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Original article

A concise synthesis of *N*-substituted fagomine derivatives and the systematic exploration of their α-glycosidase inhibition

Fu-xiang Jiang [a,1], Qiao-zhen Liu [a,1], Dan Zhao [b,1], Cui-ting Luo [a], Cui-ping Guo [a], Wen-cai Ye [a,c], Cheng Luo [b], Heru Chen [a,b,c,*]

[a] Institute of Traditional Chinese Medicine and Natural Products, College of Pharmacy, Jinan University, Huangpu Avenue West 601, Guangzhou 510632, PR China
[b] State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, PR China
[c] Guangdong Province Key Laboratory of Pharmacodynamic Constituents of TCM and New Drugs Research, Jinan University, Guangzhou 510632, PR China

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ABSTRACT

A novel and concise scheme has been developed successfully for the syntheses of *N*-substituted fagomine derivatives. The transformation of lactone (**2**) to 1,5-diol (**3**) was carried on with high yield (93–95%). The cyclization of **4** to **5** is a high stereoselective reaction (de value > 98%). It is disclosed that bulky substituent at N atom of the piperidine decreases the inhibition activity except those substituents having the ability of solvation or forming disulfide bond with M444 at the active site of α-glycosidase, which enhance the interaction with enzyme. Compounds with *S*-configuration at C-3 show greater activity than those with *R*-configuration. The structure–activity relationship study is also supported by molecular docking analysis.

1. Introduction

α-Glucosidases are membrane-bound enzymes of the GH31 family that hydrolyze larger carbohydrate molecules to glucose and related monosaccharides [1]. It has been disclosed nowadays that most of these enzymes are located in the brush border of the small intestine involved in numerous fundamental biological process, such as intestinal digestion, posttranslational processing of the sugar chain of glycoproteins, quality-control systems in the endoplasmic reticulum (ER) and the ER-associated degradation (ERAD) mechanism, and the lysosomal catabolism of glycoconjugates [2]. Therefore, it's no problem to understand that inhibition of glycosidases will bring about profound effects on carbohydrate catabolism in the intestines, maturation, transport, secretion of glycoproteins, and can alter cell–cell or cell-virus recognition processes. Obviously, this is why glycosidase inhibitors show potential applications in viral infection, cancer, and genetic disorder.

Polyhydroxyated piperidines (azasugars), which contain a nitrogen atom instead of oxygen atom in the pyran ring of a sugar, have been identified as glycosidase inhibitors [3,4]. They have been disclosed as effective therapeutic agents for a wide range of diseases including diabetes [5], viral infection [6], tumor metastasis [7], and lysosomal storage disorder [8]. Two best-known α-glucosidase inhibitors are acarbose and miglitol (Fig. 1). The first one is a natural product isolated initially from an *Actinoplanes* strain, and the last one is an *N*-hydroxyethyl analogue of 1-deoxynojirimycin which was isolated from *Morus* spp. [1,9,10]. Unfortunately, either acarbose or miglitol produces gastrointestinal complaints [1]. Hence, many efforts have been made to identify more effective α-glycosidase inhibitors from natural sources in order to overcome the exiting problem [11,12].

As azasugars, fagomine (Fig. 1) was first isolated from Japanese buckwheat seeds (*Fagopyrum esculentum* Moench) [13] and subsequently from the leaves of *Morus multicaulis* [14], which is popular in China. Another two epi-fagomines, 4-epi-fagomine and 3,4-di-epi-fagomine (Fig. 1) were discovered from the leaves and roots of the legume *Xanthocersis zambesiaca* [15]. These compounds have been shown activity against mammalian gut α-glucosidase and β-galactosidase [16,17]. Moreover, fagomine was found having potent antihyperglycemic effect in streptozocin-induced diabetic mice and

* Corresponding author. Institute of Traditional Chinese Medicine and Natural Products, College of Pharmacy, Jinan University, Huangpu Avenue West 601, Guangzhou 510632, PR China.
E-mail address: thrchen@jnu.edu.cn (H. Chen).
[1] These three authors contribute equally to this work.

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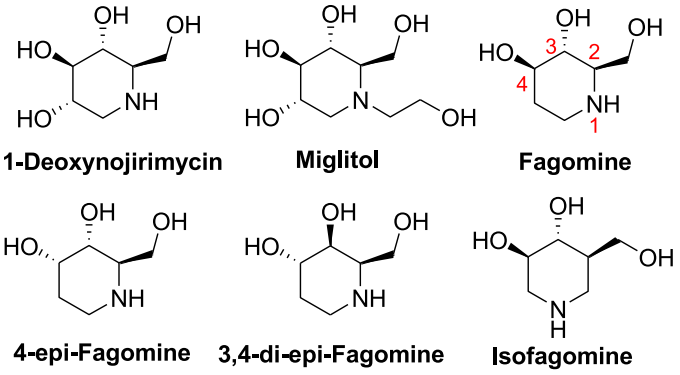


Fig. 1. Chemical structures of azasugars.

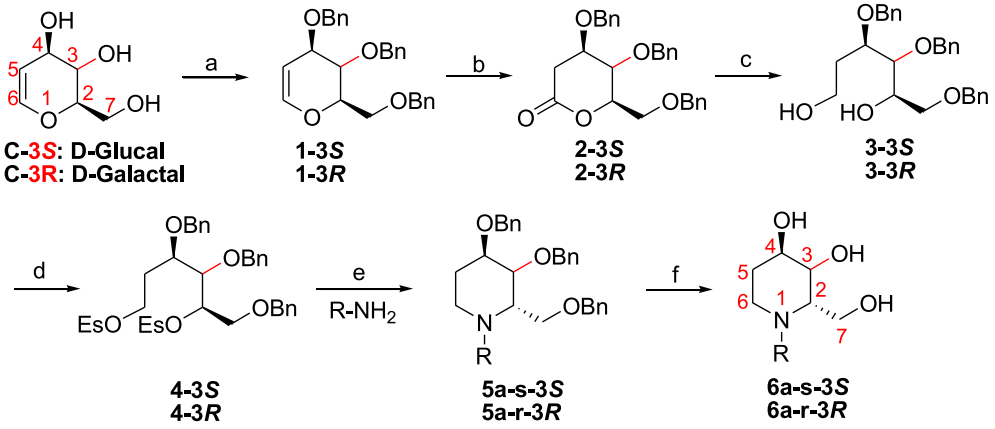
potentiating markedly the immunoreactive insulin release [18]. Interestingly, another fagomine isomer, the isofagomine was confirmed as a potent liver glycogen phosphorylase (GP) inhibitors [19]. All these facts make us believe that systematic exploration of fagomine derivatives may possibly lead to the discovery of new effective glycosidase inhibitors.

Therefore, in the current study, a concise total synthesis of *N*-substituted fagomine derivatives has been developed. The systematic investigation of their α-glycosidase inhibition, structure–activity relationship study, and molecular docking analysis were also reported here.

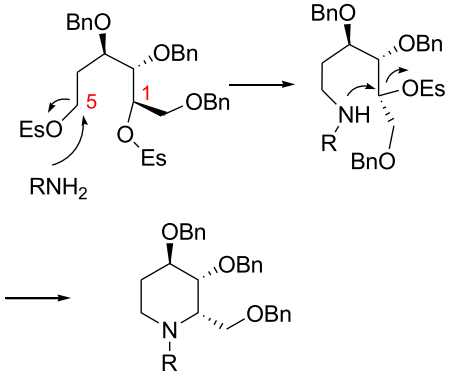
2. Chemistry

The total synthesis of fagomine derivatives was outlined in Scheme 1. Both D-glucal and D-galactal were applied as the starting materials in order to prepare epi-isomers at C-3 of the final products. Firstly, three hydroxyl groups of both D-glucal and D-galactal were protected by benzyl groups using benzyl bromide/NaH/tetrabutylammonium iodide (TBAI) as the reagents. The addition of TBAI, which was a phase transfer catalyst here, increased the yield to 98.8%. Pyridiniumchlorochromate (PCC) was applied to oxidize both **1-3*S*** and **1-3*R*** to lactones (**2-3*S*** and **2-3*R***) with yields from 72% to 83%. Two lactone isomers, **2-3*S*** and **2-3*R*** were reducted to 1,5-diols (**3-3*S*** and **3-3*R***) by $LiAlH_4$ in high yields, which were from 95% to 93%. Both 1,5-diols (**3-3*S*** and **3-3*R***) were successfully turned into ethyl 1,5-disulfonates (**4-3*S*** and **4-3*R***) applied ethylsulfonyl chloride (EsCl) and Et_3N as reagents. The yields were 72% and 82% respectively. Reactions of ethyl 1,5-disulfonates with different primary amines resulted in the cyclized products **5a-s-3*S*** and **5a-s-3*R*** with yields from good to excellence (70–93%). Removal of benzyl group by Pd catalytic hydrogenation led to target products **6a-s-3*S*** and **6a-s-3*R*** in mild to good yields (45–85%). In some cases, the low yields were caused by the loss of product during HPLC purification.

The formation of piperidine derivatives (**5a-s-3*S*** and **5a-s-3*R***) included two processes, an intermolecular S_N2 reaction with primary amines following subsequently the intramolecular nucleophilic reaction. No 1,5-diamines were found although primary amines were excessive during the reactions. This indicates that the



Scheme 1. Synthesis of fagomine derivatives. Reagents and conditions: (a) THF, NaH, BnBr, TBAI, 98.8%; (b) DCM, PCC, 72–83%; (c) $LiAlH_4$, THF, 93–95%; (d) DCM, Et_3N, EsCl, 72–82%; (e) dioxiane, 90–100 °C, 70–93%; (f) H_2, Pd/C, 0.2 M HCOOH, 45–85%.



Entry	R	de (%)
5b-3*S*	CH_2CH_2-	98.8
5c-3*S*	MeO CH_2CH_2-	99.3
5f-3*S*	HN N CH_2CH_2-	98.6
5k-3*S*	$AcNHCH_2CH_2-$	98.2

Fig. 2. Putative mechanism for the formation of piperidine derivatives and the de values of some representative reaction. The de values were determined by HPLC analysis. Column: chiral CD-Ph S5 (4.6 mm i.d.×250 mm); Eluant: ACN: 50 mM $NaClO_4$ = 60:40 (V:V); Flow rate: 0.5 ml/min; temperature: 30 °C; Detector: UV 214 nm.

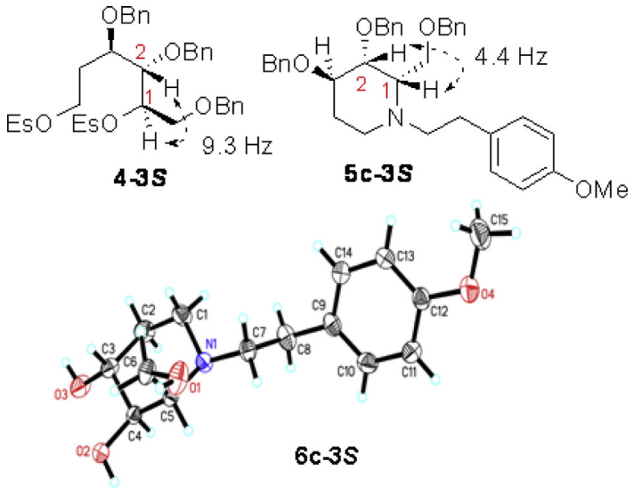


Fig. 3. Characteristic coupling constants of **4-3*S*** and **5c-3*S***. ORTEP drawing of **6c-3*S***.

formation of piperidine derivatives is preferential absolutely to the formation of 1,5-diamines.

Theoretically, as shown in Fig. 2, the intramolecular nucleophilic reaction leads to the reverse of the configuration at C-1. This is true in the current study. The optical analysis of all the resulted compounds (**5a-s-3*S*** and **5a-r-3*R***) on chiral CD-Ph S5 column (SHISEIDO CO., LTD, Japan) displayed that the stereoselectivities of all the reactions were very high. All the de values were higher than 98%. Four representative examples were listed in Fig. 2. It can be seen that more bulky of the substituent leads to higher stereoselectivity of the reaction. e.g., the de value of **5c-3*S*** was greater than that of **5k-3*S*** due to *p*-OMePhCH$_2$CH$_2$ is a more bulky group than AcNHCH$_2$CH$_2$. This is reasonable and complies obviously with the law of S_N2 reaction.

The configurations at C-1 of the domain products (**5a-s-3*S*** and **5a-r-3*R***) were confirmed reversed when compared with their precursors (**4-3*S*** and **4-3*R***). e.g., as seen in Fig. 3, transformation of **4-3*S*** to **5c-3*S*** resulted in the reversed configuration at C-1 from *R*- to *S*-, which was supported by the coupling constant of H-1 with H-2. When single crystal of the compound is available, the configuration is double supported by analysis of its X-ray data. As an example, the configuration at C-1 of **6c-3*S*** was confirmed *S*- which supported the conclusion drawn from NMR analysis.

3. Results and discussion

3.1. α-Glycosidase inhibition of N-substituted fagomine derivatives

The α-glycosidase inhibition of all the *N*-substituted fagomine derivatives was determined by an *in vitro* screening assay. Acarbose was chosen as the positive control. As shown in Table 1, the α-glycosidase inhibition of all the tested fagomine derivatives was less active than that of acarbose, and 1,2-di-epi-fagomine (**6a-3*R***) is the most active fagomine derivative. Any bulky substituents at N atom of the piperidine ring (**6b**-**6h**, **6n**) cause the loss of activity. Only **6g-3*S*** is the exception, which displays moderate activity with IC_{50} value of 215.9 ± 2.1 μM. This indicates that the sulfamide group possibly enhance the binding affinity with enzyme. As a universal law amongst all the tested derivatives, compounds with *R*-configuration at C-3 are always less active than those with *S*-configuration at C-3. It is quit interesting that **6s-3*S*** shows greater activity than either **6r-3*S*** or **6r-3*R***. This evidence implies that sulfur in place of oxygen at the same position results in higher affinity with α-glycosidase.

Table 1
α-Glucosidase inhibition of *N*-substituted fagomine derivatives.

