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N-glucosides as human sodium-dependent glucose cotransporter 2 (hSGLT2) inhibitors

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ABSTRACT

Inhibition of renal sodium-dependent glucose cotransporter 2 (SGLT2) increases urinary glucose excretion (UGE), and thus reduces blood glucose levels in hyperglycemia. A series of N-glucosides was synthesized for biological evaluation as human SGLT2 (hSGLT2) inhibitors. Among these compounds, N-glucoside **9d** possessing an indole core structure showed good in vitro activity (IC_{50} = 7.1 nM against hSGLT2). Furthermore, **9d** exhibited favorable in vivo potency with regard to UGE in rats based on good pharmacokinetic profiles.

The progressive nature of type 2 diabetes makes it difficult to maintain appropriate glycemic control with several glucose-lowering agents.[1] Thus, there is a need for new agents with complementary mechanism of action. Renal glucose reabsorption is mediated predominantly by sodium-dependent glucose cotransporter 2 (SGLT2) and, to a lesser extent, by SGLT1.[2] Inhibitor of SGLT2 increases urinary glucose excretion (UGE) and reduces blood glucose levels in hyperglycemia independently of insulin action.[3–5] Thus, inhibition of SGLT2 can be an attractive therapeutic approach for type 2 diabetes. In addition to the kidney, SGLT1 is expressed in the intestine, heart, and trachea, while SGLT2 is expressed exclusively in the kidney.[6] Therefore, selective inhibition of SGLT2, rather than SGLT1, would be desirable for anti-diabetic agent.[7]

Representative human SGLT2 (hSGLT2) inhibitors are illustrated in Figure 1. After the first disclosure of orally active phenol-O-glucoside hSGLT2 inhibitor **1b** (T-1095),[8] a large number of O-glucosides including **2b** (sergliflozin)[9] have been reported. It is noteworthy that aryl-C-glucosides such as **3**,[10] **4** (dapagliflozin)[11] and **5** (canagliflozin)[12] have been disclosed as metabolically more stable hSGLT2 inhibitors, and they exhibited excellent in vivo potencies based on their improved pharmacokinetic profiles.[7]

The general structures and our design of hSGLT2 inhibitors are depicted in Figure 2.[7] Starting from the phenol-O-glucoside **6** such as **2a**, Bristol–Myers Squibb opened the field of aryl-C-glucoside **7** such as **3** and **4** as metabolically more stable hSGLT2 inhibitors.[10,11] To explore new hSGLT2 inhibitors, we designed aniline-N-glucoside **8** and heteroaromatic-N-glucoside **9**. Herein, we describe the synthesis, in vitro hSGLT2 inhibitory activity, and in vivo profiles of novel N-glucosides.

We first explored the N-glucoside **8**, in which 2-benzylphenol aglycon of **6** was replaced with 2-benzylaniline as shown in Figure 2. Synthesis of the aniline-N-glucoside **8a**, possessing 4-ethyl group on the benzyl substituent like **3**, is described in Scheme 1. The aglycon **12** was synthesized from 1-Bromo-4-ethylbenzene **10**, wherein the *o*-nitrodiphenylcarbinol intermediate **11** was converted to **12** by a two-step reduction sequence. Condensation of aglycon **12** with D-(+)-glucose in refluxing MeOH with ammonium chloride (20 mol %)[13] gave **8a** in 56% yield.[14] In vitro hSGLT2 inhibitory activity and UGE of **8a** are presented in Table 1.[15] Compound **8a** exhibited strong hSGLT2 inhibitory activity (IC_{50} = 3.9 nM) comparable to **3** (IC_{50} = 5.1 nM). Next, the effect of **8a** on UGE in Sprague–Dawley (SD) rats was evaluated when orally administered at a dose of 30 mg/kg. Despite its excellent hSGLT2 inhibitory activity, **8a** was unable to elicit much UGE (93 mg/day) in comparison with **3** (1485 mg/day). One possible explanation for this poor result is the deactivation of **8a** by hydrolysis, because **8a** was easily hydrolyzed under acidic aqueous condition (0.5 N HCl, 37 °C) in our

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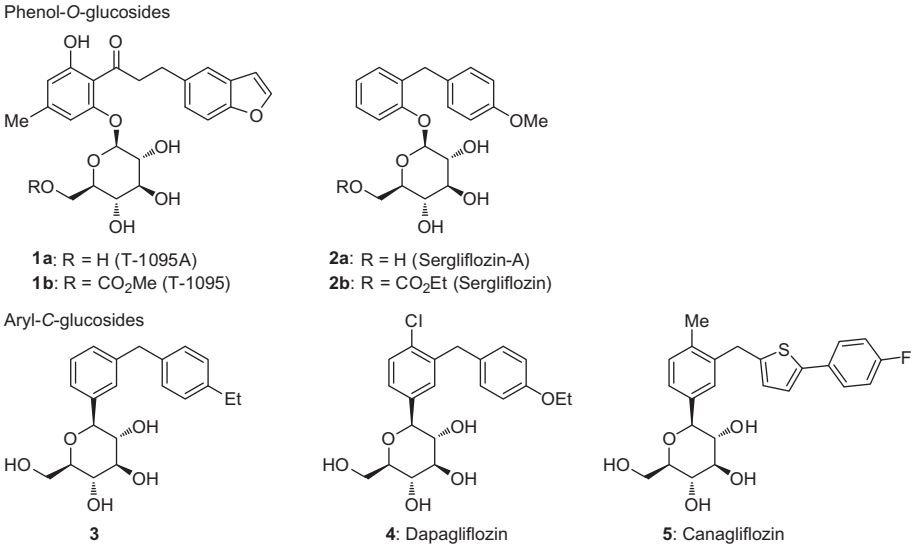


