Bioorganic & Medicinal Chemistry 20 (2012) 3263–3279

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Discovery of ipragliflozin (ASP1941): A novel *C*-glucoside with benzothiophene structure as a potent and selective sodium glucose co-transporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes mellitus

Masakazu Imamura [a,*], Keita Nakanishi [a], Takayuki Suzuki [a], Kazuhiro Ikegai [a], Ryota Shiraki [a], Takashi Ogiyama [a], Takeshi Murakami [a], Eiji Kurosaki [a], Atsushi Noda [b], Yoshinori Kobayashi [b], Masayuki Yokota [b], Tomokazu Koide [b], Kazuhiro Kosakai [b], Yasufumi Ohkura [b], Makoto Takeuchi [a], Hiroshi Tomiyama [b], Mitsuaki Ohta [a]

[a] *Drug Discovery Research, Astellas Pharma Inc., 21 Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan*
[b] *Research Laboratories, Kotobuki Pharmaceutical Co., Ltd, 6351 Sakaki-machi, Hanishina-gun, Nagano 389-0697, Japan*

ARTICLE INFO

Article history:
Received 16 February 2012
Revised 21 March 2012
Accepted 22 March 2012
Available online 29 March 2012

Keywords:
Diabetes
SGLT2 inhibitor
Benzothiophene
Ipragliflozin

ABSTRACT

A series of *C*-glucosides with various heteroaromatics has been synthesized and its inhibitory activity toward SGLTs was evaluated. Upon screening several compounds, the benzothiophene derivative (**14a**) was found to have potent inhibitory activity against SGLT2 and good selectivity versus SGLT1. Through further optimization of **14a**, a novel benzothiophene derivative (**14h**; ipragliflozin, ASP1941) was discovered as a highly potent and selective SGLT2 inhibitor that reduced blood glucose levels in a dose-dependent manner in diabetic models KK-A^{y} mice and STZ rats.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disorder markedly increasing in Westernized societies and developing countries characterized by fasting and postprandial hyperglycemia due to the impaired insulin secretion and/or insulin resistance.[1–3] Untreated hyperglycemics are at risk of micro- and macrovascular complications including retinopathy, nephropathy, stroke, amputation and myocardial infarction.[4] Therefore, therapeutic strategies for T2DM are currently focused on controlling blood glucose levels.

To date, several oral drugs that enhance insulin secretion and/or improve insulin sensitivity have been developed. However, due to their limited efficacy and adverse side effects, it is difficult to maintain good glycemic control in most T2DM patients. Recent studies suggest that only about one-third of patients treated for T2DM achieve the glycemic target: a glycosylated hemoglobin (HbA_{1c}) of <7%.[5,6] For that reason, more effective agents are needed for the successful management of T2DM. Among these, inhibitors of sodium glucose co-transporters (SGLTs) are an attractive option, because they have a distinct mechanism of action that reduces blood glucose levels independently of insulin secretion.[7]

Plasma glucose is filtered in the glomerulus and then reabsorbed in the proximal tubules of the kidney. Renal glucose reabsorption is mediated by two SGLTs: SGLT1, a low-capacity, high-affinity transporter,[8,9] and SGLT2, a high-capacity, low-affinity transporter.[10,11] While SGLT2 is mainly expressed in the S1 and S2 segments of the proximal tubules, SGLT1 is distributed mainly in the small intestine and also present in the S3 segment of the proximal tuble.[11] Humans with SGLT1 gene mutations experience glucose–galactose malabsorption, resulting in frequent, watery diarrhea and dehydration when on a glucose diet, indicating that SGLT1 is the major glucose transporter in the small intestine.[12,13] In contrast, persistent renal glucosuria is the only reported phenotype of humans with SGLT2 gene mutations.[14,15] This observation suggests that SGLT2 is responsible for the majority of renal glucose reabsorption and that selective SGLT2 inhibitors are desired to avoid the gastrointestinal side effects related to SGLT1 inhibition.

Selective SGLT2 inhibitors have recently been shown to enhance urinary glucose excretion and reduce hyperglycemia in patients with T2DM.[16,17] SGLT2 inhibitors could increase the caloric output in urine due to the urinary glucose excretion, suggesting that SGLT2 inhibitors do not result in the weight gain often seen with

* Corresponding author. Tel.: +81 29 829 6653.
E-mail address: masakazu.imamura@astellas.com (M. Imamura).

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http://dx.doi.org/10.1016/j.bmc.2012.03.051

other antihyperglycemic agents currently prescribed, making them an even more expected candidate for next-generation of antidiabetic agents.

Phlorizin (**1**) is a natural *O*-glucoside that is a well known potent nonselective SGLT inhibitor.[18] However, **1** is not considered a suitable drug candidate not only because of its inhibitory activity toward SGLT1 but also because of its poor metabolic stability due to susceptible β-glucosidase-mediated degradation.

In a series of previous reports,[19–25] researchers at Mitsubishi Tanabe Pharma Co. disclosed the structure–activity relationships (SARs) of **1** and the discovery of another selective, potent SGLT2 inhibitor, T-1095A (**2**). However, to achieve glucose lowering in diabetic mice, oral administration of the methyl carbonate prodrug of **2**, T-1095 (**3**), was needed due to the β-glucosidase-mediated metabolic instability of the *O*-glucoside linkage in T-1095A. On the other hand, *C*-glucoside derivatives, such as compounds **4**[26] and **5**[27,28] were found to be potent SGLT2 inhibitors that are metabolically more stable than *O*-glucosides.

Here, we describe the *C*-glucoside derivatives containing heteroaromatics as SGLT2 inhibitors (compounds **6** and **7** in Fig. 1). A number of compounds with various heteroaromatics were synthesized and evaluated, including SAR studies, which culminated in the discovery of a novel benzothiophene derivative, **14h** (Ipragliflozin, ASP1941), a potent and selective SGLT2 inhibitor[29] that exhibits properties warranting a clinical development for the treatment of T2DM mellitus.

2. Chemistry

Preparation of thiophen-3-yl *C*-glucoside derivative **8** is outlined in Scheme 1. Addition of a Grignard reagent to aldehyde **20** followed by reduction of the resulting alcohol **21** with triethylsilane (Et_3SiH) and boron trifluoride ethyl ether complex ($BF_3{\cdot}OEt_2$) gave **22**. Lithium halogen exchange of **22** followed by the addition of a lithiated aromatic to gluconolactone **23**[30] yielded lactol, which was reduced by treatment with Et_3SiH and $BF_3{\cdot}OEt_2$ to give compound **24**. Removal of the benzyl groups from **24** with boron trichloride (BCl_3) generated thiophen-3-yl *C*-glucoside derivative **8**.

Pyrrol-3-yl *C*-glucoside derivative **9** was synthesized as shown in Scheme 2. Aglycon **26** was prepared by adding a Grignard reagent generated by pyrrole **25** and isopropyl magnesium bromide (*i*PrMgBr) to benzylbromide. Substitution of glucosyl fluoride **27**[31] with a Grignard reagent prepared from **26** and *i*PrMgBr gave compound **28**. Removal of the benzyl groups in **28** by hydrogenation yielded pyrrol-3-yl *C*-glucoside derivative **9**.

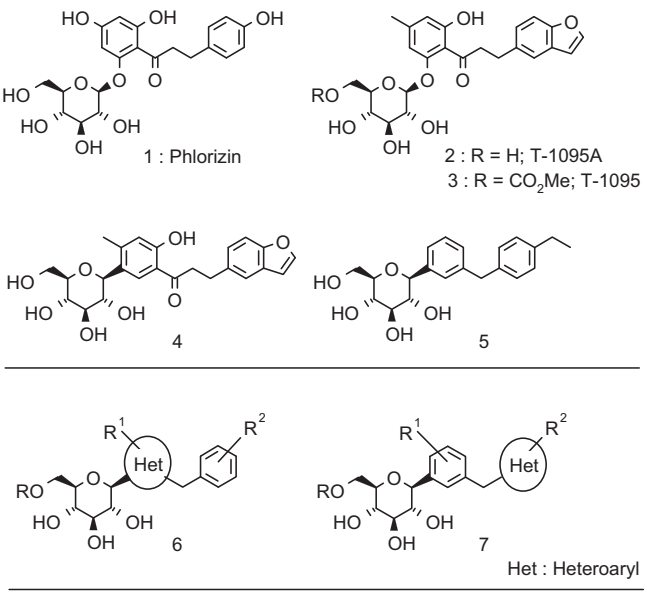


Figure 1. Structure of SGLT2 inhibitors.

Scheme 3 shows the synthesis of pyridyl *C*-glucoside derivative **10**. Lithium halogen exchange of 2,6-dibromopyridine **29** followed by the addition of a lithiated aromatic to gluconolactone **23** yielded lactol, which was then reduced by treatment with Et_3SiH and trifluoroacetic acid (TFA) to give pyridyl *C*-glucoside **30**. Hydroxycarbonylation was carried out on **30** under atmosphere of CO to give picolinic acid derivative **31**. Compound **31** was converted to Weinreb amide **32**, which was reduced to an aldehyde. A Grignard reagent prepared from 4-ethyliodobenzene and *i*PrMgBr was added to the aldehyde to give compound **33**. Barton reduction of the generated alcohol yielded compound **34**. Removal of the benzyl groups from **34** by BCl_3 afforded pyridyl *C*-glucoside derivative **10**.

Synthesis of pyrazin-2-yl *C*-glucoside derivative **11** is depicted in Scheme 4. 2,6-dichloropyrazine was lithiated by lithium diisopropyl amide (LDA) and then a lithiated aromatic was added to gluconolactone **23** to give lactol. Reduction of lactol by treatment with Et_3SiH and TFA gave pyrazin-2-yl *C*-glucoside **36**. Lithiation of **36** with lithium tetramethylpiperidide (LiTMP) followed by the addition of a lithiated aromatic to 4-ethylbenzaldehyde and reduction of the nascent alcohol with Et_3SiH and TFA yielded compound **37**. Dechlorination of **37** by hydrogenation followed by removal of the benzyl groups by treatment with BCl_3 generated pyrazin-2-yl *C*-glucoside derivative **11**.

Preparation of key intermediate **43** is shown in Scheme 5. 3-Bromobenzylalcohol (**39**) was protected with a *tert*-butyldiphenylsilyl (TBDPS) group to give compound **40**. Lithium halogen exchange of **40** followed by the addition of a lithiated aromatic to gluconolactone **23** yielded lactol, which was reduced by treatment with Etr_3SiH and $BF_3{\cdot}OEt_2$ to give phenyl *C*-glucoside **41**. Removal of the TBDPS group by tetrabutylammoniumfluoride (TBAF) followed by the oxidation of benzylalcohol to benzaldehyde with manganese (IV) oxide (MnO_2) afforded the key intermediate **43**.

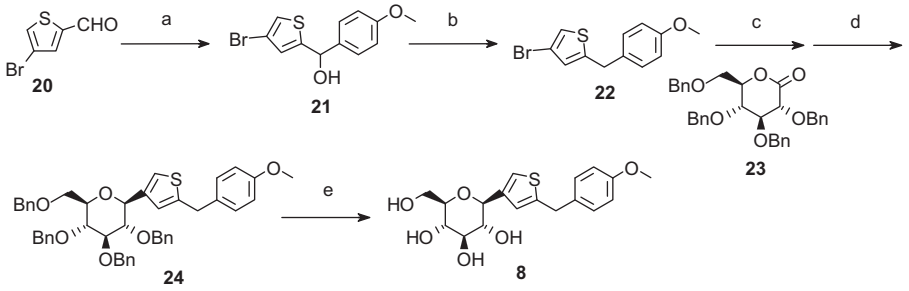
Compounds **12** and **19** were synthesized as shown in Scheme 6. 2-Bromopyridine (**44**) and *N*-methylbenzimidazole (**45**) were lithiated and added to **43** to give alcohols **46** and **47**. Barton reduction of these alcohols yielded compounds **48** and **49**, while subsequent removal of the benzyl groups by BCl_3 afforded pyridine derivative **12** and *N*-methylbenzimidazole derivative **19**.

Scheme 7 shows the synthesis of benzothiophene derivative **14a** and benzofuran derivative **15**. The lithiation of benzothiophene (**50**) and benzofuran (**51**) followed by the addition of a lithiated aromatic to **43** yielded lactols, which were reduced by treatment with Et_3SiH and $BF_3{\cdot}OEt_2$ to give compounds **52** and **53**. The benzyl groups of these compounds were removed by treatment with BCl_3 to give compounds **14a** and **15**.

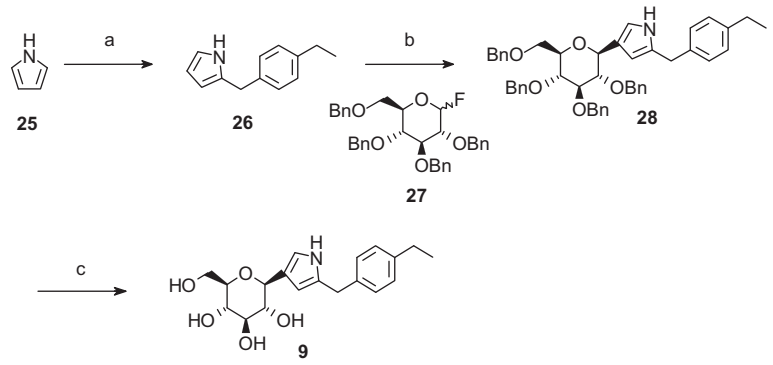
Synthesis of C-glucosylated benzylbromide **56** is depicted in Scheme 8. Conversion of the benzyl groups in **41** to acetyl groups followed by removal of the TBDPS group yielded benzylalcohol **55**. Bromination of **55** with carbon tetrabromide and triphenylphosphine gave the desired intermediate **56**.

Preparation of *N*-methylindole derivative **16** is outlined in Scheme 9. Conversion of *N*-methylindole **57** to organo stannyl reagent, followed by Stille coupling of this organo stannyl reagent to **56** using a palladium catalyst yielded compound **58**. Removal of the acetyl groups from **58** in a basic condition generated **16**.

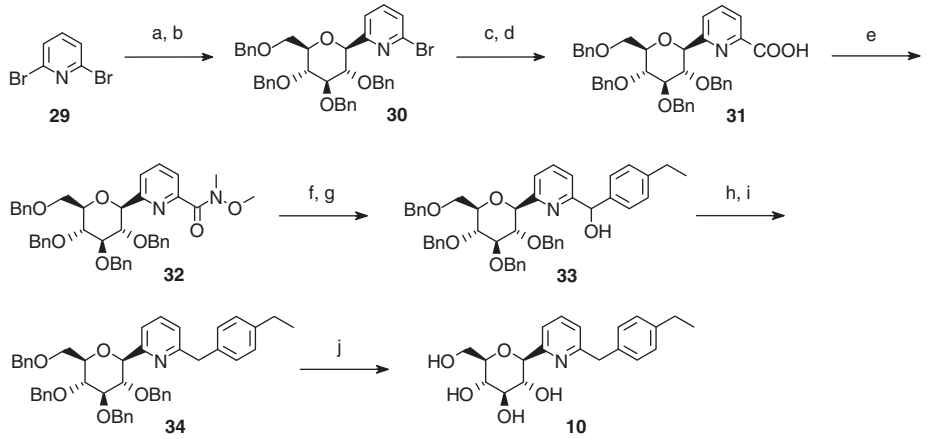
Conversion of compound **56** to an organo zinc reagent followed by Negishi coupling with 2-methylthiopyrazine, 2-chlorobenzothiazole and 2-chlorobenzoxazole using a palladium catalyst gave compounds **59**, **60** and **61**, respectively. The acetyl groups of these compounds were removed in a basic condition to give pyrazine derivative **13**, benzothiazole derivative **17** and benzoxazole derivative **18** (Scheme 10).