Compounds	IC_{50} (μM) ± SEM	Compounds	IC_{50} (μM) ± SEM
[a]Acarbose	39.8 ± 0.3	**6j-3*S***	161.2 ± 0.6
6a-3*S*	124.5 ± 1.5	**6j-3*R***	141.2 ± 0.5
6a-3*R*	110.0 ± 0.8	**6k-3*S***	235.2 ± 2.1
6b-3*S*	–	**6l-3*S***	184.2 ± 1.6
6b-3*R*	–	**6m-3*S***	186.0 ± 0.7
6c-3S	–	**6m-3*R***	166.0 ± 0.7
6c-3*R*	–	**6n-3*S***	–
6d-3S	–	**6n-3*R***	–
6d-3*R*	–	**6o-3*S***	170.2 ± 1.3
6e-3*S*	–	**6o-3*R***	158.8 ± 2.2
6e-3*R*	–	**6p-3*S***	168.1 ± 0.6
6f-3*S*	–	**6p-3*R***	151.9 ± 0.4
6g-3S	215.9 ± 2.1	**6q-3*S***	151.7 ± 0.5
6h-3*S*	–	**6q-3*R***	147.4 ± 0.7
6h-3*R*	–	**6r-3*S***	217.0 ± 1.2
6i-3*S*	216.2 ± 1.5	**6r-3*R***	203.7 ± 2.3
6i-3*R*	139.3 ± 1.1	**6s-3S**	121.9 ± 0.9

IC_{50} values expressed as SEM (Standard Error of Mean), where $n = 3$.
[a] Positive control; – Less than 50% inhibition at 500 μM.

3.2. Explanation from structure

It was pointed out that the binding of acarbose at the active site of α-glycosidase involves numerous hydrogen bonds, particularly with the acarvosine rings. Besides, hydrophobic interactions also mediate binding of acarbose with the enzyme [20] (Fig. 4A). As the same with acarbose, the molecular docking of **6a-3*R*** to α-glucosidase shows that **6a-3*R*** locates at the inner active site. It also forms strong hydrogen bonds and hydrophobic interactions with surrounding residues of the enzyme (Fig. 4B). When bulky substituents locate at the N atom of the piperidine ring, steric clash tends to weaken the binding force of small molecules with α-glucosidase. This is in accordance with the experimental results that from **6b** to **6h** all the activities decrease. However, as shown in Fig. 4C, **6g-3*S*** with 4-sulphonamidophenethyl group at N atom could point out to the solution environment. The sulfonamide group actually possesses relative higher polarity and solvates in the solution more easily when compared with other groups at compounds **6b**-**6h**. The solvation may compensate partially the loss of interaction caused by steric clash. This may be the reason why **6g-3S** has a relative higher enzymatic activity.

Comparing the *R*- and *S*- configuration at C-3, it was found that from *R*- to *S*- configuration the compounds flip to a position which form more hydrogen bond interaction with surrounding residues of the enzyme. This flip of conformation is particularly obvious in **6a**, **6m** and **6r** (Fig. 5). The overall enhanced hydrogen bond interaction may be the reason why compounds with *S*-configuration at C-3 are always more active than those with *R*-configuration.

Interestingly, we found that the sulfur atom of **6s-3*S*** has the trend of forming disulfide bond with M444 of the enzyme (Fig. 6). The disulfide bond may greatly strengthen the interaction between **6s-3*S*** and the enzyme. Thus, **6s-3*S*** shows greater activity than either **6r-3*S*** or **6r-3*R*** and most of the other compounds.

4. Conclusions

A series of *N*-substituted fagomine derivatives has been synthesized by a novel and concise scheme. The transformation of lactone (**2**) to 1,5-diol (**3**) was carried out easily in high yield (93–95%). The cyclization of **4** to **5** includes the intermolecular nucleophilic substitution (S_N2) following immediately an intramolecular nucleophilic substitution with high stereoselectivity (de

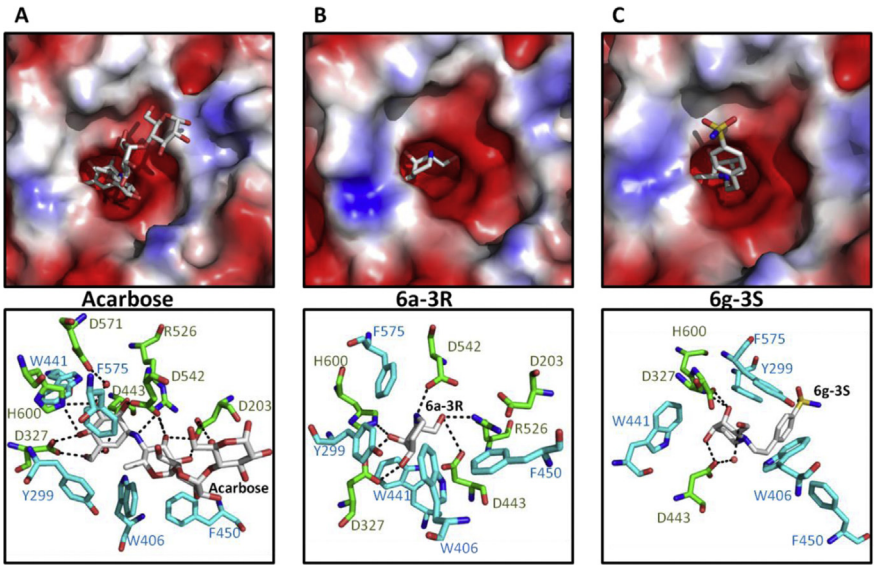


Fig. 4. Complex models of α-Glucosidase with Acarbose (**A**), **6a-3*R*** (**B**) and **6g-3*S*** (**C**). Upper panel shows the structural electrostatic surfaces (the blue color indicates positive charge and red color indicates negative charge). Water molecules are shown as red spheres. Acarbose, **6a-3*R*** and **6g-3*S*** are shown as sticks. Lower panel shows detailed interactions. Residues which could form hydrogen bond with Acarbose, **6a-3*R*** or **6g-3*S*** are shown as green sticks and hydrophobic residues are shown as blue sticks. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

value > 98%). The inhibition of all the prepared compounds to α-glycosidase has been systematically investigated. It is disclosed that any bulky substitution at N atom of the piperidine basically decreases the inhibition activity. Interestingly, compounds (**6a**, **6m** and **6r**) with *S*-configuration at C-3 show greater inhibition activity than those with *R*-configuration. Compounds with substituents having the ability of solvation (**6g-3S**) or forming disulfide bond with M444 of α-glycosidase (**6s-3S**) show greater activity than those with bulky substituents only. The structure–activity relationship study is supported by molecular docking analysis.

5. Experimental section

5.1. Materials and methods

5.1.1. Materials

Alpha-glucosidase (maltase) was purchased from ORIENTAL YEAST Co. Ltd. (Japan). All other chemicals were purchased from Aldrich or Adamas without further purification. Silica gel for column chromatography was purchased from Qingdao Marine Chemicals Inc, China. Chromatographic grade methanol was bought from Shandong YuWang Reagent Company (China).

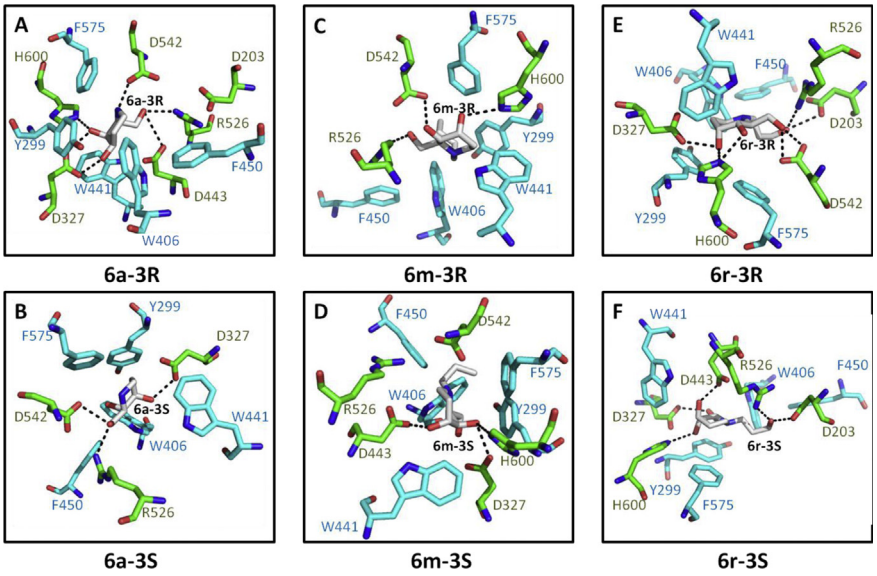


Fig. 5. Comparison of detailed interactions between **6a-3*R*/*S*** (**Fig. A/B**), **6m-3*R*/*S*** (**Fig. C/D**) and **6r-3*R*/*S*** (**Fig. E/F**). Residues which could form hydrogen bond with **6a-3*R*/*S***, **6m-3*R*/*S*** or **6r-3*R*/*S*** are shown as green sticks and hydrophobic residues are shown as blue sticks. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

5.1.2. General experimental procedures

NMR spectra were recorded on Bruker AV-300 (Bruker Biospin, Swiss), TMS was used as internal standard. ESI-MS were recorded on Finnigan LCQ Advantage MAX mass spectrometer. HPLC was performed on either LC-100 liquid chromatograph equipped with a tunable LC-100 UV detector (Shanghai Wufeng Inc., China) or Agilent 1200 series liquid chromatograph equipped with an Agilent 1200 Series UV detector (Agilent Technologies, USA). Column used were Cosmosil $5C_{18}$ (Nacalai Tesque Inc., Japan) for general purification and chiral CD-Ph S5 (SHISEIDO CO., LTD, Japan) for optical analysis. Pre-coated thin-layer chromatography (TLC) plates (Institute of Yantai Chemical Industry, China) were used for TLC. Spots on TLC plates were detected by either a ZF-7A portable UV detector or spraying Bismuth potassium iodide solution followed subsequent heating. Ethanol was reluxed over Fresh magnesium ribbon for 5 h and redistilled.

5.1.3. X-ray crystallographic study

Data collections of compound **6c-3*S*** were performed on a Bruker Smart Apex CCD diffractometer with Mo-Kα radiation (λ = 0.71073 Å), using frames of 0.3° oscillation ($2\theta \leq 56°$). The structures were solved with direct methods and refined with the full-matrix least-squares technique with the SHELXTL programs. Anisotropic thermal parameters were applied to all non-hydrogen atoms. The hydrogen atoms were generated geometrically (C–H = 0.960 Å). The crystallographic calculations were conducted with the *SHELXL-97* programs [21].

5.1.4. Molecular docking

The *N*-substituted fagomine derivatives were docked to α-Glucosidase (PDB entry: 2QMJ) [20] using Glide program [22] in its XP mode in a standard procedure. The three water molecules at the active site were all retained. The *N*-substituted fagomine derivatives were sketched by ChemBio3D Ultra 11.0 [23] and processed by LigPrep under its default parameters. The docked conformations of the compounds with the lowest energy were selected for further analysis.

5.1.5. In vitro α-glucosidase inhibition assay

α-Glucosidase activity was assayed in 0.1 M sodium phosphate buffer (pH 6.8) with *p*-nitrophenyl-α-D-glucopyranoside as a substrate. The concentration of α-glucosidase was 0.2 U/mL in each experiment. The enzyme (20 ml) along with 100 ml of phosphate buffered saline was incubated with various concentrations of tested compounds at 37 °C. The pre-incubation time was 15 min, then 20 ml of substrate (0.7 mM) was added and reaction was carried on at 37 °C for 30 min. Enzymatic activity was quantified by measuring the absorbance of *p*-nitrophenol at 400 nm on a microtitre plate spectrophotometer (Spectra Max, Molecular Devices, USA). One unit of α-glucosidase was defined as the amount of enzyme liberating 1.0 mmol of *p*-nitrophenol per minute under the conditions specified [24]. Acarbose was used as the positive control (IC_{50} = 39.75 ± 0.06 μM) (Table 1). The percent inhibition of *p*-nitrophenol formation in the test sample versus control was calculated for each compound by using the following formula:

$$\%\text{inhibition} = 100 - \left(\frac{OD_{sample}}{OD_{control}}\right) \times 100$$

5.1.6. Statistical analysis

Results are presented as means ± SEM from three experiments as indicated in each figure legend. IC_{50} values were determined by using EZ-FIT, Enzyme kinetics software by Perrella Scientific Inc., USA.

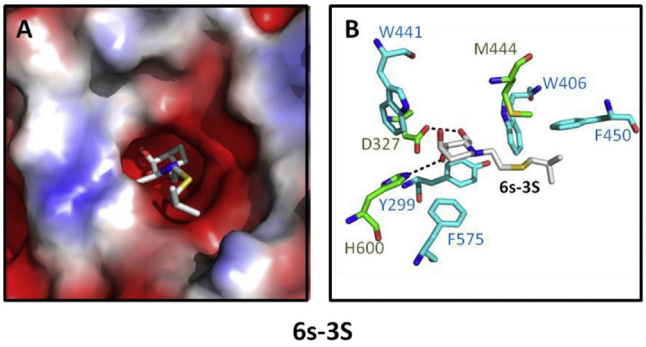


Fig. 6. Complex model of α-Glucosidase with **6s-3S**. The structural electrostatic surfaces are shown as Fig. 3A. And detailed interactions are shown as Fig. 3B. Residues which could form hydrogen bond with **6s-3*S*** are shown as green sticks and hydrophobic residues are shown as blue sticks. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

5.2. Synthetic process

*5.2.1. Synthesis of (2R,3S,4R)-3,4-bis-benzyloxy-2-benzyloxymethyl-3,4-dihydro-2H-pyran (**1-3S**)*

To a solution of D-glucal (1.46 g, 10 mmol) in dry THF (20 ml) was added NaH (1.44 g, 60 wt% dispersion in mineral oil, 36 mmol) and tetrabutylammonium iodide (TBAI) at room temperature. The suspension was stirred for 30 min then cooled in an ice-bath. Benzyl bromide (4.4 ml, 36 mmol) was added dropwise over a 5-min period, and after 10 min the ice bath was removed. The reaction mixture was stirred overnight. Then 10 ml of methanol was added slowly to dispose the excess NaH. The solvents were removed under reduced pressure at 35 °C. The residue was then dissolved in 200 ml of dichloromethane (DCM) and washed with water and brine respectively. Then the mixture was dried over anhydrous $MgSO_4$. Removal of MgSO4 was carried on, and the filtrate was evaporated to give a yellow oil, which solidified to a yellow solid after submitted to high vacuum overnight. Further purification by column chromatography (silica gel, EtOAc/Petroleum ether = 1:20, *V*:*V*) gave **1-3*S*** as a colorless semisolid (4.05 g, 98.8%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37–7.21 (m, 15H, Ph-H), 6.42 (dd, *J* = 6.1, 1.2 Hz, 1H, H-6), 4.87 (dd, *J* = 6.1, 2.7 Hz, 1H, H-5), 4.85–4.50 (m, 6H, $PhCH_2$–), 4.21 (ddd, *J* = 6.1, 2.3, 1.4 Hz, 1H, H-2), 4.06 (m, 1H, H-7a), 3.86 (dd, *J* = 8.7, 6.2 Hz, 1H, H-4); 3.77 (m, 2H, H-3, H-7b); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 144.8, 138.4, 138.3, 138.1, 128.5 (6C), 127.8 (3C), 127.7 (6C), 100.0, 76.8, 75.8, 74.5, 73.8, 73.6, 70.5, 68.6; ESI-MS (*m*/*z*): 439.4[M + Na^+].

