Med Chem Res (2015) 24:3174–3193
DOI 10.1007/s00044-015-1370-4

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Stereo-selective synthesis, structural and antibacterial studies of novel glycosylated $\beta^{2,3}$-amino acid analogues

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Received: 26 November 2014 / Accepted: 15 April 2015 / Published online: 28 April 2015

Abstract Ten β-lactam derivatives (**6a–j**) with an *O*-phenyl group at C-2, a glycoside at C-3 and various substituted phenyl rings on the nitrogen, were formed *via* a series of reactions starting with the glycoside precursors, functionalizing this to the aldehyde, forming the imines and finally the lactams, which were modified, removing the benzyl group on the glycoside producing a further set of lactams (**7a–j**) and converting them to the $\beta^{2,3}$ amino acids (**8a–j**) in the final stage of the synthesis. The synthesis and structural elucidation of the three sets of compounds are discussed here. In addition, the crystal structure of **6e** is also discussed, which shows the absolute configuration of the molecule to be *2S*,*3R*. The Hirshfeld interactions are calculated to be Cl···H (11.1 %), O···H (8.0 %) and N···H (0.4 %). The reaction mechanism for the formation of the β-lactam is also proposed. The three sets of compounds were evaluated for their antibacterial activity against three gram-positive (*Pseudomonas aeruginosa*, *Bacillus subtilis* and *Staphylococcus aureus*) and one gram-negative strain (*Escherichia coli*). The $\beta^{2,3}$-amino acids **8a**, **8b** and **8h** showed good antibacterial activity against all strains with MIC values between 0.17 and 1.44 mM, comparable to the standard ampicillin. All three compounds showed better activity to *E. coli* than ampicillin. Interestingly, molecular docking to the penicillin-binding protein (PBP 2X) showed the same three compounds **8a**, **8b** and **8h** to have a better MolDock score than ampicillin and the free carboxyl groups in the β-amino acid to bind to Ser337, blocking it from further binding with peptidoglycan for cross-linking and subsequent transpeptidation.

Keywords β-Lactam glycosides · β-Amino acids · Antibacterial activity · Molecular docking

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Introduction

The overuse of antibiotics resulting in antibiotic resistance is a topic of great concern. There is thus a need to develop new antimicrobials with higher potency and less toxicity (Fisher *et al.*, 2005; Ritter and Wong, 2001). One such approach is molecular hybridization, where two or more different classes of biologically active compounds are linked to create a hybrid molecule with enhanced therapeutic effects (Mehta and Singh, 2002). Glycofuranose and other sugar derivatives have demonstrated significant anticancer (Tripathi *et al.*, 2001), and antimycobacterial activity (Maddry *et al.*, 1998; Tripathi *et al.*, 2002), enhanced drug delivery (Namane *et al.*, 1992; Negre *et al.*, 1992) and improved aqueous solubility and oral activity (Fisher *et al.*, 1991), while enantiomerically pure β-amino acids (hydrolysis products of β-lactams) have received great attention due to their interesting pharmacological properties and occurrence in natural products (Juaristi and Soloshonok, 1997).

$\beta^{2,3}$-Amino acids have a three carbon core skeleton with side chains at C-2 and C-3. Examples of compounds with these core skeletons are the natural products: majusculamide-

C (Carter *et al.*, 1984), onchidin (Rodriguez *et al.*, 1994), guineamide-C (Tan *et al.*, 2003), malevamide D (Horgen *et al.*, 2002) and ulongapeptin (Williams *et al.*, 2003). Peptides containing β-amino acids are known to display interesting biological properties and are increasingly finding applications in medicinal chemistry (Juaristi and Lopez-Ruiz, 1999; Aguilar *et al.*, 2007; Ruf *et al.*, 2012). In addition, these β-amino acids have shown antibacterial (Hicks *et al.*, 2013), anticancer (Hansen *et al.*, 2012), proteasome inhibiting activity (Zhu *et al.*, 2010) and anti-HIV activity (Hamada *et al.*, 2002). A number of natural products possess a β-amino acid core, namely taxol or taxotere with anticancer activity (Wani *et al.*, 1971), cryptophycin (Smith *et al.*, 1994) and microginin (Tatsufumi *et al.*, 1993) with angiotensin-converting-enzyme-inhibiting activity, amastatin, an aminopeptidase inhibitor (Aoyagi *et al.*, 1978) and jasplakinolide with antifungal activity (Scott *et al.*, 1988).

Several attractive asymmetric catalytic methods for the synthesis of enantiomerically pure β-amino acids have been reviewed in the literature (Ma, 2003; Sewald, 2003; Weiner *et al.*, 2010). Furthermore, a significant amount of work with respect to methodology and synthesis has been reported for sugar β-lactams and β-amino acid derivatives (Ramesh *et al.*, 2012; Shaikh *et al.*, 2007; Chincholkar *et al.*, 2007; Sanap *et al.*, 2010; Deshmukh *et al.*, 2004); however, to the best of our knowledge, there have been no reports on the synthesis of glycosylated $\beta^{2,3}$-amino acids, with side chains at C-2 and C-3. Herein, we report a non-catalytic method for the stereo-selective synthesis of sugar β-lactams and glycosylated $\beta^{2,3}$-amino acid derivatives, their structural elucidation with NMR and single crystal X-ray diffraction and their antibacterial activity along with molecular docking studies.

Results and discussion

Chemistry

In our synthetic approach, we have used the methodologies of Agrofoglio *et al.* (1997) and Arun *et al.* (2003) with modifications. The synthesis started with formation of the furanose ring from D-glucose, together with selective acetal protection forming **1** (Fig. 1). The free hydroxy group on **1** was then protected with a benzyl group in **2**, before selectively removing the acetal group at C-5 and C-6 resulting in **3**. Oxidation with sodium periodate produced the aldehyde intermediate **4**, from which the imines **5a–j** were formed from several substituted anilines. The β-lactams **6a–j** were then formed from the imines with phenoxyacetyl chloride. The position of the substituent on aniline was important as the yields were best with substituents at the *para* position and poorer with the *meta* substituted anilines. The reaction did not occur with *ortho* substituted anilines due to steric hindrance between the *ortho* substituents on the imine and phenoxyacetyl chloride. The structures of **6a–j** were confirmed by NMR spectroscopy. Single crystal X-ray diffraction and coupling constants ($J_{\text{H-2/H-3}} = 5.6$ Hz) indicated that only the *cis 2S,3R* diastereomer formed in the reaction.

Using **6b** as an example of a benzyl-protected β-lactam, the IR spectrum showed an amide carbonyl absorption at 1750 cm^{-1}. The ^{1}H NMR spectrum showed the β-lactam protons H-2 and H-3 as a doublet and double doublet at δ 5.28 ($J = 5.6$ Hz) and δ 4.73 ($J = 8.9$, 5.6 Hz), respectively. The β-lactam carbonyl resonance was observed at δ 164.1. The glycoside proton resonances appeared at δ 4.60–4.61 (m, H-5), δ 4.39 (d, $J = 3.3$ Hz, H-6), δ 4.67 (d, $J = 3.8$ Hz, H-7) and δ 6.06 (d, $J = 3.8$ Hz, H-8). The acetonide tertiary carbon C-9 appeared at δ 111.9 and C-10 and C-11 appeared at δ 26.8 and 26.3 in the ^{13}C NMR spectrum.

The benzyl-protected group was indicated by the diastereotopic protons H-7a_1 and H-7a_2 as two doublets at δ 4.27 and δ 4.60 each with $J = 11.4$ Hz and the aromatic protons as a multiplet at δ 7.14–7.21. The oxygenated phenyl ring on the β-lactam core structure was indicated by the presence of multiplets at δ 7.00–7.07 (H-2c/4c/6c) and δ 7.25–7.23 (H-3c/5c). For the *N*-substituted 3-fluorophenyl ring, the H-2b and H-4b resonances appeared as a doublet of triplets at δ 7.47 ($J = 10.6$, 2.2 Hz) and triplet of doublets at δ 6.79 ($J = 8.4$, 2.3 Hz). H-6b occurred as a double doublet at δ 7.54 with $J = 8.1$ and 1.4 Hz and H-5b overlapped with H-3c/5c at δ 7.25–7.30.

The COSY correlation between H-3 and H-5 indicated that the glycoside was attached to C-3 of the lactam ring. The HMBC correlation from H-2 to the aromatic singlet resonance of C-1c confirms the attachment of the phenoxy group to the lactam ring. HMBC correlations from H-2 and H-3 to the carbonyl carbon C-1 confirmed the formation of the lactam ring. The HMBC correlation from H-6 to C-7a confirmed that the hydroxy at C-6 was benzyl-protected and the acetonide methyl groups H-10 and H-11 showed HMBC correlations to C-9, allowing this carbon to be assigned. Weak NOESY interactions between H-3 and H-2b and H-6b confirmed that the 3-fluorophenyl group was attached to the nitrogen of the lactam ring. NOESY interactions between H-10 and both H-5 and H-6 indicate that these protons are on the same side of the plane, and likewise, NOESY interactions between H-11 and both H-7 and H-8 indicate that these protons are on the other side of the plane. This allowed us to differentiate H-10 from H-11. Selected HMBC and NOESY interactions are given in Figs. 2 and 3.

There are two possible conformations for the attachment of the sugar to the β-lactam ring in the synthesized

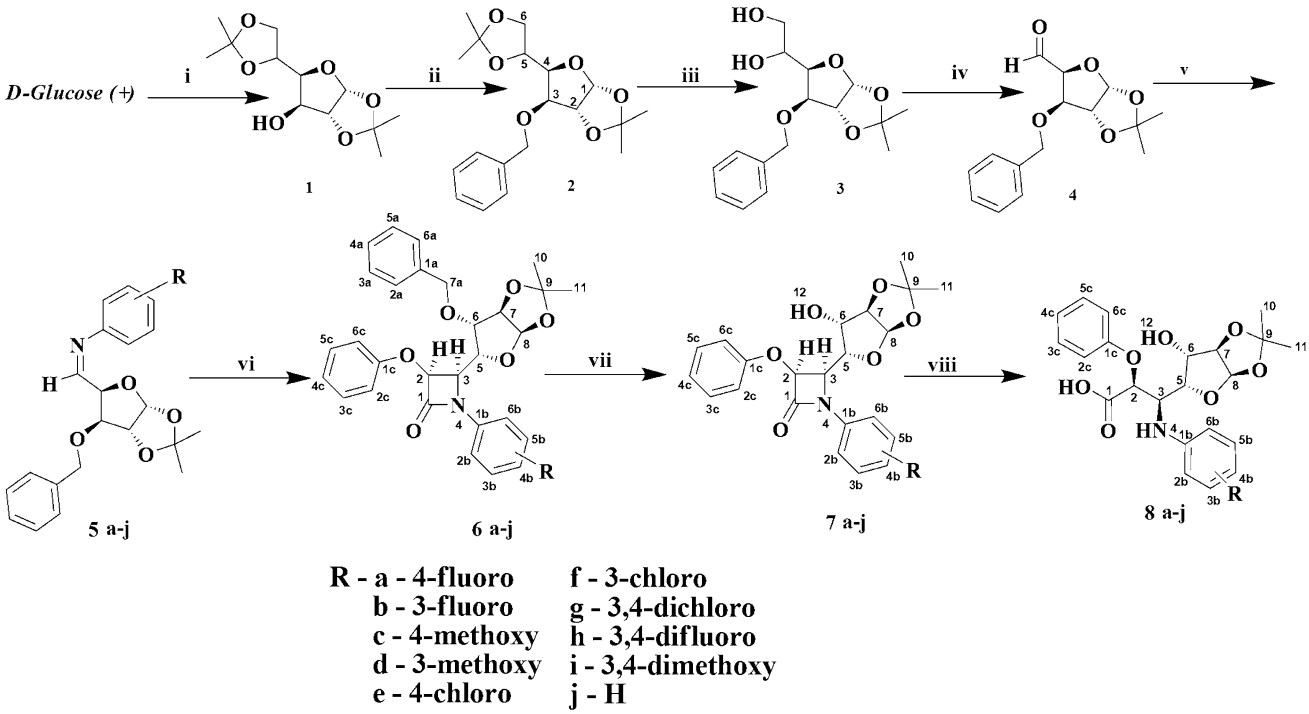


Fig. 1 Synthetic scheme for the synthesis of the β-amino acids **8a–j** via hydrolysis of the β-lactams. Reagents and conditions: *i* $CuSO_4$, acetone, H_2SO_4, rt, 30 h; *ii* NaH, TBAI, benzyl bromide, THF, 2 h; *iii* 70 % acetic acid in water, rt, 16 h; *iv* $NaIO_4$, 0 °C, 2 h; *v:* substituted $ArNH_2$, $MgSO_4$, CH_2Cl_2, reflux 8–9 h; *vi* $PhOCH_2COCl$, Et_3N, CH_2Cl_2, 0 °C to rt, 15 h; *vii* Pd/C, MeOH, rt; *viii* LiOH/THF, 0–10 °C, 2 h

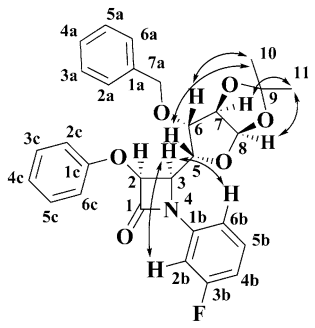


Fig. 2 Selected NOESY interactions for **6b**

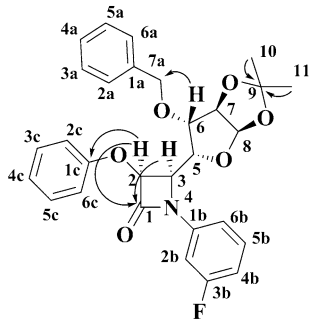


Fig. 3 Selected HMBC correlations for **6b**

derivatives **6a–j**. The crystal structure of **6e** (Fig. 4) shows that H-3 and H-5 are anti. The coupling constant (***J***) between these two protons was found to be 8.9 ± 0.2 Hz for all the derivatives. This coupling constant was consistent with a dihedral angle of 171.69° observed between H-3 and H-5 in the crystal structure of **6e**. Likewise, the coupling constant $J_{H2,H3}$ of 5.6 Hz was consistent with the almost eclipsed protons which had a dihedral angle of 0.5° from the crystal structure.

Debenzylation of **6a–j** with hydrogen on a palladium–carbon catalyst resulted in **7a–j** with a free hydroxy group at C-6. This was indicated by the OH absorption at 3477 cm^{-1} in the IR spectrum as well as the loss of the five proton multiplet at δ 7.14–7.21 for the benzyl group and the two H-7a proton resonances in the ^1H NMR spectrum. The C-6 carbon resonance to which the benzyl group was attached was also observed more upfield in **7b** at δ 75.6 as opposed to δ 83.1 in **6b**.