Scheme 1. Reagents and conditions: (a) 4-methoxyphenylmagnesiumbromide, THF, 0 °C, 96%; (b) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −20 °C, 70%; (c) *n*-BuLi (1.6 M in hexane), THF, −78 °C then **23**, 71%; (d) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C to −20 °C, quant.; (e) BCl_3 (1.0 M in heptane), pentamethylbenzene, CH_2Cl_2, −78 °C, 46%.

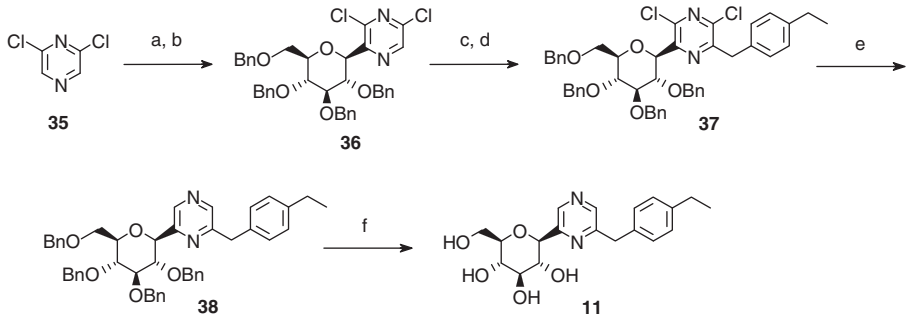


Scheme 2. Reagents and conditions: (a) *i*PrMgBr, then 4-ethylbenzylbromide, benzene, 60 °C, 19%; (b) *i*PrMgBr, THF, rt then **27**, 38%; (c) $Pd(OH)_2$, H_2, EtOAc–MeOH, rt, 13%.

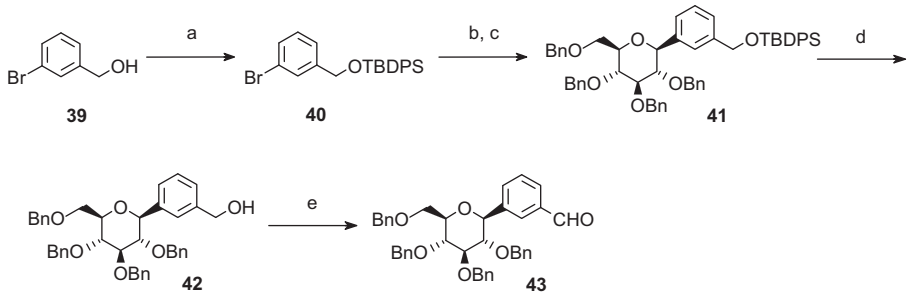


Scheme 3. Reagents and conditions: (a) *n*-BuLi (1.6 M in hexane), THF, −78 °C then **23**, 67%; (b) Et_3SiH, TFA, CH_2Cl_2, rt, 70%; (c) $Pd(OAc)_2$, dppp, CO, Et_3N, DMSO-MeOH, 70 °C, 76%; (d) 1 M NaOH aq, THF–MeOH, rt, quant.; (e) *N*,*O*-dimethylhydroxylamine hydrochloride, WSC-HCl, HOBt, Et_3N, DMF, rt, 84%; (f) DIBAL-H, CH_2Cl_2, 0 °C, 62%; (g) 4-Ethyliodobenzene, *i*PrMgCl, THF, −30 °C, 90%; (h) NaH, CS_2, MeI, THF, rt; (i) *n*-Bu_3SnH, AIBN, toluene, reflux, 70% (2 steps); (j) BCl_3 (1.0 M in heptane), pentamethylbenzene, CH_2Cl_2, −78 °C, 81%.

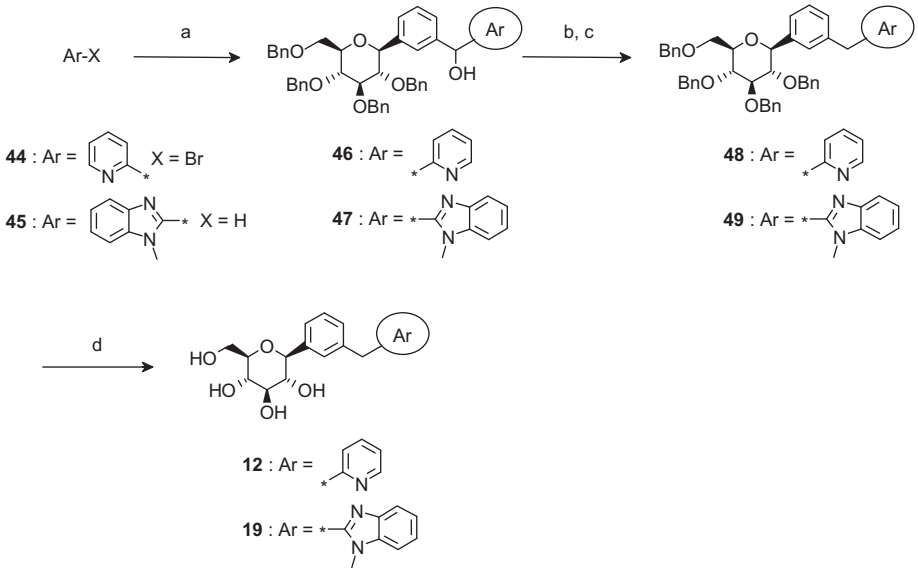
Schemes 11 and 12 show the synthesis of benzothiophene derivatives having several substitution groups on the central benzene ring. Lithiation of **50** followed by the addition of a lithiated aromatic to compounds **64** or **65**, which were prepared from the hydroxybenzaldehydes **62** or **63**, respectively, yielded alcohols those were reduced with Et_3SiH and $BF_3{\cdot}OEt_2$ to give aglycons **66** and **67**. Lithium halogen exchange of **66** and **67** followed by the addition of a lithiated aromatic to gluconolactone **23** yielded lactols those were reduced by treatment with Et_3SiH and $BF_3{\cdot}OEt_2$ to give compounds **68** and **69**. Successive removal of the methoxymethyl group and benzyl groups generated compounds **14b** and **14f**, both having a hydroxy group on the central benzene ring, although at different position (Scheme 11). Methylation of intermediates **70** and **71** followed by removal of the benzyl groups gave methoxy derivatives **14c** and **14g** (Scheme 11). Compounds with fluorine or chlorine on the central benzene ring (compounds **14d**, **14e**, **14h** and **14i**) were synthesized using a procedure similar to Scheme 11 (Scheme 12). Aglycons **74**, **75**, **76** and **77** were prepared by adding lithiated benzothiophene to the corresponding benzaldehydes and reducing the alcohol. The addition of lithiated aglycons generated by lithium



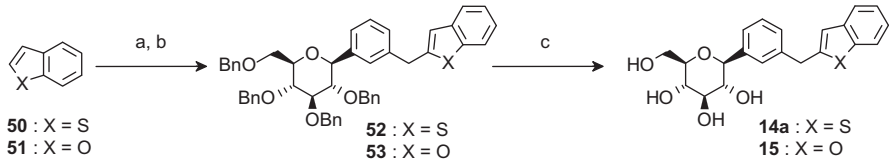
Scheme 4. Reagents and conditions: (a) LDA, THF, −78 °C then **23**, 66%; (b) Et_3SiH, TFA, CH_2Cl_2, rt, 28%; (c) LiTMP, THF, −78 °C then 4-ethylbenzaldehyde, 34%; (d) Et_3SiH, TFA, CH_2Cl_2, rt, 63%; (e) 10% Pd/C, H_2, MeOH–THF, rt, 50%; (f) BCl_3 (1.0 M in heptane), pentamethylbenzene, CH_2Cl_2, −78 °C, 43%.



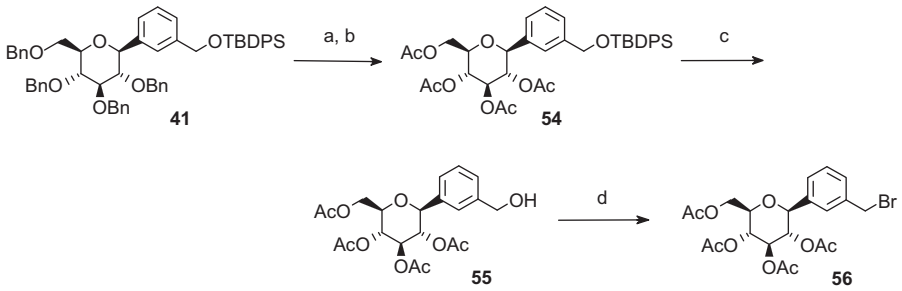
Scheme 5. Reagents and conditions: (a) TBDPSCl, imidazole, DMF, rt, quant.; (b) *n*-BuLi (1.6 M in hexane), THF, −78 °C then **23**; (c) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −20 °C, 29% (2 steps); (d) TBAF (1.0 M in THF), THF, rt, 46%; (e) MnO_2, CH_2Cl_2, rt, 92%.



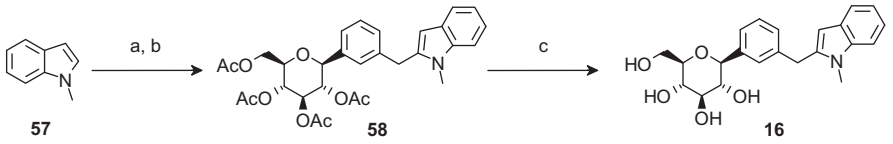
Scheme 6. Reagents and conditions: (a) *n*-BuLi (1.6 M in hexane), THF, −78 °C then **43**, 63% (**46**), 35% (**47**); (b) NaH, CS_2, MeI, THF, rt; (c) *n*-Bu_3SnH, AIBN, toluene, reflux, 87% (2 steps) (**48**), 82% (2 steps) (**49**); (d) BCl_3 (1.0 M in heptane), pentamethylbenzene, CH_2Cl_2, −78 °C, 84% (**12**), 20% (**19**).



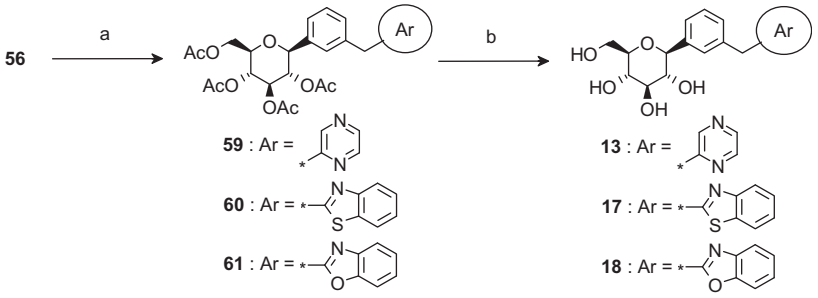
Scheme 7. Reagents and conditions: (a) *n*-BuLi (1.6 M in hexane), THF, −78 °C then **43**; (b) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 60% (2 steps) (**52**), 62% (2 steps) (**53**); (c) BCl_3 (1.0 M in heptane), pentamethylbenzene, CH_2Cl_2, −78 °C, 60% (**14a**), 52% (**15**).



Scheme 8. Reagents and conditions: (a) 10% Pd/C, H_2, THF–MeOH, rt; (b) Ac_2O, DMAP, pyridine, rt, 98% (2 steps); (c) TBAF (1.0 M in THF), THF, rt, 44%; (d) CBr_4, PPh_3, CH_2Cl_2, rt, 71%.



Scheme 9. Reagents and conditions: (a) *n*-BuLi (1.6 M in hexane), *n*-Bu_3SnCl, THF, 0 °C to rt, 96% (b) **56**, $Pd_2(dba)_3$, 2-(dicyclohexylphosphino)biphenyl, KF, Cs_2CO_3, dioxane, 60 °C, 51%; (c) NaOMe, MeOH-THF, rt, 61%.



Scheme 10. Reagents and conditions: (a) Zn, 1,2-dibromoethane, TMSCl, reflux then Ar-X (X = Cl or SMe), $Pd(PPh_3)_4$, reflux, 75% (**59**), 47% (**60**), 31% (**61**); (b) NaOMe, MeOH, rt, 32% (**13**), 69% (**17**), 72% (**18**).

halogen exchange to gluconolactone **23** followed by the reduction of lactol and removal of the benzyl groups afforded halogenated derivatives **14d**, **14e**, **14h** and **14i**.

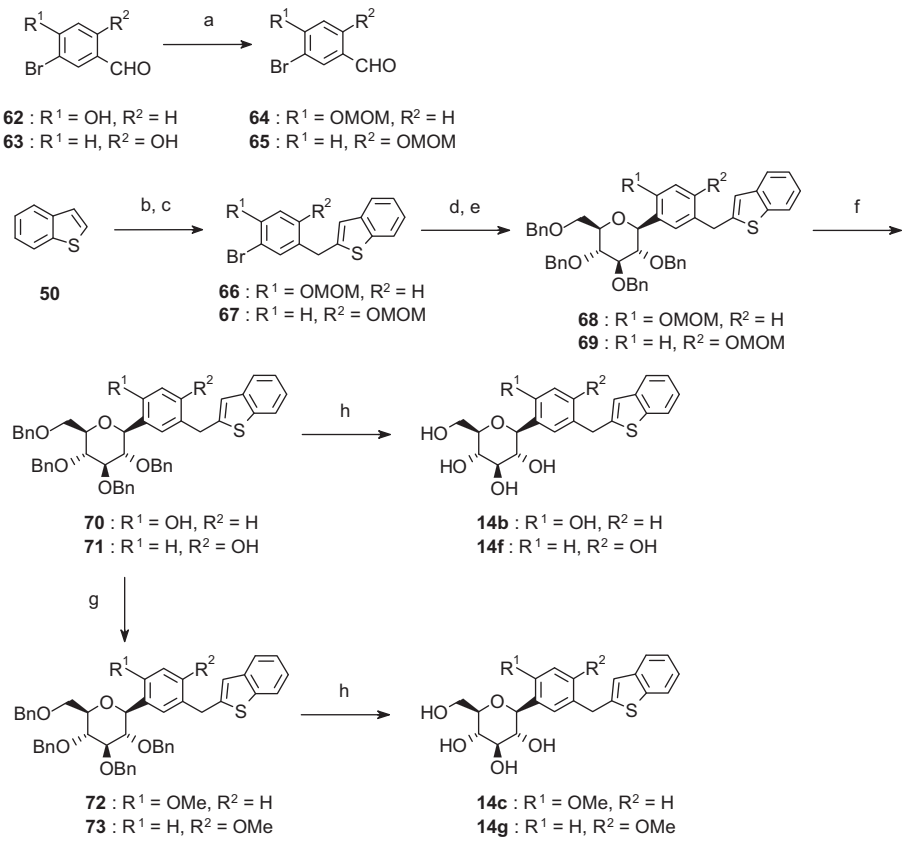
3. Result and discussion

The in vitro SGLT inhibitory potential (IC_{50}) of all synthesized compounds was assessed by monitoring the inhibition of accumulating [^{14}C] methyl-α-D-glucopyranoside (AMG) in Chinese hamster ovary cells expressing human SGLT2 or SGLT1.[32]

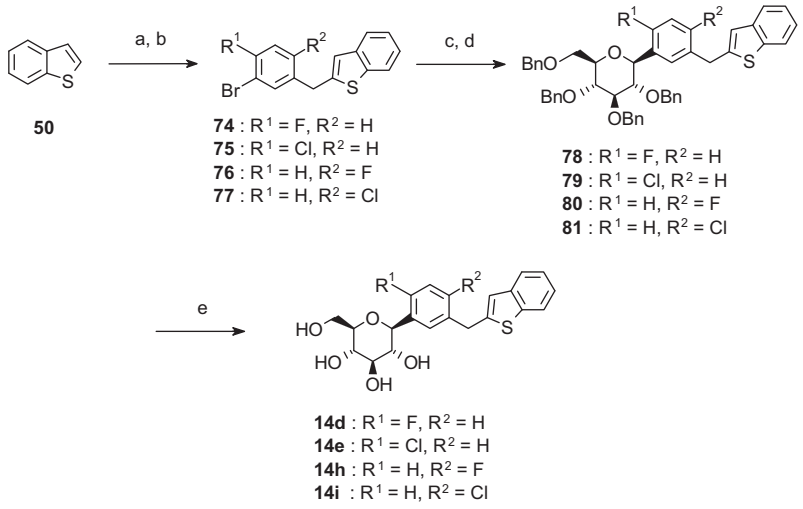
Compound **5** was found to be a very potent SGLT2 inhibitor with an IC_{50} value of 10 nM and also to have a excellent SGLT2 selectivity versus SGLT1 (1000-fold). Table 1 shows the results of replacing the central benzene ring in **5** with various heteroaromatics. Although replacement with a thiophene ring (**8**) or a pyrrole ring (**9**) caused a decrease in inhibitory activity (IC_{50} values of 100 and 70 nM, respectively), the decrease was not extreme and both structures had a good selectivity versus SGLT1 (160-fold, 230-fold, respectively). These results suggest their utility as SGLT2 inhibitors. Replacement with a pyridine or a pyrazine (**10** and **11**) resulted in a much more significant decrease in SGLT2 inhibitory activity (IC_{50} value of 610 and 4900 nM, respectively), indicating that lipophilic aromatics are preferred at this position when designing SGLT2 inhibitors.