*5.2.2. Synthesis of compounds (2R,3R,4R)-3,4-bis-benzyloxy-2-benzyloxymethyl-3,4-dihydro-2H-pyran (**1-3R**)*

Followed the process as described in 5.2.1.1. D-galactal (0.73 g, 5.0 mmol), NaH (1.8 g, 60 wt% dispersion in mineral oil, 75 mmol), benzyl bromide (2.2 ml, 18 mmol) were added. No TBAI was added. The final purification by column chromatography (silica gel, EtOAc/Petroleum ether = 1:10, *V*:*V*) gave **1-3*R*** as a colorless solid (1.92 g, 92.3%). R_f = 0.36; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.20–7.30(m, 15H, Ph-H), 6.33 (dd, *J* = 6.2, 1.3 Hz, 1H), 4.80–4.84 (m, 2H), 4.34–4.60(m, 6H), 4.10–4.17(m, 2H), 3.89 (m, 1H), 3.74–3.80 (m, 1H), 3.62–3.67 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 144.0, 138.4, 138.3, 137.9, 128.6 (6C), 127.7 (3C), 127.8 (6C), 99.9, 75.5, 73.3, 73.2, 71.2, 70.7, 70.6, 68.3; ESI-MS (*m*/*z*): 417.5[M + $H]^+$.

*5.2.3. Synthesis of (2R,3S,4R)-3,4-bis-benzyloxy-2-benzyloxymethyl-tetrahydro-pyran-5-one (**2-3S**)*

To a solution of **1-3*S*** (4.1 g, 10 mmol) in DCM (25 ml), PCC (12.9 g, 60 mmol) was added in portions following the addition of about 5 g silica gel. The mixture was stirred at ambient temperature for 12 h. Then the reaction mixture was submitted to a funnel filled

with diatomite for removal of silica gel and insoluble substances. All the filtrates were combined, and the solvent was evaporated under reduced pressure. The residue was further purified by column chromatography (silica gel, EtOAc/Petroleum ether = 1:4, *V*:*V*) to give **2-3S** as a colorless oil (3.11 g, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33–7.16 (m, 15H, Ph-H), 4.64–4.42 (m, 6H, $PhCH_2$–), 4.26 (m, 1H), 3.88 (m, 2H), 3.68 (m, 2H), 2.77 (m, 2H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 169.5, 137.9, 137.5 (2C), 128.6 (2C), 128.5 (2C), 128.2 (2C), 128.1 (3C), 127.9 (6C), 79.4, 75.2, 74.9, 73.6, 72.9, 71.1, 69.0, 33.8; ESI-MS (*m/z*): 455.3[M + Na^+].

*5.2.4. Synthesis of (2R,3R,4R)-3,4-bis-benzyloxy-2-benzyloxymethyl-tetrahydro-pyran-5-one (**2-3R**)*

Followed the process as described in 5.2.2.1. **1-3*R*** (1.6 g, 3.8 mmol) in DCM (20 ml), PCC (3.3 g, 15.4 mmol) and 3 g silica gel were added. The final purification by column chromatography (silica gel, EtOAc/Petroleum ether = 1:1, *V*:*V*) gave **2-3R** as a colorless oil (1.4 g, 82.3%), R_f = 0.34. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39–7.26 (m, 15H, Ar–H), 4.92 (d, *J* = 11.5 Hz, 1H), 4.64–4.41 (m, 1H), 4.31 (ddd, *J* = 7.6, 5.7, 1.6 Hz, 1H), 4.14 (m, 1H), 3.87–3.81 (m, 1H), 3.76–3.62(m, 2H), 3.00–2.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.0, 138.0, 137.5, 137.4, 128.6 (2C), 128.5 (2C), 128.2 (2C), 128.0 (3C), 127.4 (6C), 78.1, 74.4, 74.2, 73.6, 70.7, 70.3, 67.9, 33.0; ESI-MS (*m/z*): 433.5 [M + H]$^+$, 455.1 [M + Na]$^+$.

*5.2.5. Synthesis of (2R,3R,4R)-1,3,4-tris(benzyloxy)hexane-2,5-diol (**3-3S**)*

To a solution of **2-3S** (3 g, 7 mmol) in anhydrous THF (25 ml), $LiAlH_4$ (2.2 g, 60 mmol) was added in portions with stirring in an ice-water bath. After the completion of the addition, the mixture was stirred for another 2 h at ambient temperature. The excess hydride was destroyed by addition of 2 mol/L HCl in ice-water bath until no gas was observed. The reaction mixture was extracted with EtOAc (4 × 100 mL). The combined organic layers were washed with water and brine respectively, and were dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (silica gel, EtOAc/Petroleum ether = 1:3, *V*:*V*) to give **3-3*S*** as a colorless oil (3.6 g, 95%). ^{1}H NMR(300 MHz, $CDCl_3$) δ: 7.39–7.21 (m, 15H, Ph-H), 4.57 (m, 6H, $PhCH_2$–), 4.01 (m, 1H), 3.86 (m, 1H), 3.73–3.53 (m, 4H), 3.42 (dd, *J* = 9.1, 9.3 Hz, 1H), 1.87 (m, 2H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 138.1, 138.0, 137.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9 (3C), 127.8 (6C), 78.5, 77.9, 73.7, 73.6, 72.8, 71.3, 70.8, 59.8, 33.0; ESI-MS (*m/z*): 459.3[M + Na]$^+$.

*5.2.6. Synthesis of (2R,3S,4R)-1,3,4-tris(benzyloxy)hexane-2,5-diol (**3-3R**)*

Followed the process as described in 5.2.3.1. **2-3*R*** (1.5 g, 3.4 mmol) in DCM (15 ml), and $LiAlH_4$ (1.02 g, 26.8 mmol) were added. The final purification by column chromatography (silica gel, EtOAc/Petroleum ether = 1:1, *V*:*V*) gave **3-3*R*** in slight yellow oil (1.14 g, 78.2%), R_f = 0.23. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.23–7.29 (m, 15H), 4.40–4.75 (m, 6H), 3.86 (m, 1H), 3.68–3.54 (m, 4H), 3.50 (d, *J* = 5.7, 5.3 Hz, 1H), 1.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.2, 138.1, 138.0, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 127.9 (3C), 127.5 (6C), 79.4, 78.0, 74.0, 73.5, 72.6, 71.2, 70.2, 59.6, 33.6,; ESI-MS (*m/z*): 459.3[M + Na]$^+$.

*5.2.7. Synthesis of (2R,3R,4R)-1,3,4-tris(benzyloxy)hexane-2,5-diethylsulfonate (**4-3S**)*

3-3*S* (3 g, 7 mmol) was dissolved in 25 ml of dried dichloromethane and dried over molecular sieves in order to remove any moisture if present. Triethylamine (1.2 ml, 7.2 mmol) was then added and the reaction mixture was cooled to 0 °C. After 5 min, ethylsulfonyl chloride (1.35 ml, 14.7 mmol) was added and the reaction mixture was stirred for 3 h at 0 °C. The reaction mixture was then quenched with saturated Na_2CO_3 solution (10 ml) and extracted with dichloromethane (3 × 50 ml). The combined organic layer was washed with saturated sodium bicarbonate solution and then with water. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was submitted to column chromatography (silica gel, EtOAc/Petroleum ether = 1:4, *V*:*V*) led to **4-3*S*** as a colorless oil (3.6 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40–7.23 (m, 15H, Ph-H), 4.96 (dt, *J* = 6.4, 3.1 Hz, 1H), 4.81–4.44 (m, 6H, $PhCH_2$–), 4.17 (m, 2H), 3.95 (dd, *J* = 4.9, 2.9 Hz, 1H), 3.85 (m, 2H), 3.72 (dt, *J* = 9.3, 4.6 Hz, 1H), 3.24–2.94 (m, 4H, –CH_2SO_2–), 1.97 (m, 2H), 1.33 (m, 6H, CH_3–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.7, 137.5, 137.4, 128.5 (2C), 128.4 (2C), 128.1 (2C), 128.0 (3C), 127.9 (6C), 82.2, 80.0, 5.2, 74.3, 73.2, 73.1, 69.0, 66.3, 45.6, 44.8, 30.8, 8.2 (2C); ESI-MS (*m/z*): 643.5[M + Na]$^+$.

*5.2.8. Synthesis of (2R,3S,4R)-1,3,4-tris(benzyloxy)hexane-2,5-diethylsulfonate (**4-3R**)*

Followed the process as described in 5.2.4.1. **3-3*R*** (1.35 g, 3.1 mmol) in DCM (20 ml), and Et_3N (1.0 ml, 6.8 mmol), ethylsulfonyl chloride (0.6 ml, 6.5 mmol) were added. The final purification by column chromatography (silica gel, EtOAc/Petroleum ether = 1:3, *V*:*V*) gave **4-3*R*** in slight yellow oil (1.39 g, 72.3%), R_f = 0.30. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.24–7.39 (m, 15H, Ar–H), 4.82 (m, 2H), 4.64 (dd, *J* = 11.3, 6.0 Hz, 2H), 4.49 (m, 3H), 4.32 (m, 2H), 4.01 (dd, *J* = 5.6, 3.0 Hz, 1H), 3.82(m, 1H), 3.73 (d, *J* = 4.7 Hz, 2H), 3.21–2.93 (m, 4H, –CH_2SO_2–), 2.04 (m, 2H), 1.31 (m, 6H, CH_3–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.1, 138.0, 137.5, 128.8 (2C), 128.6 (2C), 128.5 (2C), 128.1 (3C), 127.9 (6C), 81.2, 78.6, 75.7, 74.7, 73.9, 72.5, 69.6, 67.0, 46.1, 45.1, 30.8, 8.4 (2C); ESI-MS (*m/z*): 643.1 [M + Na]$^+$.

*5.2.9. General procedure for the syntheses of **5a-s-3S** and **5a-r-3R***

Either **4-3*S*** or **4-3*R*** [(310.1 mg, 0.5 mmol), ortherwise marked out] and amines (3–5 ml) were sealed together in a dried 10-ml pressure reactor. The reaction mixture was stirred at 80–90 °C over an oil-bath for scheduled time (12–18 h). Then, the mixture was quenched with 8 ml of 1.0 mol/L hydrochloric acid and extracted with dichloromethane (3 × 50 ml). The combined organic layer was washed with saturated sodium bicarbonate solution and water respectively. The organic layer was then dried over anhydrous $MgSO_4$, filtered and concentrated. The residues were submitted to column chromatography (silica gel, EtOAc/Petroleum ether) or RP-HPLC for purification.

*5.2.9.1. Synthesis of (2S,3R,4R)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-1-(furan-2-ylmethyl)piperidine (**5a-3S**).* Purified by silica gel column chromatography (EtOAc/Petroleum ether, 1:4, *V*:*V*) to afford **5a-3*S*** as slight yellow oil (218.7 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39–7.20 (m, 16H, Ar–H), 6.28 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.14 (d, *J* = 3.1 Hz, 1H), 4.65–4.43 (m, 6H, $PhCH_2$–), 3.93–3.64 (m, 5H), 3.49 (m, 1H), 3.22 (dd, *J* = 9.8, 4.4 Hz, 1H), 2.61 (m, 2H), 1.97 (m, 1H), 1.63 (m, 1H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 152.5, 141.9, 139.0, 138.7, 138.5, 128.4, 128.3, 128.2 (4C), 127.7 (2C), 127.6 (2C), 127.4 (3C), 110.1, 108.7, 78.2, 74.3, 72.8, 71.1, 70.2, 67.6, 59.2, 50.9, 45.8, 27.6; ESI-MS (*m/z*): 498.5[M + H]$^+$.

*5.2.9.2. Synthesis of (2S,3S,4R)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-1-(furan-2-ylmethyl)piperidine (**5a-3R**).* Purified by RP-HPLC (methanol:H_2O = 4:1, *V*:*V*) to give **5a-3*R*** as slight yellow oil (221.7 mg, 89.2%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.18–7.36 (m, 16H), 6.24 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.07 (d, *J* = 3.1 Hz, 1H), 4.44–4.58 (m, 5H), 4.33 (d, *J* = 11.6 Hz, 1H), 3.76–3.85 (m, 5H), 3.64 (dd, *J* = 9.2, 2.8 Hz, 1H), 2.85 (m, 1H), 2.64 (m, 2H), 1.90 (m, 1H), 1.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.8, 141.6, 138.5, 138.1, 138.0, 128.3, 128.2, 128.1 (4C), 127.5 (2C), 127.3 (2C), 127.1 (3C), 109.7, 108.6, 76.8, 73.2,

71.2, 70.7, 70.2, 65.5, 58.8, 49.2, 46.1, 26.9; ESI-MS (*m/z*): 498.4 $[M + H]^+$, 520.3 $[M + Na]^+$.