In the last step of the reaction, the lactams **7a–j** were hydrolysed to the β-amino acids using lithium hydroxide in THF to produce **8a–j**. This was indicated by the change in carbonyl resonance from δ 164.0 in the lactam (**7b**) to δ 173.1 in **8b**. The H-2 and H-3 resonances also shifted to δ 5.07 (d, $J = 2.2$ Hz) and δ 4.54 (dd, $J = 8.8$, 2.2 Hz) in **8b**, respectively, from δ 5.46 (d, $J = 5.6$ Hz) and δ 4.69 (dd, $J = 8.6$, 5.6 Hz) in **7b**. The change in $J_{H2,H3}$ from 5.6

to 2.2 Hz is evident from the fact that the lactam ring was hydrolysed and from the fact that the dihedral angle between H-2 and H-3 approached 90°. Final confirmation was obtained by the HRMS of each of the synthesized compounds **8a**–**j**.

The proposed mechanism for the stereo-selective synthesis of the sugar-based β-lactams (**6a**–**j**) is illustrated in Fig. 5. The reaction can occur either *via* an endo or exo attack by the pi electrons of the imine on the LUMO of the ketene. However, due to the bulky sugar moiety, causing steric hindrance, only the exo attack occurs resulting in the intermediate INT1 and transition state TS1. It is important to note that the exo attack in INT1 results in the electron donor of the ketene occupying the outward position at C-3 with lower-energy conrotatory transition state structures resulting in the *2S,3R* diastereomer (Tang *et al.*, 2010; Lopez *et al.*, 1993).

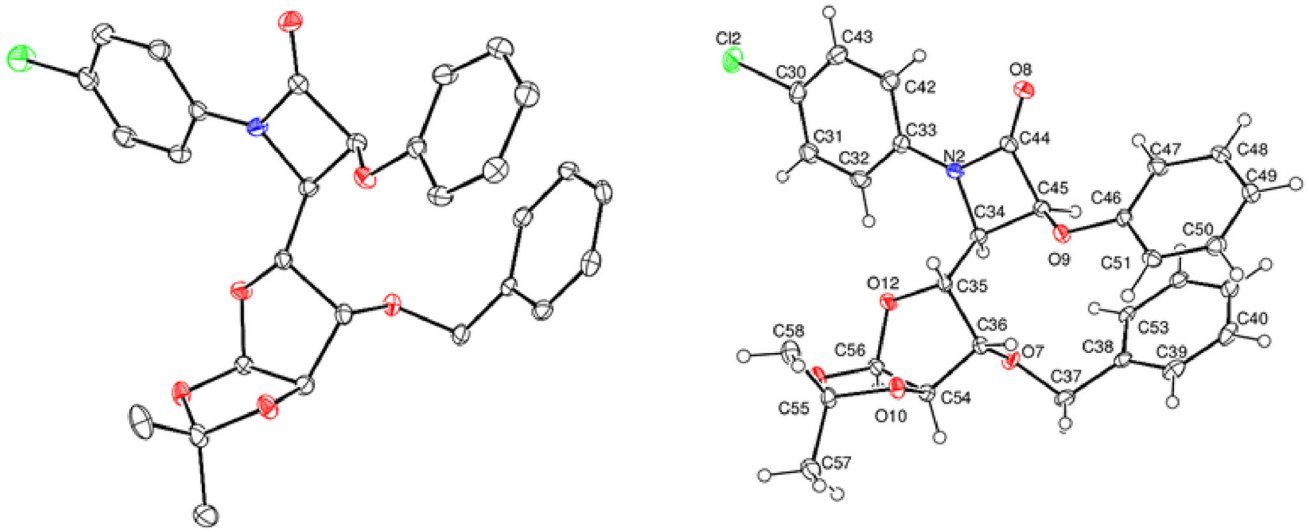


Fig. 4 Ortep diagrams for **6e**

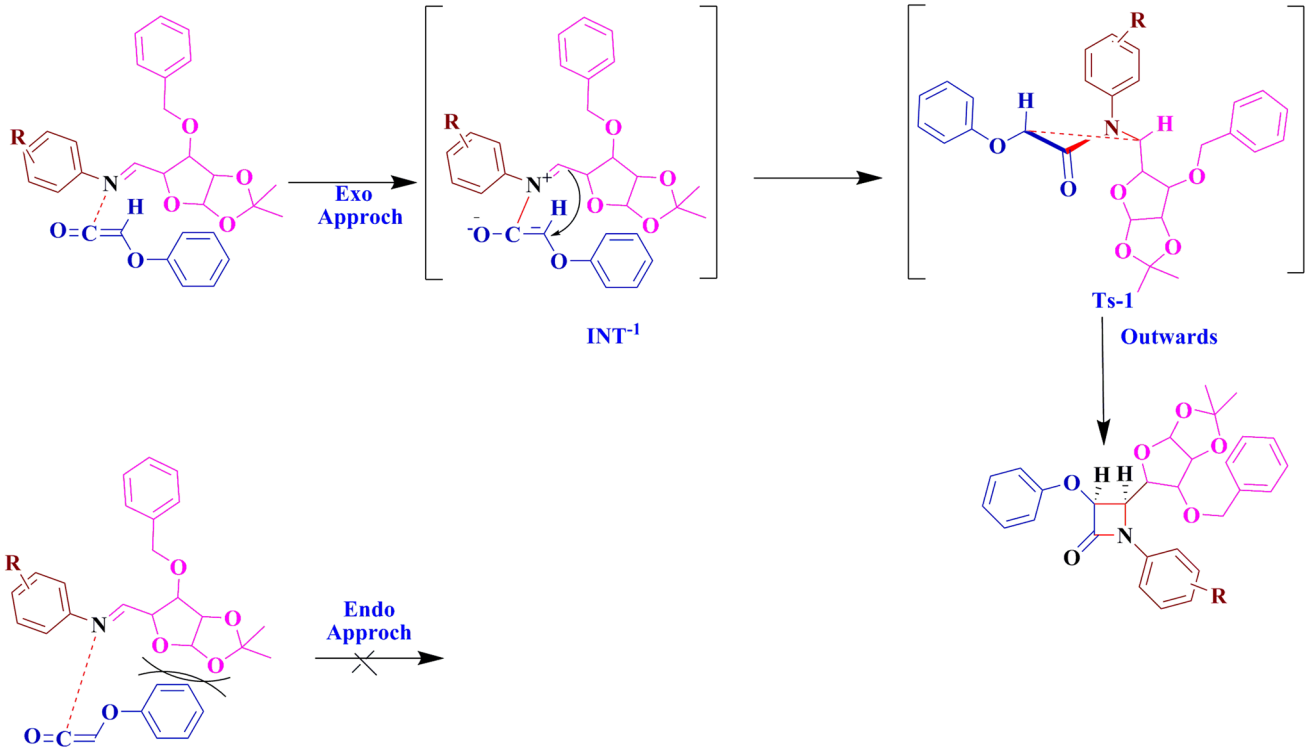


Fig. 5 Proposed reaction mechanism for the Staudinger reaction

Crystal structure

Crystal and structure refinement data for **6e** are shown in Table 1. **6e** crystallizes in the orthorhombic $P2_12_12_1$ space group with two molecules in the asymmetric unit. The benzyl and phenyl rings are pointed away from each other at opposite ends of the lactam ring, with the sugar moiety situated orthogonal to the phenyl moiety on the nitrogen. The two benzyl rings on the sugar and the lactam are almost parallel to each other. Bond distances in the lactam rings all display single-bond characters with the N–C bond lengths being 1.368(3) and 1.370(3) for the amide bond and 1.493(3) and 1.490(5) for the other N–C-bond for the two molecules (Table 2). The two sets of C–C bond distances for the two molecules are 1.538(3) and 1.552(3), and 1.536(3) and 1.558(3) Å. The difference in the lactam ring bond distances causes some strain in the ring; thus, the bond angles of the lactam ring lie between 86.4(2)° and 99.2(2)° for both molecules. As explained in the NMR section, H(25) and H(8) are antiperiplanar with a dihedral angle of above 170.0° and H(8) and H(9) are eclipsed with a dihedral angle of 0.5°. In the crystal, weak C–H…O hydrogen bonding interactions (Table 3) link the molecules in a 3D network (Fig. 6). Figure 7 represents fingerprint plots corresponding to Hirshfeld surface–surface interactions and percentage contribution of interactions. The Hirshfeld interactions for **6e** are Cl···H (11.1 %) > O···H (8.0 %) > N···H (0.4 %).

Table 1 Crystal data and X-ray data collection parameters for **6e**

Empirical formula	$C_{29}H_{28}ClNO_6$
Formula weight	521.97
Temperature (K)	173
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions (Å,°)	$a = 7.4706(6)$
	$b = 23.0503(16)$
	$c = 29.525(2)$
Volume (Å^3)	5084.2 (6)
Z	8
Density$_{calc}$ (mg/m^3)	1.364
Absorption coefficient (mm^{-1})	0.196
$F(000)$	2192
Crystal size (mm^3)	0.79 × 0.77 × 0.33
Theta range for data collection (°)	1.21–25.00
Index ranges	$-8 \le h \le 8$, $-27 \le k \le 28$, $-35 \le l \le 35$
Reflections collected	111,939
Independent reflections	8942 [R(int) = 0.0390]
Completeness to theta = 25.242°	97.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.937 and 0.917
Refinement method	Full-matrix least squares on F^2
Data/restraints/parameters	8942/0/671
Goodness-of-fit on F^2	1.041
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0284$, $wR_2 = 0.0616$
R indices (all data)	$R_1 = 0.0345$, $wR_2 = 0.0643$
Absolute structure parameter	0.007(12)
Extinction coefficient	N/A
Largest diff. peak and hole (e Å^{-3})	0.150 and −0.250

In vitro antibacterial activity

All the above-mentioned synthesized compounds (**6a–j**, **7a–j** and **8a–j**) were evaluated for antibacterial activity against four bacterial strains (three gram-positive (+) and one gram-negative). Disc diffusion assays were initially used to gauge whether or not the compounds had activity and to select compounds on which to determine the MIC values. The results are presented in Tables 4 and 5. Compounds **6a–j** with an *O*-benzyl group at C-6 on the sugar moiety were the least active in the disc diffusion assay. By removing the benzyl group at C-6 resulting in the free hydroxy group, the activity of the resultant compounds **7a–j** increased, having a broader spectrum of activity in that some of the compounds were now also active against *Escherichia coli* and *Staphylococcus aureus*. *E. coli* and *S. aureus* were resistant to **6a–j**. However, the highest activity was shown by the glycosyl $\beta^{2,3}$-amino acid derivatives (**8a–j**) with all compounds having a broad spectrum of activity and only **8i** and **8j** (the 3,4-dimethoxy and unsubstituted derivatives) being inactive against *S. aureus*.

Amongst the glycosyl $\beta^{2,3}$-amino acid derivatives (**8a–j**), the highest activity was shown by **8h**, followed by **8b** and **8a**. These were all the fluoro derivatives substituted at the 3,4-position, 3-position and 4-position, respectively. These results indicate that the fluorine atom substituted on the

Table 2 Selected bond lengths/Å and angles/° for **6e**

N(1)–C(18)	1.368(3)
C(9)–C(18)	1.538(3)
C(8)–C(9)	1.552(3)
N(1)–C(8)	1.493(3)
C(8)–N(1)–C(18)	95.20(16)
C(9)–C(18)–N(1)	91.76(17)
C(8)–C(9)–C(18)	86.35(16)
C(9)–C(8)–N(1)	86.61(15)

N-phenyl ring is essential for antibacterial activity and that both C-3 and C-4 substitutions are equally important, with fluorine substitution at both positions showing the best activity. The MIC values of these three compounds (**8a**, **8b** and **8h**) were then determined to further evaluate their antibacterial activity. These results also indicated that **8h** was the best antibacterial compound overall and **8a**, **8b** and **8h** all showed good-to-moderate activity against the bacterial strains tested against. All three compounds **8a**, **8b** and **8h** showed at least twofold better activity (0.17 mM) than ampicillin (0.37 mM) against *E. coli*. In addition, **8h** showed slightly better activity (0.33 mM) than ampicillin (0.37 mM) against *P. aeruginosa*.

These results indicate that the $\beta^{2,3}$ amino acid core is better than the lactam moiety in these molecules with regard to antibacterial activity. These results also showed the importance of the free hydroxy group at C-6 and fluorine substitution at the 3- and 4-positions on the *N*-phenyl ring.

Docking studies

To validate these results, molecular docking studies for **8a**, **8b** and **8h** were carried out using Molegro Virtual Docker (MVD-2013, 6.0). Recently, Nagarajan *et al.* (2012) reported the synthesis and antimicrobial activity of sugar-based azetidin-2-one derivatives of which many compounds displayed great affinity towards penicillin-binding protein (PBP) and inactivate PBPs by interfering with the process of transpeptidation. It was also reported that Ser337, Ser395, Ser548 and Thr550 are important residues of PBP 2X for the binding of β-lactam glycosides to the target PBP (Nagarajan *et al.*, 2012). β-Lactam antibiotics such as cefditoren (CDS) exhibit potent antimicrobial activity by targeting PBPs, which are membrane-associated enzymes that catalyse polymerization and cross-linking of peptidoglycan precursors in bacterial cell wall biosynthesis. The involvement of the active-site serine residue of PBPs is found to be crucial during the cross-link formation and subsequent transpeptidation (Mcdonough *et al.*, 2002).

The trypsin-digested PBP 2X is composed of a short cytoplasmic region, a transmembrane region and a periplasmic unit containing three domains: the N-terminal, transpeptidase and *C*-terminal domains. The crystal structure of CDS-acylated PBP 2X from *Streptococcus pneumonia* (**2Z2M**) exists as a homodimeric assembly, and the inhibitor CDS is bound to two chains (B and E) of the structure, but none of the binding sites come in the interface of two domains or two different chains (Yamada *et al.*, 2007). The protein data bank (PDB) structure **2Z2M** bound to the inhibitor CDS shows a true binding site for each of the subunits and was considered as the centre of search space for docking. Hence, to identify other residual interactions of the tested compounds, a grid box (including residues within a 10.0 Å radius) large enough to accommodate the active site was constructed. An essential feature of the binding site is the conservation of hydrogen bonds and aromatic π–π stacking interactions.

The molecular docking results for **8a**, **8b** and **8h** are summarized in Table 6. The MolDock score ranged from −142.7 to −147.7 kcal mol^{-1}, while the MolDock score of standard drugs AMP (Ampicillin) and CDS was −139.5 and −196.6 kcal mol^{-1}, respectively. Based on the MolDock score, the conformations were ranked with the criteria that the lower the MolDock score, the higher the binding affinity. Thus, all the test compounds exhibited better affinities compared to ampicillin (AMP) towards PBP 2X. Compounds **8h** and **8a** (MolDock score: −147.7 and −147.8 kcal mol^{-1}, respectively) displayed similar affinity towards PBP 2X followed by **8b** (−142.7 kcal mol^{-1}). MVD could predict the correct pose of the ligand. The docked pose displays the proper conformation and better interaction than the co-crystallized ligand. The best poses (orientations) of the docked compounds and of standard drugs (AMP and CDS) are represented in Fig. 8. Compounds **8a**, **8b** and **8h** exhibited well-conserved interactions with PBP 2X such as hydrogen bonding, hydrophobic bonding and van der Waal's interactions with one or more amino acid residues in the active pocket. Compound **8h** displayed the highest number (8) of conserved hydrogen bond interactions (−22.6 kcal mol^{-1}) with amino acid residues Ser337, Ser395, Asn397 and Thr550, while compound **8a** exhibited three hydrogen bond interactions (−12.5 kcal mol^{-1}) with Ser337, Ser395 and Asn397. In compound **8b** (−8.7 kcal mol^{-1}), prominent hydrogen bonding interactions were observed with Ser337 and Gln552 residues.