Next, we investigated the effects of replacing the terminal benzene ring of **5** with various heteroaromatics (Table 2). Replacement with a pyridine (**12**) and a pyrazine (**13**) resulted in complete loss of the inhibitory activity toward SGLT2, indicating that nitrogen-containing heteroaromatics are unfavorable at the terminal benzene ring position. This tendency was also seen when replacing with fused heteroaromatics. Conversion of the terminal benzene ring in compound **5** to nitrogen-containing heteroaromatic, such as an indole (**16**) a benzothiazole (**17**), a benzoxazole (**18**) and a benzimidazole (**19**), also resulted in a significant decrease of the inhibitory activity toward SGLT2. Among these heteroaryl derivatives, the benzothiophene derivative **14a** was a potent SGLT2 inhibitor with a good selectivity versus SGLT1. On the basis of these results, we selected **14a** as the lead compound for further optimizations.

We next studied the effects of the substitution groups on the central benzene ring of compound **14a** (Table 3). Substitution of hydroxyl (**14b**) or methoxy (**14c**) groups at the *ortho* position to the glycoside of the benzene ring (6-position; R^1) were found to effectively increase inhibitory activity against SGLT2 (IC_{50} values of 9.8 and 13 nM, respectively) while retaining a good selectivity versus SGLT1 (107-fold and 510-fold, respectively). Additionally, the introduction of a fluorine atom (**14d**) maintained the potency of **14a**, while that of a chlorine atom (**14e**) led to a three-fold decrease. These results indicates that the introduction of oxy-functional groups onto this position should improve the inhibitory activity against SGLT2. On the other hand, similar hydroxyl (**14f**) or methoxy (**14g**) group substitutions at the *para* position to the



Scheme 11. Reagents and conditions: (a) NaH, MOMCl, DMF, rt, 91% (**64**), 98% (**65**); (b) *n*-BuLi (1.6 M in hexane), THF, −78 °C then **64** or **65**; (c) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −20 °C, 86% (2 steps) (**66**), 76% (2 steps) (**67**); (d) *n*-BuLi (1.6 M in hexane), THF, −78 °C then **23**; (e) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −20 °C, 58% (2 steps) (**68**), 14% (2 steps) (**69**); (f) HCl (4.0 M in dioxane) , 91% (**70**), 82% (**71**); (g) K_2CO_3, MeI, DMF, rt , 95% (**72**), 92% (**73**); (h) BCl_3 (1.0 M in heptane), pentamethylbenzene, CH_2Cl_2, −78 °C, 45% (**14b**), 29% (**14c**) , 73% (**14f**), 27% (**14g**).

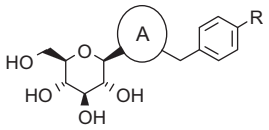


Scheme 12. Reagents and conditions: (a) *n*-BuLi (1.6 M in hexane), THF, −78 °C then benzaldehydes; (b) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 36% (2 steps) (**74**), 48% (2 steps) (**75**) , 64% (2 steps) (**76**), 46% (2 steps) (**77**); (c) *n*-BuLi (1.6 M in hexane), THF, −78 °C then **43**; (d) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 22% (2 steps) (**78**), 34% (2 steps) (**79**) , 61% (2 steps) (**80**), 14% (2 steps) (**81**); (e) BCl_3 (1.0 M in heptane), pentamethylbenzene, CH_2Cl_2, −78 °C, 24% (**14d**), 86% (**14e**) , 64% (**14h**) , 70% (**14i**).

glycoside of the benzene ring (4-position; R^2) resulted in a poor selectivity versus SGLT1. Substitution with a fluorine atom at this position (**14h**) resulted in a very good in vitro profile with an IC_{50} value of 7.4 nM and a 254-fold selectivity versus SGLT1, while introduction of a chlorine atom (**14i**) improved the inhibitory activity against SGLT2 significantly (IC_{50} = 3.7 nM), but with a consequent loss of selectivity versus SGLT1 (47-fold).

Among the aforementioned benzothiophene derivatives, compound **14h** was chosen for further in vivo studies. As shown in Figure 2, single oral doses (0.01–10 mg/kg) of **14h** induced urinary

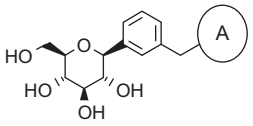
Table 1
In vitro inhibitory activity and selectivity of *C*-glucosides **5**–**11**

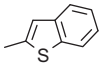
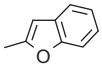
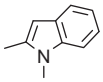
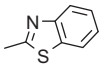
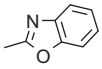
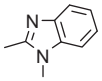


Compound	A	R	hSGLT2 IC_{50}[a] (nM)	Selectivity vs hSGLT1[a] (fold)
5		Et	10	1000
8		OMe	100	160
9		Et	70	230
10		Et	610	>160
11		Et	4900	>20

[a] The data were obtained from at least two independent experiments.

Table 2
In vitro inhibitory activity and selectivity of *C*-glucosides **12**–**19**



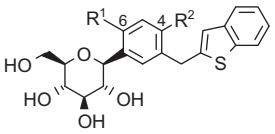
Compound	A	hSGLT2 IC_{50}[a] (nM)	Selectivity vs hSGLT1[a] (fold)
12		>100,000	–
13		>100,000	––
14a		30	210
15		675	127
16		6300	7
17		650	130
18		2300	>43
19		>100,000	–

[a] The data were obtained from at least two independent experiments.

glucose excretion in a dose-dependent manner in both normal and in KK-A^y mice, a type 2 diabetes model.[29] To assess antihyperglycemic effects, KK-A^y mice and streptozotocin-induced diabetic rats (STZ rats, a type 1 diabetes model) were used to evaluate the efficacy of **14h** for lowering blood glucose levels. Figure 3 shows that single administrations of **14h** (0.1, 0.3 and 1 mg/kg) dose-dependently reduces blood glucose level in both KK-A^y mice and STZ rats.[29]

Administration of a single 0.3 mg/kg dose intravenously and a single 1 mg/kg dose orally to rats revealed that compound **14h** has good bioavailability with a value of 71.7% (Table 4). Furthermore, the extensive blood glucose lowering effect of **14h** should reflect excellent pharmacokinetic properties in vivo as well as strong inhibitory activity against SGLT2.

Table 3
In vitro inhibitory activity and selectivity of *c*-glucosides with benzothiophene **14a**–**i**



Compound	R^1	R^2	hSGLT2 IC_{50}[a] (nM)	Selectivity vs hSGLT1[a] (fold)
14a	H	H	30	210
14b	OH	H	9.8	107
14c	OMe	H	13	510
14d	F	H	47	110
14e	Cl	H	92	120
14f	H	OH	75	43
14g	H	OMe	14	11
14h	H	F	7.4	254
14i	H	Cl	3.7	47

[a] The data were obtained from at least two independent experiments.

4. Conclusion

The synthesis and structure–activity relationships (SARs) of *C*-glucosides with various heteroaromatics as SGLT2 inhibitors have been explored. Based on these SAR studies, the benzothiophene derivative compound **14a** was found to be a potent and selective SGLT2 inhibitor. Further optimization of compound **14a** culminated in the discovery of a novel compound, (1*S*)-1,5-anhydro-1-[3-(1-benzothiophen-2-ylmethyl)-4-fluorophenyl]-D-glucitol (**14h**), that is a highly potent and selective inhibitor for SGLT2. Oral administration of compound **14h** caused a remarkable increase in urinary glucose excretion and anti-hyperglycemic effects in the diabetic models KK-A^y mice and STZ rats. These findings, combined with its favorable pharmacokinetic profile, have prompted clinical evaluation of **14h**. Currently, this benzothiophene derivative (Ipragliflozin, ASP1941) is being developed for the treatment of type 2 diabetes mellitus.

5. Experimental

5.1. Chemistry

^{1}H NMR and ^{13}C NMR spectra were obtained on a JEOL JNM-EX400 spectrometer and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Abbreviations of ^{1}H NMR signal patterns are as follows: s, singlet; d, doublet; dd, double doublet; ddd, double double doublet; dt, double triplet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were obtained on a JEOL JMS-DX300 or HITACHI M-80 spectrometer. Column chromatography on silica gel was performed with Kieselgel 60 (E. Merck).

5.1.1. (4-Bromo-2-thienyl)(4-methoxyphenyl)methanol (21)

To an ice-cooled solution of 4-bromothiophene-2-carbaldehyde (1.91 g, 10.0 mmol) in THF (20 mL) was added 4-methoxyphenylmagnesiumbromide (0.5 M in THF; 24 mL, 12.0 mmol) and the mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched by adding saturated aqueous ammonium chloride

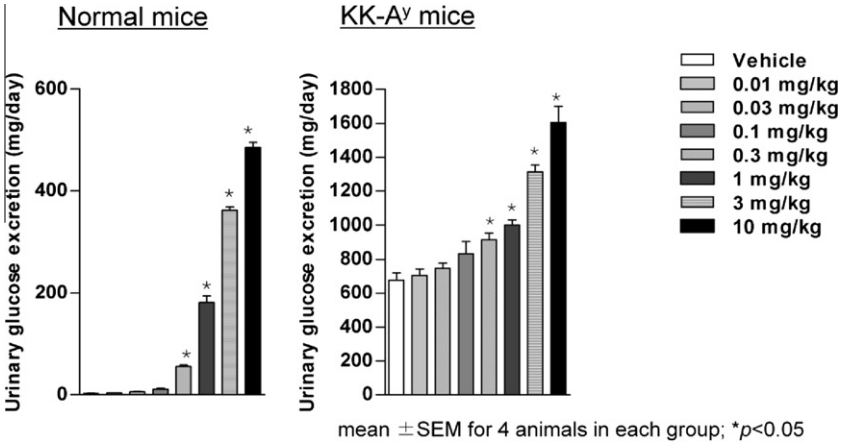


Figure 2. Effects of single oral dosings of compound **14h** on urinary glucose excretion in Institute of Cancer Research normal mice and KK-A^y mice. Values are mean or mean ± SEM for four animals in each group. Each parameter was analyzed statistically over 24 h. *p<0.05 vs. vehicle using Dunnett's multiple range test.

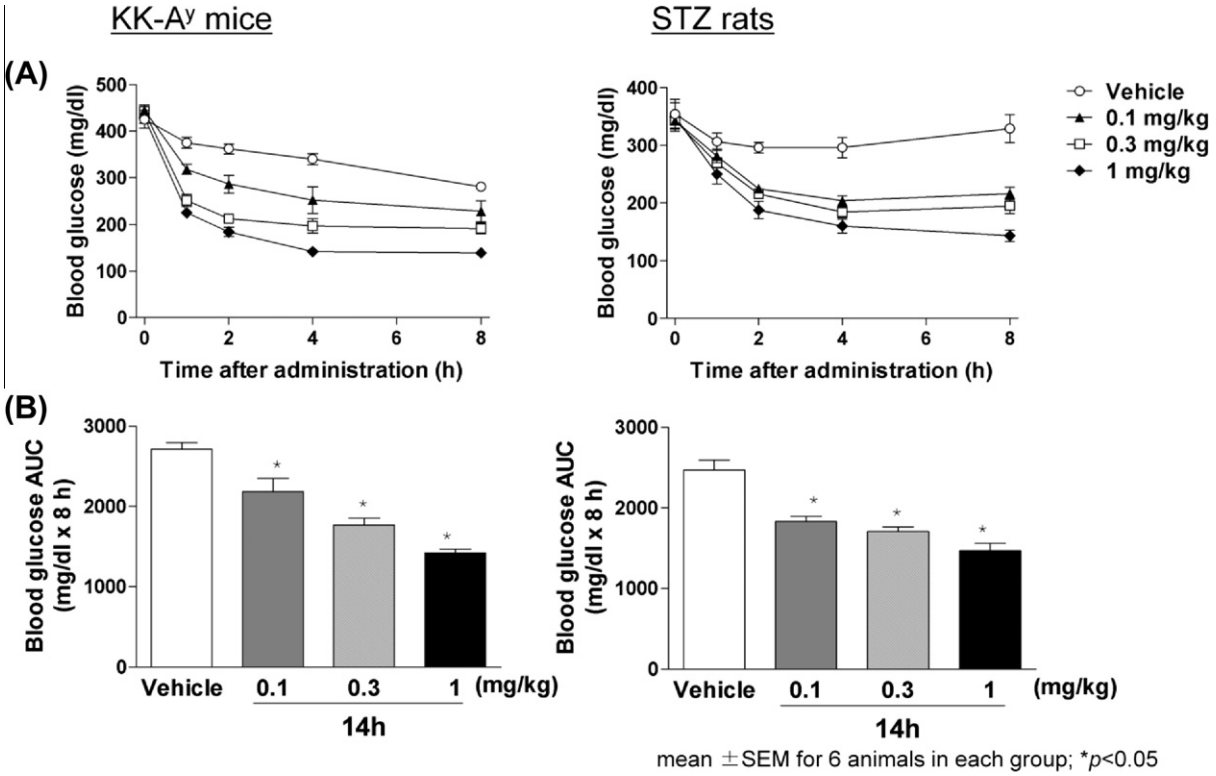


Figure 3. Effects of single oral dosings of **14h** on blood glucose level in KK-A^y mice and STZ rats. (A) Change in blood glucose levels. (B) Suppression of glucose AUC. Values are expressed as mean ± SEM for four animals in each group. *p<0.05 versus vehicle using Dunnett's multiple range test.

Table 4
Pharmacokinetic properties of **14h** in rats

Route	Dose (mg/kg)	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24h} (ng∗h/mL)	AUC_{inf} (ng∗h/mL)	CL_{tot} (L/h/kg)	V_{dss} (L/kg)	BA%
iv	0.3	3.85			686	692	0.43	1.68	
po	1	3.61	1	331	1638	1654			71.7

solution and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the titled compound **21** (2.86 g, 96%) as a light brown solid.