*5.2.9.3. Synthesis of (2S,3R,4R)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-1-phen-ethylpiperidine (**5b-3S**).* Purified by silica gel column chromatography (EtOAc/Petroleum ether, 1:4, *V*:*V*) to afford **5b-3*S*** as slight yellow oil (234.5 mg, 90%). ^{1}H NMR (300 MHz, CD_3COCD_3) δ: 7.42–7.19 (m, 20H, Ar–H), 4.65 (s, 2H, $PhCH_2$–), 4.63 (s, 2H, $PhCH_2$–), 4.50 (s, 2H, $PhCH_2$–), 3.86 (m, 1H), 3.74 (m, 1H), 3.63 (m, 2H), 3.45 (m, 1H), 2.93–2.61 (m, 6H), 2.01 (m, 1H), 1.59 (m, 1H); ^{13}C NMR(75 MHz, CD_3COCD_3) δ: 141.9, 140.5, 140.2, 139.8, 129.7 (2C), 129.1 (2C), 129.0 (2C), 129.0 (2C), 128.5 (2C), 128.4 (2C), 128.2 (2C), 128.1 (2C), 128.0 (3C), 126.5, 80.2, 75.7, 72.8, 72.2, 71.0, 66.3, 59.7, 56.5, 45.5, 33.6, 29.0; ESI-MS (*m/z*): 522.5$[M + H]^+$.

*5.2.9.4. Synthesis of (2S,3S,4R)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-1-phen-ethylpiperidine (**5b-3R**).* Purified by RP-HPLC (methanol:H_2O = 17:1, *V*:*V*) to give **5b-3*R*** as slight yellow oil (219.6 mg, 84.3%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.19–7.36 (m, 18H), 7.03 (m, 2H), 4.50–4.84 (m, 4H), 4.39(d, *J* = 8.9 Hz, 2H), 3.84 (m, 1H), 3.62–3.74 (m, 3H), 3.00 (d, *J* = 12.0 Hz, 1H), 2.64–2.75 (m, 6H), 1.96 (m, 1H),1.66 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.6, 138.9, 138.4, 138.0, 128.5 (2C), 128.2 (2C), 128.1 (2C), 128.0 (2C), 127.5 (2C), 127.4 (2C), 127.2 (2C), 127.1 (2C), 127.0 (3C), 125.8, 73.4, 71.4, 71.3, 70.7, 65.4, 55.3, 58.9, 50.3, 46.1, 31.1, 27.3; ESI-MS (*m/z*): 522.4 $[M + H]^+$, 544.5$[M + Na]^+$.

*5.2.9.5. Synthesis of (2S,3R,4R)-1-(4-methoxyphenethyl)-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5c-3S**).* Purified by silica gel column chromatography (EtOAc/Petroleum ether, 1:4, *V*:*V*) to afford **5c-3*S*** as faint yellow oil (246.0 mg, 89%). ^{1}H NMR(300 MHz, CD_3COCD_3) δ: 7.42–7.19 (m, 15H, Ar–H), 7.11 (m, 2H, Ar–H), 6.80 (m, 2H, Ar–H), 4.65 (s, 2H, $PhCH_2$–), 4.63(s, 2H, $PhCH_2$–), 4.50 (s, 2H, $PhCH_2$–), 3.83 (m, 1H), 3.73 (s, 3H, CH_3O–), 3.71 (m, 1H), 3.61 (m, 2H), 3.45 (m, 1H), 2.98–2.61 (m, 6H), 1.98 (m, 1H), 1.56 (m, 1H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ: 158.9, 139.7, 139.3, 139.0, 132.9, 129.7 (2C), 128.2 (3C), 128.1 (3C), 127.6 (3C), 127.5 (2C), 127.4 (2C), 127.3, 127.1, 113.5 (2C), 81.1, 78.6, 73.5, 72.8, 71.9, 67.2, 60.8, 57.5, 55.4, 46.5, 33.6, 28.9; ESI-MS (*m/z*): 552.4 $[M + H]^+$.

*5.2.9.6. Synthesis of (2S,3S,4R)-1-(4-methoxyphenethyl)-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5c-3R**).* Purified by RP-HPLC (methanol:H_2O = 4:1, *V*:*V*) to give **5c-3*R*** as colorless oil (270.9 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.21–7.36 (m, 15H), 6.96 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 2.8 Hz, 2H), 4.38–4.64 (m, 6H), 3.84 (m, 1H), 3.74 (s, 3H), 3.61–3.71 (m, 3H), 2.99 (d, *J* = 8.9 Hz, 1H), 2.84 (m, 3H), 2.67 (dd, *J* = 13.2, 5.9 Hz, 3H), 1.96(m, 1H), 1.66 (ddd, *J* = 11.8, 9.7, 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.9, 139.0, 138.5, 138.1, 132.7, 129.6 (2C), 128.6 (3C), 128.5 (3C), 127.6 (3C), 127.5 (2C), 127.4 (2C), 127.3, 127.2, 113.8 (2C), 77.0, 73.6, 71.6, 71.5, 70.8, 65.6, 59.1, 55.6, 55.3, 46.3, 30.4, 27.4; ESI-MS (*m/z*):552.5 $[M + H]^+$.

*5.2.9.7. Synthesis of (2R,3R,4R)-1-(4-fluorophenethyl)-3,4-bis(benzyloxy)-2- (benzyloxymethyl) piperidine (**5d-3S**).* Purified by silica gel column chromatography (EtOAc/Petroleum ether, 1:4, *V*:*V*) to afford **5d-3*S*** as slight yellow oil (218.3 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52–6.90 (m, 19H, Ar–H), 4.81–4.48 (m, 6H, $PhCH_2$–), 3.89 (m, 1H, H-7a), 3.74 (ddd, 1H, *J* = 13.5, 8.2, 3.8 Hz), 3.64 (m, 2H), 3.44 (m, 1H), 3.07–2.70 (m, 6H), 2.12 (m, 1H), 1.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.7, 138.8, 138.5, 138.2, 136.3, 129.9 (2C), 128.2 (3C), 128.2 (3C), 128.0 (3C), 127.7, 127.5, 127.4 (2C), 127.3 (2C), 114.9, 114.6, 78.7, 74.6, 73.4, 72.7, 71.4, 67.9, 59.2, 55.6, 46.1, 31.6, 28.1; ESI-MS (*m/z*): 540.5 $[M + H]^+$.

*5.2.9.8. Synthesis of (2S,3S,4R)-1-(4-fluorophenethyl)-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5d-3R**).* Purified by RP-HPLC (methanol:H_2O = 17:3, *V*:*V*) to give **5d-3*R*** as slight yellow oil (246.9 mg, 91.6%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.24–7.36 (m, 15H), 6.86–6.98 (m, 4H), 4.53–4.65 (m, 4H), 4.41(dd, *J* = 11.9, 7.1 Hz, 2H), 3.85 (s, 1H), 3.60–3.72 (m, 3H), 2.99 (d, *J* = 8.9 Hz, 1H), 2.62–2.88 (m, 6H), 1.97 (m, 1H), 1.65 (ddd, *J* = 11.8, 9.7, 2.5 Hz, 1H),; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.7, 139.0, 138.5, 138.0, 136.3, 130.0, 127.42–128.37(16C), 115.2, 114.9, 76.9, 73.5, 71.6, 71.5, 70.8, 65.1, 59.1, 55.4, 46.2, 30.5, 27.4; ESI-MS (*m/z*): 540.5 $[M + H]^+$, 562.5$[M + Na]^+$.

*5.2.9.9. Synthesis of (2S,3R,4R)-1-(3-fluorophenethyl)-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5e-3S**).* Purified by silica gel column chromatography (EtOAc/Petroleum ether, 1:4, *V*:*V*) to afford **5e-3*S*** as slight yellow oil (212.9 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40–6.88 (m, 19H, Ph-H), 4.66–4.35 (m, 6H, $PhCH_2$–), 3.75 (m, 1H), 3.61 (m, 2H), 3.49 (m, 1H), 3.30 (m, 1H), 3.07–2.70 (m, 6H), 1.97 (m, 1H), 1.65 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.8, 143.5, 138.9, 138.6, 138.4, 131.1, 128.3 (3C), 128.1 (3C), 127.6 (3C), 127.5 (2C), 127.4 (2C), 127.4 (2C), 123.8, 115.2, 114.9, 78.7, 74.7, 73.4, 72.7, 71.4, 67.8, 59.3, 54.9, 46.0, 28.1, 25.9; ESI-MS (*m/z*): 540.5 $[M + H]^+$.

*5.2.9.10. Synthesis of (2S,3S,4R)-1-(3-fluorophenethyl)-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5e-3R**).* Purified by RP-HPLC (methanol:H_2O = 17:3, *V*:*V*) to give **5d-3*R*** as slight yellow oil (262.9 mg, 95.1%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.28–7.41 (m, 15H), 6.90–7.03 (dt, *J* = 22.2, 8.5 Hz, 4H), 4.57–4.70 (m, 4H), 4.43 (dd, *J* = 11.9, 7.9 Hz, 2H), 3.89 (s, 1H), 3.65–3.76 (m, 3H), 3.03 (d, *J* = 8.7 Hz, 1H), 2.66–2.92 (m, 6H), 2.01 (dd, *J* = 13.8, 3.6 Hz, 1H), 1.69 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.8, 139.0, 138.5, 138.0, 136.3, 130.0, 127.42–128.37(16C), 115.18, 114.90, 76.9, 73.5, 71.6, 71.5, 70.8, 65.7, 59.1, 55.4, 46.2, 30.5, 27.4; ESI-MS (*m/z*): 540.5 $[M + H]^+$, 562.5$[M + Na]^+$.

*5.2.9.11. Synthesis of (2S,3R,4R)-1-(2-(1H-imidazol-4-yl)ethyl)-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5f-3S**).* Purified by silica gel column chromatography (EtOAc/Petroleum ether, 1:2, *V*:*V*) to afford **5f-3*S*** as slight yellow oil (178.9 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.10 (s, 1H, –NH–), 7.47–7.24 (m, 15H, Ph-H), 6.80 (m, 2H), 4.77–4.43 (m, 6H, $PhCH_2$–), 3.72 (m, 4H), 3.30 (m, 1H), 2.97–2.60 (m, 6H), 2.01 (m, 1H), 1.78 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.7, 138.3, 137.8, 134.3, 131.4, 128.6 (2C), 128.4 (2C), 128.1, 128.0, 127.6 (3C), 127.5 (6C), 122.6, 74.6, 73.5, 73.1, 71.4, 68.4, 60.3, 53.5, 52.3, 44.5, 26.9, 22.6; ESI-MS (*m/z*): 512.5$[M + H]^+$.

*5.2.9.12. Synthesis of (2S,3R,4R)-1-(4-sulphonamidophenethyl)-3,4-bis(benzyloxy)-2 -(benzyloxy methyl) piperidine (**5g-3S**).* Purified by silica gel column chromatography (EtOAc/Petroleum ether, 1:3, *V*:*V*) to afford **5g-3*S*** as slight yellow oil (195.0 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.73–7.07 (m, 19H, Ph-H), 4.64–4.32 (m, 6H, $PhCH_2$–), 3.72 (dd, *J* = 10.0, 6.4 Hz, 1H), 3.60 (m, 1H), 3.51 (m, 2H), 3.23 (m, 1H), 2.93–2.53 (m, 6H), 1.97 (m, 1H), 1.67 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.3, 139.7, 138.8, 138.4, 138.2, 128.5 (2C), 128.4 (2C), 128.3 (2C), 128.1 (2C), 127.9 (3C), 127.8 (2C), 127.7 (2C), 127.5 (2C), 126.4 (2C), 78.2, 73.9, 73.4, 72.7, 71.3, 68.5, 58.8, 55.8, 45.9, 31.7, 27.5; ESI-MS (*m/z*): 601.4$[M + H]^+$.

*5.2.9.13. Synthesis of (2S,3R,4R)-1-(4-methylphenethyl)-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5h-3S**).* Purified by silica gel column chromatography (EtOAc/Petroleum ether, 1:4, *V*:*V*) to afford **5h-3*S*** as slight yellow oil (246.6 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45–7.15 (m, 15H, Ph-H), 7.00 (q, *J* = 8.0 Hz, 4H, Ar–H), 4.70–4.35 (m, 6H, $PhCH_2$–), 3.77 (dd, *J* = 9.8, 6.0 Hz, 1H),

3.62 (m, 2H), 3.51 (m, 1H), 3.30 (m, 1H), 2.76 (m, 6H), 2.29 (s, 3H, CH_3–), 1.95 (m, 1H), 1.67 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.1, 138.8, 138.5, 137.7, 135.3, 129.1 (2C), 128.8 (3C), 128.3 (3C), 127.8 (3C), 127.6 (2C), 127.5 (2C), 127.1 (2C), 127.0 (2C), 78.4, 74.5, 73.4, 72.8, 71.4, 67.8, 59.2, 56.7, 46.2, 31.9, 28.0, 21.2; ESI-MS (*m/z*): 536.4 $[M + H]^+$.

*5.2.9.14. Synthesis of (2S,3S,4R)-1-(4-methylphenethyl)-3,4-bis(benzyloxy)-2- (benzyloxymethyl) piperidine (**5h-3R**).* Purified by RP-HPLC (methanol:H_2O = 17:3, *V*:*V*) to give **5h-3*R*** as slight yellow oil (240.2 mg, 89.6%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.28–7.42 (m, 15H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.98 (d, *J* = 7.9 Hz, 2H), 4.44–4.71 (m, 6H), 3.91 (m, 1H), 3.67–3.77 (m, 3H), 3.03 (d, *J* = 9.0 Hz, 1H), 2.69–2.92 (m, 6H), 2.36 (s, 3H), 2.02 (m, 1H), 1.71 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.0, 138.5, 138.1, 137.6, 135.3, 129.0 (2C), 128.7 (3C), 128.2 (3C), 127.7 (3C), 127.5 (2C), 127.4 (2C), 127.1 (2C), 127.0 (2C), 76.9, 73.5, 71.5, 71.4, 70.7, 65.4, 58.9, 55.4, 46.2, 30.6, 27.4, 21.0; ESI-MS (*m/z*): 536.5$[M + H]^+$, 558.4 $[M + Na]^+$.