Figure 1. Structures of hSGLT2 inhibitors.

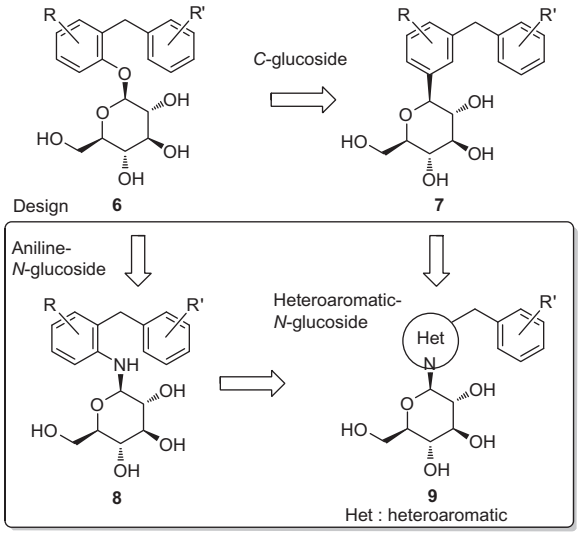


Figure 2. General structures of hSGLT2 inhibitors and our design for novel N-glucoside.

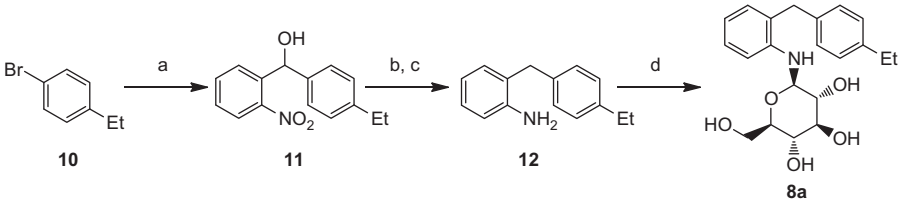
preliminary experiments (data not shown),[16] and in fact, aglycon **12** was observed in the pharmacokinetic studies of **8a** in rats.

Aiming at more stable N-glucosides, we next designed a series of heteroaromatic-N-glucoside **9**, of which the key concept was to combine aryl-C-glucoside **7** and aniline-N-glucoside **8** as shown in Figure 2. Synthesis of the heteroaromatic-N-glucosides **9a**–**9f** is outlined in Scheme 2.[17] As a N-glucosylation method of heteroaromatic aglycons, a patent literature reports that benzimidazole-2-thione is silylated by *N,O*-bis(trimethylsilyl)acetamide (BSA) followed by coupling with 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose **14** in the presence of trimethylsilyl triflate (TMSOTf).[18] Using this method, desired protected heteroaromatic-N-glucosides **15a**–**15d** could be obtained from their corresponding aglycons **13a**–**13d**, respectively, although in poor to moderate yields (4–44%). Then **15a**–**15d** were deprotected with sodium methoxide to give the target compounds **9a**–**9d**.[19,20] The coupling reaction of indazole **13e** with **14** mainly generated 2-glucosylated product **15e** accompanied by small amount of 1-isomer **15f** as an inseparable mixture. After deprotection of the mixture, **9e** and **9f** were successfully obtained in 42% and 5% yields (based on **13e**), respectively.[21]

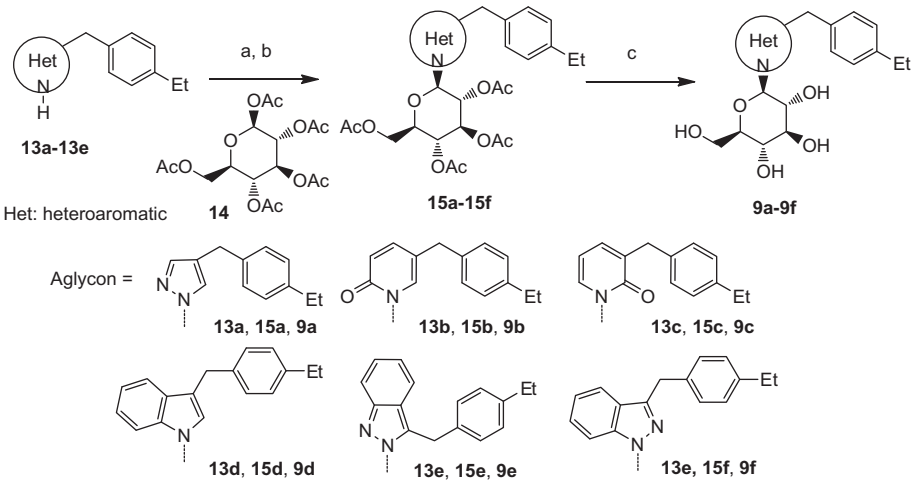
Table 1
SAR exploration of aniline- and heteroaromatic-N-glucosides[15]