Table 3 H bond interactions for **6e**

Donor···H···Acceptor	D–H	H···A	D···A	D–H···A	Symmetry code
C(9)···H(9)···O(8)	1.00	2.57	3.394(3)	140	$2 - x, 1/2 + y, 1/2 - z$
C(27)···H(27B)···O(4)	0.98	2.58	3.507(3)	158	$-1/2 + x, 1/2 - y, - z$
C(40)···H(40)···O(5)	0.95	2.44	3.310(3)	152	$1 + x, y, z$
C(58)···H(58A)···O(7)	0.98	2.27	3.232(3)	165	$-1 + x, y, z$
C(58)···H(58B)···O(11)	0.98	2.56	3.464(3)	153	$-1/2 + x, 1/2 - y, 1 - z$

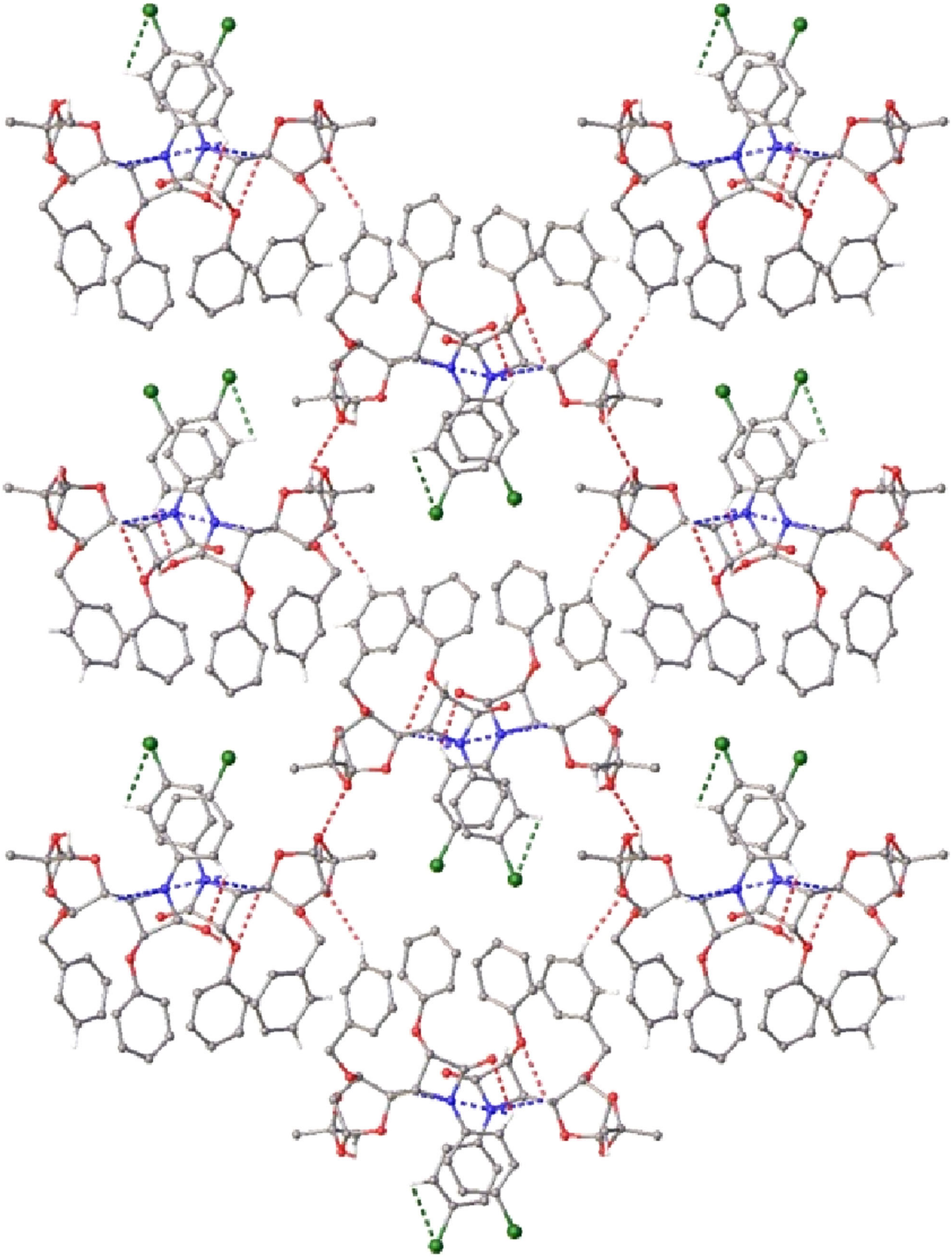
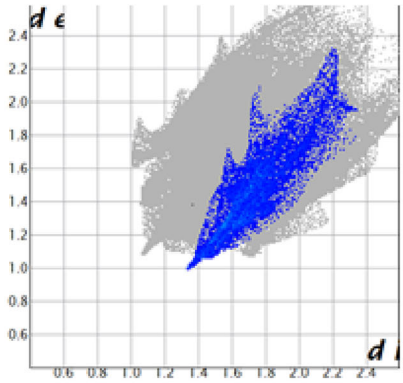
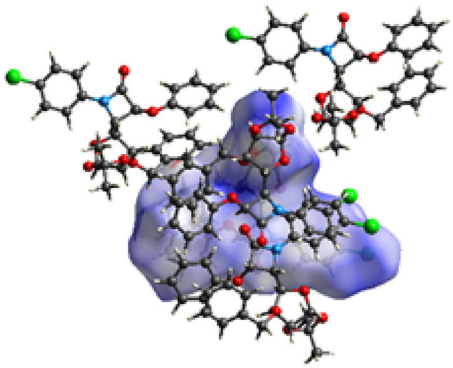


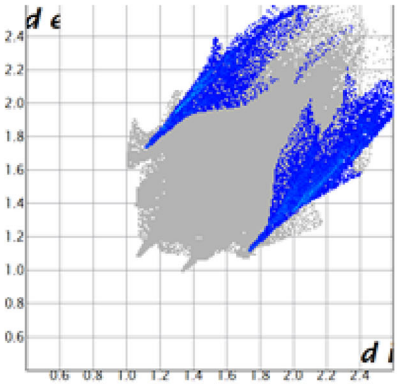
Fig. 6 Crystal packing diagram of **6e**



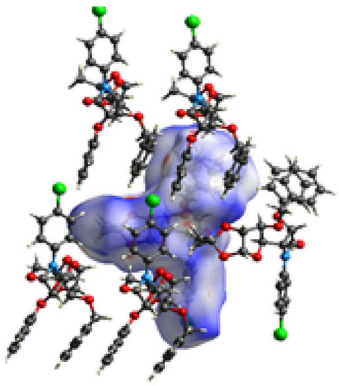
Fingerprint plot, O---H interaction, 8.0%



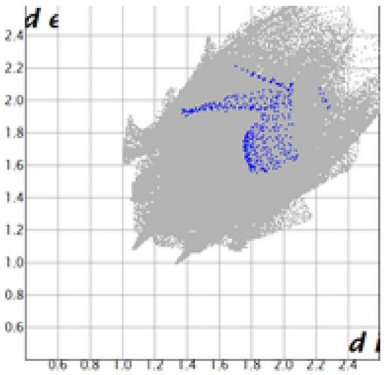
Hirshfeld Surface of the central molecule mapped with *d* norm, O---H interaction



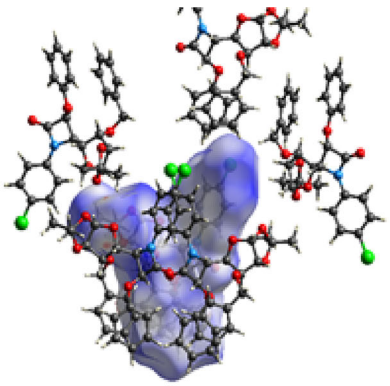
Fingerprint plot, Cl---H interaction, 11.1%



Hirshfeld Surface of the central molecule mapped with *d*norm, Cl---H interaction



Fingerprint plot, N---H interaction, 0.4%



Hirshfeld Surface of the central molecule mapped with *d*norm, N---H interaction

Fig. 7 Hirshfeld analysis of **6e**

Table 4 In vitro antibacterial activity (Zone of inhibition in mm) of **6a–j**, **7a–j**, and **8a–j** by the disc diffusion method

No.[b]	*P. aeruginosa*	*E. coli*	*B. subtillis*	*S. aureus*
6a	–	–	7.9	–
6b	9	–	8.1	–
6c	11	–	7.5	–
6d	10	–	8	–
6e	–	–	7.5	–
6f	–	–	7.5	–
6g	–	–	8	–
6h	–	–	8	–
6i	10	–	7	–
6j		–	8	–
7a	10	10	10	12
7b	8	8	9	14
7c	9	–	11	10
7d	9	8	13	14
7e	–	–	8	12
7f	–	–	10	10
7g	–	8	12	12
7h	9	9	8	–
7i	7		7	–
7j	11	–	8	–
8a	12	28	30	22
8b	12	30	30	23
8c	9	28	18	17
8d	9	28	18	16
8e	10	30	25	20
8f	8	30	25	21
8g	9	28	25	20
8h	18	28	30	28
8i	10	9	10	–
8j	10	10	10	–
Amp[a]	–	20	38	20

[a] Ampicillin control (570 μg mL^{-1})

[b] Test compounds have a concentration of 400 μg mL^{-1}

Table 5 In vitro antibacterial activity (MIC in mM) of compounds **8a**, **8b** and **8h**

No.	*P. aeruginosa*	*E. coli*	*B. subtillis*	*S. aureus*
8a	1.44	0.17	0.72	1.44
8b	1.44	0.17	0.72	1.44
8h	0.33	0.17	0.33	1.38
Amp	0.37	0.37	0.18	0.37

Besides hydrogen bonding interactions, steric and aromatic π–π stacking interactions were also evident with the various amino acid residues in the active site of **2Z2M**. These are essential for the inhibition of PBP 2X. The present study indicated that in general, free carboxyl groups in the β-amino acid bind to Ser337, blocking it from further binding with peptidoglycan for cross-linking and subsequent transpeptidation. Thus, the in silico results provide strong evidence that **8a**, **8b** and **8h** play a vital role in binding with **2Z2M**, which could eventually lead to effective inhibition of PBPs.

Materials and methods

Reagents and chemicals were purchased from Sigma-Aldrich *via* Capital Laboratories, South Africa. Organic solvents were purified by re-distillation and dried according to standard procedures. Melting points were determined on a Thermonik Campbell melting point apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 341 digital polarimeter under standard conditions. Infrared spectra were recorded on a Bruker infrared spectrophotometer, Model 599-B. The purity of the compounds was determined on an analytical HPLC (Shimadzu-20A5) fitted with a C8 (150 mm × 5 μm) column using a mobile phase (A) (25 %) with 0.1 % formic acid buffer and (B) acetonitrile (75 %) in an isocratic system over a period of 30–60 min. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ or CD_3OD at room temperature using a Bruker Avance 400 MHz instrument. Chemical shifts (δ) are noted against the internal standard tetramethylsilane. 2D NMR (COSY, NOESY, HSQC and HMBC) was used to confirm the structure of the synthesized compounds. ESI-MS analysis was carried out in the positive mode on a Shimadzu mass spectrometer 2020, and HRMS was recorded on a Waters Synapt G2 quadrupole time-of-flight mass spectrometer, also in the positive mode (Milford, MA, USA).

Crystals suitable for X-ray diffraction were obtained by slow evaporation in a combination of dichloromethane, acetone and *n*-hexane at room temperature. The data collection and cell refinement was done using Bruker APEX2 and SAINT-Plus software packages, respectively. Data reduction was performed with SAINT-Plus and XPREP. SHELXS-97 (Sheldrick, 2008) was used to solve and refine the structure. ORTEP-3 (Farrugia, 1999) and WinGX (Farrugia, 1999) were used to prepare the graphics for publication. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB21EZ, UK. Copies of the data can be obtained free of charge on quoting the depository number CCDC-1035534 (Fax: +44-1223-336-033; E-Mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk).

Hirshfeld analysis

Crystal Explorer 3.0 software was used to determine the Hirshfeld surface in the crystal structure and its associated fingerprint analysis and to view the molecular contacts between the molecules (Spackman and McKinnon, 2002). The different colour intensities presented indicate the strength of interactions for short and long contacts. The program was run with the *cif* file. Bond lengths to hydrogen atoms were set to typical neutron values of C–H = 1.083 Å. The Hirshfeld surface mapped with d_{norm} of the molecule, and Cl···H, O···H and N···H contacts are coloured with white-to-blue, indicating that the molecular contacts are close to van der Waals separations in the structures. Accordingly, at each point on the *iso*-surface, two distances are defined: d_e and d_i. The distance from a point to the nearest nucleus external to the surface is denoted as d_e, while the distance from a point to the nearest nucleus internal to the surface is denoted as d_i (Mckinnon *et al.*, 2004, 2007). The normalized distance (d_{norm}) based on d_e and d_i is given by:

$$d_{\text{norm}} = \left(d_i - r_i^{\text{vdw}}\right)/r_i^{\text{vdw}} + \left(d_e - r_e^{\text{vdw}}\right)/r_e^{\text{vdw}}$$

where r_i^{vdw} and r_e^{vdw} are the van der Waals radii of the atoms.

The parameter d_{norm} defines a surface with a red–white–blue colour scheme, where red is used to highlight short contacts, white for contacts around the van der Waals separation and blue for long contacts. Hirshfeld surface fingerprint plots were generated using d_i and d_e as 2D histograms.

Docking methodology

Chemdraw10.0 was used to construct the compounds **8a**, **8b** and **8h**, and the 2D structures converted into energy-minimized 3D structures which were saved as MDL MolFiles (.mol2). The coordinate file and crystal structure of trypsin-digested PBP 2X (PDB ID: **2M2Z**) were obtained from the protein data bank (http://www.rscb.org/pdb). The protein file was prepared by the removal of water molecules, addition of polar hydrogens and removal of other bound ligands. In the present study, the binding site was selected based on the amino acid residues of the prepared protein as obtained from the protein data bank which are involved in binding with CDS. This binding site would be considered as the most probable region based on crystallographic data. The docking protocol was carried out for the synthesized compounds as listed in Table 6 using MVD-2013 (6.0) software and standard operating procedures.