*5.2.9.15. Synthesis of (2S,3R,4R)-1-(3-morpholin-N-yl-propyl)-3,4-bis(benzyloxy)-2- (benzyloxymethyl) piperidine (**5i-3S**).* Purified by silica gel column chromatography (EtOAc/Petroleum ether, 1:2, *V*:*V*) to afford **5i-3*S*** as slight yellow oil (228.5 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42–7.26 (m, 15H, Ph-H), 4.73–4.40 (m, 6H, $PhCH_2$-), 3.82–3.50 (m, 8H), 3.24 (m, 1H), 2.63 (m, 4H), 2.41 (m, 4H), 2.30 (m, 2H), 1.99 (m, 1H), 1.69 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.0, 138.7, 138.5, 128.3 (3C), 128.1 (3C), 127.6 (3C), 127.5 (3C), 127.4 (3C), 78.8, 74.8, 73.2, 72.6, 71.4, 67.3 (2C), 60.3 (2C), 56.9, 52.5 (2C), 46.2, 45.9, 28.1 (2C); ESI-MS (*m/z*): 545.4$[M + H]^+$.

*5.2.9.16. Synthesis of (2S,3S,4R)-1-(3-morpholin-N-yl-propyl)-3,4-bis(benzyloxy)-2- (benzyloxymethyl) piperidine (**5i-3R**).* Purified by RP-HPLC (methanol:H_2O = 17:3, *V*:*V*) to give **5i-3*R*** as slight yellow oil (223.1 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.21–7.34 (m, 15H), 4.37–4.62 (m, 6H), 3.82 (m, 1H), 3.56–3.73 (m, 7H), 2.89 (d, *J* = 8.7 Hz, 1H), 2.52–2.79 (m, 4H), 2.37 (m, 4H), 2.22 (m, 2H), 1.94 (m, 1H), 1.59–1.70 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.6, 138.2, 137.9, 128.2 (3C), 128.1 (3C), 127.5 (3C), 127.3 (3C), 127.3 (3C), 76.5, 73.1, 71.2, 71.1, 70.4, 66.6 (2C), 65.4, 59.3, 56.8, 53.4 (2C), 50.9, 45.8, 26.9, 21.7; ESI-MS (*m/z*): 545.5$[M + H]^+$, 567.4$[M + Na]^+$.

*5.2.9.17. Synthesis of (2S,3R,4R)-1-(N,N-dimethylaminoethyl)-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5j-3S**).* Purified by silica gel column chromatography (EtOAc/Petroleum ether, 1:2, *V*:*V*) to afford **5j-3*S*** as slight yellow oil (202.5 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41–7.21 (m, 15H, Ph-H), 4.73–4.38 (m, 6H, $PhCH_2$–), 3.75 (dd, *J* = 9.8, 6.1 Hz, 1H), 3.63 (m, 2H), 3.49 (m, 1H), 3.21 (dd, *J* = 9.8, 4.1 Hz, 1H), 2.74 (m, 2H), 2.64 (m, 2H), 2.45 (m, 2H), 2.24 (s, 6H, CH_3-), 1.99 (m, 1H), 1.65 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.0, 138.7, 138.5, 128.3 (3C), 128.0 (3C), 127.6, 127.6 (2C), 127.5 (2C), 127.4 (2C), 78.8, 74.9, 73.2, 72.7, 71.4, 67.3, 60.3, 56.9, 52.5, 46.2, 45.9 (2C), 28.1; ESI-MS (*m/z*): 489.5$[M + H]^+$.

*5.2.9.18. Synthesis of (2S,3S,4R)-1-(N,N-dimethylaminoethyl)-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5j-3R**).* Purified by RP-HPLC (methanol:H_2O = 4:1, *V*:*V*) to give **5j-3*R*** as slight yellow oil (194.4 mg, 79.7%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.23–7.35 (m, 15H), 4.36–4.60 (m, 6H), 3.82 (m, 1H), 3.73 (dd, *J* = 10.3, 2.7 Hz), 3.62 (m, 2H), 2.88 (ddd, *J* = 14.9, 9.8, 5.4 Hz, 2H), 2.61–2.74 (m, 3H), 2.43 (m, 2H), 2.17 (s, 6H), 1.93 (ddd, *J* = 11.7, 7.1, 3.6 Hz, 1H), 1.61 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.9, 138.5, 138.1, 128.3 (3C), 128.0 (3C), 127.6, 127.6 (2C), 127.5 (2C), 127.4 (2C), 76.7, 73.4, 71.4, 71.4, 70.7, 65.8, 60.0, 55.7, 51.2, 46.6, 45.83 (2C), 27.2; ESI-MS (*m/z*): 489.4$[M + H]^+$, 511.3$[M + Na]^+$.

*5.2.9.19. Synthesis of (2S,3R,4R)-1-(2′-acetlyaminoethyl)-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5k-3S**).* Purified by silica gel column chromatography (EtOAc/Petroleum ether, 1:2, *V*:*V*) to afford **5k-3*S*** as slight yellow oil (208.3 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41–7.21 (m, 15H, Ar–H), 6.97 (s, 1H, –CONH–), 4.71–4.46 (m, 6H, $PhCH_2$–), 3.78 (dd, *J* = 10.1, 7.5 Hz), 3.60 (m, 3H), 3.33 (m, 3H), 2.84 (m, 2H), 2.70 (m, 2H), 1.97 (m, 1H), 1.65 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.4, 138.7, 138.4, 138.1, 128.5 (3C), 128.4 (3C), 127.9 (3C), 127.8 (3C), 127.5 (3C), 78.4, 74.7, 73.3, 72.7 (2C), 71.5, 67.4, 59.7, 51.5, 44.9, 36.8, 28.8, 23.0; ESI-MS (*m/z*): 503.5$[M + H]^+$.

*5.2.9.20. Synthesis of (2S,3R,4R)-1-(3′-ethoxypropyl)-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5l-3S**).* Purified by silica gel column chromatography (EtOAc/Petroleum ether, 1:4, *V*:*V*) to afford **5l-3*S*** as slight yellow oil (201.2 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42–7.17 (m, 15H, Ph-H), 4.70–4.36 (m, 6H, $PhCH_2$–), 3.75 (m, 1H), 3.63 (m, 2H), 3.51 (m, 1H), 3.40 (m, 4H), 3.24 (dd, *J* = 9.5, 4.1 Hz, 1H), 2.63 (m, 4H), 1.96 (m, 1H), 1.76 (m, 2H), 1.63 (m, 1H), 1.17 (t, *J* = 7.0 Hz, 3H, CH_3–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.0, 138.7, 138.6, 128.3 (3C), 128.0 (3C), 127.6 (3C), 127.5 (3C), 127.4 (3C), 78.8, 74.9, 73.2, 72.7, 71.4, 69.0, 67.3, 66.1, 59.6, 51.2, 45.7, 28.0, 26.6, 15.3; ESI-MS (*m/z*): 504.5$[M + H]^+$.

*5.2.9.21. Synthesis of (2S,3R,4R)-1-propyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5m-3S**).* Purified by silica gel column chromatography (EtOAc/Petroleum ether, 1:3, *V*:*V*) to afford **5m-3*S*** as slight yellow oil (211.2 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45–7.18 (m, 15H, Ph-H), 4.64–4.41 (m, 6H, $PhCH_2$–), 3.73 (dd, *J* = 9.8, 5.8 Hz, 1H), 3.63 (m, 2H), 3.50 (m, 1H), 3.22 (dd, *J* = 9.5, 4.2 Hz, 1H), 2.68–2.48 (m, 4H), 1.97 (m, 1H), 1.65 (m, 1H), 1.46 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.1, 138.8, 138.6, 128.3 (3C), 128.1 (3C), 127.6 (3C), 127.5 (3C), 127.4 (3C), 78.8, 75.0, 73.2, 72.7, 71.4, 67.3, 59.7, 56.4, 45.8, 28.2, 19.5, 11.9; ESI-MS (*m/z*): 460.3 $[M + H]^+$.

*5.2.9.22. Synthesis of (2S,3S,4R)-1-propyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5m-3R**).* Purified by RP-HPLC (methanol:H_2O = 17:3, *V*:*V*) to give **5m-3*R*** as slight yellow oil (191.0 mg, 83.2%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.21–7.34 (m, 15H), 4.37–4.62 (m, 6H), 3.81 (dd, *J* = 4.6, 2.4 Hz, 1H), 3.53–3.82 (m, 3H), 2.86 (dt, *J* = 8.8, 2.5 Hz, 1H), 2.46–2.67 (m, 4H), 1.92 (m, 1H), 1.40–1.66 (m, 3H), 0.81 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.0, 138.6, 138.2, 128.2 (3C), 128.1 (3C), 127.6 (3C), 127.4 (3C), 127.3 (3C), 76.8, 73.3, 71.4, 70.6, 65.4, 59.5, 55.2, 46.1, 40.8, 27.2, 18.0, 11.9; ESI-MS (*m/z*): 460.4$[M + H]^+$, 482.3$[M + Na]^+$.

*5.2.9.23. Synthesis of (2S,3R,4R)-1-isopropyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5n-3S**).* Purified by silica gel column chromatography (EtOAc/Petroleum ether, 1:3, *V*:*V*) to afford **5n-3*S*** as slight yellow oil (212.2 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44–7.20 (m, 15H, Ph-H), 4.68–4.41 (m, 6H, $PhCH_2$–), 3.74 (dd, *J* = 9.8, 5.7 Hz, 1H), 3.61 (m, 2H), 3.47 (m, 1H), 3.34 (dd, *J* = 9.5, 4.1 Hz, 1H), 3.02 (m, 1H), 2.59 (m, 2H), 1.93 (m, 1H), 1.60 (m, 1H), 1.10 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.2, 138.9, 138.6, 128.4 (3C), 128.3 (3C), 127.6(3C), 127.5 (3C), 127.4 (3C), 79.3, 75.1, 73.1, 72.6, 71.3, 68.1, 58.2, 50.3, 39.5, 28.8, 21.4, 17.6; ESI-MS (*m/z*): 460.3 $[M + H]^+$.

*5.2.9.24. Synthesis of (2S,3S,4R)-1-isopropyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5n-3R**).* Purified by RP-HPLC (methanol:H_2O = 17:3, *V*:*V*) to give **5n-3*R*** as slight yellow oil (196.4 mg, 86.1%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.20–7.34 (m, 15H), 4.33–4.58 (m, 6H), 3.84 (s, 1H), 3.78 (dd, *J* = 10.4, 2.4 Hz, 1H), 3.63 (ddd, *J* = 13.0, 9.9, 2.6 Hz, 2H), 3.30 (m, 1H), 2.98 (d, *J* = 9.3 Hz, 1H),

2.56 (m, 2H), 1.93 (m, 1H), 1.57 (m, 1H), 1.14 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.9, 138.5, 138.1, 128.3 (3C), 128.2 (3C), 127.5(3C), 127.4 (3C), 127.3 (3C), 77.2, 73.2, 71.3, 71.2, 71.0, 65.2, 58.3, 47.6, 37.3, 27.4, 21.5, 13.6; ESI-MS (m/z): 460.4[M + H]$^+$, 482.3[M + Na]$^+$.

*5.2.9.25. Synthesis of (2S,3R,4R)-1-butyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5o-3S**).* Purified by silica gel column chromatography (EtOAc/Petroleum ether, 1:3, *V*:*V*) to afford **5o-3*S*** as slight yellow oil (200.7 mg, 85%). ^{1}H NMR(300 MHz, $CDCl_3$) δ: 7.44–7.20 (m, 15H, Ph-H), 4.68–4.41 (m, 6H, $PhCH_2$–), 3.75 (dd, J = 9.9, 5.8 Hz, 1H, H-7a), 3.63 (m, 2H), 3.51 (m, 1H), 3.24 (dd, J = 9.6, 4.1 Hz, 1H), 2.63 (m, 4H), 1.98 (m, 1H), 1.65 (m, 1H), 1.45 (m, 2H), 1.26 (m, 2H), 0.90 (t, J = 4.3 Hz, 3H, CH_3–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.2, 138.9, 138.6, 128.4 (3C), 128.3 (3C), 127.6 (3C), 127.5 (3C), 127.4 (3C), 78.5, 74.6, 73.2, 72.7, 71.4, 67.2, 59.7, 54.2, 45.8, 28.0, 27.9, 20.7, 14.1; ESI-MS (m/z): 474.3[M + H]$^+$.

*5.2.9.26. Synthesis of (2S,3S,4R)-1-butyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5o-3R**).* Purified by RP-HPLC (methanol:H_2O = 17:3, *V*:*V*) to give **5o-3*R*** as slight yellow oil (211.1 mg, 89.4%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.21–7.34 (m, 15H), 4.36–4.62 (m, 6H), 3.81 (m, 1H), 3.54–3.69 (m, 3H), 2.86 (d, J = 8.9 Hz, 1H), 2.47–2.74 (m, 4H), 1.92 (m, 1H), 1.63 (m, 1H), 1.42 (m, 2H), 1.22 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.0, 138.6, 138.2, 1128.4 (3C), 128.3 (3C), 127.6 (3C), 127.5 (3C), 127.4 (3C), 76.8, 73.3, 71.4, 71.4, 70.6, 65.4, 59.5, 53.0, 46.1, 27.3, 27.0, 20.8, 14.1; ESI-MS (m/z): 474.5[M + H]$^+$, 496.3 [M + Na]$^+$.

*5.2.9.27. Synthesis of (2S,3R,4R)-1-isobutyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5p-3S**).* Purified by silica gel column chromatography (EtOAc/Petroleum ether, 1:3, *V*:*V*) to afford **5p-3*S*** as slight yellow oil (200.2 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43–7.16 (m, 15H, Ph-H), 4.75–4.39 (m, 6H, $PhCH_2$–), 3.75 (dd, J = 9.9, 5.8 Hz, 1H), 3.67 (m, 2H), 3.50 (m, 1H), 3.31 (m, 1H), 2.59 (m, 2H), 2.38 (d, J = 6.6 Hz, 2H), 1.94 (m, 1H), 1.70 (m, 1H), 1.54 (m, 1H), 0.86 (d, J = 6.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.2, 138.9, 138.7, 128.3 (3C), 127.8 (3C), 127.7 (3C), 127.5 (3C), 127.4 (3C), 79.6, 73.2, 72.6, 71.8, 65.9, 62.7, 62.6, 60.8, 45.7, 29.5, 26.4, 20.9 (2C); ESI-MS (m/z): 474.3[M + H]$^+$.