^{1}H NMR (DMSO-d_6) δ: 3.32 (1H, s), 3.74 (3H, s), 5.85 (1H, d, J = 4.0 Hz), 6.26 (1H, d, J = 4.0 Hz), 6.80 (1H, d, J = 1.6 Hz), 6.91 (2H, d, J = 8.4 Hz), 7.31 (2H, d, J = 8.4 Hz), 7.49 (1H, d, J = 1.6 Hz). MS (FAB) m/z: 300 (M^++H), calcd for $C_{12}H_{11}BrO_2S$: 299

5.1.2. 4-Bromo-2-(4-methoxybenzyl)thiophene (22)

To a cold (−78 °C) solution of **21** (2.78 g, 9.29 mmol) in CH_2Cl_2 (60 mL) was added Et_3SiH (3.0 mL, 19.0 mmol) and $BF_3{\cdot}OEt_2$

(1.3 mL, 10.0 mmol) and the mixture was warmed up to −20 °C and stirred at −20 °C for 2 h. The reaction mixture was quenched by adding saturated aqueous sodium bicarbonate solution and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the titled compound **22** (1.85 g, 70%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 3.80 (3H, s), 4.04 (2H, s), 6.68 (1H, d, J = 1.6 Hz), 6.85 (2H, d, J = 9.6 Hz), 7.02 (1H, d, J = 1.6 Hz), 7.14 (2H, d, J = 9.6 Hz). MS (FAB) m/z: 284 (M^++H), calcd for $C_{12}H_{11}BrOS$: 283

5.1.3. (1*S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-[5-(4-methoxybenzyl)-3-thienyl]-D-glucitol (24)

To a cold (−78 °C) solution of **22** (1.78 g, 6.29 mmol) in THF–toluene (1:1; 40 mL) was added *n*-BuLi (1.60 M in hexane; 4.0 mL, 6.4 mmol) and the mixture was stirred at −78 °C for 10 min. To the reaction mixture was added a solution of **23** in THF–toluene (1:1; 30 mL) and the mixture was stirred at −78 °C for 2 h. The reaction mixture was quenched by adding saturated aqueous ammonium chloride solution and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give a lactol (2.98 g, 71%) as a pale yellow oil. To a cold (−78 °C) solution of the lactol obtained above (2.26 g, 3.04 mmol) in CH_2Cl_2 (50 mL) was added Et_3SiH (1.46 mL, 9.14 mmol) and $BF_3{\cdot}OEt_2$ (0.42 mL, 3.30 mmol) and the mixture was warmed up to −20 °C and stirred at −20 °C for 4.5 h. The reaction mixture was quenched by adding saturated aqueous sodium bicarbonate solution and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the titled compound **24** (2.30 g, quant.) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 3.46–3.57 (2H, m), 3.72–3.77 (7H, m), 3.96 (1H, d, J = 10.3 Hz), 4.06 (2H, s), 4.27 (1H, d, J = 10.3 Hz), 4.43–4.65 (4H, m), 4.81–4.95 (3H, m), 6.79 (2H, d, J = 6.3 Hz), 6.87 (1H, s), 6.97–7.01 (2H, m), 7.12–7.34 (21H, m). MS (ESI) m/z: 749 (M^++Na), calcd for $C_{46}H_{46}O_6S$: 726.

5.1.4. (1*S*)-1,5-Anhydro-1-[5-(4-methoxybenzyl)-3-thienyl]-D-glucitol (8)

To a cold (−78 °C) solution of **24** (0.73 g, 1.00 mmol) in CH_2Cl_2 (35 mL) were added pentamethylbenzene (2.22 g, 15.0 mmol) and BCl_3 (1.0 M in heptane; 5.0 mL, 5.0 mmol) and the mixture was stirred at −78 °C for 4 h. The reaction mixture was quenched by adding MeOH at −78 °C then warmed up to rt. The mixture was evaporated in vacuo and the resulting residue was purified by column chromatography on silica gel (MeOH–$CHCl_3$) to give the titled compound **8** (0.167 g, 46%) as a white solid.

^{1}H NMR (CD_3OD) δ: 3.32–3.45 (4H, m), 3.66 (1H, dd, J = 5.3, 11.7 Hz), 3.76 (3H, s), 3.86 (1H, d, J = 11.7 Hz), 4.04 (2H, s), 4.15 (1H, d, J = 9.3 Hz), 6.80–6.92 (3H, m), 7.13–7.18 (3H, m). MS (FAB) m/z: 367 (M^++H), calcd for $C_{18}H_{22}O_6S$: 366

5.1.5. 2-(4-Ethylbenzyl)-1*H*-pyrrole (26)

To pyrrole **25** (8.00 g, 119 mmol) was added *i*PrMgBr (0.71 M in THF; 202 mL, 143 mmol) and the mixture was stirred at rt for 1 h, then the solvent was removed in vacuo. The resulting residue was dissolved in benzene (150 mL) and 4-ethylbenzylbromide (25.9 g, 130 mmol) was added to the solution, then the mixture was stirred at 60 °C for 1 h. To the reaction mixture was added saturated aqueous ammonium chloride solution then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the titled compound **26** (4.19 g, 19%) as a brown oil.

^{1}H NMR ($CDCl_3$) δ: 1.22 (3H, t, J = 6.9 Hz), 2.62 (2H, q, J = 7.5, 15 Hz), 3.44 (2H, s), 5.96–6.01 (1H, m), 6.14 (1H, dd, J = 2.7, 5.7 Hz), 6.65 (1H, dd, J = 2.7, 5.7 Hz), 7.00–7.28 (4H, m). MS (FAB) m/z: 186 (M^++H), calcd for $C_{13}H_{15}N$: 185.

5.1.6. (1*S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-[5-(4-ethylbenzyl)-1*H*-pyrrol-2-yl]-D-glucitol (28)

To a solution of **26** (4.14 g, 22.3 mmol) in THF (10 mL) was added *i*PrMgBr (0.71 M in THF; 27.6 mL, 21.0 mmol) and the mixture was stirred at rt for 2 h. To the reaction mixture was added **27** (3.80 g, 7.0 mmol) and the mixture was stirred at rt for 1.5 h. To the reaction mixture was added saturated aqueous ammonium chloride solution then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the titled compound **28** (1.89 g, 38%) as a brown oil.

^{1}H NMR ($CDCl_3$) δ: 1.19 (3H, t, J = 7.5 Hz), 2.59 (2H, q, J = 7.8, 15 Hz), 3.40–3.98 (8H, m), 4.22 (1H, d, J = 9.6 Hz), 4.33 (1H, d, J = 9.6 Hz), 4.45–4.62 (4H, m), 4.80–4.96 (3H, m), 5.95 (1H, t, J = 3.3 Hz), 6.18 (1H, t, J = 3.3 Hz), 6.85–7.33 (24H, m), 8.17 (1H, s). MS (FAB) m/z: 708 (M^++H), calcd for $C_{44}H_{49}NO_5$: 707.

5.1.7. (1*S*)-1,5-Anhydro-1-[5-(4-ethylbenzyl)-1*H*-pyrrol-2-yl]-D-glucitol (9)

To a solution of **28** (400 mg, 0.57 mmol) in MeOH–EtOAc (1:5, 12 mL) was added $Pd(OH)_2$ (20 wt% on carbon; 150 mg) and the mixture was stirred at rt for 86 h under H_2 atmosphere. The reaction mixture was filtered through celite and the filtrate was evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (MeOH–$CHCl_3$) to give the titled compound **9** (25 mg, 13%) as a white solid.

^{1}H NMR (CD_3OD) δ: 1.19 (3H, t, J = 7.8 Hz), 2.58 (2H, q, J = 7.8 Hz), 3.24–3.46 (4H, m), 3.65 (1H, dd, J = 4.8, 11.7 Hz), 3.80–3.86 (4H, m), 4.15 (1H, d, J = 9.3 Hz), 5.73 (1H, d, J = 3.0 Hz), 6.02 (1H, d, J = 3.0 Hz), 7.07 (2H, d, J = 8.3 Hz), 7.12 (2H, d, J = 8.3 Hz). MS (FAB) m/z: 348 (M^++H), calcd for $C_{19}H_{25}NO_5$: 347.

5.1.8. (1*S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-(6-bromopyridin-2-yl)-D-glucitol (30)

To a cold (−78 °C) solution of 2,6-dibromopyridine (**29**) (7.10 g, 30.0 mmol) in THF (90 mL) was added *n*-BuLi (1.60 M in hexane; 18.9 mL, 30.0 mmol) and the mixture was stirred at −78 °C for 25 min. To the reaction mixture was added a solution of **23** (15.4 g, 28.5 mmol) in THF (30 mL) and the mixture was stirred at −78 °C for 3.5 h. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with Brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give lactol (13.3 g, 67%) as a pale yellow oil. To a cold (0 °C) solution of the lactol obtained above (13.2 g, 18.9 mmol) in CH_2Cl_2 (135 mL) was added Et_3SiH (30.2 mL, 189 mmol) and trifluoroacetic acid (TFA) (14.5 mL, 189 mmol) and the mixture was warmed up to rt and stirred at rt for 7 days. The reaction mixture was quenched by adding saturated aqueous sodium bicarbonate solution and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the titled compound **30** (9.05 g, 70%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 3.62 (1H, dt, J = 4.0, 9.6 Hz), 3.73–3.78 (2H, m), 3.82–3.87 (2H, m), 4.08–4.13 (2H, m), 4.37 (1H, d, J = 9.2 Hz), 4.50–4.62 (4H, m), 4.83–4.96 (3H, m), 6.93–6.98 (2H, m), 7.15–7.36 (18H, m), 7.40–7.53 (3H, m). MS (FAB) m/z: 681 (M^++H), calcd for $C_{39}H_{38}BrNO_5$: 680

5.1.9. (1*S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-(6-carboxypyridin-2-yl)-D-glucitol (31)

To a solution of **30** (1.15 g, 1.67 mmol) in DMSO–MeOH (2:3; 10.0 mL) was added $Pd(OAc)_2$ (135 mg, 0.6 mmol), diphenylphosphino propane (248 mg, 0.6 mmol) and triethylamine (0.61 mL, 4.40 mmol). The mixture was stirred at 70 °C under CO atmosphere for 24 h. The reaction mixture was evaporated in vacuo and to the resulting residue was added EtOAc. The insoluble portion was filtered through celite and the filtrate was washed with water. The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give yellow oil (0.84 g, 76%). To a solution of this yellow oil (0.80 g, 1.21 mmol) in THF–MeOH (1:1; 16 mL) was added 1 M aqueous sodium hydroxide solution (8.0 mL) and the mixture was stirred at rt for 2 h and the reaction mixture was evaporated in vacuo . The resulting residue was dissolved in $CHCl_3$ then washed with 1 M aqueous hydrogen chloride solution. The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo then dried up to give the titled compound **31** (0.78 g, quant.) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 3.62–3.97 (8H, m), 4.41–4.65 (4H, m) 4.87 (1H, d, J = 10.8 Hz), 4.95 (2H, s), 6.75–6.78 (2H, m), 7.07–7.38 (18H, m), 7.61 (1H, d, J = 8.0 Hz), 7.87 (1H, t, J = 8.0 Hz), 8.13 (1H, d, J = 8.0 Hz). MS (FAB) *m/z*: 646 (M^++H), calcd for $C_{40}H_{39}NO_7$: 645.

5.1.10. (1*S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-{6-[methoxy(methyl)carbamoyl]pyridin-2-yl-D-glucitol (32)

To a solution of **31** (2.98 g , 4.41 mmol) in DMF (18 mL) was added *N*,*O*-dimethylhydroxylamine hydrochloride (646 mg, 6.62 mmol), triethylamine (0.93 mL, 6.62 mmol), HOBt (743 mg, 4.85 mmol) and WSC HCl (1.27 g, 6.62 mmol) and the mixture was stirred at rt overnight. The reaction mixture was diluted with EtOAc then washed with water and saturated aqueous sodium bicarbonate solution. The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the titled compound **32** (2.55 g, 84%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 3.37 (3H, s), 3.61–3.89 (9H, m), 3.95 (1H, d, J = 10.8 Hz), 4.41–4.65 (5H, m), 4.85–4.97 (3H, m), 6.87 (2H, m), 7.12–7.35 (19H, m), 7.46 (1H, d, J = 8.4 Hz), 7.77 (1H, t, J = 8.4 Hz). MS (FAB) *m/z*: 689 (M^++H), calcd for $C_{42}H_{44}N_2O_7$: 688.

5.1.11. (1*S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-{6-[(4-ethylphenyl)(hydroxy)methyl]pyridin-2-yl-D-glucitol (33)

To a cold (−78 °C) solution of **32** (440 mg, 0.639 mmol) in CH_2Cl_2 (30 mL) was added diisobutylalminiumhydride (1.0 M in hexane; 0.96 mL, 0.96 mmol) and the mixture was stirred at 0 °C for 3 h. To the reaction mixture was added saturated aqueous ammonium chloride solution then the resulting insoluble portion was filtered through celite. The filtrate was extracted with $CHCl_3$ and the organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give aldehyde (250 mg, 62%) as a colorless oil. To a cold (−30 °C) solution of 1-ethyl-4-iodobenzene (0.29 mL, 1.98 mmol) in THF (10 mL) was added *i*PrMgCl (2.0 M in THF; 0.95 mL, 1.90 mmol) and the mixture was stirred at −30 °C for 2 h. To the reaction mixture was added a solution of aldehyde obtained above (250 mg, 0.40 mmol) in THF (10 mL) and the mixture was stirred at rt for 2.5 h. To the reaction mixture was added saturated aqueous ammonium chloride solution then extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the title compound (**33**) (274 mg, 90%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.15 (3H, t, J = 6.8 Hz), 2.56 (2H, q, J = 6.8 Hz), 3.62–4.01 (7H, m), 4.37–4.68 (5H, m), 4.84–4.97 (3H, m), 5.72 (1H, br s), 6.76–6.85 (2H, m), 7.02–7.36 (24H, m), 7.57 (1H, t, J = 8.0 Hz). MS (FAB) *m/z*: 736 (M^++H), calcd for $C_{48}H_{49}NO_6$: 735.

5.1.12. (1*S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-[6-(4-ethylbenzyl)pyridin-2-yl]-D-glucitol (34)

To a solution of **33** (310 mg, 0.41 mmol) in THF (15 mL) was added NaH (55% on mineral oil; 36 mg, 0.81 mmol). The mixture was stirred at ambient temp. for 10 min, then CS_2 (0.184 mL, 3.05 mmol) was added and the mixture was stirred at rt for 1 h. To the reaction mixture was added MeI (0.05 mL, 0.81 mmol) and the mixture was stirred at rt for 2 h. The reaction mixture was diluted with EtOAc then washed with brine. The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. To a solution of resulting residue in toluene (10 mL) was added *n*-Bu_3SnH (0.55 mL, 2.03 mmol) and α,α′-azoisobutyronitrile (AIBN) (33 mg, 0.20 mmol) and the mixture was stirred under reflux condition 5 h. The reaction mixture was cooled down to rt then evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the title compound (**34**) (205 mg, 70%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.08 (3H, t, J = 8.2 Hz), 2.47 (2H, q, J = 8.2 Hz), 3.54–3.90 (7H, m), 4.05 (2H, q, J = 15.2 Hz), 4.29–4.55 (5H, m), 4.79 (1H, d, J = 10.4 Hz), 4.83 (2H, q, J = 11.2 Hz), 6.71–6.74 (2H, m), 6.92–7.28 (24H, m), 7.46 (1H, t, J = 7.6 Hz). MS (FAB) *m/z*: 720 (M^++H), calcd for $C_{48}H_{49}NO_5$: 719.

5.1.13. (1*S*)-1,5-Anhydro-1-[6-(4-ethylbenzyl)pyridin-2-yl]-D-glucitol (10)

The title compound was prepared in the same manner as described for **8** using **34** instead of **24** in 81% yield.