Table 6 Molecular docking results by MVD-2013 (6.0) based on MolDock score against **2Z2M**

No.	MolDock score kcal mol^{-1}	E-inter (protein–ligand) kcal mol^{-1}	Residues involved in hydrophobic and steric interactions (within 5 Å)	Residues involved in hydrogen bonding	H-bonds[a]		Heavy atoms count	LE1[b]	LE3[c]	Docking score kcal mol^{-1}	Rerank score kcal mol^{-1}
					No.	kcal mol^{-1}					
8a	−147.855	−160.474	Glu334, Asn377, Glu378, Ser395, Thr550	Ser337, Ser395, Asn397	03	−12.5000	31	−4.7695	−3.6416	−464.006	−112.890
8b	−142.667	−153.38	Glu334, Ser337, Thr550, Ala551	Ser337, Gln552	05	−8.7173	31	−4.6021	−1.4880	−473.793	−46.129
8h	−147.718	−169.785	Gly336, Ser337, Asp373, Thr550, Gln552	Ser337, Ser395, Asn397, Thr550	08	−22.6022	32	−4.6161	−3.5277	−479.106	−112.888
AMP[d]	−139.546	−138.552	Gln552, Thr560	Glu334, Ser337, Ser395, Ser348, Thr550	07	−12.0332	25	−5.5818	−3.9849	−481.997	−99.623
CDS[e]	−196.551	−184.475	Trp374, His394, Gln452, Thr526, Thr550, Ala551, Tyr561	Glu334, Ser337, Asn397, Ser548, Thr550, Ala551, Gln552	12	−24.5485	33	−5.9561	−1.7029	−641.603	−56.196

[a] Hydrogen bonding energy between protein and ligand

[b] Ligand Efficiency: MolDock score divided by heavy atoms count

[c] Ligand efficiency: Rerank score divided by heavy atoms count

[d] Ampicillin (Penicillin derivative)

[e] Cefditoren (Cephalosporin derivative)

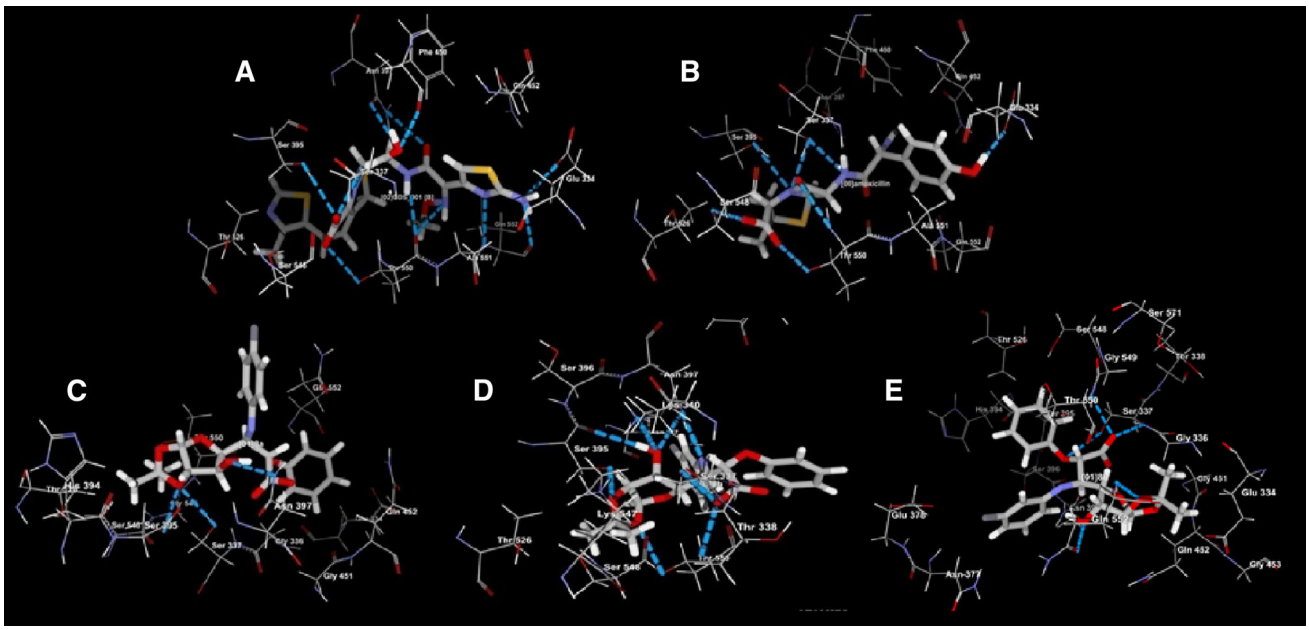


Fig. 8 The docked pose of compounds in the active site of PBP 2X; Hydrogen bonds are represented by *broken lines* (*blue*). **a** Cefdfitoren, **b** Ampicillin, **c 8a**, **d 8h**, **e 8b** (Color figure online)

The MolDock scoring function is used by the MVD program and is defined by $E_{score} = E_{inter} + E_{intra}$, where, E_{score} = MolDock score, E_{inter} = ligand–Protein interaction and E_{intra} = internal energy of the ligand. MolDock is based on a heuristic search algorithm that combines differential evolution with a cavity prediction algorithm. The docking scoring function of MolDock is an extension of the piecewise linear potential (PLP) including new hydrogen bonding and electrostatic terms. To further improve docking accuracy, a re-ranking scoring function was introduced, which identifies the most promising docking explanation from the results obtained by the docking algorithm (Thomsen and Christensen, 2006).

Antibacterial assay

The synthesized compounds **6a–j**, **7a–j** and **8a–j** were evaluated for antibacterial activity using the disc diffusion method (Clinical and Laboratory Standards Institute, 2007) against gram-positive and gram-negative bacteria, *Staphylococcus aureus* 29263, *Pseudomonas aeruginosa* 2758, *Escherichia coli* 25922 and *Bacillus subtilis* 6623. The standard antibiotic ampicillin was used as a control for comparison. Briefly, Mueller Hilton agar was prepared (38 g in 1 L of water) and poured into sterile prelabeled petri dishes, which were then allowed to set and dry at room temperature. The bacterial organisms were standardized using a 0.5 McFarland standard turbidity and then swabbed onto the agar plates. Paper discs were dissolved in sample and control discs were placed onto the agar plates which were inverted and incubated at 35–37 °C for 24 h. The diameter of the zone of inhibition was measured in mm. Based on these results, the most active compounds, **8a**, **8b** and **8h**, were selected to determine their MIC values using the broth microdilution assay with ampicillin as the control and following the method in Andrews (2001).

Briefly, the cultures were grown overnight on TSA and diluted to an equivalent of a 0.5 McFarland standard. 96-well microtiter plates were inoculated with 100 µL of cell suspension, 100 µL of Mueller-Hinton (MH) broth and twofold serial dilutions of compounds **8a**, **8b** and **8h** dissolved in DMSO (2500–39 µg mL^{-1}) and the antimicrobial agent ampicillin (128–4 µg mL^{-1}). The plates were then incubated at 30 °C for 24 h without shaking. The negative control wells contained MH broth only, and the positive control wells contained the respective cell suspensions with no compound/antimicrobial agents added. This was done in duplicate. The MIC was the lowest concentration of antimicrobial agent, which inhibited the visible growth of the bacteria.

Synthesis of intermediate 4

The synthesis of compound **4** was carried out following the procedures reported in Agrofoglio *et al.* (1997) and Arun *et al.* (2003). This involved acetonide protection of glucose, benzyl protection of the free hydroxyl group, subsequent acetonide deprotection and oxidation to the aldehyde (**4**).

Synthesis of the imines (5a–j)

Anhydrous $MgSO_4$ (2.0 g) was added to a solution of substituted anilines (2.0 mmol) and aldehyde **4** (556.0 mg, 2.0 mmol) in dichloromethane (DCM) (30 mL), and the mixture was stirred under reflux for 8 h. The solution was filtered and the solvent removed under reduced pressure to afford the imines **5a–j** as brown or colourless oils, which were used immediately for the next step.

Synthesis of the β-lactams (6a–j)

A solution of phenoxyacetyl chloride (255.0 mg, 1.5 mmol) in dry DCM was added to a solution of the respective imine (**5a–j**) (1 mmol) and triethylamine (454.0 mg, 4.5 mmol) in dry DCM (20 mL) at 0–5 °C under nitrogen. Upon completion, the mixture was allowed to attain room temperature and stirred overnight. Completion of the reaction was monitored by TLC. On completion, the solvent was concentrated under reduced pressure to afford the crude β-lactams (**6a–j**) as white solids, which were purified by column chromatography using silica gel and 20 % ethyl acetate in n-hexane.

(**6a**) *((3S,4R)-4-((3aR,5R,6S,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-1-(4-fluorophenyl)-3-phenoxyazetidin-2-one)* White solid (60 % yield); mp 120–122 °C; $[\alpha]_D^{20} = -4.32°$ (*c* 0.02, MeOH); IR υ_{max} 2934 (C–H), 1744 (C=O); 1590, 1511, 1493 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.70 (2H, dd, *J* = 9.1, 4.8 Hz, H-2b/6b), 7.26–7.30 (2H, m, H-3c/5c), 7.14–7.19 (5H, m, H-2a-H-6a), 7.03–7.08 (3H, m, H-2c/4c/6c), 6.98 (2H, t, *J* = 8.8 Hz, H-3b/5b), 6.04 (1H, d, *J* = 3.8 Hz, H-8), 5.28 (1H, d, *J* = 5.6 Hz, H-2), 4.71 (1H, dd, *J* = 8.8, 5.6 Hz, H-3), 4.65 (1H, d, *J* = 3.9 Hz, H-7), 4.60 (2H, d, *J* = 11.8 Hz, H-$7a_2$, H-5), 4.39 (1H, d, *J* = 3.3 Hz, H-6), 4.29 (1H, d, *J* = 11.4 Hz, H-$7a_1$), 1.47 (3H, s, H-10), 1.31 (3H, s, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.7(C, C-1), 159.6 (C, d, *J* = 242.3 Hz, C-4b), 157.3(C, C-1c), 137.0 (C, C-1a), 133.6 (C, C-1b), 129.7 (CH, C-3c/5c), 128.5 (CH, C-3a/5a), 128.1 (CH, C-4a), 127.6 (CH, C-2a/6a), 122.6 (CH, C-4c), 119.9 (CH, d, *J* = 7.9 Hz, C-2b/6b), 115.6 (CH, C-2c/6c), 115.5 (CH, d, *J* = 22.4 Hz, C-3b/5b), 111.9 (C, C-9), 105.0 (CH, C-8), 83.1(CH, C-6), 81.9 (CH, C-7), 81.3 (CH, C-5), 79.2 (CH, C-2), 72.0 (CH_2, C-7a), 58.5 (CH, C-3), 26.8 (CH_3, C-11), 26.3 (CH_3, C-10); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −117.49; MS (*m/z*) (pos): 506 (M^+).

(**6b**) *((3S,4R)-4-((3aR,5R,6S,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-1-(3-fluorophenyl)-3-phenoxyazetidin-2-one)* White solid (45 % yield); mp 108–109 °C; $[\alpha]_D^{20} = -3.80°$ (*c* 0.02, MeOH); IR υ_{max} 2990 (C–H), 2934 (C–H), 1750 (C=O), 1613, 1591, 1494 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.54 (1H, dd, *J* = 8.1, 1.4 Hz, H-6b), 7.47 (1H, dt, *J* = 10.6, 2.2 Hz, H-2b), 7.25–7.30 (3H, m, H-3c/5c, H-5b), 7.14–7.21 (5H, m, H-2a-H-6a), 7.01–7.07 (3H, m H-2c/4c/6c), 6.78 (1H, td, *J* = 8.4, 2.3 Hz, H-4b), 6.05 (1H, d, *J* = 3.8 Hz, H-8), 5.28 (1H, d, *J* = 5.7 Hz, H-2), 4.73 (1H, dd, *J* = 8.9, 5.6 Hz, H-3), 4.66 (1H, d, *J* = 3.8 Hz, H-7), 4.60* (1H, d, *J* = 11.4 Hz, H-$7a_2$), 4.60–4.61* (1H, m, H-5), 4.39 (1H, d, *J* = 3.3 Hz, H-6), 4.27 (1H, d, *J* = 11.4 Hz, H-$7a_1$), 1.48 (3H, s, H-10), 1.32 (3H, s, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.1 (C, C-1), 162.8 (C, d, *J* = 243.5 Hz, C-3b), 157.3 (C, C-1c), 139.0 (C, d, *J* = 10.8 Hz, C-1b), 137.0 (C, C-1a), 130.0 (CH, d, *J* = 9.0 Hz, C-5b) 129.7 (CH, C-3c/5c), 128.5 (CH, C-3a/5a), 128.1 (CH, C-4a), 127.6 (CH, C-2a/6a), 122.6 (CH, C-4c), 115.6 (CH, C-2c/6c), 114.0 (CH, d, *J* = 3.0 Hz, C-6b), 111.9 (C, C-9), 111.4 (CH, d, *J* = 21.2 Hz, C-4b), 105.9 (CH, d, *J* = 26.7 Hz, C-2b), 105.0 (CH, C-8), 83.1(CH, C-6), 81.9 (CH, C-7), 81.2 (CH, C-5), 79.1 (CH, C-2), 72.0 (CH_2, C-7a), 58.6 (CH, C-3), 26.8 (CH_3, C-11), 26.3 (CH_3, C-10); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −111.50; MS (*m/z*) (pos): 506 (M^+). * resonances overlap.

(**6c**) *((3S,4R)-4-((3aR,5R,6S,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-1-(4-methoxyphenyl)-3-phenoxyazetidin-2-one)* White solid (75 % yield); mp 130–132 °C; $[\alpha]_D^{20} = -5.95°$ (*c* 0.02, MeOH); IR υ_{max} 2958 (C–H), 2936 (C–H), 1747 (C=O), 1598, 1590, 1512, 1494 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.67 (2H, d, *J* = 9.0, Hz, H-2b/6b), 7.28 (2H, t, *J* = 7.7 Hz, H-3c/5c), 7.16–7.18 (5H, m, H-2a-H-6a), 7.08 (2H, d, *J* = 8.0 Hz, H-2c/6c), 7.02 (1H, t, *J* = 7.3 Hz, H-4c), 6.83 (2H, t, *J* = 9.0 Hz, H-3b/5b), 6.04 (1H, d, *J* = 3.8 Hz, H-8), 5.28 (1H, d, *J* = 5.5 Hz, H-2), 4.69 (1H, dd, *J* = 8.8, 5.5 Hz, H-3), 4.65 (1H, d, *J* = 3.8 Hz, H-7), 4.60* (1H, d, *J* = 11.5 Hz, H-$7a_2$), 4.59–4.62* (1H, m, H-5), 4.41 (1H, d, *J* = 3.3 Hz, H-6), 4.28 (1H, d, *J* = 11.5 Hz, H-$7a_1$), 3.77 (3H, s, H-7b), 1.47 (3H, s, H-10), 1.31 (3H, s, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.5 (C, C-1), 157.4 (C, C-1c), 156.6 (C, C-4b), 137.1 (C, C-1a), 131.2 (C, C-1b), 129.7 (CH, C-3c/5c), 128.5 (CH, C-3a/5a), 128.0 (CH, C-4a), 127.6 (CH, C-2a/6a), 122.5 (CH, C-4c), 119.8 (CH, d, C-2b/6b), 115.6 (CH, C-2c/6c), 114.0 (CH, C-3b/5b), 111.9 (C, C-9), 105.0 (CH, C-8), 83.2(CH, C-6), 81.9 (CH, C-7), 81.4 (CH, C-5), 79.2 (CH, C-2), 72.0 (CH_2, C-7a), 58.5 (CH, C-3), 55.5 (CH_3, C-7b), 26.9 (CH_3, C-11), 26.3 (CH_3, C-10); MS (*m/z*) (pos): 518 (M^+). * resonances overlap.