*5.2.9.28. Synthesis of (2S,3S,4R)-1-isobutyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5p-3R**).* Purified by RP-HPLC (methanol:H_2O = 17:3, *V*:*V*) to give **5o-3*R*** as slight yellow oil (199.0 mg, 84.5%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.23–7.35 (m, 15H), 4.40–4.61 (m, 6H), 3.76 (dd, J = 5.9, 2.8 Hz, 1H), 3.66 (m, 2H), 3.56 (dd, J = 10.1, 3.9 Hz, 1H), 2.91 (dt, J = 7.2, 3.5 Hz, 1H), 2.43–2.67 (m, 3H), 2.18 (dd, J = 12.7, 5.5 Hz, 1H), 1.96 (m, 1H), 1.75 (m, 1H), 1.58 (m, 1H), 0.87 (dd, J = 12.1, 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.0, 138.8, 138.3, 128.4 (3C), 127.8 (3C), 127.7 (3C), 127.4 (3C), 127.3 (3C), 76.4, 73.2, 72.1, 71.4, 70.4, 66.8, 62.1, 61.1, 46.7, 26.7, 26.4, 21.4, 20.9; ESI-MS (m/z): 474.5[M + H]$^+$, 496.3 [M + Na]$^+$.

*5.2.9.29. Synthesis of (2S,3R,4R)-1-hydroethyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5q-3S**).* Purified by silica gel column chromatography (EtOAc/Petroleum ether, 1:1, *V*:*V*) to afford **5q-3*S*** as slight yellow oil (165.6 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38–7.14 (m, 15H, Ph-H), 4.64–4.35 (m, 6H, $PhCH_2$–), 3.80 (dd, J = 10.3, 6.9 Hz, 1H), 3.74–3.53 (m, 5H), 3.47 (m, 1H), 3.15–2.84 (m, 4H), 2.08 (m, 1H), 1.70 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.3, 137.8, 137.7, 128.5 (3C), 128.5 (3C), 127.9 (3C), 127.8 (3C), 127.6 (3C), 77.4, 77.0, 73.3, 72.8, 71.6, 66.9, 60.4, 57.8, 54.9, 46.0, 25.3; ESI-MS (m/z): 462.5[M + H]$^+$.

*5.2.9.30. Synthesis of (2S,3S,4R)-1-hydroethyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5q-3R**).* Purified by RP-HPLC (methanol:H_2O = 9:1, *V*:*V*) to give **5q-3*R*** as slight yellow oil (178.5 mg, 77.6%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.22–7.34 (m, 15H), 4.28–4.83 (m, 6H), 3.47–3.70 (m, 6H), 2.99 (m, 2H), 2.65 (dd, 12.9, 6.2 Hz, 2H), 2.54 (dt, J = 13.4, 4.0 Hz, 1H), 1.95 (ddd, J = 14.6, 10.3, 4.3 Hz, 1H), 1.57 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.7, 138.4, 137.8, 127.35–128.29(15C), 76.1, 73.2, 71.9, 71.5, 70.5, 66.3, 60.6, 58.9, 54.5, 45.9, 26.5; ESI-MS (m/z): 462.5[M + H]$^+$, 484.5 [M + Na]$^+$.

*5.2.9.31. Synthesis of (2S,3R,4R)-1-hydropropyl-3,4-bis(benzyloxy)-2-(benzyloxy -methyl) piperidine (**5r-3S**).* Purified by silica gel column chromatography (EtOAc/Petroleum ether, 1:1, *V*:*V*) to afford **5r-3*S*** as slight yellow oil (166.3 mg, 70%). ^{1}H NMR(300 MHz, $CDCl_3$) δ: 7.50–7.20 (m, 15H, Ph-H), 4.74–4.43 (m, 6H, $PhCH_2$–), 3.80 (m, 3H), 3.67 (m, 2H), 3.60 (m, 1H), 3.28 (m, 1H), 3.00 (m, 1H), 2.81 (m, 1H), 2.72 (m, 2H), 2.02 (m, 1H), 1.79 (m, 1H), 1.69 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.8, 138.6, 138.2, 128.4 (3C), 128.3 (3C), 127.7 (3C), 127.6 (3C), 127.5 (3C), 78.8, 74.4, 73.2, 72.7, 71.5, 67.7, 64.4, 60.9, 54.3, 45.5, 27.8, 27.4; ESI-MS(m/z): 476.3 [M + H]$^+$.

*5.2.9.32. Synthesis of (2S,3S,4R)-1-hydropropyl-3,4-bis(benzyloxy)-2-(benzyloxy-methyl) piperidine (**5r-3R**).* Purified by RP-HPLC (methanol:H_2O = 9:1, *V*:*V*) to give **5r-3*R*** as slight yellow oil (200.3 mg, 84.3%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.22–7.34 (m, 15H), 4.42–4.78 (m, 6H), 3.71–3.77 (m, 4H), 3.63 (m, 2H), 3.07 (m, 1H), 2.96 (m, 1H), 2.78 (m, 1H), 2.58 (m, 2H), 1.99 (ddd, J = 11.6, 9.1, 5.8 Hz, 1H), 1.82 (ddd, J = 15.9, 10.1, 4.6 Hz, 1H), 1.59 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.9, 138.5, 138.1, 127.57–128.72(15C), 76.3, 73.4, 71.9, 71.7, 70.8, 66.3, 63.4, 61.4, 52.8, 45.6, 27.8, 26.7; ESI-MS (m/z): 476.7[M + H]$^+$, 498.6[M + Na]$^+$.

*5.2.9.33. Synthesis of (2S,3R,4R)-1-(2-(thiophen-2-yl)ethyl)-3,4-bis(benzyloxy)-2-(benzyloxymethyl) piperidine (**5s-3S**).* Purified by silica gel column chromatography (EtOAc/Petroleum ether, 1:1, *V*:*V*) to afford **5s-3*S*** as slight yellow oil (237.2 mg, 90.2%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40–7.26 (m, 15H, Ph-H), 7.14 (dd, J = 5.1, 1.2 Hz, 1H), 6.93 (dd, J = 5.1, 3.3 Hz, 1H), 6.77 (d, J = 3.3 Hz, 1H), 4.73–4.43 (m, 6H, $PhCH_2$–), 3.87–3.50 (m, 4H), 3.42–3.32 (m, 1H), 3.08–2.95 (m, 4H), 2.77–2.68 (m, 2H), 2.10–1.95 (m, 1H), 1.79–1.67 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.3, 139.0, 138.7, 137.5, 128.3 (3C), 128.1 (3C), 127.7 (3C), 127.5 (3C), 126.5 (3C), 126.4, 126.2, 123.6, 79.0, 75.0, 73.3, 72.6, 71.5, 67.4, 54.6, 46.8, 30.7, 28.3, 27.0; ESI-MS (m/z): 528.3[M + H]$^+$.

*5.2.10. General procedure for the syntheses of **6a-s-3S** and **6a-r-3R***

Any of the compounds **5a-s-3*S*** and **5a-r-3*R*** (0.1–0.3 g, identified in specific reaction) was dissolved in 10% TFA in MeOH (10 ml) following the addition of 10% Pd/C (300 mg). The reaction mixture was subjected to 5 atm H_2 for 48 h with stirring at room temperature. The catalyst was filtered off through Celite and the filtrate was concentrated in vacuo followed purification by RP-HPLC.

*5.2.10.1. Synthesis of (2S,3R,4R)-2-(hydroxymethyl)piperidine-3,4-diol (**6a-3S**).* **5a-3*S*** (218.7 mg, 0.44 mmol). Purified by RP-HPLC (methanol:H_2O = 1:9, *V*:*V*) to give **6a-3*S*** as white crystal (38.8 mg, 60%). ^{1}H NMR (300 MHz, D_2O) δ: 3.83 (dd, J = 3.2, 12.6 Hz, 1H), 3.71 (m, 2H), 3.42 (dd, J = 8.2, 1.5 Hz, 1H, H-3), 3.0 (m, 1H, H-2), 2.82 (m, 2H), 2.09 (m, 1H), 1.72 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ: 65.7, 64.8, 59.5, 55.7, 38.8, 23.6; HRMS (m/z): calcd for $C_6H_{14}NO_3^+H$: 148.09737, found: 148.09741.

*5.2.10.2. Synthesis of (2S,3S,4R)-2-(hydroxymethyl)piperidine-3,4-diol (**6a-3R**).* **5a-3*R*** (215.3 mg, 0.43 mmol). Purified by RP-HPLC

(methanol:H_2O = 1:9, *V*:*V*) to give **6a-3*R*** as white crystal (58.0 mg, 91.1%). ^{1}H NMR (300 MHz, CD_3OD) δ: 3.75–4.10 (m, 4H), 3.14–3.33 (m, 3H), 1.95–2.06 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ: 66.5, 65.6, 58.1, 56.1, 38.1, 27.7; ESI-MS (*m*/*z*): 148.2[M + H]$^+$; HRMS (*m*/*z*): calc for $C_6H_{13}NO_3^+H$: 148.09737, found: 148.09743.

*5.2.10.3. Synthesis of (2S,3R,4R)-1-phenethyl-2-(hydroxymethyl) piperidine-3,4-diol (**6b-3S**).* **5b-3*S*** (234.5 mg, 0.45 mmol). Purified by RP-HPLC (methanol:H_2O = 2:3, *V*:*V*) to give **6b-3*S*** as white solid (103.9 mg, 92%). ^{1}H NMR (300 MHz, CD_3OD) δ: 7.3–7.1 (m, 5H, Ar–H), 3.83 (m, 2H), 3.70–3.60 (m, 2H), 2.99 (m, 1H), 2.98–2.60 (m, 6H), 1.95 (m, 1H), 1.58 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ: 140.4, 128.4 (2C), 128.0 (2C), 125.6, 72.2, 68.4, 61.6, 58.6, 55.8, 45.2, 32.2, 29.0; HRMS (*m*/*z*): calcd for $C_{14}H_{21}NO_3^+H$: 252.15997, found: 252.15995.

*5.2.10.4. Synthesis of (2S,3S,4R)-1-phenethyl-2-(hydroxymethyl) piperidine-3,4-diol (**6b-3R**).* **5b-3*R*** (219.6 mg, 0.42 mmol). Purified by RP-HPLC (methanol:H_2O = 2:3, *V*:*V*) to give **6b-3*R*** as white solid (103.7 mg, 98%). ^{1}H NMR (300 MHz, CD_3OD) δ: 7.23–7.37 (m, 5H, Ar–H), 3.84–4.15 (m, 4H), 2.98–3.54 (m, 7H), 1.94–2.03 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ: 138.6, 128.8 (2C), 128.6 (2C), 126.1, 68.4, 67.2, 64.3, 56.0, 48.6, 48.7, 31.3, 29.7; ESI-MS (*m*/*z*): 252.4 [M + H]$^+$, 274.3[M + Na]$^+$; HRMS (*m*/*z*): calc for $C_{14}H_{21}NO_3^+H$: 252.15997, found: 252.15989.

*5.2.10.5. Synthesis of (2S,3R,4R)-1-(4-methoxyphenethyl)-2-(hydroxymethyl) piperidine-3,4-diol (**6c-3S**).* **5c-3*S*** (246.0 mg, 0.45 mmol). Purified by RP-HPLC (methanol:H_2O = 2:3, *V*:*V*) to give **6c-3*S*** as white solid (102.5 mg, 82%). ^{1}H NMR (300 MHz, CD_3OD) δ: 7.11 (d, *J* = 8.6 Hz, 2H, Ar–H), 6.82 (d, *J* = 9.1 Hz, 2H, Ar–H), 3.83 (m, 2H), 3.74 (s, 3H, $-OCH_3$), 3.70–3.60 (m, 2H), 2.99 (m, 1H), 2.98–2.60 (m, 6H), 1.95 (m, 1H), 1.58 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ: 158.2, 132.4, 129.3 (2C), 113.6 (2C), 72.2, 68.4, 61.6, 58.6, 55.9, 54.9, 45.2, 31.3, 29.0; HRMS (*m*/*z*): calcd. for $C_{15}H_{23}NO_4^+H$: 282.17053, found: 282.16983.

*5.2.10.6. Synthesis of (2S,3S,4R)-1-(4-methoxyphenethyl)-2-(hydroxymethyl) piperidine-3,4-diol (**6c-3R**).* **5c-3*R*** (270.9 mg, 0.49 mmol). Purified by RP-HPLC (methanol:H_2O = 2:3, *V*:*V*) to give **6c-3*R*** as white solid (131.5 mg, 95.2%). ^{1}H NMR (300 MHz, CD_3OD) δ: 7.11 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 9.1 Hz, 2H), 3.93 (m, 1H), 3.91 (dd, *J* = 7.4, 3.1 Hz, 2H), 3.74 (s, 3H), 3.61 (dd, *J* = 8.6, 3.0 Hz, 1H), 2.65–2.97 (m, 7H), 1.70–1.86 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ: 158.1, 132.1, 129.3 (2C), 113.6 (2C), 68.9, 67.1, 61.7, 58.0, 55.3, 54.3, 45.1, 29.9, 29.1; ESI-MS (*m*/*z*): 282.3[M + H]$^+$, 304.2[M + Na]$^+$; HRMS (*m*/*z*): calc for $C_{15}H_{23}NO_4^+H$: 282.17053, found: 282.16981.