^{1}H NMR (CD_3OD) δ: 1.19 (3H, t, J = 7.6 Hz), 2.59(2H, q, J = 7.6 Hz), 3.41–3.62 (4H, m), 3.74 (1H, dd, J = 4.8, 12.2 Hz), 3.91(1H, d, J = 11.3 Hz), 4.10 (2H, s), 4.28 (1H, d, J = 8.8 Hz), 7.07–7.18 (5H, m), 7.41 (1H, d, J = 7.8 Hz), 7.71 (1H, t, J = 7.8 Hz). MS (FAB) *m/z*: 360 (M^++H), calcd for $C_{20}H_{25}NO_5$: 359.

5.1.14. (1*S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-(3,5-dichloropyrazin-2-yl)-D-glucitol (36)

To a cold (−78 °C) solution of *i*Pr_2NH (2.34 g, 23.1 mmol) in THF (60 mL) was added *n*-BuLi (1.60 M in hexane; 13.2 mL, 21.0 mmol), then the mixture was warmed up to 0 °C and stirred for 30 min. The mixture was cooled down to −78 °C and 2,6-dichloropyrimidine (**35**) (2.98 g, 20.0 mmol) was added to the mixture. After stirring at −78 °C for 10 min., the solution was added to a solution of **23** (10.8 g, 20.0 mmol) in THF (100 mL) and the mixture was stirred at −78 °C for 3 h. The reaction mixture was diluted with saturated aqueous ammonium chloride solution then extracted with Et_2O. The organic layer was dried over MgSO4, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give lactol (9.07 g, 66%). The title compound was prepared in the same manner as described for **30** using this lactol in 28% yield.

^{1}H NMR ($CDCl_3$) δ: 3.66–3.73 (4H, m), 3.91 (1H, t, J = 9.2 Hz), 4.07 (1H, t, J = 9.2 Hz), 4.38 (1H, d, J = 11.6 Hz), 4.48 (1H, d, J = 12.0 Hz), 4.54 (1H, d, J = 12.0 Hz), 4.59 (1H, d, J = 10.8 Hz), 4.72 (1H, d, J = 11.6 Hz), 4.81 (1H, d, J = 9.2 Hz), 4.85 (1H, d, J = 10.8 Hz), 4.96 (2H, s), 6.89 (2H, d, J = 7.2 Hz), 7.13–7.37 (18H, m), 8.21 (1H, s). MS (FAB) *m/z*: 671 (M^++H), calcd for $C_{38}H_{36}Cl_2N_2O_5$: 670.

5.1.15. (1*S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-[3,5-dichloro-6-(4-ethylbenzyl)pyrazin-2-yl]-D-glucitol (37)

To a cold (−78 °C) solution of *n*-BuLi (1.60 M in hexane; 2.15 mL, 3.42 mmol) in THF (20 mL) was slowly added 2,2,6,6-tetramethylpiperidine (0.64 mL, 3.80 mmol) and the mixture was warmed up to 0 °C and then stirred for 1 h. The mixture was cooled down to −78 °C, then a solution of **36** (2.09 g, 3.11 mmol) in THF (20 mL) was added to the mixture and stirred at −78 °C for 1 h. To the reaction mixture was added 4-ethylbenzaldehyde (1.28 mL, 9.34 mmol) and the mixture was stirred at −78 °C for 1.5 h. To the reaction mixture was added saturated aqueous ammonium chloride solution and Et_2O then the organic layer was separated. The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give alcohol (0.84 g, 34%). The title compound was prepared in the same manner as described for **30** using this alcohol in 63% yield.

^{1}H NMR ($CDCl_3$) δ: 1.10 (3H, t, J = 7.6 Hz), 2.50 (2H, q, J = 7.6 Hz), 3.64–3.68 (1H, m), 3.72–3.82 (3H, m), 3.90 (1H, t, J = 9.0 Hz), 4.10–4.23 (4H, m), 4.49 (1H, d, J = 12.0 Hz), 4.59–4.66 (3H, m), 4.78 (1H, d, J = 10.0 Hz), 4.86–4.97 (3H, m), 6.78 (2H, d, J = 6.8 Hz), 6.97 (2H, d, J = 8.0 Hz), 7.09–7.33 (20H, m). MS (ESI) *m/z*: 789 (M^++H), calcd for $C_{47}H_{46}Cl_2N_2O_5$: 788.

5.1.16. (1*S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-[6-(4-ethylbenzyl)pyrazin-2-yl]-D-glucitol (38)

To a solution of **37** (0.10 g, 0.13 mmol) in MeOH–THF (3:1; 4.0 mL) was added Pd (10 wt% on carbon) (0.10 g) and Et_3N (0.035 mL, 0.25 mmol). The mixture was stirred at rt under H_2 atmosphere for 22 h. The insoluble portion was filtered through celite and washed with MeOH. The filtrate was evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the title compound (**38**) (0.046 g, 50%) as a pale yellow oil.

^{1}H NMR ($CDCl_3$) δ: 1.15 (3H, t, J = 7.8 Hz), 2.54 (2H, q, J = 7.8 Hz), 3.63–3.68 (1H, m), 3.74–3.81 (3H, m), 3.87 (1H, t, J = 9.0 Hz), 3.93–4.00 (2H, m), 4.11 (2H, s), 4.43 (1H, d, J = 9.6 Hz), 4.48 (1H, d, J = 10.8 Hz), 4.53 (1H, d, J = 12.2 Hz), 4.59 (1H, d, J = 12.2 Hz), 4.62 (1H, d, J = 10.8 Hz), 4.87 (1H, d, J = 10.4 Hz), 4.92 (2H, s), 6.75 (2H, d, J = 8.4 Hz), 7.04 (2H, d, J = 8.4 Hz), 7.08–7.34 (20H, m), 8.36 (1H, s), 8.48 (1H, s). MS (ESI) *m/z*: 721 (M^++H), calcd for $C_{47}H_{48}N_2O_5$: 720.

5.1.17. (1*S*)-1,5-Anhydro-1-[6-(4-ethylbenzyl)pyrazin-2-yl]-D-glucitol (11)

The title compound was prepared in the same manner as described for **8** using **38** instead of **24** in 43% yield.

^{1}H NMR (CD_3OD) δ: 1.20 (3H, t, J = 7.8 Hz), 2.60 (2H, q, J = 7.8 Hz), 3.45–3.56 (3H, m), 3.64 (1H, t, J = 9.1 Hz), 3.70–3.75 (1H, m), 3.89 (1H, dd, J = 1.4, 12.2 Hz), 4.17 (2H, s), 4.37 (1H, d, J = 9.2 Hz), 7.13 (2H, d, J = 8.1 Hz), 7.19 (2H, d, J = 8.1 Hz), 8.40 (1H, s), 8.56 (1H, s). MS (ESI) *m/z*: 361 (M^++H), calcd for $C_{19}H_{22}N_2O_5$: 360.

5.1.18. [(3-bromobenzyl)oxy](*tert*-butyl)diphenylsilane (40)

To a cold (0 °C) solution of 3-bromophenylethanol (**39**) (50 g, 267 mmol) and imidazole (27 g, 401 mmol) in DMF (500 mL) was added *tert*-butylchlorodiphenylsilane (83 mL, 320 mmol) and the mixture was warmed up to rt then stirred at rt for 8 h. To the reaction mixture was added saturated aqueous ammonium chloride solution and EtOAc. The organic layer was separated and washed with brine then dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the title compound (**40**) (117 g, quant.) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 1.10 (9H, s), 4.72 (2H, s), 7.16–7.27 (2H, m), 7.35–7.48 (8H, m), 7.66–7.69 (4H, m). MS (FAB) *m/z*: 425 (M^+), calcd for $C_{23}H_{25}BrOSi$: 425.

5.1.19. (1*S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-[3-({[tert-butyl(diphenyl)silyl]oxy}methyl)phenyl]-D-glucitol (41)

The title compound was prepared in the same manner as described for **24** using **40** instead of **22** in 29% yield.

^{1}H NMR ($CDCl_3$) δ: 1.09 (9H, s), 3.49–3.80 (7H, m), 4.22–4.97 (10H, m), 6.88–7.72 (34H, m). MS (FAB) *m/z*: 869 (M^++H), calcd for $C_{56}H_{60}O_6Si$: 868.

5.1.20. (1*S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-[3-(hydroxymethyl)phenyl]-D-glucitol (42)

To a solution of **41** (18.5 g, 21.3 mmol) in THF (200 mL) was added tetrabutylammonium fluoride (1.0 M in THF; 30.8 mL, 20.8 mmol) and the mixture was stirred at rt for 30 min. The reaction mixture was evaporated in vacuo and the resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the title compound (**42**) (6.17 g, 46%) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 3.50 (1H, t, J = 9.3 Hz), 3.60–3.87 (8H, m), 4.26 (1H, d, J = 9.3 Hz), 4.42 (1H, d, J = 10.6 Hz), 4.56 (1H, d, J = 12.3 Hz), 4.62–4.67 (1H, m), 4.66 (2H, s), 4.87 (1H, d, J = 10.6 Hz), 4.90–4.93 (1H, m), 4.96 (1H, d, J = 11.0 Hz), 6.89–6.92 (2H, m), 7.18–7.42 (22H, m). MS (FAB) *m/z*: 631 (M^++H), calcd for $C_{41}H_{42}O_6$: 630.

5.1.21. (1*S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-(3-formylphenyl)-D-glucitol (43)

To a solution of **42** (4.12 g, 6.53 mmol) in chloroform (50 mL) was added manganese (IV) oxide (MnO_2) (28.4 g, 327 mmol) and the mixture was stirred at rt for 1 day. The reaction mixture was filtered through celite and the filtrate was evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the title compound (**43**) (3.79 g, 92%) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 3.48 (1H, t, J = 9.2 Hz), 3.75–3.87 (5H, m), 4.32 (1H, d, J = 9.2 Hz), 4.47 (1H, d, J = 10.6 Hz), 4.54–4.68 (4H, m), 4.87 (1H, d, J = 10.6 Hz), 4.94 (2H, m), 6.85–6.88 (2H, m), 7.13–7.52 (19H, m), 7.70 (1H, d, J = 7.7 Hz), 7.85 (1H, d, J = 7.7 Hz), 7.93 (1H, brs), 9.97 (1H, s). MS (FAB) *m/z*: 651 (M^++Na), calcd for $C_{41}H_{40}O_6$: 628.

5.1.22. (1*S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-{3-[hydroxy(pyridin-2-yl)methyl]phenyl}-D-glucitol (46)

To a cold (−78 °C) solution of 2-bromopyridine (**44**) (774 mg, 4.87 mmol) in THF (25 mL) was added *n*-BuLi (1.60 M in hexane; 3.10 mL, 4.87 mmol) and the mixture was stirred at −78 °C for 1 h. To the reaction mixture was added a solution of **43** (2.55 g, 4.06 mmol) in THF (60 mL) and the mixture was stirred at −78 °C for 3 h. To the reaction mixture was added H_2O and EtOAc, then the organic layer was separated and washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the title compound (**46**) (1.82 g, 63%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 3.48–3.60 (2H, m), 3.71–3.81 (5H, m), 4.24 (1H, dd, J = 6.8, 9.6 Hz), 4.33 (1H, dd, J = J = 6.8, 9.6 Hz), 4.54 (1H, t, J = 12.0 Hz), 4.61–4.65 (3H, m), 4.85–4.95 (2H, m), 5.23 (1H, brs), 5.75 (1H, brs), 6.84–6.98 (4H, m) 7.00–7.50 (23H, m), 8.52 (1H, dd, J = 4.8, 9.6 Hz). MS (FAB) *m/z*: 708 (M^++H), calcd for $C_{38}H_{36}Cl_2N_2O_5$: 670, calcd for $C_{46}H_{45}NO_6$: 707.

5.1.23. (1*S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-[3-(pyridin-2-ylmethyl)phenyl]-D-glucitol (48)

The title compound was prepared in the same manner as described for **34** using **46** instead of **33** in 87% yield.

^{1}H NMR ($CDCl_3$) δ: 3.48–3.81 (7H, m), 4.16 (2H, s), 4.22 (1H, d, J = 9.6 Hz), 4.34 (1H, d, J = 10.4 Hz), 4.52–4.65 (3H, m), 4.85–4.94 (3H, m), 6.87–6.89 (2H, m), 7.00–7.06 (2H, m), 7.15–7.36 (22H, m), 7.45 (1H, dt, J = 2.0, 7.2 Hz), 8.48–8.51 (1H, m). MS (FAB) *m/z*: 692 (M^++H), calcd for $C_{46}H_{45}NO_5$: 691.

5.1.24. (1*S*)-1,5-Anhydro-1-[3-(pyridin-2-ylmethyl)phenyl]-D-glucitol (12)

The title compound was prepared in the same manner as described for **8** using **48** instead of **24** in 84% yield.

^{1}H NMR (CD_3OD) δ: 3.32–3.49 (4H, m), 3.69 (1H, dd, J = 5.4, 12.2 Hz), 3.87 (1H, dd, J = 1.8, 12.2 Hz), 4.10 (1H, d, J = 9.3 Hz), 4.14 (2H, s), 7.17 (1H, dt, J = 2.1, 6.9 Hz), 7.18–7.31 (4H, m), 7.36 (1H, s), 7.73 (1H, dt, J = 2.1, 7.9 Hz), 8.40–8.43 (1H, m). MS (FAB) *m/z*: 332 (M^++H), calcd for $C_{18}H_{21}NO_5$: 331.

5.1.25. (1*S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-{3-[hydroxy-(1-methyl-1*H*-benzimidazole-2-yl)methyl]phenyl}-D-glucitol (47)

The title compound was prepared in the same manner as described for **46** using 1-methyl-1*H*-benzimidazole (**45**) instead of **44** in 35% yield.

^{1}H NMR ($CDCl_3$) δ: 3.36–3.81 (11H, m), 4.23 (1H, d, J = 9.6 Hz), 4.38 (1H, dd, J = 6.0, 9.6 Hz), 4.51 (1H, dd, J = 4.8, 12.4 Hz), 4.58–4.64 (2H, m), 4.84–4.94 (3H, m), 6.04 (1H, d, J = 12.4 Hz), 6.89–6.94 (2H, m), 7.14–7.77 (26H, m). MS (FAB) *m/z*: 761 (M^++H), calcd for $C_{49}H_{48}N_2O_6$: 760.

5.1.26. (1*S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-{3-[(1-methyl-1*H*-benzimidazole-2-yl)methyl]phenyl}-D-glucitol (49)

The title compound was prepared in the same manner as described for **34** using **47** instead of **33** in 82% yield.

^{1}H NMR ($CDCl_3$) δ: 3.36–3.62 (6H, m), 4.21 (1H, d, J = 9.2 Hz), 4.30 (2H, s), 4.54 (2H, q, J = 10.8 Hz), 4.60 (2H, q, J = 11.2 Hz), 4.83–4.97 (7H, m), 6.84–6.90 (2H, m), 7.12–7.78 (26H, m). MS (FAB) *m/z*: 745 (M^++H), calcd for $C_{49}H_{48}N_2O_5$: 744.

5.1.27. (1*S*)-1,5-Anhydro-1-{3-[(1-methyl-1*H*-benzimidazole-2-yl)methyl]phenyl}-D-glucitol (19)

The title compound was prepared in the same manner as described for **8** using **49** instead of **24** in 20% yield.

^{1}H NMR (CD_3OD) δ: 3.29–3.50 (4H, m), 3.64–3.70 (1H, m), 3.70 (3H, s), 3.86 (1H, dd J = 4.8, 9.4 Hz), 4.09 (1H, d, J = 9.4 Hz), 4.35 (2H, s), 7.18 (1H, d, J = 7.4 Hz), 7.21–7.37 (5H, m), 7.43 (1H, dd, J = 1.8, 6.8 Hz), 7.60 (1H, dd, J = 2.4, 6.8 Hz). MS (FAB) *m/z*: 385 (M^++H), calcd for $C_{21}H_{24}N_2O_5$: 384.