(**6d**) *((3S,4R)-4-((3aR,5R,6S,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-1-(3-methoxyphenyl)-3-phenoxyazetidin-2-one)* White solid (50 % yield); mp 80–81 °C; $[\alpha]_D^{20} = -5.26°$ (*c* 0.02, MeOH); IR υ_{max} 2955 (C–H), 2930 (C–H), 1755 (C=O), 1599, 1591, 1491 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (1H, t, $J = 2.1$ Hz, H-5b), 7.34–7.36 (1H, m, H-4b), 7.26–7.30 (3H, m, H-2b/3c/5c), 7.14–7.21 (5H, m, H-2a-H-6a), 7.08 (2H, d, $J = 7.8$ Hz, H-2c/6c), 7.02 (1H, t, $J = 7.2$ Hz, H-4c), 6.65 (1H, dd, $J = 8.5$, 2.6 Hz, H-6b), 6.05 (1H, d, $J = 3.9$ Hz, H-8), 5.29 (1H, d, $J = 5.6$ Hz, H-2), 4.72 (1H, dd, $J = 8.7$, 5.6 Hz, H-3), 4.67 (1H, d, $J = 4.0$ Hz, H-7), 4.67 (1H, d, $J = 4.0$ Hz, H-7), 4.60–4.67 (2H, m, H-7a_2/H-5), 4.43 (1H, d, $J = 3.3$ Hz, H-6), 4.29 (1H, d, $J = 11.4$ Hz, H-7a_1), 3.78 (3H, s, H-7b), 1.48 (3H, s, H-10), 1.32 (3H, s, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.1 (C, C-1), 159.9 (C, C-3b), 157.3 (C, C-1c), 138.8 (C, C-1b), 137.1 (C, C-1a), 129.7 (CH, C-3c/5c), 129.5 (CH, C-5b), 128.5 (CH, C-3a/5a), 128.0 (CH, C-4a), 127.6 (CH, C-2a/6a), 122.5 (CH, C-4c), 115.6 (CH, C-2c/6c), 111.9 (C, C-9), 111.0 (CH, C-6b), 110.8 (CH, C-4b), 105.0 (CH, C-8), 103.8 (CH, C-2b), 83.2 (CH, C-6), 82.0 (CH, C-7), 81.3 (CH, C-5), 79.0 (CH, C-2), 72.0 (CH_2, C-7a), 58.7 (CH, C-3), 55.3 (CH_3, C-7b), 26.8 (CH_3, C-11), 26.3 (CH_3, C-10); MS (*m/z*) (pos): 518 (M^+).

(**6e**) *((3S,4R)-4-((3aR,5R,6S,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-1-(4-chlorophenyl)-3-phenoxyazetidin-2-one)* White solid (65 % yield); mp 110–112 °C; $[\alpha]_D^{20} = -7.72°$(c 0.02, MeOH); IR υ_{max} 2969 (C–H), 2927 (C–H), 1744 (C=O), 1595, 1491 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (2H, d, $J = 8.8$ Hz, H-2b/6b), 7.24–7.29 (4H, m, H-3b/5b, H-3c/5c), 7.13–7.20 (5H, m, H-2a-H-6a), 7.00–7.06 (3H, m, H-2c/4c/6c), 6.03 (1H, d, $J = 3.8$ Hz, H-8), 5.28 (1H, d, $J = 5.6$ Hz, H-2), 4.71 (1H, dd, $J = 8.8$, 5.6 Hz, H-3), 4.65 (1H, d, $J = 3.8$ Hz, H-7), 4.58–4.61 (2H, m, H-5/7a_2), 4.38 (d, $J = 3.3$ Hz, H-6), 4.25 (1H, d, $J = 11.5$ Hz, H-7a_1), 1.46 (3H, s, H-10), 1.32 (3H, s, H-11). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.9 (C, C-1), 157.3 (C, C-1c), 137.0 (C, C-1a), 136.2 (C, C-4b), 129.7 (CH, C-3c/5c), 128.8 (CH, C-2b/6b), 128.5 (CH, C-3a/5a), 128.1 (CH, C-4a), 127.6 (CH, C-2a/6a), 122.6 (CH, C-4c), 119.7 (CH, C-3b/5b), 115.6 (CH, C-2c/6c), 112.0 (C, C-9), 105.0 (CH, C-8), 83.1 (CH, C-6), 81.9 (CH, C-7), 81.3 (CH, C-5), 79.2 (CH, C-2), 72.0 (CH_2, C-7a), 58.5 (CH, C-3), 26.8 (CH_3, C-11), 26.3 (CH_3, C-10); MS (*m/z*) (pos): 522 (M^+).

(**6f**) *((3S,4R)-4-((3aR,5R,6S,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-1-(3-chlorophenyl)-3-phenoxyazetidin-2-one)* White solid (45 % yield); mp 112–114 °C; $[\alpha]_D^{20} = -4.80°$ (*c* 0.02, MeOH); IR υ_{max} 2986 (C–H), 2943 (C–H), 1752 (C=O), 1595, 1485 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (1H, t, $J = 1.7$ Hz, H-2b), 7.50 (1H, dd, $J = 8.2$, 1.7 Hz, H-6b), 7.28 (2H, t, $J = 8.5$ Hz, H-3c/5c), 7.23 (1H, d, $J = 10.2$ Hz, H-5b), 7.14–7.21 (5H, m, H-2a-H-6a), 7.01–7.06 (4H, m, H-4b, H-2c/4c/6c), 6.06 (1H, d, $J = 3.9$ Hz, H-8), 5.28(1H, d, $J = 5.7$ Hz, H-2), 4.74 (1H, dd, $J = 8.9$, 5.7 Hz, H-3), 4.67 (1H, d, $J = 3.9$ Hz, H-7), 4.60–4.63 (2H, m, H-5/H-7a_2), 4.38 (1H, d, $J = 3.3$ Hz, H-6), 4.27 (1H, d, $J = 11.5$ Hz, H-7a_1), 1.48 (3H, s, H-10), 1.32 (3H, s, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.2 (C, C-1), 157.4 (C, C-1c), 138.8 (C, C-1b), 137.1 (C, C-1a), 134.6 (C, C-3b), 130.0 (CH, C-5b), 129.8 (CH, C-3c/5c), 128.7 (CH, C-3a/5a), 128.2 (CH, C-4a), 127.6 (CH, C-2a/6a), 124.8 (CH, C-4b), 122.8 (CH, C-4c), 118.6 (CH, C-6b), 116.6 (CH, C-2b), 115.7 (CH, C-2c/6c), 112.0 (C, C-9), 105.1 (CH, C-8), 83.2 (CH, C-6), 82.0 (CH, C-7), 81.4 (CH, C-5), 79.3(CH, C-2), 72.2 (CH_2, C-7a), 58.6 (CH, C-3), 27.0 (CH_3, C-11), 26.4 (CH_3, C-10); MS (*m/z*) (pos): 522 (M^+).

(**6g**) *(3S,4R)-4-((3aR,5R,6S,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-1-(3,4-dichlorophenyl)-3-phenoxyazetidin-2-one)* White solid (40 % yield); mp 109–110 °C; $[\alpha]_D^{20} = -3.15°$ (*c* 0.02, MeOH); IR υ_{max} 2922 (C–H), 1746 (C=O), 1592, 1477 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (1H, d, $J = 2.4$ Hz, H-2b), 7.59 (1H, dd, $J = 8.7$, 2.4 Hz, H-6b), 7.34 (1H, d, $J = 8.8$ Hz, H-5b), 7.28 (2H, t, $J = 7.7$ Hz, H-3c/5c), 7.14–7.21 (5H, m, H-2a-H-6a), 7.02–7.06 (3H, m, H-2c/4c/6c), 6.05 (1H, d, $J = 3.9$ Hz, H-8), 5.28 (1H, d, $J = 5.6$ Hz, H-2), 4.72 (1H, dd, $J = 9.0$, 5.7 Hz, H-3), 4.67 (1H, d, $J = 3.9$ Hz, H-7), 4.58–4.63 (2H, m, H-5/H-7a_2), 4.37 (1H, d, $J = 3.3$ Hz, H-6), 4.27 (1H, d, $J = 11.4$ Hz H-7a_1), 1.47 (3H, s, H-10), 1.32 (3H, s, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.0 (C, C-1), 157.2 (C, C-1c), 136.93 (C, C-4b), 136.90 (C, C-1a), 132.6 (C, C-1b), 130.4 (CH, C-6b), 129.7 (CH, C-3c/5c), 128.5 (CH, C-3a/5a), 128.1 (CH, C-4a), 127.9 (C, C-3b), 127.6 (CH, C-2a/6a), 122.7 (CH, C-4c), 120.1 (CH, C-5b), 117.8 (CH, C-2b), 115.6 (CH, C-2c/6c), 112.0 (C, C-9), 105.0 (CH, C-8), 83.0 (CH, C-6), 81.9 (CH, C-7), 81.2 (CH, C-5), 79.3 (CH, C-2), 72.0 (CH_2, C-7a), 58.6 (CH, C-3), 26.8 (CH_3, C-11), 26.3 (CH_3, C-10), MS (*m/z*) (pos): 556 (M^+).

(**6h**) *((3S,4R)-4-((3aR,5R,6S,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-1-(3,4-difluorophenyl)-3-phenoxyazetidin-2-one)* White solid (40 % yield); mp 134–135 °C; $[\alpha]_D^{20} = -3.14°$ (*c* 0.02, MeOH); IR υ_{max} 2986 (C–H), 2943 (C–H), 1752 (C=O), 1595, 1485 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 (1H, ddd, $J = 11.9$, 7.0, 2.5 Hz, H-2b), 7.46–7.51 (1H, m, H-6b), 7.26–7.30 (2H, m, H-3c/5c), 7.13–7.20 (5H, m, H-2a-H-6a), 7.02–7.11 (4H, m, H-5b, H-2c/4c/6c), 6.05 (1H, d, $J = 3.9$ Hz, H-8), 5.28 (1H, d, $J = 5.6$ Hz, H-2), 4.66–4.71 (2H, m, H-3/H-7), 4.58–4.63 (2H, m, H-5/H-7a_2), 4.38 (1H, d, $J = 3.6$ Hz, H-6), 4.27 (1H, d, $J = 11.4$ Hz, H-7a_1), 1.48 (3H, s, H-10), 1.32 (3H, s, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.9 (C, C-1), 157.2 (C, C-1c), 149.6 (C, dd, $J = 259.3$, 13.5 Hz, C-3b), 149.6 (C, dd, $J = 257.3$, 13.0 Hz, C-4b), 137.0 (C, C-1a),

134.0 (C, C-1b), 129.7 (CH, C-3c/5c), 128.5 (CH, C-3a/5a), 128.1 (CH, C-4a), 127.6 (CH, C-2a/6a), 122.7 (CH, C-4c), 117.2 (CH, d, $J = 17.9$ Hz, C-5b), 115.6 (CH, C-2c/6c), 114.3 (CH, dd, $J = 5.9$, 3.8 Hz, C-6b), 112.0 (C, C-9), 108.1 (CH, d, $J = 21.8$ Hz, C-2b), 105.0 (CH, C-8), 83.0 (CH, C-6), 81.6 (CH, C-7), 81.2 (CH, C-5), 79.3 (CH, C-2), 72.0 (CH_2, C-7a), 58.8 (CH, C-3), 26.8 (CH_3, C-11), 26.3 (CH_3, C-10); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −135.79; −142.25; MS (*m/z*) (pos): 524 (M^+).

(**6i**) *((3S,4R)-4-((3aR,5R,6S,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-1-(3,4-dimethoxyphenyl)-3-phenoxyazetidin-2-one)* White solid (65 % yield); mp 120–121 °C; $[\alpha]_D^{20} = -2.88°$ (*c* 0.02, MeOH); IR υ_{max} 2961 (C–H), 1754 (C=O), 1590, 1510, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 (1H, d, $J = 2.4$ Hz, H-2b), 7.26–7.30 (3H, m, H-6b, H-3c/5c), 7.13–7.20 (5H, m, H-2a-H-6a), 7.08–7.10 (2H, m, H-2c/6c), 7.00–7.04 (1H, t, $J = 7.4$ Hz, H-4c), 6.79 (1H, d, $J = 8.7$, H-5b), 6.03 (1H, d, $J = 3.8$ Hz, H-8), 5.29 (1H, d, $J = 5.4$ Hz, H-2), 4.66–4.70 (2H, m, H-3/H-7), 4.59–4.63 (2H, m, H-5/H-7a_2), 4.46 (1H, d, $J = 3.2$ Hz, H-6), 4.29 (1H, d, $J = 11.4$ Hz, H-7a1), 3.84 (3H, s, H-7b), 3.87 (3H, s, H-8b), 1.47 (3H, s, H-10), 1.32 (3H, s, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.7 (C, C-1), 157.5 (C, C-1c), 149.0 (C, C-3b), 146.2 (C, C-4b), 137.2 (C, C-1a), 131.6 (C, C-1b), 129.8 (CH, C-3c/5c), 128.6 (CH, C-3a/5a), 128.2 (CH, C-4a), 127.8 (CH, C-2a/6a), 122.6 (CH, C-4c), 115.8 (CH, C-2c/6c), 112.1 (C, C-9), 111.3 (CH, C-5b), 110.5 (CH, C-6b), 105.1 (CH, C-8), 103.3 (CH, C-2b), 83.4 (CH, C-6), 82.1 (CH, C-7), 81.4 (CH, C-5), 79.3 (CH, C-2), 72.2 (CH_2, C-7a), 59.2 (CH, C-3), 56.2 (CH_3, C-7b), 56.0 (CH_3, C-8b), 27.0 (CH_3, C-11), 26.5 (CH_3, C-10); MS (*m/z*) (pos): 548 (M^+).