*5.2.10.7. Synthesis of (2S,3R,4R)-1-(4-fluorophenethyl)-2-(hydroxymethyl) piperidine-3,4-diol (**6d-3S**).* **5d-3*S*** (218.3 mg, 0.40 mmol). Purified by RP-HPLC (methanol:H_2O = 3:7, *V*:*V*) to give **6d-3*S*** as white solid (77.4 mg, 71%). ^{1}H NMR (300 MHz, CD_3OD) δ: 7.23 (m, 2H, Ar–H), 7.03 (m, 2H, Ar–H), 3.83 (m, 2H), 3.70–3.60 (m, 2H), 3.01 (dd, *J* = 8.4, 5.1 Hz), 2.97–2.68 (m, 6H), 1.98 (m, 1H), 1.60 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ: 162.6, 136.1, 129.9 (2C), 114.7 (2C), 72.2, 68.5, 61.7, 58.8, 55.5, 45.2, 31.3, 29.0; HRMS (*m*/*z*): calcd. for $C_{14}H_{20}FNO_3^+H$: 270.15055, found: 270.15027.

*5.2.10.8. Synthesis of (2S,3S,4R)-1-(4-fluorophenethyl)-2-(hydroxymethyl) piperidine-3,4-diol (**6d-3R**).* **5d-3*R*** (246.9 mg, 0.46 mmol). Purified by RP-HPLC (methanol:H_2O = 9:11, *V*:*V*) to give **6d-3*R*** as white solid (120.2 mg, 97.6%). ^{1}H NMR (300 MHz, CD_3OD) δ: 7.32 (m, 2H, Ar–H), 7.06 (m, 2H, Ar–H), 3.84–4.12 (m, 4H), 3.07–3.45 (m, 7H), 2.01 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ: 162.6, 134.8, 132.6 (2C), 117.4 (2C), 68.7, 67.3, 64.6, 56.6, 55.8, 48.3, 30.8, 29.5; ESI-MS (*m*/*z*): 270.3 [M + H]$^+$, 292.3[M + Na]$^+$; HRMS (*m*/*z*): calc for $C_{14}H_{20}FNO_3^+H$: 270.15055, found: 270.15022.

*5.2.10.9. Synthesis of (2S,3R,4R)-1-(3-fluorophenethyl)-2-(hydroxymethyl) piperidine-3,4-diol (**6e-3S**).* **5e-3*S*** (212.9 mg, 0.39 mmol). Purified by RP-HPLC (methanol:H_2O = 3:7, *V*:*V*) to give **6e-3*S*** as white solid (53.9 mg, 52%). ^{1}H NMR (300 MHz, CD_3OD) δ: 7.23 (m, 2H, Ar–H), 6.97 (m, 2H, Ar–H), 3.83 (m, 2H), 3.70–3.60 (m, 2H), 3.01 (dd, *J* = 8.6, 5.3 Hz, 1H), 2.95–2.67 (m, 6H), 1.96 (m, 1H), 1.57 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ: 162.8, 139.9, 130.9, 123.9, 114.6, 112.7, 72.1, 68.4, 61.5, 58.6, 54.1, 45.1, 31.4, 29.0; HRMS (ESI): calcd. for $C_{14}H_{20}FNO_3^+H$: 270.15055, found: 270.15027.

*5.2.10.10. Synthesis of (2S,3S,4R)-1-(3-fluorophenethyl)-2-(hydroxymethyl) piperidine-3,4-diol (**6e-3R**).* **5e-3*R*** (262.9 mg, 0.49 mmol). Purified by RP-HPLC (methanol:H_2O = 9:11, *V*:*V*) to give **6e-3*R*** as white solid (123.7 mg, 94.3%). ^{1}H NMR (300 MHz, CD_3OD) δ: 7.22 (m, 2H, Ar–H), 7.04 (m, 2H, Ar–H), 3.65–3.87 (m, 4H), 2.67–3.01 (m, 7H), 1.95 (m, 1H), 1.57 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ: 161.8, 133.1, 129.9 (2C), 117.7, 117.0, 74.4, 70.7, 63.8, 60.9, 56.3, 47.3, 31.2, 27.7; ESI-MS (*m*/*z*): 270.3 [M + H]$^+$, 292.2[M + Na]$^+$; HRMS (*m*/*z*): calc for $C_{14}H_{20}FNO_3^+H$: 270.15055, found: 270.15022.

*5.2.10.11. Synthesis of (2S,3R,4R)-1-(2-(1H-imidazol-4-yl)ethyl)-2-(hydroxymethyl) piperidine-3,4-diol (**6f-3S**).* **5f-3*S*** (178.9 mg, 0.35 mmol). Purified by RP-HPLC (methanol:H_2O = 1:9, *V*:*V*) to give **6f-3*S*** as colorless oil (39.6 mg, 47%). ^{1}H NMR (300 MHz, CD_3OD) δ: 7.44 (d, *J* = 8.3 Hz, 1H), 6.73 (d, *J* = 9.1 Hz, 1H), 3.79–3.60 (m, 4H), 3.27 (m, 1H), 2.93–2.50 (m, 6H), 1.95 (m, 1H), 1.76 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ: 134.3, 131.4, 122.6, 73.5, 73.1, 71.4, 60.3, 52.3, 44.5, 29.0, 26.8; HRMS (*m*/*z*): calcd for $C_{11}H_{19}N_3O_3^+H$: 242.14992, found: 242.14969.

*5.2.10.12. Synthesis of (2S,3R,4R)-1-(4-sulphonamidophenethyl)-2-(hydroxymethyl) piperidine-3,4-diol (**6g-3S**).* **5g-3*S*** (195.0 mg, 0.32 mmol). Purified by RP-HPLC (methanol:H_2O = 1:4, *V*:*V*) to give **6g-3*S*** as colorless oil (69.7 mg, 60%). ^{1}H NMR (300 MHz, D_2O) δ: 7.66 (d, *J* = 8.4 Hz, 2H, Ar–H), 7.27 (d, *J* = 8.4 Hz, 2H, Ar–H), 3.70 (m, 2H), 3.58 (m, 2H), 2.97 (m, 1H), 2.88–2.34 (m, 6H), 1.81 (m, 1H), 1.45 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ: 145.5, 139.8, 129.5 (2C), 125.8 (2C), 71.7, 68.3, 61.6, 57.1, 54.6, 44.8, 31.7, 28.8; HRMS (*m*/*z*): calcd for $C_{14}H_{22}N_2O_5^+H$: 331.13222, found: 331.13177.

*5.2.10.13. Synthesis of (2S,3R,4R)-1-(4-methylphenethyl)-2-(hydroxymethyl) piperidine-3,4-diol (**6h-3S**).* **5h-3*S*** (246.6 mg, 0.46 mmol). Purified by RP-HPLC (methanol:H_2O = 2:3, *V*:*V*) to give **6h-3*S*** as white solid (87.8 mg, 72%). ^{1}H NMR (300 MHz, CD_3OD) δ: 7.10 (m, 4H, Ar–H), 3.86 (m, 2H), 3.71 (m, 2H), 3.10 (m, 1H), 2.98 (m, 2H), 2.82 (m, 2H), 2.28 (s, 3H), 2.03 (m, 1H), 1.63 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ: 136.6, 135.3, 128.7 (2C), 128.3 (2C), 71.8, 67.9, 61.5, 58.8, 55.5, 45.3, 31.2, 28.3, 19.7; HRMS (*m*/*z*): calcd for $C_{15}H_{23}NO_3^+H$: 266.17507, found: 266.17511.

*5.2.10.14. Synthesis of (2S,3S,4R)-1-(4-methylphenethyl)-2-(hydroxymethyl) piperidine-3,4-diol (**6h-3R**).* **5h-3*R*** (240.2 mg, 0.45 mmol). Purified by RP-HPLC (methanol:H_2O = 2:3, *V*:*V*) to give **6h-3*R*** as white solid (111.0 mg, 93.3%). ^{1}H NMR (300 MHz, CD_3OD) δ: 7.10 (s, 4H, Ar–H), 3.94 (m, 1H), 3.89 (d, *J* = 4.0 Hz, 2H), 3.65 (m, 1H), 2.83–3.07 (m, 7H), 2.29 (s, 3H, CH_3), 1.82 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ: 138.6, 136.5, 130.1 (2C), 129.6 (2C), 70.3, 68.5, 63.1, 59.5, 56.6, 46.4, 30.6, 30.1, 21.1; ESI-MS (*m*/*z*): 266.3[M + H]$^+$, 288.2 [M + Na]$^+$; HRMS (*m*/*z*): calc for $C_{15}H_{23}NO_3^+H$: 266.17507, found: 266.17507 [M + H]$^+$.

*5.2.10.15. Synthesis of (2S,3R,4R)-1-(3-morpholin-N-yl-propyl)-2-(hydroxymethyl) piperidine-3,4-diol (**6i-3S**).* **5i-3*S*** (228.5 mg, 0.42 mmol). Purified by RP-HPLC (methanol:H_2O = 1:9, *V*:*V*) to give **6i-3*S*** as colorless oil (73.7 mg, 64%). ^{1}H NMR (300 MHz, D_2O) δ: 3.73 (m, 2H), 3.58 (m, 6H), 2.91 (m, 1H), 2.62–2.33 (m, 8H), 2.26 (t, *J* = 7.8 Hz, 2H), 1.82 (m, 1H), 1.62 (m, 2H), 1.45 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ: 71.9, 68.4, 66.1 (2C), 61.8, 56.8, 56.0, 52.4 (2C), 51.3, 44.9, 29.0, 22.0; HRMS (*m/z*): calcd for $C_{13}H_{26}N_2O_4^+H$: 275.19708, found: 275.19712.

*5.2.10.16. Synthesis of (2S,3S,4R)-1-(3-morpholin-N-yl-propyl)-2-(hydroxymethyl) piperidine-3,4-diol (**6i-3R**).* **5i-3*R*** (223.1 mg, 0.42 mmol). Purified by RP-HPLC (methanol:H_2O = 2:3, *V*:*V*) to give **6i-3*R*** as colorless oil (92.8 mg, 82.6%). ^{1}H NMR (300 MHz, CD_3OD) δ: 3.95 (d, *J* = 4.2 Hz, 1H), 3.89 (d, *J* = 2.6 Hz, 2H), 3.72 (m, 4H), 3.63 (dd, *J* = 8.9, 3.0 Hz, 1H), 2.96 (m, 1H), 2.36–2.73 (m, 10H), 1.26–1.42 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD) δ: 69.9, 68.4, 67.4 (2C), 63.7, 58.8, 57.9, 54.7 (2C), 51.5, 46.3, 30.6, 22.6; ESI-MS (*m/z*): 275.3 $[M + H]^+$, 297.3$[M + Na]^+$; HRMS (*m/z*): calc for $C_{13}H_{26}N_2O_4^+H$: 275.19708, found: 275.19703.

*5.2.10.17. Synthesis of (2S,3R,4R)-1-(N,N-dimethylaminoethyl)-2-(hydroxymethyl) piperidine-3,4-diol (**6j-3S**).* **5j-3*S*** (202.5 mg, 0.41 mmol). Purified by RP-HPLC (methanol:H_2O = 1:9, *V*:*V*) to give **6j-3*S*** as white solid (40.7 mg, 45%). ^{1}H NMR (300 MHz, D_2O) δ: 3.69 (m, 2H), 3.60–3.45 (m, 2H), 2.86 (dd, *J* = 9.5, 4.3 Hz, 1H), 2.78–2.36 (m, 6H), 2.14 (s, 6H), 1.78 (m, 1H), 1.41 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ: 71.7, 68.4, 62.8, 56.9, 55.1, 50.2, 44.9, 44.0 (2C), 28.9; HRMS (*m/z*): calcd for $C_{10}H_{22}N_2O_3^+H$: 219.17087, found: 219.17081.

*5.2.10.18. Synthesis of (2S,3S,4R)-1-(N,N-dimethylaminoethyl)-2-(hydroxymethyl) piperidine-3,4-diol (**6j-3R**).* **5j-3*R*** (194.4 mg, 0.40 mmol). Purified by RP-HPLC (methanol:H_2O = 3:7, *V*:*V*) to give **6j-3*R*** as white solid (75.8 mg, 87.3%). ^{1}H NMR (300 MHz, CD_3OD) δ: 3.79–3.88 (m, 3H), 3.61 (dd, *J* = 7.8, 3.0 Hz, 1H), 2.92 (dt, *J* = 13.5, 6.7 Hz, 1H), 2.49–2.75 (m, 6H), 2.31 (s, 6H, $2CH_3$), 1.19–1.31 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ: 70.2, 68.5, 64.7, 59.2, 57.6, 51.6, 46.5, 45.6 (2C), 30.3; ESI-MS (*m/z*): 219.1$[M + H]^+$, 241.2$[M + Na]^+$; HRMS (*m/z*): calcd for $C_{10}H_{22}N_2O_3^+H$: 219.17087, found: 219.17104.

*5.2.10.19. Synthesis of (2S,3R,4R)-1-(2′-acetlyaminoethyl)-2-(hydroxymethyl) piperidine-3,4-diol (**6k-3S**).* **5k-3*S*** (208.3 mg, 0.41 mmol). Purified by RP-HPLC (methanol:H_2O = 1:9, *V*:*V*) to give **6k-3*S*** as white solid (59.7 mg, 62%). ^{1}H NMR (300 MHz, CD_3OD) δ: 3.81 (m, 2H), 3.70–3.60 (m, 2H), 3.30 (m, 2H), 3.02–2.60 (m, 5H), 1.96 (s, 3H), 1.91 (m, 1H), 1.57 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ: 170.9, 71.9, 68.6, 62.8, 58.8, 52.3, 44.9, 36.9, 28.9, 21.2; HRMS (*m/z*): calcd for $C_{10}H_{20}N_2O_4^+H$: 233.15013, found: 233.14981.

*5.2.10.20. Synthesis of (2S,3R,4R)-1-(3′-ethoxypropyl)-2-(hydroxymethyl) piperidine-3,4-diol (**6l-3S**).* **5l-3*S*** (201.2 mg, 0.40 mmol). Purified by RP-HPLC (methanol:H_2O = 3:7, *V*:*V*) to give **6l-3*S*** as colorless oil (62.4 mg, 67%). ^{1}H NMR (300 MHz, D_2O) δ: 3.74 (m, 2H), 3.61 (m, 2H), 3.53–3.36 (m, 4H), 2.91 (m, 1H), 2.56 (m, 4H), 1.84 (m, 1H), 1.68 (m, 2H), 1.47 (m, 1H), 1.08 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, D_2O) δ: 71.8, 68.6, 68.3, 66.2, 61.9, 56.9, 50.2, 44.9, 28.8, 25.5, 14.1; HRMS (*m/z*): calcd for $C_{11}H_{23}NO_4^+H$: 234.17053, found: 234.16992.