5.1.28. (1*S*)-1,5-Anhydro-1-[3-(1-benzothiophen-2-ylmethyl)-phenyl]-2,3,4,6-tetra-*O*-benzyl-D-glucitol (52)

To a cold (−78 °C) solution of benzothiophene (**50**) (818 mg, 6.09 mmol) in THF (16 mL) was added *n*-BuLi (1.60 M in hexane; 3.90 mL, 6.09 mmol) and the mixture was stirred at −78 °C for 1 h. To the reaction mixture was added a solution of **43** (2.55 g, 4.06 mmol) in THF (45 mL) and the mixture was stirred at −78 °C for 3 h. To the reaction mixture was added H_2O and EtOAc, then the organic layer was separated and washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give alcohol (2.48 g, 80%) as a yellow foam. To a solution of this alcohol (2.47 g, 3.63 mmol) in CH_2Cl_2 (45 mL) was added Et_3SiH (1.16 mL, 7.26 mmol) and $BF_3{\cdot}OEt_2$ (567 mg, 3.99 mmol) and the mixture was stirred at 0 °C for 4 h. To the reaction mixture was added saturated aqueous sodium bicarbonate solution and the organic layer was separated, dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the title compound (**52**) (2.04 g, 75%) as a light orange oil.

^{1}H NMR ($CDCl_3$) δ: 3.50–3.61 (2H, m), 3.73–3.81 (6H, m), 4.21 (2H, s), 4.30 (2H, q, J = 9.6 Hz), 4.59 (2H, q, J = 12.4 Hz), 4.86 (1H, d, J = 10.8 Hz), 4.90 (2H, q, J = 10.8 Hz), 6.87–6.89 (2H, m), 6.97 (1H, s), 7.13–7.40 (24H, m), 7.66 (1H, d, J = 10.8 Hz), 7.68 (1H, d, J = 10.8 Hz). MS (FAB) *m/z*: 747 (M^++H), calcd for $C_{49}H_{46}O_5S$: 746.

5.1.29. (1*S*)-1,5-Anhydro-1-[3-(1-benzothiophen-2-ylmethyl)-phenyl]-D-glucitol (14a)

The title compound was prepared in the same manner as described for **8** using **52** instead of **24** in 60% yield.

^{1}H NMR (CD_3OD) δ: 3.34–3.49 (4H, m), 3.67 (1H, dd, J = 5.4, 11.9 Hz), 3.87 (1H, d, J = 2.0, 11.9 Hz), 4.12 (1H, d, J = 9.3 Hz), 4.24 (2H, s), 7.06 (1H, s), 7.07–7.33 (5H, m), 7.40 (1H, s), 7.65 (1H, d, J = 7.8 Hz), 7.72 (1H, d, J = 7.8 Hz). MS (FAB) *m/z*: 387 (M^++H), calcd for $C_{21}H_{22}O_5S$: 386.

5.1.30. (1*S*)-1,5-Anhydro-1-[3-(1-benzofuran-2-ylmethyl)phenyl]-2,3,4,6-tetra-O-benzyl-D-glucitol (53)

The title compound was prepared in the same manner as described for **52** using **51** instead of **50** in 62% yield.

^{1}H NMR ($CDCl_3$) δ: 3.48–3.60 (2H, m), 3.73–3.81 (5H, m), 4.10 (2H, s), 4.24 (1H, d, J = 12.7 Hz), 4.37 (1H, d, J = 12.7 Hz), 4.58 (2H, q, J = 16.6 Hz), 4.63 (1H, d, J = 14.2 Hz), 4.86 (1H, d, J = 14.2 Hz), 4.91 (2H, q, J = 14.2 Hz), 6.32 (1H, d, J = 1.2 Hz), 6.87–6.90 (2H, m), 7.11–7.43 (26H, m). MS (ESI) *m/z*: 753 (M^++Na), calcd for $C_{49}H_{46}O_6$: 730.

5.1.31. (1*S*)-1,5-Anhydro-1-[3-(1-benzofuran-2-ylmethyl)phenyl]-D-glucitol (15)

The title compound was prepared in the same manner as described for **8** using **53** instead of **24** in 52% yield.

^{1}H NMR (CD_3OD) δ: 3.35–3.50 (4H, m), 3.69 (1H, dd, J = 4.7, 11.7 Hz), 3.87 (1H, dd, J = 1.4, 11.7 Hz), 4.10 (2H, s), 4.13 (1H, d, J = 9.3 Hz), 6.44 (1H, s), 7.13–7.18 (2H, m), 7.26–7.36 (4H, m), 7.41 (1H, brs), 7.45–7.47 (1H, m). MS (FAB) *m/z*: 371 (M^++H), calcd for $C_{21}H_{22}O_6$: 370.

5.1.32. (1*S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-[3-({[tert-butyl(diphenyl)silyl]oxy}methyl)phenyl]-D-glucitol (54)

To a solution of **41** (5.93 g, 6.82 mmol) in MeOH-THF (1:1; 90 mL) was added Pd (10 wt% on carbon) (500 mg) and the mixture was stirred at rt under H_2 atmosphere for 1 day. The reaction mixture was filtered through celite and washed with MeOH. The filtrate was evaporated in vacuo, then dried in vacuo. To a solution of the resulting residue in pyridine (40 mL) was added acetic anhydride (2.68 mL, 28.4 mmol) and 4-dimethylaminopyridine (catalytic amount). The mixture was stirred at rt for 1 day, then MeOH was added to the reaction mixture. The reaction mixture was evaporated in vacuo. The resulting residue was dissolved in EtOAc and washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo and then dried in vacuo to give the titled compound (**54**) (4.48 g, 98%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.10 (9H, s), 1.79, 2.01, 2.06, 2.07 (each 3H, each s), 3.84 (1H, ddd, J = 2.9, 6.1, 12.9 Hz), 4.15(1H, dd, J = 2.9, 16.1 Hz), 4.28 (1H, dd, J = 6.1, 16.1 Hz), 4.39 (1H, d, J = 12.4 Hz), 4.76 (2H, s), 5.11 (1H, t. J = 12.4 Hz), 5.23 (1H, t, J = 12.4 Hz), 5.34 (1H, t, J = 12.4 Hz), 7.30–7.47 (10H, m), 7.65–7.72(4H, m). MS (FAB) *m/z*: 677 (M^++H), calcd for $C_{37}H_{44}O_{10}Si$: 676.

5.1.33. (1*S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-[3-(hydroxymethyl)phenyl]-D-glucitol (55)

The title compound was prepared in the same manner as described for **42** using **54** instead of **41** in 44% yield.

^{1}H NMR ($CDCl_3$) δ: 1.81, 2.00, 2.06, 2.09 (each 3H, each s), 3.84 (1H, ddd J = 3.2, 6.4, 13.2 Hz), 4.14(1H, dd, J = 3.2, 16.6 Hz), 4.30 (1H, dd, J = 6.4, 16.6 Hz), 4.41 (1H, d, J = 13.2 Hz), 4.69 (2H, s), 5.14 (1H, t, J = 13.2 Hz), 5.23 (1H, t, J = 13.2 Hz), 5.34 (1H, t, J = 13.2 Hz), 7.22–7.35 (3H, m), 7.37 (1H, brs). MS (FAB) m/z: 439 (M^++H), calcd for $C_{21}H_{26}O_{10}$: 438.

5.1.34. (1*S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-[3-(bromomethyl)phenyl]-D-glucitol (56)

To a cold (0 °C) solution of **55** (1.29 g, 2.94 mmol) in CH_2Cl_2 (40 mL) was added triphenylphosphine (926 mg, 3.53 mmol) and carbontetrabromide (1.17 g, 3.53 mmol) and the mixture was stirred at rt for 30 min. To the reaction mixture was added saturated aqueous sodium bicarbonate solution and the organic layer was separated, dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the title compound (**56**) (1.04 g, 71%) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 1.84, 2.00, 2.06, 2.10 (each 3H, each s), 3.85 (1H, ddd, J = 3.2, 6.6, 13.2 Hz), 4.17 (1H, dd, J = 3.2, 16.6 Hz), 4.30 (1H, dd, J = 6.4, 16.6 Hz), 4.41 (1H, d, J = 12.9 Hz), 4.48 (2H, s), 5.10 (1H, t, J = 12.9 Hz), 5.23 (1H, t, J = 12.9 Hz), 5.34 (1H, t, J = 12.9 Hz), 7.30–7.37 (4H, m). MS (FAB) m/z: 502 (M^++H), calcd for $C_{21}H_{25}BrO_9$: 501.

5.1.35. (1*S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{3-[(1-methyl-1*H*-indol-2-yl)methyl]phenyl}-D-glucitol (58)

To a cold (0 °C) solution of 1-methyl-1*H*-indol (**57**) (3.32 g, 25.31 mmol) in THF (40 mL) was added *n*-BuLi (1.60 M in hexane; 16.1 mL, 25.3 mmol) and the mixture was stirred at 0 °C for 1 h. To the reaction mixture was added a solution of tributyl(chloro)stannane (7.42 g, 22.78 mmol) in THF (10 mL) and the mixture was stirred at rt for 1.5 h. To the reaction mixture was added brine and EtOAc, then the organic layer was separated and dried over $MgSO_4$, filtered and evaporated in vacuo to give a orange syrup (10.2 g, 96%). To a solution of this syrup (546 mg, 1.3 mmol) and **56** (501 mg, 1.0 mmol) in dioxane (10 mL) was added tris(dibenzylideneacetone)palladium (0) (92 mg, 0.1 mmol), dicyclohexylphosphinobiphenyl (88 mg, 0.25 mmol), potassium fluoride (174 mg, 3.0 mmol) and cesium carbonate (652 mg, 2.0 mmol). The mixture was stirred at 60 °C under Ar atmosphere overnight. The reaction mixture was cooled down to rt, then filtered through celite and washed with dioxane. The filtrate was evaporated in vacuo and the resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the title compound (**58**) (280 mg, 51%) as a light orange foam.

^{1}H NMR ($CDCl_3$) δ: 1.68, 1.98, 2.05, 2.06 (each 3H, each s), 3.54 (3H, s), 3.81 (1H, ddd, J = 2.0, 4.6, 9.6 Hz), 4.11–4.19 (3H, m), 4.28 (1H, dd, J = 4.6, 12.4 Hz), 4.35 (1H, d, J = 10.0 Hz), 5.10 (1H, t, J = 10.0 Hz), 5.22 (1H, t, J = 10.0 Hz), 5.30 (1H, t, J = 10.0 Hz), 6.24 (1H, s), 7.06–7.20 (4H, m), 7.21–7.31 (3H, m), 7.54 (1H, d, J = 12.0 Hz). MS (FAB) m/z: 552 (M^++H), calcd for $C_{30}H_{33}NO_9$: 551.

5.1.36. (1*S*)-1,5-Anhydro-1-{3-[(1-methyl-1*H*-indol-2-yl)methyl]phenyl}-D-glucitol (16)

To a solution of **58** (270 mg, 0.49 mmol) in THF–MeOH (1:1; 20 mL) was added sodium methoxide (catalytic amount) and the mixture was stirred at rt for 1 h. To the reaction mixture was added ion exchange resign (Dowex 50 W-x8, H^+ form) and filtered. The filtrate was evaporated in vacuo and the resulting residue was purified by column chromatography on silica gel (MeOH-$CHCl_3$) to give the title compound (**16**) (118 mg, 61%) as a white foam.

^{1}H NMR (CD_3OD) δ: 3.32–3.48 (4H, m), 3.57 (3H, s), 3.67 (1H, dd, J = 5.4, 11.7 Hz), 3.86 (1H, dd, J = 1.4, 11.7 Hz), 4.09 (1H, d, J = 9.3 Hz), 4.17 (2H, s), 6.22 (1H, s), 6.97 (1H, dt, J = 1.0, 7.6 Hz), 7.08 (1H, dt, J = 1.0, 7.6 Hz), 7.14 (1H, dt, J = 2.1, 6.9 Hz), 7.24–7.32 (4H, m), 7.43 (1H, d, J = 7.6 Hz). MS (FAB) m/z: 384 (M^++H), calcd for $C_{22}H_{25}NO_5$: 383.

5.1.37. (1*S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-[3-(pyrazin-2-ylmethyl)phenyl]-D-glucitol (59)

To a suspension of zinc (157 mg, 2.39 mmol) in THF (3.0 mL) was added 1,2-dibromoethane (1 drop) and the mixture was refluxed for 5 min under Ar atmosphere, then the mixture was cooled down to rt and chlorotrimethylsilane (1 drop) was added to the mixture. The mixture was stirred at rt for 15 min under Ar atmosphere. To the reaction mixture was added a solution of **56** (300 mg, 0.60 mmol) in THF (3.0 mL) and the mixture was refluxed for 1 h under Ar atmosphere. Then 2-chloropyrazine (68 mg, 0.60 mmol) and tetrakis(triphenylphosphine)palladium (0) (69 mg, 0.24 mmol) was added to the mixture and the mixture was refluxed for 2 h under Ar atmosphere. The reaction mixture was cooled down to rt, then filtered. The filtrate was evaporated in vacuo and the resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the title compound (**59**) (223 mg, 75%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.75, 1.99, 2.06, 2.08 (each 3H, each s), 3.82 (1H, ddd, J = 2.4, 4.8, 9.6 Hz), 4.11–4.14 (1H, m), 4.17 (2H, s), 4.27 (1H, dd, J = 4.8, 12.4 Hz), 4.37 (1H, d, J = 9.6 Hz), 5.11 (1H, t, J = 9.6 Hz), 5.22 (1H, t, J = 9.6 Hz), 5.31 (1H, t, J = 9.6 Hz), 7.21–7.32 (4H, m), 8.43 (2H, m), 8.53 (1H, s). MS (ESI) m/z: 501 (M^++H), calcd for $C_{25}H_{28}N_2O_9$: 500.

5.1.38. (1*S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-[3-(1,3-benzothiazol-2-ylmethyl)phenyl]-D-glucitol (60)

The title compound was prepared in the same manner as described for **59** using 2-methylthiobenzothiazole instead of 2-chloropyrazine in 47% yield.

^{1}H NMR ($CDCl_3$) δ: 1.77, 1.96, 2.04, 2.09 (each 3H, each s), 3.78 (1H, ddd, J = 2.1, 4.2, 9.4 Hz), 4.08 (1H, dd, J = 2.1, 11.8 Hz), 4.22 (2H, s), 4.24 (1H, dd, J = 4.2, 11.8 Hz), 4.34 (1H, d, J = 9.8 Hz), 5.08 (1H, t, J = 9.8 Hz), 5.16 (1H, t, J = 9.8 Hz), 5.29 (1H, t, J = 9.8 Hz), 7.26–7.38 (4H, m), 7.67–7.84 (4H, m). MS (FAB) m/z: 556 (M^++H), calcd for $C_{28}H_{29}NO_9S$: 555.

5.1.39. (1*S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-[3-(1,3-benzoxazol-2-ylmethyl)phenyl]-D-glucitol (61)

The title compound was prepared in the same manner as described for **59** using 2-chlorobenzoxazole instead of 2-chloropyrazine in 31% yield.

^{1}H NMR ($CDCl_3$) δ: 1.71, 1.99, 2.06, 2.11 (each 3H, each s), 3.80–4.16 (2H, m), 4.25 (2H, s), 4.27 (1H, dd, J = 5.2, 12.8 Hz), 4.39 (1H, d, J = 9.6 Hz), 5.10 (1H, t, J = 9.6 Hz), 5.22 (1H, t, J = 9.6 Hz), 5.31 (1H, t, J = 9.6 Hz), 7.28–7.68 (8H, m). MS (ESI) m/z: 540 (M^++H), calcd for $C_{28}H_{29}NO_{10}$: 539.