(**6j**) *((3S,4R)-4-((3aR,5R,6S,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-3-phenoxy-1-phenylazetidin-2-one)* White solid (65 % yield); mp 118–119 °C; $[\alpha]_D^{20} = -3.68°$ (*c* 0.02, MeOH); IR υ_{max} 2928 (C–H), 1753 (C=O), 1597, 1489 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (2H, d, $J = 7.8$ Hz, H-2b/6b), 7.26–7.32 (4H, m, H-3b/5b, H-3c/5c), 7.15–7.20 (5H, m, H-2a-H-6a), 7.07–7.11 (3H, m, H-4b, H-2c/6c), 7.03 (1H, t, $J = 7.2$ Hz, H-4c), 6.05 (1H, d, $J = 3.9$ Hz, H-8), 5.28 (1H, d, $J = 5.6$ Hz, H-2), 4.76 (1H, dd, $J = 8.9$, 5.6 Hz, H-3), 4.66 (1H, d, $J = 3.9$ Hz, H-7), 4.60–4.64 (2H, m, H-5/H-7a_2), 4.41 (1H, d, $J = 3.4$ Hz, H-6), 4.28 (1H, d, $J = 11.4$ Hz, H-7a_1), 1.47 (3H, s, H-10), 1.31 (3H, s, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.2(C, C-1), 157.5 (C, C-1c), 137.8 (C, C-1b), 137.3 (C, C-1a), 129.8 (CH, C-3c/5c), 128.9 (CH, C-3b/5b), 128.7 (CH, C-3a/5a), 128.2 (CH, C-4a), 127.7 (CH, C-2a/6a), 124.8 (CH, C-4b), 122.7 (CH, C-4c), 118.5 (CH, C-2b/6b), 115.8 (CH, C-2c/6c), 112.0 (C, C-9), 105.1 (CH, C-8), 83.3 (CH, C-6), 82.0 (CH, C-7), 81.5 (CH, C-5), 79.2 (CH, C-2), 72.1 (CH_2, C-7a), 58.5 (CH, C-3), 27.0 (CH_3, C-11), 26.4 (CH_3, C-10); MS (*m/z*) (pos): 488 (M^+).

Debenzylation of 6a–j to produce the lactams 7a–j

The β-lactams (**6a–j**) (2.0 mmol) in 20 mL MeOH were treated with 10 % Pd/C (0.06 g), under hydrogen pressure for 2 h. Completion of the reaction was monitored by TLC, and on completion, the catalyst was removed by filtration and the solvent evaporated under reduced pressure to afford the crude compounds (**7a–j**) as white solids, which was then purified by column chromatography using silica gel and 35 % ethyl acetate in n-hexane.

(**7a**) *((3S,4R)-1-(4-fluorophenyl)-4-((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-3-phenoxyazetidin-2-one)* White solid (80 % yield); mp 165–167 °C; $[\alpha]_D^{20} = -3.99°$ (*c* 0.02, MeOH); IR υ_{max} 3477 (O–H), 1757 (C=O) cm^{-1}, 1600, 1509, 1496; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (2H, dd, $J = 6.9$, 4.7 Hz, H-2b/6b), 7.31 (2H, t, $J = 8.5$ Hz, H-3c/5c), 7.14 (2H, d, $J = 8.0$ Hz, H-2c/6c), 6.98–7.06 (3H, m, H-3b/5b, H-4c), 6.03 (1H, d, $J = 3.7$ Hz, H-8), 5.46 (1H, d, $J = 5.6$ Hz, H-2), 4.67 (1H, dd, $J = 8.6$, 5.6 Hz, H-3), 4.59 (1H, d, $J = 2.9$ Hz, H-6), 4.54 (1H, dd, $J = 8.7$ Hz, 2.9 Hz, H-5), 4.48 (1H, d, $J = 3.7$ Hz, H-7), 1.45 (3H, s, H-10), 1.29 (3H, s, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.7 (C, C-1), 159.6 (C, d, $J = 242.4$ Hz, C-4b), 157.5 (C, C-1c), 133.8 (C, C-1b), 129.8 (CH, C-3c/5c), 122.8 (CH, C-4c), 120.0 (CH, d, $J = 7.9$ Hz, C-2b/6b), 115.7 (CH, C-2c/6c), 115.6 (CH, d, $J = 22.4$ Hz, C-3b/5b), 112.0 (C, C-9), 104.6 (CH, C-8), 85.6 (CH, C-7), 81.6 (CH, C-5), 79.4 (CH, C-2), 75.6 (CH, C-6), 58.9 (CH, C-3), 26.8 (CH_3, C-11), 26.2 (CH_3, C-10); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −117.32; MS (*m/z*) (pos): 416 (M^+).

(**7b**) *((3S,4R)-1-(3-fluorophenyl)-4-((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-3-phenoxyazetidin-2-one*) White solid (82 % yield); mp 156–157 °C; $[\alpha]_D^{20} = -3.61°$ (*c* 0.02, MeOH); IR υ_{max} 3421(O–H), 1757 (C=O), 1610, 1589, 1493 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (1H, dd, $J = 8.0$, 1.1 Hz, H-6b), 7.50 (1H, dt, $J = 10.6$, 2.2 Hz, H-2b), 7.31 (2H, t, $J = 8.5$ Hz, H-3c/5c), 7.25–7.27 (1H, m, H-5b), 7.15 (2H, d, $J = 8.8$, H-2c/6c), 7.05 (1H, t, $J = 7.4$, H-4c), 6.80 (1H, td, $J = 8.5$, 2.3 Hz, H-4b), 6.05 (1H, d, $J = 3.7$, H-8), 5.46 (1H, d, $J = 5.6$ Hz, H-2), 4.69 (1H, dd, $J = 8.6$, 5.6 Hz, H-3), 4.59 (1H, d, $J = 2.9$, H-6), 4.55(1H, dd, $J = 8.6$, 3.0 Hz, H-5), 4.49 (1H, d, $J = 3.8$ Hz, H-7), 1.45 (3H, s, H-10), 1.29 (3H, s, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.0 (C, C-1), 161.6 (C, d, $J = 243.5$ Hz, C-3b), 157.5 (C, C-1c), 138.9 (C, d, $J = 10.6$ Hz, C-1b), 130.1 (CH, d, $J = 9.2$ Hz, C-5b), 129.8 (CH, C-3c/5c), 122.9 (CH, C-4c),

115.7 (CH, C-2c/6c), 114.0 (CH, d, $J = 2.9$ Hz, C-6b), 112.9 (C, C-9), 111.5 (CH, d, $J = 21.2$ Hz, C-4b), 105.9 (CH, d, $J = 26.3$ Hz, C-2b), 104.6 (CH, C-8), 85.6 (CH, C-7), 81.5 (CH, C-5), 79.3 (CH, C-2), 75.6 (CH, C-6), 59.0 (CH, C-3), 26.8 (CH_3, C-11), 26.2 (CH_3, C-10); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −111.33; MS (*m/z*) (pos): 416 (M^+).

(**7c**) *((3S,4R)-4-((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-1-(4-methoxyphenyl)-3-phenoxyazetidin-2-one)* White solid (85 % yield); mp 148–150 °C; $[\alpha]_D^{20} = -4.58°$ (*c* 0.02, MeOH); IR υ_{max} 3477 (O–H), 1757 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (2H, d, $J = 9.0$, Hz, H-2b/6b), 7.31 (2H, t, $J = 8.3$, H-3c/5c), 7.13 (2H, d, $J = 8.0$ Hz, H-2c/6c), 7.02 (1H, t, $J = 7.3$ Hz, H-4c), 6.84 (2H, d, $J = 9.0$ Hz, H-3b/5b), 6.02 (1H, d, $J = 3.7$ Hz, H-8), 5.39 (1H, d, $J = 5.5$ Hz, H-2), 4.63 (1H, dd, $J = 8.6$, 5.5 Hz, H-3), 4.57–4.58 (1H, m, H-6), 4.52 (1H, dd, $J = 8.6$, 2.8 Hz, H-5), 4.47 (1H, d, $J = 3.7$ Hz, H-7), 3.76 (3H, s, H-7b), 2.15 (1H, s, H-12), 1.44 (3H, s, H-10), 1.27 (3H, s, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4 (C, C-1), 157.6 (C, C-1c), 156.7 (C, C-4b), 131.1 (C, C-1b), 129.8 (CH, C-3c/5c), 122.7 (CH, C-4c), 119.9 (CH, C-2b/6b), 115.7 (CH, C-2c/6c), 114.0 (CH, C-3b/5b), 111.9 (C, C-9), 104.6 (CH, C-8), 85.6 (CH, C-7), 81.6 (CH, C-5), 79.3 (CH, C-2), 75.6 (CH, C-6), 58.9 (CH, C-3), 55.5 (CH_3, C-7b), 26.8 (CH_3, C-11), 26.3 (CH_3, C-10); MS (*m/z*) (pos): 428 (M^+).

(**7d**) *((3S,4R)-4-((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-1-(3-methoxyphenyl)-3-phenoxyazetidin-2-one)* White solid (79 % yield); mp 169–170 °C; $[\alpha]_D^{20} = -3.27°$ (*c* 0.02, MeOH); IR υ_{max} 3420(O–H), 1755 (C=O), 1599, 1586, 1494 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29–7.38 (4H, m, H-2b/6b, H-3c/5c), 7.22 (1H, t, $J = 8.2$ Hz, H-5b), 7.15 (2H, d, $J = 8.2$ Hz, H-2c/6c), 7.04 (1H, t, $J = 7.3$ Hz, H-4c), 6.66 (1H, dd, $J = 8.0$, 1.8 Hz, H-4b), 6.04 (1H, d, $J = 3.7$ Hz, H-8), 5.44 (1H, d, $J = 5.6$ Hz, H-2), 4.69 (1H, dd, $J = 8.5$, 5.6 Hz, H-3), 4.62 (1H, d, $J = 2.9$ Hz, H-6), 4.55 (1H, dd, $J = 8.5$, 2.9 Hz, H-5), 4.49 (1H, d, $J = 3.8$ Hz, H-7), 3.79 (3H, s, H-7b), 1.45 (3H, s, H-10), 1.29 (3H, s, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.0 (C, C-1), 159.9 (C, C-3b), 157.5 (C, C-1c), 138.7 (C, C-1b), 129.8 (CH, C-3c/5c), 129.7 (CH, C-5b), 122.8 (CH, C-4c), 115.7 (CH, C-2c/6c), 112.0 (C, C-9), 111.1 (CH, C-6b), 110.8 (CH, C-4b), 104.6 (CH, C-8), 103.8 (CH, C-2b), 85.6 (CH, C-7), 81.6 (CH, C-5), 79.2 (CH, C-2), 75.7 (CH, C-6), 59.0 (CH, C-3), 55.3 (CH_3, C-7b), 26.8 (CH_3, C-11), 26.3 (CH_3, C-10); MS (*m/z*) (pos): 428 (M^+).

(**7e**) *((3S,4R)-1-(4-chlorophenyl)-4-((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-3-phenoxyazetidin-2-one)* White solid (78 % yield); mp 184–185 °C; $[\alpha]_D^{20} = -4.62°$ (*c* 0.02, MeOH); IR υ_{max} 3454 (O–H), 1754(C=O), 1595, 1491 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (2H, d, $J = 8.8$ Hz, H-2b/6b), 7.29–7.33 (2H, m, H-3c/5c), 7.27 (2H, d, $J = 8.8$ Hz, H-3b/5b), 7.13 (2H, d, $J = 8.2$ Hz, H-2c/6c), 7.04 (1H, t, $J = 7.4$ Hz, H-4c), 6.03 (1H, d, $J = 3.7$ Hz, H-8), 5.45 (1H, d, $J = 5.6$ Hz, H-2), 4.68 (1H, dd, $J = 8.7$, 5.7 Hz, H-3), 4.58 (1H, d, $J = 2.8$ Hz, H-6), 4.53 (1H, dd, $J = 8.7$, 2.9 Hz, H-5), 4.48 (1H, d, $J = 3.7$ Hz, H-7), 1.44 (3H, s, H-10), 1.28 (3H, s, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.8 (C, C-1), 157.5 (C, C-1c), 136.1 (C, C-1b), 129.8 (CH, C-3c/5c), 129.0 (CH, C-2b/6b), 122.8 (CH, C-4c), 119.6 (CH, C-3b/5b), 115.7 (CH, C-2c/6c), 112.0 (C, C-9), 104.6 (CH, C-8), 85.6 (CH, C-7), 81.6 (CH, C-5), 79.4 (CH, C-2), 75.6 (CH, C-6), 58.8 (CH, C-3), 26.8 (CH_3, C-11), 26.2 (CH_3, C-10); MS (*m/z*) (pos): 432 (M^+).

(**7f**) *((3S,4R)-1-(3-chlorophenyl)-4-((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-3-phenoxyazetidin-2-one*) White solid (83 % yield); mp 160–161 °C; $[\alpha]_D^{20} = -5.01°$ (*c* 0.02, MeOH); IR υ_{max} 3422 (O–H), 1752 (C=O), 1594, 1484 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (1H, t, $J = 2.0$ Hz, H-2b), 7.64 (1H, ddd, $J = 8.0$, 1.9, 0.7 Hz, H-6b), 7.32 (2H, t, $J = 8.5$ Hz, H-3c/5c), 7.20–7.26 (1H, m, H-5b), 7.14 (2H, d, $J = 8.6$ Hz, H-2c/6c), 7.03-7.09 (2H, m, H-4b, H-4c), 6.05 (1H, d, $J = 3.8$ Hz, H-8), 5.45 (1H, d, $J = 5.6$ Hz, H-2), 4.70 (1H, dd, $J = 8.6$, 5.6 Hz, H-3), 4.56 (1H, d, $J = 3.0$ Hz, H-6), 4.53 (1H, dd, $J = 8.6$, 3.0 Hz, H-5), 4.49 (1H, d, $J = 3.8$ Hz, H-7), 1.69 (1H, s, H-12), 1.45 (3H, s, H-10), 1.29 (3H, s, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.0 (C, C-1), 157.5 (C, C-1c), 138.6 (C, C-1b), 134.6 (C, C-3b), 129.0 (CH, C-5b), 129.8 (CH, C-3c/5c), 124.8 (CH, C-4c), 122.9 (CH, C-2b), 118.5 (CH, C-4b), 116.5 (CH, C-6b), 115.7 (CH, C-2c/6c), 112.0 (C, C-9), 104.6 (CH, C-8), 85.6 (CH, C-7), 81.5 (CH, C-5), 79.3 (CH, C-2), 75.6 (CH, C-6), 58.8 (CH, C-3), 26.8 (CH_3, C-11), 26.2 (CH_3, C-10); MS (*m/z*) (pos): 432 (M^+).