*5.2.10.21. Synthesis of (2S,3R,4R)-1-propyl-2-(hydroxymethyl)piperidine-3,4-diol (**6m-3S**).* **5m-3*S*** (211.2 mg, 0.46 mmol). Purified by RP-HPLC (methanol:H_2O = 1:9, *V*:*V*) to give **6m-3*S*** as white solid (36.5 mg, 42%). ^{1}H NMR (300 MHz, D_2O) δ: 3.71 (m, 2H), 3.65–3.51 (m, 2H), 2.92 (dd, *J* = 9.0, 4.5 Hz, 1H), 2.55 (m, 2H), 2.45 (m, 2H), 1.81 (m, 1H), 1.38 (m, 3H), 0.74 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, D_2O) δ: 71.9, 62.3, 61.7, 56.7, 55.2, 45.0, 28.9, 18.7, 11.1; HRMS (*m/z*): $C_9H_{19}NO_3^+H$: 190.14432, found 190.14356.

*5.2.10.22. Synthesis of (2S,3S,4R)-1-propyl-2-(hydroxymethyl)piperidine-3,4-diol (**6m-3R**).* **5m-3*R*** (191.0 mg, 0.42 mmol). Purified by RP-HPLC (methanol:H_2O = 2:3, *V*:*V*) to give **6m-3*R*** as white solid (63.9 mg, 81.2%). ^{1}H NMR (300 MHz, CD_3OD) δ: 3.90 (m, 1H), 3.82 (d, *J* = 3.6 Hz, 2H), 3.60 (dd, *J* = 8.7, 3.1 Hz, 1H), 2.53–2.71 (m, 5H), 1.73 (m, 2H), 1.54 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, CD_3OD) δ: 70.4, 68.5, 63.4, 59.5, 56.5, 46.4, 30.6, 19.1, 12.2; ESI-MS (*m/z*): 190.3$[M + H]^+$, 212.3$[M + Na]^+$; HRMS (*m/z*): calc for $C_9H_{19}NO_3^+H$: 190.14432, found: 190.14377.

*5.2.10.23. Synthesis of (2S,3R,4R)-1-isopropyl-2-(hydroxymethyl) piperidine-3,4-diol (**6n-3S**).* **5n-3*S*** (212.2 mg, 0.46 mmol). Purified by RP-HPLC (methanol:H_2O = 1:9, *V*:*V*) to give **6n-3*S*** as white solid (61.2 mg, 70%). ^{1}H NMR (300 MHz, D_2O) δ: 3.74 (m, 2H), 3.67–3.52 (m, 2H), 2.96 (dd, *J* = 9.7, 5.1 Hz, 1H), 2.67 (m, 1H), 2.47 (m, 1H), 1.83 (m, 1H), 1.43 (m, 1H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, D_2O) δ: 72.1, 68.3, 59.3, 57.6, 49.2, 39.8, 28.9, 20.1, 16.8; HRMS (*m/z*): calc for $C_9H_{19}NO_3^+H$: 190.14432, found: 190.14356.

*5.2.10.24. Synthesis of (2S,3S,4R)-1-isopropyl-2-(hydroxymethyl) piperidine-3,4-diol (**6n-3R**).* **5n-3*R*** (196.4 mg, 0.43 mmol). Purified by RP-HPLC (methanol:H_2O = 2:3, *V*:*V*) to give **6n-3*R*** as white solid (68.4 mg, 84.6%). ^{1}H NMR (300 MHz, CD_3OD) δ: 3.92 (dt, *J* = 9.0, 4.5 Hz, 1H), 3.86 (d, *J* = 3.3 Hz, 2H), 3.60 (dd, *J* = 9.0, 3.1 Hz, 1H), 3.38 (dt, *J* = 13.1, 6.6 Hz, 1H), 2.69 (dt, *J* = 8.9, 3.3 Hz, 1H), 1.73 (m, 2H), 2.59 (m, 2H), 1.14 (d, *J* = 6.7 Hz, 3H, CH_3), 0.98 (d, *J* = 6.5 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, CD_3OD) δ: 70.5, 68.7, 61.7, 59.2, 49.2, 38.0, 31.0, 21.6, 14.2; ESI-MS (*m/z*): 190.4 $[M + H]^+$, 212.4$[M + Na]^+$; HRMS (*m/z*): calc for $C_9H_{19}NO_3^+H$: 190.14432, found: 190.14377.

*5.2.10.25. Synthesis of (2S,3R,4R)-1-butyl-2-(hydroxymethyl)piperidine-3,4-diol (**6o-3S**).* **5o-3*S*** (200.7 mg, 0.42 mmol). Purified by RP-HPLC (methanol:H_2O = 1:9, *V*:*V*) to give **6o-3*S*** as white solid (40.5 mg, 47%). ^{1}H NMR (300 MHz, D_2O) δ: 3.70 (m, 2H), 3.70–3.50 (m, 2H), 2.91 (dd, *J* = 9.7, 5.1 Hz, 1H), 2.68–2.38 (m, 4H), 1.80 (m, 1H), 1.53–1.57 (m, 3H), 1.16 (m, 2H), 0.77 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz,D_2O) δ: 72.0, 68.4, 61.8, 56.8, 53.2, 45.0, 29.9, 27.6, 20.2, 13.3; HRMS (*m/z*): calc for $C_{10}H_{21}NO_3^+H$: 204.15997, found: 204.15942.

*5.2.10.26. Synthesis of (2S,3S,4R)-1-butyl-2-(hydroxymethyl)piperidine-3,4-diol (**6o-3R**).* **5o-3*R*** (211.1 mg, 0.45 mmol). Purified by RP-HPLC (methanol:H_2O = 3:2, *V*:*V*) to give **6o-3*R*** as white solid (69.6 mg, 76.8%). ^{1}H NMR (300 MHz, D_2O) δ: 3.61–3.78 (m, 4H), 2.93 (m, 1H), 2.52 (m, 4H), 1.82 (m, 1H), 1.33–1.45 (m, 3H), 1.18 (dd, *J* = 14.2, 7.0 Hz, 2H), 0.79 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, D_2O) δ: 72.0, 68.4, 61.8, 56.8, 53.2, 45.0, 27.6, 29.0, 20.2, 13.3; ESI-MS (*m/z*): 204.2$[M + H]^+$, 226.1$[M + Na]^+$; HRMS (*m/z*): calc for $C_{10}H_{21}NO_3^+H$: 204.15997, found: 204.15998.

*5.2.10.27. Synthesis of (2S,3R,4R)-1-isobutyl-2-(hydroxymethyl) piperidine-3,4-diol (**6p-3S**).* **5p-3*S*** (200.2 mg, 0.42 mmol). Purified by RP-HPLC (methanol:H_2O = 1:9, *V*:*V*) to give **6p-3*S*** as white solid (44.8 mg, 52%). ^{1}H NMR (300 MHz, D_2O) δ: 3.70 (m, 2H),3.58 (m, 2H), 2.92 (m, 1H, H-2), 2.66–2.40 (m, 2H), 2.32 (m, 2H), 1.72 (m, 2H), 1.48 (m, 1H), 0.78 (t, *J* = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, D_2O) δ: 71.6, 68.7, 62.5, 61.3, 56.5, 45.3, 28.8, 25.5, 20.4, 20.4; HRMS (*m/z*): calc for $C_{10}H_{21}NO_3^+H$: 204.15997, found: 204.15942.

*5.2.10.28. Synthesis of (2S,3S,4R)-1-isobutyl-2-(hydroxymethyl) piperidine-3,4-diol (**6p-3R**).* **5p-3*R*** (199.0 mg, 0.42 mmol). Purified

by RP-HPLC (methanol:H_2O = 3:2, *V*:*V*) to give **6p-3*R*** as white solid (69.3 mg, 81.2%). ^{1}H NMR (300 MHz, D_2O) δ: 3.90 (m, 1H), 3.73 (dd, *J* = 7.7, 3.2 Hz, 2H), 3.60 (m, 1H), 2.66 (dd, *J* = 10.5, 5.8 Hz, 1H), 2.35–2.47 (m, 3H), 2.18 (dd, *J* = 12.8, 4.9 Hz, 2H), 1.69–1.73 (m, 3H), 0.78–0.80 (m, 6H); ^{13}C NMR (75 MHz, D_2O) δ: 68.5, 67.0, 62.9, 61.5, 58.4, 45.5, 27.8, 25.2, 20.9, 20.4; ESI-MS (*m*/*z*): 204.2[M + H]$^+$, 226.2 [M + Na]$^+$; HRMS (*m*/*z*): calc for $C_{10}H_{21}NO_3^+H$: 204.15997, found: 204.15998.

*5.2.10.29. Synthesis of (2S,3R,4R)-1-hydroethyl-2-(hydroxymethyl) piperidine-3,4-diol (**6q-3S**).* **5q-3*S*** (165.6 mg, 0.36 mmol). Purified by RP-HPLC (methanol:H_2O = 5:95, *V*:*V*) to give **6q-3*S*** as white solid (31.6 mg, 46%). ^{1}H NMR (300 MHz, D_2O) δ: 3.73 (m, 2H), 3.68–3.50 (m, 4H), 2.94 (m, 1H), 2.73 (t, *J* = 6.1 Hz), 2.61 (m, 2H), 1.80 (m, 1H), 1.46 (m, 1H); ^{13}C NMR(75 MHz, D_2O) δ: 71.3, 68.2, 62.8, 58.5, 57.2, 54.5, 44.9, 28.4; HRMS (*m*/*z*): calc for $C_8H_{17}NO_4^+H$: 192.12358, found: 192.12357.

*5.2.10.30. Synthesis of (2S,3S,4R)-1-hydroethyl-2-(hydroxymethyl) piperidine-3,4-diol (**6q-3R**).* **5q-3*R*** (178.5 mg, 0.39 mmol). Purified by RP-HPLC (methanol:H_2O = 3:97, *V*:*V*) to give **6q-3*R*** as white solid (54.8 mg, 74.1%). ^{1}H NMR (300 MHz, D_2O) δ: 3.90 (dd, 1H), 3.75 (m, 2H), 3.64 (t, *J* = 6.2 Hz, 2H), 3.57 (dd, *J* = 8.8, 3.1 Hz, 1H), 2.87 (dt, *J* = 13.0, 6.3 Hz, 1H), 2.58–2.69 (m, 4H), 1.68 (m, 2H); ^{13}C NMR (75 MHz, D_2O) δ: 68.2, 66.9, 62.1, 57.8, 57.4, 53.8, 45.5, 28.1; ESI-MS (*m*/*z*): 192.3[M + H]$^+$, 214.3[M + Na]$^+$; HRMS (*m*/*z*): calc for $C_8H_{17}NO_4^+H$: 192.12358, found: 192.12312.

*5.2.10.31. Synthesis of (2S,3R,4R)-1-hydropropyl-2-(hydroxymethyl) piperidine-3,4-diol (**6r-3S**).* **5r-3*S*** (166.3 mg, 0.35 mmol). Purified by RP-HPLC (methanol:H_2O = 5:95, *V*:*V*) to give **6r-3*S*** as white solid (34.4 mg, 48%). ^{1}H NMR (300 MHz, D_2O) δ: 3.73 (m, 2H), 3.62 (m, 2H), 3.51 (t, *J* = 6.3 Hz, 2H), 2.97 (m, 1H), 2.65 (m, 4H), 1.85 (m, 1H), 1.64 (m, 2H), 1.46 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ: 71.5, 67.9, 61.8, 60.2, 57.1, 50.4, 45.0, 28.3, 27.5; HRMS (*m*/*z*): calc for $C_9H_{19}NO_4^+H$: 206.13923, found: 206.13848.

*5.2.10.32. Synthesis of (2S,3S,4R)-1-hydropropyl-2-(hydroxymethyl) piperidine-3,4-diol (**6r-3R**).* **5r-3*R*** (200.3 mg, 0.42 mmol). Purified by RP-HPLC (methanol:H_2O = 3:97, *V*:*V*) to give **6r-3*R*** as white solid (54.2 mg, 62.7%). ^{1}H NMR (300 MHz, D_2O) δ: 3.83 (m, 2H), 3.71 (m, 2H), 3.60 (t, *J* = 6.3 Hz, 2H), 3.06 (dd, *J* = 8.8, 4.6 Hz, 1H), 1.92 (m, 1H), 2.74 (m, 4H), 1.75 (m, 2H), 1.56 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ: 71.5, 67.9, 61.8, 60.2, 57.1, 50.4, 45.0, 28.3, 27.5; ESI-MS (*m*/*z*): 206.3[M + H]$^+$; HRMS (*m*/*z*): calc for $C_9H_{19}NO_4^+H$: 206.13923, found: 206.13848.

*5.2.10.33. Synthesis of (2S,3R,4R)-1-(2-(thiophen-2-yl)ethyl)-2-(hydroxymethyl) piperidine-3,4-diol (**6s-3S**).* **5s-3*S*** (237.2 mg, 0.45 mmol). Purified by RP-HPLC (methanol:H_2O = 5:95, *V*:*V*) to give **6s-3*S*** as white solid (35.8 mg, 58.2%). ^{1}H NMR (300 MHz, CD_3OD) δ: 7.36 (d, *J* = 3.6 Hz, 1H), 6.67 (d, *J* = 3.6 Hz, 1H), 3.88–3.73 (m, 2H), 3.70 (dd, *J* = 6.8, 3.8 Hz, 1H), 3.64 (td, *J* = 7.1, 3.8 Hz, 1H), 3.02–2.90 (m, 5H), 2.77–2.68 (m, 2H), 2.02–1.87 (m, 1H), 1.64–1.49 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ: 147.0, 129.2, 128.5, 124.7, 72.3, 68.6, 61.9, 58.5, 55.4, 45.1, 29.3, 27.2; HRMS (*m*/*z*): calcd for $C_{12}H_{19}NO_3S$ + H: 258.11639, found: 258.11597.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.03.004.

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