5.1.40. (1*S*)-1,5-Anhydro-1-[3-(pyrazin-2-ylmethyl)phenyl]-D-glucitol (13)

The title compound was prepared in the same manner as described for **16** using **59** instead of **58** in 32% yield.

^{1}H NMR (CD_3OD) δ: 3.36–3.56 (5H, m), 3.77 (1H, dd, J = 5.2, 12.0 Hz), 4.16 (1H, d, J = 9.6 Hz), 4.20 (2H, s), 7.19–7.37 (4H, m), 8.42 (1H, d, J = 2.8 Hz), 8.49 (2H, m). MS (ESI) m/z: 332 (M^+), calcd for $C_{17}H_{20}N_2O_5$: 332.

5.1.41. (1*S*)-1,5-Anhydro-1-[3-(1,3-benzothiazol-2-ylmethyl)-phenyl]-D-glucitol (17)

The title compound was prepared in the same manner as described for **16** using **60** instead of **58** in 69% yield.

^{1}H NMR (CD_3OD) δ: 3.35–3.50 (4H, m), 3.67–3.72 (1H, m), 3.88 (1H, dd J = 1.9, 12.2 Hz), 4.14 (1H, d, J = 9.8 Hz), 4.49 (2H, s), 7.32–7.43 (4H, m), 7.48–7.53 (2H, m), 7.91–7.93 (2H, m). MS (FAB) m/z: 388 (M^++H), calcd for $C_{20}H_{21}NO_5S$: 387.

5.1.42. (1*S*)-1,5-Anhydro-1-[3-(1,3-benzoxazol-2-ylmethyl)phenyl]-D-glucitol (18)

The title compound was prepared in the same manner as described for **16** using **61** instead of **58** in 72% yield.

^{1}H NMR (CD_3OD) δ: 3.41–3.48 (2H, m), 3.54–3.58 (2H, m), 3.77 (1H, dd, J = 5.3, 12.0 Hz), 3.86–3.89 (1H, m), 4.17 (1H, d, J = 9.6 Hz), 4.28 (2H, s), 7.31–7.38 (5H, m), 7.44 (1H, s), 7.48–7.62 (2H, m). MS (ESI) m/z: 372 (M^++H), calcd for $C_{20}H_{21}NO_{10}$: 371.

5.1.43. 3-bromo-4-(methoxymethoxy)benzaldehyde (64)

To a cold (0 °C) solution of 3-bromo-4-hydroxybenzaldehyde (**62**) (10.5 g, 52.3 mmol) in DMF (120 mL) was added sodium hydride (60% in mineral oil) (2.14 g, 55.4 mmol) and the mixture was stirred at 0 °C for 15 min. To the reaction mixture was added chloromethylmethylether (4.73 mL, 62.9 mmol) and the mixture was stirred at rt overnight. The reaction mixture was diluted with EtOAc and washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the title compound (**64**) (11.7 g, 91%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 3.53 (3H, s), 5.35 (2H, s), 7.27 (1H, d, J = 8.4 Hz), 7.79 (1H, dd, J = 2.0, 8.4 Hz), 8.09 (1H, d, J = 3.4 Hz), 9.86 (1H, s). MS (FAB) m/z: 245 (M^+), calcd for $C_9H_9BrO_3$: 245.

5.1.44. 3-bromo-5-(methoxymethoxy)benzaldehyde (65)

The title compound was prepared in the same manner as described for **64** using 3-bromo-5-hydroxybenzaldehyde (**63**) instead of **62** in 98% yield.

^{1}H NMR ($CDCl_3$) δ: 3.52 (3H, s), 5.29 (2H, s), 7.15 (1H, d, J = 11.9 Hz), 7.61 (1H, dd, J = 3.4, 8.4 Hz), 7.94 (1H, d, J = 3.4 Hz), 10.42 (1H, s). MS (FAB) m/z: 245 (M^+), calcd for $C_9H_9BrO_3$: 245.

5.1.45. 2-[3-bromo-4-(methoxymethoxy)benzyl]-1-benzothiophene (66)

To a cold (−78 °C) solution of **50** (16.6 g, 124 mmol) in THF (200 mL) was added *n*-BuLi (1.60 M in hexane; 78.5 mL, 124 mmol) and the mixture was stirred at −78 °C for 1.5 h. To the reaction mixture was added a solution of **64** (29.0 g, 118 mmol) in THF (300 mL) and the mixture was stirred at −78 °C for 2 h. To the reaction mixture was added H_2O and Et_2O and the organic layer was separated, dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give alcohol as a pale yellow oil. To a cold (−20 °C) solution of this oil (43.3 g, 114 mmol) in CH_2Cl_2 (800 mL) was added Et_3SiH (36.5 mL, 229 mmol) and $BF_3{\cdot}OEt_2$ (15.2 mL, 120 mmol) and the mixture was stirred at −20 °C for 30 min. To the reaction mixture was added saturated aqueous sodium bicarbonate solution and the organic layer was separated, dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the title compound (**66**) (35.6 g, 86%) as a pale yellow oil.

^{1}H NMR ($CDCl_3$) δ: 3.51 (3H, s), 4.14 (2H, s), 5.22 (2H, s), 7.00 (1H, s), 7.09 (1H, d, J = 4.8 Hz), 7.16 (1H, dd, J = 2.0, 8.4 Hz), 7.22–7.33 (2H, m), 7.47 (1H, d, J = 2.0 Hz), 7.66 (1H, d, J = 7.2 Hz), 7.73 (1H, d, J = 12.0 Hz). MS (FAB) m/z: 364 (M^++H), calcd for $C_{17}H_{15}BrO_2S$: 363.

5.1.46. 2-[3-bromo-5-(methoxymethoxy)benzyl]-1-benzothiophene (67)

The title compound was prepared in the same manner as described for **66** using **65** instead of **64** in 76% yield.

^{1}H NMR ($CDCl_3$) δ: 3.38 (3H, s), 4.22 (2H, s), 5.16 (2H, q, J = 9.0 Hz), 6.93 (1H, d, J = 11.7 Hz), 7.01 (1H, s), 7.16–7.30 (4H, m), 7.59 (1H, dd, J = 2.2, 8.8 Hz), 7.70 (1H, dd, J = 2.9, 13.0 Hz). MS (FAB) m/z: 364 (M^++H), calcd for $C_{17}H_{15}BrO_2S$: 363

5.1.47. (1*S*)-1,5-Anhydro-1-[5-(1-benzothiophen-2-ylmethyl)-2-(methoxymethoxy)phenyl]-2,3,4,6-tetra-*O*-benzyl-D-glucitol (68)

The title compound was prepared in the same manner as described for **24** using **66** instead of **22** in 57% yield.

^{1}H NMR ($CDCl_3$) δ: 3.35 (3H, s), 3.59–3.61 (1H, m), 3.72–3.82 (4H, m), 3.93 (1H, d, J = 9.7 Hz), 4.17 (2H, q J = 17.0 Hz), 4.43 (1H, d, J = 10.7 Hz), 4.55 (2H, q, J = 12.2 Hz), 4.75 (2H, q, J = 10.7 Hz), 4.92 (2H, q, J = 10.7 Hz), 5.04 (2H, q, J = 12.2 Hz), 5.0 (2H, q, J = 7.0 Hz), 6.85–6.88 (2H, m), 6.96 (1H, s), 7.09–7.31 (22H, m), 7.42 (1H, d, J = 2.0 Hz), 7.56 (1H, d, J = 7.6 Hz), 7.55 (1H, d, J = 7.6 Hz). MS (ESI) m/z: 830 (M^++Na), calcd for $C_{51}H_{50}O_7S$: 807.

5.1.48. (1*S*)-1,5-Anhydro-1-[3-(1-benzothiophen-2-ylmethyl)-4-(methoxymethoxy)phenyl]-2,3,4,6-tetra-*O*-benzyl-D-glucitol (69)

The title compound was prepared in the same manner as described for **24** using **67** instead of **22** in 14% yield.

^{1}H NMR ($CDCl_3$) δ: 3.43 (3H, s), 3.45–3.60 (1H, m), 3.72–4.01 (5H, m), 4.15–4.38 (4H, m), 4.51–4.70 (4H,m), 4.83–4.94 (3H, m), 5.23 (2H, s), 6.85–7.40 (26H, m), 7.54 (1H, d, J = 7.6 Hz), 7.64 (1H, d, J = 7.6 Hz). MS (ESI) m/z: 830 (M^++Na), calcd for $C_{51}H_{50}O_7S$: 807.

5.1.49. (1*S*)-1,5-Anhydro-1-[5-(1-benzothiophen-2-ylmethyl)-2-hydroxyphenyl]-2,3,4,6-tetra-*O*-benzyl-D-glucitol (70)

To a cold (0 °C) solution of **68** (21.7 g, 26.9 mmol) in EtOAc (135 mL) was added 4 M HCl solution in EtOAc (135 mL, 540 mmol) and the mixture was stirred at rt overnight. The reaction mixture was evaporated in vacuo and the resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the title compound (**70**) (18.6 g, 91%) as a pale yellow oil.

^{1}H NMR ($CDCl_3$) δ: 3.54–3.58 (1H, m), 3.67–3.77 (4H, m), 3.83–3.97 (2H, m), 4.05–4.17 (2H, m), 4.37–4.48 (3H, m), 4.52–4.62 (2H, m), 4.83–4.95 (3H, m), 6.90–7.70 (28H, m). MS (FAB) m/z: 785 (M^++Na), calcd for $C_{49}H_{46}O_6S$: 762.

5.1.50. (1*S*)-1,5-Anhydro-1-[3-(1-benzothiophen-2-ylmethyl)-4-hydroxyphenyl]-2,3,4,6-tetra-*O*-benzyl-D-glucitol (71)

The title compound was prepared in the same manner as described for **70** using **69** instead of **68** in 82% yield.

^{1}H NMR ($CDCl_3$) δ: 3.44–3.65 (2H, m), 3.70–3.92 (4H, m), 4.13–4.27 (3H, m), 4.37 (1H, d, J = 13.7 Hz), 4.50–4.67 (4H, m), 4.80–4.96 (4H, m), 6.75–7.05 (3H, m), 7.08–7.35 (23H, m), 7.56 (1H, d, J = 9.0 Hz), 7.67 (1H, d, J = 10.8 Hz). MS (FAB) m/z: 761 (M^+-H), calcd for $C_{49}H_{46}O_6S$: 762.

5.1.51. (1*S*)-1,5-Anhydro-1-[5-(1-benzothiophen-2-ylmethyl)-2-hydroxyphenyl]-D-glucitol (14b)

The title compound was prepared in the same manner as described for **8** using **70** instead of **24** in 45% yield.

^{1}H NMR (CD_3OD) δ: 3.39–3.43 (2H, m), 3.44–3.58 (2H, m), 3.67–3.73 (2H, m), 3.86 (1H, dd, J = 1.7, 11.8 Hz), 4.14 (2H, s), 4.57 (1H, d, J = 9.3 Hz), 6.78 (1H, d, J = 8.3 Hz), 7.02 (1H, s), 7.08 (1H, dd, J = 2.0, 7.8 Hz), 7.22–7.24 (1H, m), 7.31 (1H, d, J = 7.8 Hz), 7.64 (1H, d, J = 7.3 Hz), 7.71 (1H, d, J = 7.6 Hz). MS (FAB) m/z: 401 (M^+-H), calcd for $C_{21}H_{22}O_6S$: 402.

5.1.52. (1*S*)-1,5-Anhydro-1-[3-(1-benzothiophen-2-ylmethyl)-4-hydroxyphenyl]-D-glucitol (14f)

The title compound was prepared in the same manner as described for **8** using **71** instead of **24** in 73% yield.

^{1}H NMR (CD_3OD) δ: 3.33–3.46 (4H, m), 3.62–3.68 (1H, m), 3.84 (1H, dd, J = 1.7, 11.8 Hz), 4.02 (1H, d, J = 9.3 Hz), 4.18 (2H, q, J = 15.7 Hz), 6.80 (1H, d, J = 8.3 Hz), 7.03 (1H, d, J = 1.0 Hz), 7.11–7.27 (4H, m), 7.62 (1H, d, J = 7.0 Hz), 7.69 (1H, d, J = 7.0 Hz). MS (FAB) m/z: 401 (M^+-H), calcd for $C_{21}H_{22}O_6S$: 402.

5.1.53. (1*S*)-1,5-Anhydro-1-[5-(1-benzothiophen-2-ylmethyl)-2-methoxyphenyl]-2,3,4,6-tetra-*O*-benzyl-D-glucitol (72)

To a solution of **70** (763 mg, 1.00 mmol) in DMF (10 mL) was added potassium carbonate (207 mg, 1.50 mmol) and iodomethane (0.1 mL, 1.5 mmol). The mixture was stirred at rt overnight. The reaction mixture was diluted with EtOAc and washed with H_2O, brine. The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the title compound (**72**) (736 mg, 95%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 3.58–3.62 (1H, m), 3.71–3.82 (9H, m), 3.92 (1H, d, J = 10.8 Hz), 4.15–4.19 (2H, m), 4.40 (1H, d, J = 10.8 Hz), 4.52 (1H, d, J = 12.0 Hz), 4.61–4.65 (2H, m), 4.84–4.88 (2H, m), 4.94 (1H, d, J = 10.8 Hz), 6.84–6.89 (3H, m), 6.95 (1H, s), 7.11–7.31 (21H, m), 7.42 (1H, d, J = 2.0 Hz), 7.56 (1H, d, J = 7.0 Hz), 7.65 (1H, d, J = 7.0 Hz). MS (ESI) m/z: 799 (M^++Na), calcd for $C_{50}H_{48}O_6S$: 776.

5.1.54. (1*S*)-1,5-Anhydro-1-[3-(1-benzothiophen-2-ylmethyl)-4-methoxyphenyl]-2,3,4,6-tetra-*O*-benzyl-D-glucitol (73)

The title compound was prepared in the same manner as described for **72** using **71** instead of **70** in 92% yield.

^{1}H NMR ($CDCl_3$) δ: 3.47–3.78 (1H, m), 3.87 (3H, s), 4.13–4.29 (6H, m), 4.33 (1H, d, J = 10.5 Hz), 4.49–4.75 (5H, m), 4.84–4.94 (4H, m), 6.86–6.95 (3H, m), 7.06–7.37 (23H, m), 7.58 (1H, d, J = 6.8 Hz), 7.66 (1H, d, J = 7.7 Hz). MS (FAB) m/z: 775 (M^+-H), calcd for $C_{50}H_{48}O_6S$: 776.

5.1.55. (1*S*)-1,5-Anhydro-1-[5-(1-benzothiophen-2-ylmethyl)-2-methoxyphenyl]-D-glucitol (14c)

The title compound was prepared in the same manner as described for **8** using **72** instead of **24** in 29% yield.

^{1}H NMR (CD_3OD) δ: 3.36–3.39 (2H, m), 3.46–3.54 (2H, m), 3.63–3.68 (1H, m), 3.81–3.86 (4H, m), 4.12 (2H, s), 4.69 (1H, d, J = 9.2 Hz), 6.94 (1H, d, J = 8.3 Hz), 7.04 (1H, s), 7.20–7.28 (3H, m), 7.39 (1H, d, J = 2.5 Hz), 7.64 (1H, d, J = 7.6 Hz), 7.71 (1H, d, J = 7.6 Hz). MS (FAB) m/z: 417 (M^++H), calcd for $C_{22}H_{24}O_6S$: 416.

5.1.56. (1*S*)-1,5-Anhydro-1-[3-(1-benzothiophen-2-ylmethyl)-4-methoxyphenyl]-D-glucitol (14g)

The title compound was prepared in the same manner as described for **8** using **73** instead of **24** in 27% yield.