(**7g**) *((3S,4R)-1-(3,4-dichlorophenyl)-4-((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro [3,2-d][1,3]dioxol-5-yl)-3-phenoxyazetidin-2-one*) White solid (86 % yield); mp 165–167 °C; $[\alpha]_D^{20} = -4.02°$ (*c* 0.02, MeOH); IR υ_{max} 3464 (O–H), 2990 (C–H), 2977 (C–H), 2928 (C–H), 1762 (C=O), 1590, 1478, 1468 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (1H, d, $J = 2.5$ Hz, H-2b), 7.60 (1H, dd, $J = 8.7$, 2.4 Hz, H-6b), 7.35 (1H, d, $J = 8.7$ Hz, H-5b), 7.32 (2H, t, $J = 8.5$ Hz, H-3c/5c), 7.13 (2H, d, $J = 7.8$ Hz, H-2c/6c), 7.04 (1H, t, $J = 7.4$ Hz, H-4c), 6.04 (1H, d, $J = 3.8$ Hz, H-8), 5.47 (1H, d, $J = 5.6$ Hz, H-2), 4.69 (1H, dd, $J = 8.7$, 5.7 Hz, H-3), 4.56 (1H, br s, H-6), 4.53 (1H, dd, $J = 8.7$, 2.9 Hz, H-5), 4.48 (1H, d, $J = 3.8$ Hz, H-7), 1.83 (1H, s, H-12), 1.45 (3H, s, H-10), 1.29 (3H, s, H-11); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 163.9 (C, C-1), 157.4 (C,

C-1c), 136.8 (C, C-4b), 132.7 (C, C-1b), 130.5 (CH, C-6b), 129.8 (CH, C-3c/5c), 128.0 (C, C-3b), 122.7 (CH, C-4c), 120.1 (CH, C-5b), 117.7 (CH, C-2b), 115.7 (CH, C-2c/6c), 112.1 (C, C-9), 104.6 (CH, C-8), 85.6 (CH, C-7), 81.4 (CH, C-5), 79.4 (CH, C-2), 75.6 (CH, C-6), 58.9 (CH, C-3), 26.8 (CH_3, C-11), 26.2 (CH_3, C-10); MS (*m/z*) (pos): 466 (M^+).

(**7h**) *((3S,4R)-1-(3,4-difluorophenyl)-4-((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro [3,2-d][1,3]dioxol-5-yl)-3-phenoxyazetidin-2-one)* White solid (77 % yield); mp 159–160 °C; $[\alpha]_D^{20} = -2.85°$ (*c* 0.02, MeOH); IR 3472 (O–H), 2986 (C–H), 2926 (C–H), 1759 (C=O),1611, 1600, 1515, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.65 (1H, ddd, $J = 11.8, 7.1, 2.5$ Hz, H-2b), 7.68 (1H, d, $J = 9.0$ Hz, H-6b), 7.32 (2H, t, $J = 8.3$ Hz, H-3c/5c), 7.13 (2H, d, $J = 7.9$ Hz, H-2c/6c), 7.03–7.11 (1H, m, H-5b/H-4c), 6.05 (1H, d, $J = 3.8$ Hz, H-8), 5.47 (1H, d, $J = 5.6$ Hz, H-2), 4.67 (1H, dd, $J = 8.6, 5.6$ Hz, H-3), 4.58 (1H, br s, H-6), 4.53 (1H, dd, $J = 8.7, 2.9$ Hz, H-5), 4.49 (1H, d, $J = 3.8$ Hz, H-7), 1.47 (3H, s, H-10), 1.29 (3H, s, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.8 (C, C-1), 157.4 (C, C-1c), 150.0 (C, dd, $J = 245.9, 13.4$ Hz, C-3b), 150.0 (C, dd, $J = 244.5, 12.6$ Hz, C-4b), 134.0 (C, C-1b), 129.8 (CH, C-3c/5c), 122.9 (CH, C-4c), 117.9 (CH, d, $J = 18.4$ Hz, C-5b), 115.7 (CH, C-2c/6c), 114.2 (CH, dd, $J = 6.0, 3.9$ Hz, C-6b), 112.1 (C, C-9), 108.1 (CH, d, $J = 21.8$ Hz, C-2b), 104.6 (CH, C-8), 85.6 (CH, C-7), 81.5 (CH, C-5), 79.4 (CH, C-2), 75.6 (CH, C-6), 59.1 (CH, C-3), 26.8 (CH_3, C-11), 26.2 (CH_3, C-10); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −135.64, −142.06; MS (*m/z*): 434 (M^+).

(**7i**) *((3S,4R)-4-((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-1-(3,4-dimethoxyphenyl)-3-phenoxyazetidin-2-one*) White solid (82 % yield); mp 145–146 °C; $[\alpha]_D^{20} = -4.26°$ (*c* 0.02, MeOH); IR υ_{max} 3463 (O–H), 1740 (C=O), 1598, 1517, 1458 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.48 (1H, d, $J = 2.4$ Hz, H-2b), 7.27–7.33 (3H, m, H-6b, H-3c/5c), 7.15 (2H, d, $J = 8.0$ Hz, H-2c/6c), 7.03 (1H, t, $J = 7.4$ Hz, H-4c), 6.80 (1H, d, $J = 8.8$ Hz, H-5b), 6.02 (1H, d, $J = 3.7$ Hz, H-8), 5.43 (1H, d, $J = 5.5$ Hz, H-2), 4.62–4.66 (2H, m, H-3, H-6), 4.54 (1H, dd, $J = 8.4, 2.9$ Hz, H-5), 4.49 (1H, d, $J = 3.7$ Hz, H-7), 3.87 (3H, s, H-8b), 3.84 (3H, s, H-7b), 1.79 (1H, br s, H-12), 1.44 (3H, s, H-10), 1.29 (3H, s, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.5 (C, C-1), 157.5 (C, C-1c), 148.9 (C, C-3b), 146.1 (C, C-4b), 131.3 (C, C-1b), 129.8 (CH, C-3c/5c), 122.7 (CH, C-4c), 115.7 (CH, C-2c/6c), 112.0 (C, C-9), 111.3 (CH, C-5b), 110.4 (CH, C-2b), 104.6 (CH, C-8), 103.1 (CH, C-6b), 85.6 (CH, C-7), 81.6 (CH, C-5), 79.3 (CH, C-2), 75.6 (CH, C-6), 59.4 (CH, C-3), 56.1 (CH_3, C-7b), 55.9 (CH_3, C-8b), 26.8 (CH_3, C-11), 26.3 (CH_3, C-10); MS (*m/z*) (pos): 458 (M^+).

(**7j**) *((3S,4R)-4-((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-3-phenoxy-1-phenylazetidin-2-one)* White solid (84 % yield); mp 167–168 °C; $[\alpha]_D^{20} = -4.04°$ (*c* 0.02, MeOH); IR υ_{max} 3454 (O–H), 1749 (C=O), 1597, 1492 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 7.74 (2H, d, $J = 7.8, 4.7$ Hz, H-2b/6b), 7.31 (4H, t, $J = 7.8$ Hz, H-3c/5c, H-3b/5b), 7.15 (2H, d, $J = 8.1$ Hz, H-2c/6c), 7.11 (1H, t, $J = 7.4$ Hz, H-4b), 7.04 (1H, t, $J = 7.3$ Hz, H-4c), 6.04 (1H, d, $J = 3.7$ Hz, H-8), 5.45 (1H, d, $J = 5.6$ Hz, H-2), 4.71 (1H, dd, $J = 8.6, 5.6$ Hz, H-3), 4.61 (1H, d, $J = 2.9$ Hz, H-6), 4.55 (1H, dd, $J = 8.6, 2.9$ Hz, H-5), 4.49 (1H, d, $J = 3.7$ Hz, H-7), 1.66 (1H, br s, H-12), 1.44 (3H, s, H-10), 1.28 (3H, s, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.9 (C, C-1), 157.5 (C, C-1c), 137.6 (C, C-1b), 129.8 (CH, C-3c/5c), 128.8 (CH, C-3b/5b), 124.7 (CH, C-4b), 122.8 (CH, C-4c), 118.3 (CH, C-2b/6b), 115.7 (CH, C-2c/6c), 112.0 (C, C-9), 104.6 (CH, C-8), 85.6 (CH, C-7), 81.6 (CH, C-5), 79.2 (CH, C-2), 75.7 (CH, C-6), 58.7 (CH, C-3), 26.8 (CH_3, C-11), 26.3 (CH_3, C-10); MS (*m/z*) (pos): 398 (M^+).

Hydrolysis of the lactams 7a–j to the β-amino acids 8a–j

LiOH (48.0 mg, 2.0 mmol) in 5 mL water was added to a solution of **7a–j** (1.0 mmol) in THF (20 mL), and the mixture stirred at 0–10 °C for 2 h. On completion, the solvent was removed under reduced pressure and the pH of the residue adjusted to 2–3 using aqueous HCl at 0–5 °C to afford white solids (**8a–j**).

(8a) *((2S,3R)-3-(4-fluorophenylamino)-3-((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro [3,2-d][1,3]dioxol-5-yl)-2-phenoxypropanoic acid)* White solid (83 % yield); mp 109–110 °C; $[\alpha]_D^{20} = 33.25°$ (*c* 0.02, MeOH); IR υ_{max} 3491 (O–H), 3412 (N–H), 2989 (C–H), 2920 (C–H), 1684 (C=O), 1590, 1492 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 7.30 (2H, t, $J = 7.6$ Hz, H-3c/5c), 7.00 (1H, t, $J = 7.2$ Hz, H-4c), 6.93 (2H, d, $J = 8.1$ Hz, H-2c/6c), 6.76–6.84 (4H, m, H-2b/3b/5b/6b), 5.90 (1H, d, $J = 3.7$ Hz, H-8), 5.05 (1H, d, $J = 2.0$ Hz, H-2), 4.49 (1H, d, $J = 3.8$ Hz, H-7), 4.41–4.46 (2H, m, H-3, H-5), 3.89 (1H, d, $J = 2.2$ Hz, H-6), 1.47 (3H, s, H-10), 1.28 (3H, s, H-11); ^{13}C NMR (CD_3OD, 100 MHz) δ 173.2 (C, C-1), 159.4 (C, C-1c), 157.2 (C, d, $J = 231.7$ Hz, C-4b), 146.0 (C, C-1b), 130.7 (CH, C-3c/5c), 122.9 (CH, C-4c), 116.2 (CH, C-2c/6c), 116.0 (CH, d, $J = 7.2$ Hz, C-2b/6b), 115.9 (CH, d, $J = 22.3$ Hz, C-3b/5b), 112.7 (C, C-9), 106.0 (CH, C-8), 87.0 (CH, C-7), 83.2 (CH, C-5), 78.1 (CH, C-2), 75.4 (CH, C-6), 57.5 (CH, C-3), 27.1(CH_3, C-10), 26.5 (CH_3, C-11); ^{19}F NMR (CD_3OD, 376.5 MHz) δ −130.50; HRMS (*m/z*) (pos): 434.1612 $[M + H]^+$ (calculated for $C_{22}H_{25}NO_7F$: 434.1615).

(**8b**) *((2S,3R)-3-(3-fluorophenylamino)-3-((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro [3,2-d][1,3]dioxol-5-yl)-2-phenoxypropanoic acid)* White solid (88 % yield); mp 115–117 °C; $[\alpha]_D^{20} = 28.25°$ (*c* 0.02, MeOH); IR υ_{max} 3390 (O–H), 1730 (C=O), 1616, 1590, 1492 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 7.31 (2H, t, $J = 7.8$ Hz, H-3c/5c), 6.99–7.05 (2H, m, H-5b, H-4c), 6.95 (2H, d, $J = 8.1$ Hz, H-2c/6c), 6.56 (1H, d, $J = 8.2$ Hz, H-6b), 6.51 (1H, d, $J = 12.2$ Hz, H-2b), 6.26 (1H, td, $J = 8.5$, 2.0 Hz, H-4b), 5.90 (1H, d, $J = 3.7$, H-8), 5.07 (1H, d, $J = 2.2$ Hz, H-2), 4.54 (1H, dd, $J = 8.8$, 2.2 Hz, H-3), 4.49 (1H, d, $J = 3.7$ Hz, H-7), 4.43 (1H, dd, $J = 8.9$, 2.6 Hz, H-5), 3.87 (1H, d, $J = 2.5$ Hz, H-6), 1.47 (3H, s, H-10), 1.28 (3H, s, H-11); ^{13}C NMR (CD_3OD, 100 MHz) δ 173.1 (C, C-1), 164.2 (C, d, $J = 243.5$ Hz, C-3b), 159.4 (C, C-1c), 151.8 (C, d, $J = 10.8$ Hz, C-1b), 130.8 (CH, d, $J = 9.0$ Hz, C-5b), 130.7 (CH, C-3c/5c), 123.0 (CH, C-4c), 116.2 (CH, C-2c/6c), 112.7 (C, C-9), 110.6 (CH, d, $J = 3.0$ Hz, C-6b), 106.0 (CH, C-8), 103.9 (CH, d, $J = 21.2$ Hz, C-4b), 101.1 (CH, d, $J = 26.7$ Hz, C-2b), 87.0 (CH, C-7), 83.2 (CH, C-5), 78.1 (CH, C-2), 75.3 (CH, C-6), 56.3 (CH, C-3), 27.0 (CH_3, C-10), 26.5 (CH_3, C-11); ^{19}F NMR (CD_3OD, 376.5 MHz) δ −115.90; HRMS (*m/z*) (pos): 434.1615 $[M + H]^+$ (calculated for $C_{22}H_{25}NO_7F$: 434.1615).

(**8c**) *((2S,3R)-3-((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-3-(4-methoxyphenylamino)-2-phenoxypropanoic acid)* White solid (87 % yield); mp 113–115 °C; $[\alpha]_D^{20} = 23.04°$ (*c* 0.02, MeOH); IR υ_{max} 3400 (O–H), 1727 (C=O), 1619, 1590, 1511, 1493 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 7.30 (2H, t, $J = 7.9$ Hz, H-3c/5c), 7.00 (1H, t, $J = 7.4$ Hz, H-4c), 6.92 (1H, d, $J = 8.2$ Hz, H-2c/6c), 6.81 (2H, d, $J = 8.5$ Hz, H-3b/5b), 6.73 (2H, d, $J = 8.9$ Hz, H-2b/6b), 5.90 (1H, d, $J = 3.6$ Hz, H-8), 4.97 (1H, d, $J = 1.8$ Hz, H-2), 4.49 (1H, d, $J = 3.7$ Hz, H-7), 4.44 (1H, dd, $J = 8.1$, 2.0 Hz, H-3), 4.39 (1H, d, $J = 7.4$ Hz, H-5), 3.95 (1H, d, $J = 2.2$ Hz, H-6), 3.72 (3H, s, H-7b), 1.47 (3H, s, H-10), 1.29 (3H, s, H-11); ^{13}C NMR (CD_3OD, 100 MHz) δ 173.5 (C, C-1), 159.4 (C, C-1c), 154.1 (C, C-4b), 143.1 (C, C-1b), 130.6 (CH, C-3c/5c), 122.9 (CH, C-4c), 117.3 (CH, C-3b/5b),116.2 (CH, C-2c/6c), 115.6 (CH, C-2b/6b), 112.8 (C, C-9), 106.0 (CH, C-8), 87.0 (CH, C-7), 82.7 (CH, C-5), 78.0 (CH, C-2), 75.8 (CH, C-6), 58.3 (CH_3, C-7b), 56.3 (CH, C-3), 27.1 (CH_3, C-10), 26.5 (CH_3, C-11); HRMS (*m/z*) (pos): 446.1808 $[M + H]^+$ (calculated for $C_{23}H_{28}NO_8$: 446.1815).