^{1}H NMR (CD_3OD) δ: 3.34–3.45 (4H, m), 3.65–3.69 (2H, m), 3.85 (3H, s), 4.06 (1H, d, J = 9.3 Hz), 4.20 (2H, d, J = 7.3 Hz), 6.96 (1H, d, J = 7.8 Hz), 7.00 (1H, d, J = 1.0 Hz), 7.18–7.31 (4H, m), 7.61 (1H, d, J = 8.3 Hz), 7.69 (1H, d, J = 8.3 Hz). MS (FAB) m/z: 415 (M^+-H), calcd for $C_{22}H_{24}O_6S$: 416.

5.1.57. 2-(3-bromo-4-fluorobenzyl)-1-benzothiophene (74)

The title compound was prepared in the same manner as described for **66** using 3-bromo-4-fluorobenzaldehyde instead of **64** in 36% yield.

^{1}H NMR ($CDCl_3$) δ: 4.16 (2H, s), 7.11 (1H, t, J = 8.8 Hz), 7.14 (1H, s), 7.30 (1H, dd, J = 1.2, 6.8 Hz), 7.33 (1H, dd, J = 1.6, 7.2 Hz), 7.35–7.40 (1H, m), 7.69–7.71 (2H, m), 7.78 (1H, d, J = 7.3 Hz). MS (FAB) m/z: 322 (M^++H), calcd for $C_{10}H_{15}BrFS$: 321.

5.1.58. 2-(3-bromo-4-chlorobenzyl)-1-benzothiophene (75)

The title compound was prepared in the same manner as described for **66** using 3-bromo-4-chlorobenzaldehyde instead of **64** in 48% yield.

^{1}H NMR ($CDCl_3$) δ: 4.19 (2H, s), 7.11 (1H, s), 7.17 (1H, t, J = 9.2 Hz), 7.23–7.38 (4H, m), 7.73 (1H, d, J = 7.4 Hz), 7.82 (1H, d, J = 7.4 Hz). MS (FAB) m/z: 338 (M^++H), calcd for $C_{10}H_{15}BrClS$: 337.

5.1.59. 2-(5-bromo-2-fluorobenzyl)-1-benzothiophene (76)

The title compound was prepared in the same manner as described for **66** using 5-bromo-2-fluorobenzaldehyde instead of **64** in 64% yield.

^{1}H NMR ($CDCl_3$) δ: 4.20 (2H, s), 6.95 (1H, t, J = 9.2 Hz), 7.02 (1H, s), 7.25–7.40 (4H, m), 7.67 (1H, d, J = 7.3 Hz), 7.74 (1H, d, J = 7.3 Hz). MS (FAB) m/z: 322 (M^++H), calcd for $C_{10}H_{15}BrFS$: 321.

5.1.60. 2-(5-bromo-2-chlorobenzyl)-1-benzothiophene (77)

The title compound was prepared in the same manner as described for **66** using 5-bromo-2-chlorobenzaldehyde instead of **64** in 46% yield.

^{1}H NMR ($CDCl_3$) δ: 4.23 (2H, s), 7.14 (1H, s), 7.22 (1H, t, J = 9.6 Hz), 7.27–7.41 (4H, m), 7.69 (1H, d, J = 7.2 Hz), 7.76 (1H, d, J = 7.2 Hz). MS (FAB) m/z: 338 (M^++H), calcd for $C_{10}H_{15}BrClS$: 337.

5.1.61. (1*S*)-1,5-Anhydro-1-[5-(1-benzothiophen-2-ylmethyl)-2-fluorophenyl]-2,3,4,6-tetra-*O*-benzyl-D-glucitol (78)

The title compound was prepared in the same manner as described for **24** using **74** instead of **22** in 22% yield.

^{1}H NMR ($CDCl_3$) δ: 3.60–3.68 (1H, m), 3.73–3.85 (3H, m), 3.92–4.23 (3H, m), 4.42–4.78 (8H, m), 4.83–4.95 (2H, m), 6.85–6.98 (3H, m), 7.05–7.39 (23H, m), 7.54–7.61 (1H, m), 7.62–7.69 (1H, m). MS (ESI) m/z: 787 (M^++Na), calcd for $C_{49}H_{45}FO_5S$: 764.

5.1.62. (1*S*)-1,5-Anhydro-1-[5-(1-benzothiophen-2-ylmethyl)-2-chlorophenyl]-2,3,4,6-tetra-*O*-benzyl-D-glucitol (79)

The title compound was prepared in the same manner as described for **24** using **75** instead of **22** in 34% yield.

^{1}H NMR ($CDCl_3$) δ: 3.61–3.66 (2H, m), 3.71–3.88 (3H, m), 3.95 (1H, d, J = 10.2 Hz), 4.18 (2H, s), 4.37 (1H, d, J = 10.2 Hz), 4.51–4.65 (4H, m), 4.83–4.94 (4H, m), 6.93–6.96 (3H, m), 7.13–7.31 (21H, m), 7.35 (1H, d, J = 4.8 Hz), 7.48 (1H, d, J = 2.4 Hz), 7.58 (1H, d, J = 7.2 Hz), 7.67 (1H, d, J = 7.2 Hz). MS (ESI) m/z: 803 (M^++Na), calcd for $C_{49}H_{45}ClO_5S$: 780.

5.1.63. (1*S*)-1,5-Anhydro-1-[3-(1-benzothiophen-2-ylmethyl)-4-fluorophenyl]-2,3,4,6-tetra-*O*-benzyl-D-glucitol (80)

The title compound was prepared in the same manner as described for **24** using **76** instead of **22** in 61% yield.

^{1}H NMR ($CDCl_3$) δ: 3.42–3.48 (1H, m), 3.55–3.58 (1H, m), 3.72–3.78 (3H, m), 3.83 (1H, d, J = 10.7 Hz), 4.14–4.30 (3H, m), 4.39 (1H, d, J = 10.7 Hz), 4.51–4.67 (3H, m), 4.83–4.94 (4H, m), 6.86–6.90 (1H, m), 6.98 (1H, brs), 7.06–7.37 (24H, m), 7.57–7.60 (1H, m), 7.66–7.69 (1H, m). MS (ESI) m/z: 787 (M^++Na), calcd for $C_{49}H_{45}FO_5S$: 764.

5.1.64. (1*S*)-1,5-Anhydro-1-[3-(1-benzothiophen-2-ylmethyl)-4-chlorophenyl]-2,3,4,6-tetra-*O*-benzyl-D-glucitol (81)

The title compound was prepared in the same manner as described for **24** using **77** instead of **22** in 14% yield.

^{1}H NMR ($CDCl_3$) δ: 3.42–3.48 (1H, m), 3.50–3.64 (1H, m), 3.72–3.78 (4H, m), 3.88 (1H, d, J = 9.6 Hz), 4.19 (1H, d, J = 9.6 Hz), 4.22–4.34 (2H, m), 4.35–4.45 (1H, m), 4.50–4.65 (2H, m), 4.85–4.90 (4H, m), 6.90 (2H, d, J = 7.6 Hz), 6.94 (1H, s), 7.10–7.42 (23H, m), 7.56 (1H, d, J = 7.2 Hz), 7.65 (1H, d, J = 7.2 Hz). MS (ESI) m/z: 803 (M^++Na), calcd for $C_{49}H_{45}ClO_5S$: 780.

5.1.65. (1*S*)-1,5-Anhydro-1-[5-(1-benzothiophen-2-ylmethyl)-2-fluorophenyl]-D-glucitol (14d)

The title compound was prepared in the same manner as described for **8** using **78** instead of **24** in 24% yield.

^{1}H NMR (CD_3OD) δ: 3.34–3.52 (4H, m), 3.66–3.72 (1H, m), 3.87 (1H, d, J = 11.2 Hz), 4.22 (2H, s), 4.52 (1H, d, J = 9.3 Hz), 7.02 (1H.

dd, J = 8.3, 9.8 Hz), 7.06 (1H, s), 7.18–7.32 (3H, m), 7.49 (1H, dd, J = 2.2, 8.8 Hz), 7.66 (1H, d, J = 7.6 Hz), 7.72 (1H, d, J = 7.6 Hz). MS (FAB) m/z: 405 (M^++H), calcd for $C_{21}H_{21}FO_5S$: 404.

5.1.66. (1*S*)-1,5-Anhydro-1-[5-(1-benzothiophen-2-ylmethyl)-2-chlorophenyl]-D-glucitol (14e)

The title compound was prepared in the same manner as described for **8** using **79** instead of **24** in 86% yield.

^{1}H NMR (CD_3OD) δ: 3.41–3.44 (2H, m), 3.49–3.55 (2H, m), 3.66–3.70 (1H, m), 3.86 (1H, d, J = 10.4 Hz), 4.24 (2H, s), 4.73 (1H, d, J = 9.6 Hz), 7.07 (1H, s), 7.21–7.29 (3H, m), 7.34 (1H, d, J = 2.4 Hz), 7.55 (1H, s), 7.66 (1H, d, J = 7.2 Hz), 7.73 (1H, d, J = 7.2 Hz). MS (FAB) m/z: 419 (M^+-H), calcd for $C_{21}H_{21}ClO_5S$: 420.

5.1.67. (1*S*)-1,5-Anhydro-1-[3-(1-benzothiophen-2-ylmethyl)-4-fluorophenyl]-D-glucitol (14h)

The title compound was prepared in the same manner as described for **24** using **80** instead of **24** in 64% yield.

^{1}H NMR (CD_3OD) δ: 3.35–3.49 (4H, m), 3.68 (1H, dd, J = 5.4, 11.7 Hz), 3.87 (1H, dd, J = 1.9, 11.7 Hz), 4.11 (1H, d, J = 9.3 Hz), 4.23 (2H, q, J = 15.6 Hz), 7.05 (1H, s), 7.07 (1H, dd, J = 8.3, 9.8 Hz), 7.21–7.30 (2H, m), 7.35 (1H, ddd, J = 2.2, 4.9, 8.3 Hz), 7.43 (1H, dd, J = 2.2, 7.6 Hz), 7.66 (1H, d, J = 7.6 Hz), 7.72 (1H, d, J = 7.6 Hz). ^{13}C NMR (DMSO-d_6) δ: 29.51, 61.34, 70.30, 74.72, 78.33, 80.68, 81.24, 114.62, 121.61, 122.24, 123.06, 123.82, 124.32, 125.49, 128.31, 130.52, 136.83, 138.90, 139.60, 143.81, 159.58. MS (FAB) m/z: 405 (M^++H), calcd for $C_{21}H_{21}FO_5S$: 404. IR ν: 3309, 3193, 3067, 2973, 2909, 1506, 1084, 1062 cm^{-1}. Anal. Calcd for $C_{21}H_{21}FO_5S$: C, 62.36; H, 5.23; F, 4.70; S, 7.93. Found: C, 62.25; H, 5.47; F, 4.52; S, 7.76.

5.1.68. (1*S*)-1,5-Anhydro-1-[3-(1-benzothiophen-2-ylmethyl)-4-chlorophenyl]-D-glucitol (14i)

The title compound was prepared in the same manner as described for **24** using **81** instead of **24** in 70% yield.

^{1}H NMR (CD_3OD) δ: 3.26–3.52 (4H, m), 3.69 (1H, dd, J = 5.4, 11.9 Hz), 3.87 (1H, dd, J = 2.0, 11.9 Hz), 4.12 (1H, d, J = 9.3 Hz), 4.36 (2H, q, J = 15.8 Hz), 7.01 (1H, s), 7.20–7.29 (2H, m), 7.34 (1H, dd, J = 1.9, 8.3 Hz), 7.40 (1H, d, J = 8.3 Hz), 7.48 (1H, d, J = 1.9 Hz), 7.64 (1H, d, J = 7.8 Hz), 7.73 (1H, d, J = 7.8 Hz). MS (FAB) m/z: 421 (M^++H), calcd for $C_{21}H_{21}ClO_5S$: 420.

5.2. Pharmacology

5.2.1. In vitro pharmacology

5.2.1.1. SGLT2 and SGLT1 inhibition assay. Human, rat, and mouse SGLT2 or SGLT1 full-length complementary deoxyribonucleic acid (cDNA) sequences were cloned and stably transfected into Chinese hamster ovary (CHO) cells using standard techniques as described previously (Katsuno et al. 2007). Cells were seeded into 96-well plates at a density of 3×10^4 cells/well in Ham's F12 medium containing 10% fetal bovine serum (FBS). The cells were used 1 day after plating. Test compounds were initially dissolved in dimethyl sulfoxide (DMSO) and diluted to the desired concentration with sodium assay buffer (140 mM NaCl, 2 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM *N*-2-hydroxyethylpiperazine-*N*'-2-ethanesulfonic acid [HEPES], 5 mM tris–HCl, pH 7.4). After the medium was removed, the cells were preincubated in 100 μl choline assay buffer (NaCl in sodium assay buffer was replaced with the same concentration of choline chloride) at 37 °C for 20 min. They were then incubated in the test compound solution (25 μl) containing ^{14}C-AMG (2.2 μCi/ml) and nonlabeled AMG (final concentration 55 μM) at 37 °C for 2 h. Cells were washed twice with 200 μl ice-cold wash buffer (choline assay buffer containing 10 mM AMG) and then solubilized in 0.5% sodium dodecyl sulphate (SDS) solution (25 μl). The cell lysate was mixed with 75 μl MicroScint MS-40 (Packard Instrument Co., Meriden, CT, USA) and radioactivity was measured using a Top Count Microplate Scintillation Counter (Packard Instrument Co., Meriden, CT, USA).

5.2.2. In vivo pharmacology

5.2.2.1. Animals. Male Sprague–Dawley rats were purchased from Charles River Laboratories Japan (Kanagawa, Japan) at age 5–7 weeks. STZ was dissolved in 50 mM citric acid buffer before intravenous administration at 50 mg/kg. Blood glucose levels were measured in the diabetic rats 1 week later, after which the rats were grouped such that the blood glucose levels were similar in each group. Male Institute of Cancer Research normal and KK-A^y type 2 diabetic mice, which exhibit hyperglycemia, insulin resistance, hyperinsulinemia, hyperlipidemia, and obesity, were purchased from Japan SLC, Inc. (Shizuoka, Japan) and CLEA Japan (Kanagawa, Japan), respectively, at the age of 5–6 weeks. The diabetic mice were also grouped such that each group had similar blood glucose levels. All animals were housed under conventional conditions with controlled temperature, humidity, and light (12-h light–dark cycle) and were provided with a standard commercial diet and water (ad libitum). Animals were handled and cared for in accordance with the *Guide for the Care and Use of Laboratory Animals*, and all procedures were approved by the Animal Ethical Committee of Astellas Pharma Inc.

5.2.2.2. Effect of 14h on urinary glucose excretion in normal mice. 6. 14 h (0.01–10 mg/kg) was administered to non-fasted normal mice, and spontaneously voided urine was collected for 24 h after administration while the animals were kept in metabolic cages. After the urine volume had been measured, the glucose concentration in the urine was measured using the Glucose CII test reagent (Wako, Osaka, Japan).

5.2.2.3. Effect of single administration of 14h in diabetic animals. To investigate its antihyperglycemic effect, **14h** (0.1–1 mg/kg) was administered to STZ-induced type 1 diabetic rats and KK-A^y type 2 diabetic mice in the fed condition. Blood glucose levels were then measured for 8 h under fasting conditions, in order to eliminate the influence of feeding during the experiment.

Acknowledgments

We thank Dr. Susumu Watanuki and Dr. Yasuhiro Yonetoku for their useful advice. We are also grateful to Dr. Atsuo Tahara, Mr. Masanori Yokono, Mr. Daisuke Yamajuku, Ms. Rumi Kihara , Ms. Takako Furukawa and Dr. Fumihiko Ushigome for performing the biological experiments, and members of the Division of Analytical Science Laboratories for elemental analysis and spectral measurements.

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