(**8d**) *((2S,3R)-3-((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-3-(3-methoxyphenylamino)-2-phenoxypropanoic acid)* White solid (86 % yield); mp 99–100 °C; $[\alpha]_D^{20} = 22.08°$ (*c* 0.02, MeOH); IR υ_{max} 3394 (O–H), 1730(C=O), 1620, 1597, 1511, 1494 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 7.30 (2H, t, $J = 7.6$ Hz, H-3c/5c), 6.93–7.02 (4H, m, H-5b, H-2c/4c/6c), 6.38–6.40 (2H, m, H-2b/4b), 6.18 (1H, dd, $J = 7.7$, 1.8 Hz, H-6b), 5.90 (1H, d, $J = 3.7$ Hz, H-8), 5.04 (1H, s, H-2), 4.52 (1H, dd, $J = 8.5$, 2.1 Hz, H-3), 4.49 (1H, d, $J = 3.8$ Hz, H-7), 4.43 (1H, dd, $J = 8.6$, 2.6 Hz, H-5), 3.89 (1H, d, $J = 2.6$ Hz, H-6), 3.73 (3H, s, H-7b), 1.47 (3H, s, H-10), 1.28 (3H, s, H-11); ^{13}C NMR (CD_3OD, 400 MHz) δ 162.0 (C, C-1), 159.4 (C, C-1c), 150.9 (C, C-1b), 150.9 (C, C-3b), 130.7 (CH, C-3c/5c), 130.5 (CH, C-5b), 122.9 (CH, C-4c), 116.2 (CH, C-2c/6c), 112.7 (C, C-9), 107.9 (CH, C-6b), 106.0 (CH, C-8), 104.0 (CH, C-4b), 100.6 (CH, C-2b), 87.0 (CH, C-7), 83.1 (CH, C-5), 78.1 (CH, C-2), 75.4 (CH, C-6), 56.5 (CH, C-3), 55.5 (CH_3, C-7b), 27.0 (CH_3, C-10), 26.5 (CH_3, C-11); HRMS (*m/z*) (pos): 446.1812 $[M + H]^+$ (calculated for $C_{23}H_{28}NO_8$: 446.1815).

(**8e**) *((2S,3R)-3-(4-chlorophenylamino)-3-((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro [3,2-d][1,3]dioxol-5-yl)-2-phenoxypropanoic acid)* White solid (90 % yield); mp 129–130 °C; $[\alpha]_D^{20} = 17.25°$ (*c* 0.02, MeOH); IR υ_{max} 3508 (O–H), 3410 (N–H), 1681 (C=O), 1603, 1588, 1513, 1492 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 7.32 (2H, dd, $J = 8.2$ Hz, 7.6 Hz, H-3c/5c), 6.99–7.04 (3H, m, H-2c/4c/6c), 6.94 (2H, d, $J = 8.1$ Hz, H-3b/5b), 6.75 (2H, d, $J = 8.8$ Hz, H-2b/6b), 5.89 (1H, d, $J = 3.7$ Hz, H-8), 5.06 (1H, d, $J = 2.4$ Hz, H-2), 4.49–4.53 (2H, m, H-3, H-7), 4.42 (1H, dd, $J = 8.7$, 2.6 Hz, H-5), 3.88 (1H, d, $J = 2.6$ Hz, H-6), 1.47 (3H, s, H-10), 1.28 (3H, s, H-11); ^{13}C NMR (CD_3OD, 100 MHz) δ 173.1 (C, C-1), 159.4 (C, C-1c), 148.5 (C, C-1b), 130.7 (CH, C-3c/5c), 129.5 (CH, C-3b/5b), 123.0 (CH, C-4c), 122.4 (C, C-4b), 116.2 (CH, C-2c/6c), 115.9 (CH, C-2b/6b), 112.7 (C, C-9), 106.0 (CH, C-8), 87.0 (CH, C-7), 83.3 (CH, C-5), 78.1 (CH, C-2), 75.3 (CH, C-6), 56.6 (CH, C-3), 27.0 (CH_3, C-11), 26.5 (CH_3, C-10); HRMS (*m/z*) (pos): 450.1305 $[M + H]^+$ (calculated for $C_{22}H_{25}ClNO_7$: 450.1320).

(**8f**) *((2S,3R)-3-(3-chlorophenylamino)-3-((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro [3,2-d][1,3]dioxol-5-yl)-2-phenoxypropanoic acid)* White solid (85 % yield); mp 100–102 °C; $[\alpha]_D^{20} = 19.08°$ (*c* 0.02, MeOH); IR υ_{max} 3395 (O–H), 1731(C=O), 1595, 1492 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 7.31 (2H, t, $J = 8.2$ Hz, H-3c/5c), 7.01 (2H, t, $J = 7.8$ Hz, H-4c, H-5b), 6.95 (2H, d, $J = 8.1$ Hz, H-2c/6c), 6.80 (1H, t, $J = 1.8$ Hz, H-2b), 6.69 (1H, dd, $J = 8.1$, 1.9 Hz, H-4b), 6.56 (1H, dd, $J = 7.8$, 0.7 Hz, H-6b), 5.90 (1H, d, $J = 3.8$ Hz, H-8), 5.08 (1H, d, $J = 2.4$ Hz, H-2), 4.54 (1H, dd, $J = 8.9$, 2.4 Hz, H-3), 4.50 (1H, d, $J = 3.8$ Hz, H-7), 4.43 (1H, dd, $J = 8.8$, 2.6 Hz, H-5), 3.88 (1H, d, $J = 2.6$ Hz, H-6), 1.47 (3H, s,

H-10), 1.28 (3H, s, H-11); ^{13}C NMR (CD_3OD, 100 MHz) δ 173.1 (C, C-1), 159.4 (C, C-1c), 151.2 (C, C-1b), 135.6 (C, C-3b), 130.9 (CH, C-5b), 130.7 (CH, C-3c/5c), 123.0 (CH, C-4c), 117.6 (CH, C-4b), 116.2 (CH, C-2c/6c), 114.1 (CH, C-2b), 113.1 (CH, C-6b), 112.7 (C, C-9), 106.0 (CH, C-8), 87.0 (CH, C-7), 83.2 (CH, C-5), 78.1 (CH, C-2), 75.3 (CH, C-6), 56.3 (CH, C-3), 27.0 (CH_3, C-10), 26.5 (CH_3, C-11); HRMS (*m/z*) (pos): 450.1323 $[M + H]^+$ (calculated for $C_{22}H_{25}ClNO_7$: 450.1320).

(**8g**) *((2S,3R)-3-(3,4-dichlorophenylamino)-3-((3aR,5R,6-S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro [3,2-d][1,3]-dioxol-5-yl)-2-phenoxypropanoic acid)* White solid (83 % yield); mp 135–137 °C; $[\alpha]_D^{20} = 18.50°$ (*c* 0.02, MeOH); IR υ_{max} 3480 (N–H), 3416 (N–H), 1676 (C=O), 1596, 1493 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.31 (2H, t, $J = 8.5$ Hz, H-3c/5c), 7.12 (1H, d, $J = 8.9$ Hz, H-5b), 7.01 (1H, t, $J = 7.4$ Hz, H-4c), 6.96 (1H, s, H-2b), 6.93 (2H, d, $J = 4.5$ Hz, H-2c/6c), 6.70 (1H, dd, $J = 8.8$, 2.7 Hz, H-6b), 5.90 (1H, d, $J = 3.7$ Hz, H-8), 5.07 (2H, d, $J = 2.4$ Hz, H-2), 4.49–4.52 (2H, m, H-3, H-7), 4.42 (1H, dd, $J = 9.0$, 2.6 Hz, H-5), 3.87 (1H, d, $J = 2.6$ Hz, H-6), 1.47 (3H, s, H-10), 1.28 (3H, s, H-11); ^{13}C NMR (CD_3OD, 400 MHz) δ 173.0 (C, C-1), 159.4 (C, C-1c), 149.9 (C, C-1b), 133.2 (C, C-3b), 131.2 (CH, C-5b), 130.7 (CH, C-3c/5c), 123.0 (CH, C-4c), 119.7 (C, C-4b), 116.2 (CH, C-2c/6c), 115.6 (CH, C-2b), 114.6 (CH, C-6b), 112.7 (C, C-9), 106.0 (CH, C-8), 87.0 (CH, C-7), 83.2 (CH, C-5), 78.0 (CH, C-2), 75.2 (CH, C-6), 56.5 (CH, C-3), 27.0 (CH_3, C-10), 26.5 (CH_3, C-11); HRMS (*m/z*): 484.0941 $[M + H]^+$ (calculated for $C_{22}H_{24}Cl_2NO_7$: 484.0930).

(**8h**) *((2S,3R)-3-(3,4-difluorophenylamino)-3-((3aR,5R,6-S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro [3,2-d][1,3]-dioxol-5-yl)-2-phenoxypropanoic acid)* White solid (81 % yield); mp 103–104 °C; $[\alpha]_D^{20} = 17.25°$ (*c* 0.02, MeOH); IR υ_{max} 3477 (O–H), 3412 (N–H), 1685 (C=O), 1527, 1493 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.31 (2H, d, $J = 8.5$ Hz, H-3c/5c), 7.00 (1H, t, $J = 7.2$ Hz, H-4c), 6.96 (2H, d, $J = 6.8$ Hz, H-2c/6c), 6.87–6.89 (1H, m, H-5b), 6.65 (1H, ddd, $J = 13.6$, 6.8, 2.5 Hz, H-2b), 6.50 (1H, d, $J = 8.9$ Hz, H-6b), 5.89 (1H, d, $J = 3.8$ Hz, H-8), 5.06 (2H, s, H-2), 4.48 (1H, d, $J = 3.7$ Hz, H-7), 4.42 (2H, s, H-3, H-5), 3.86 (1H, s, H-6), 1.46 (3H, s, H-10), 1.27 (3H, s, H-11); ^{13}C NMR (CD_3OD, 400 MHz) δ 173.1 (C, C-1), 159.9 (C, C-1c), 151.8 (C, dd, $J = 240.5$, 13.4 Hz, C-3b), 147.2 (C, d, $J = 9.0$ Hz, C-1b), 143.8 (C, dd, $J = 232.7$, 13.1 Hz, C-4b), 130.7 (CH, C-3c/5c), 123.0 (CH, C-4c), 117.8 (CH, d, $J = 17.7$ Hz, C-5b), 116.2 (CH, C-2c/6c), 112.7 (C, C-9), 110.0 (CH, C-6b), 105.9 (CH, C-8), 103.1 (CH, d, $J = 21.0$ Hz, C-2b), 87.0 (CH, C-7), 83.3 (CH, C-5), 78.1 (CH, C-2), 75.3 (CH, C-6), 57.1 (CH, C-3), 27.0 (CH_3, C-10), 26.5 (CH_3, C-11); ^{19}F NMR (CD_3OD, 376.5 MHz) δ −140.86, −156.61; HRMS (*m/z*) (pos): 452.1528 $[M + H]^+$ (calculated for $C_{22}H_{24}F_2NO_7$: 452.1521).

(**8i**) *((2S,3R)-3-((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-3-(3,4-dimethoxyphenylamino)-2-phenoxypropanoic acid)* White solid (80 % yield); mp 114–115 °C; $[\alpha]_D^{20} = 27.50°$ (*c* 0.02, MeOH); IR υ_{max} 3391(O–H), 2937 (C–H), 1728 (C=O), 1597, 1515, 1492 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.30 (2H, d, $J = 8.5$ Hz, H-3c/5c), 7.00 (1H, t, $J = 7.3$ Hz, H-4c), 6.92 (2H, d, $J = 8.0$ Hz, H-2c/6c), 6.74 (1H, dd, $J = 4.5$, 4.5 Hz, H-5b), 6.55 (1H, s, H-2b), 5.91 (1H, d, $J = 3.7$ Hz, H-8), 5.01 (1H, s, H-2), 4.49 (1H, d, $J = 3.7$ Hz, H-7), 4.43 (2H, s, H-3, H-5), 3.90 (1H, s, H-6), 3.80 (3H, s, H-7b), 3.74 (3H, s, H-8b), 1.47 (3H, s, H-10), 1.28 (3H, s, H-11); ^{13}C NMR (CD_3OD, 400 MHz) δ 173.4 (C, C-1), 159.4 (C, C-1c), 151.3 (C, C-3b), 144.4 (C, C-1b), 142.8 (C, C-4b), 130.7 (CH, C-3c/5c), 122.9 (CH, C-4c), 117.3 (CH, C-6b), 116.2 (CH, C-2c/6c), 115.4 (CH, C-5b), 112.8 (C, C-9), 106.0 (CH, C-8), 101.8 (CH, C-2b), 87.0 (CH, C-7), 82.8 (CH, C-5), 78.0 (CH, C-2), 75.6 (CH, C-6), 57.8* (CH, CH_3, C-3, C-8b), 56.3 (CH_3, C-7b), 27.1 (CH_3, C-10), 26.5 (CH_3, C-11); HRMS (*m/z*) (pos): 476.1917 $[M + H]^+$ (calculated for $C_{24}H_{30}NO_9$: 476.1921). * overlapping resonances.

(**8j**) *((2S,3R)-3-((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-5-yl)-2-phenoxy-3-(phenylamino)propanoic acid)* White solid (90 % yield); mp 117–118 °C; $[\alpha]_D^{20} = 27.25°$ (*c* 0.02, MeOH); IR υ_{max} 3508 (O–H), 3410 (N–H), 1682 (C=O), 1588, 1513, 1493 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.31 (2H, t, $J = 7.7$, Hz, H-3c/5c), 7.11 (2H, t, $J = 8.3$ Hz, H-3b/5b), 7.00 (1H, t, $J = 7.4$ Hz, H-4c), 6.94 (2H, d, $J = 8.1$ Hz, H-2c/6c), 6.85 (2H, d, $J = 8.0$ Hz, H-2b/6b), 6.67 (1H, t, $J = 7.2$ Hz, H-4b), 5.91 (1H, d, $J = 3.7$ Hz, H-8), 5.06 (1H, d, $J = 2.5$ Hz, H-2), 4.57 (1H, dd, $J = 8.5$, 2.5 Hz, H-3), 4.50 (1H, d, $J = 3.7$ Hz, H-7), 4.45 (1H, dd, $J = 8.4$, 2.6 Hz, H-5), 3.94 (1H, d, $J = 2.6$, H-6), 1.47 (3H, s, H-10), 1.28 (3H, s, H-11); ^{13}C NMR (CD_3OD, 100 MHz) δ 173.0 (C, C-1), 159.3 (C, C-1c), 148.5 (C, C-1b), 130.7 (CH, C-3c/5c), 129.9 (C, C-3b/5b), 123.0 (CH, C-4c), 119.3 (CH, C-4b), 116.3 (CH, C-2c/6c), 115.7 (CH, C-2b/6b), 112.8 (C, C-9), 106.1 (CH, C-8), 87.0 (CH, C-7), 82.8 (CH, C-5), 77.8 (CH, C-2), 75.5 (CH, C-6), 57.1 (CH, C-3), 27.1 (CH_3, C-10), 26.5 (CH_3, C-11); HRMS (*m/z*) (pos): 416.1711 $[M + H]^+$ (calculated for $C_{22}H_{26}NO_7$: 416.1709).

Acknowledgments This research was supported by Grants from the National Research Foundation (NRF), South Africa, and was supported by the South African Research Chairs Initiative of the Department of Science and Technology. We thank Dr Mahesh Palkel for assisting with molecular docking studies.

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