Compound	hSGLT2 IC_{50} (nM)[a]	UGE (mg/day)[b]
8a	3.9	93 ± 27
9a	381	ND[c]
9b	163	ND
9c	6671	ND
9d	7.1	1830 ± 75
9e	1098	ND
9f	69	ND
3	5.1	1485 ± 201

[a] These data were obtained by a single determination performed in duplicate.
[b] Each compound was orally administered at a dose of 30 mg/kg to male Sprague–Dawley (SD) rats. Urinary glucose excretion (UGE) data over 24 h were normalized per 200 g body weight. Values are expressed as mean ± S.E.M. (n = 3).
[c] ND = no data.



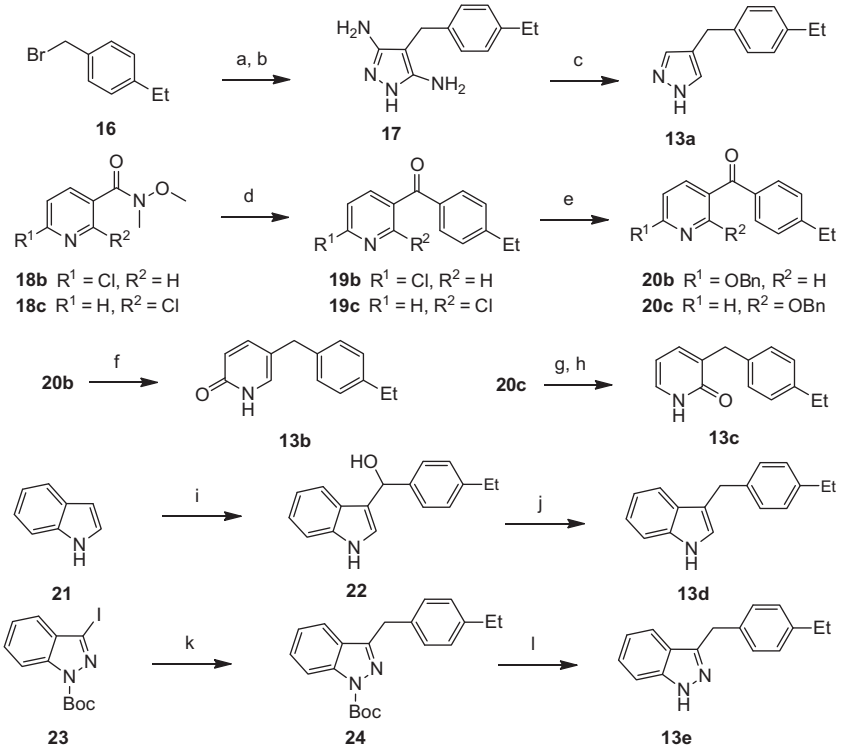
Scheme 1. Synthesis of aniline-N-glucosides **8a**. Reagents and conditions: (a) *n*-BuLi, THF, −78 °C, then *o*-nitrobenzaldehyde, THF, −78 to 0 °C (27%); (b) H_2, Pd/C, EtOH, rt (100%); (c) Et_3SiH, $BF_3{\cdot}Et_2O$, MeCN,−78 °C to rt (75%); (d) D-(+)-glucose, NH_4Cl, MeOH, reflux (56%).



Scheme 2. Synthesis of heteroaromatic-N-glucosides **9a**–**9f**. Reagents and conditions: (a) *N*,*O*-bis(trimethylsilyl)acetamide, MeCN, 60 °C; (b) **14**, trimethylsilyl triflate, 1,2-dichloroethane, 80 °C (**15a** 44%, **15b** 37%, **15c** 4%, **15d** 17%, two steps); (c) NaOMe, MeOH, rt (**9a** 78%, **9b** 82%, **9c** 48%, **9d** 48%) (**9e** 42% and **9f** 5% based on **13e**, respectively).

Synthesis of aglycons **13a**–**13e** is described in Scheme 3. Pyrazole **13a** was synthesized via double deamination reaction of diaminopyrazole **17** by Echevarría's method.[22] In the cases of pyridones **13b** and **13c**, the intermediates **20b** and **20c** were prepared by reaction of Weinreb amides **18b**[23] and **18c**[24] with 4-ethylphenylmagnesium bromide, followed by substitution reaction of **19b** and **19c** with sodium benzyloxide, respectively. Then, aglycons **13b** and **13c** were obtained by reduction of ketone and debenzylation of **20b** and **20c**, respectively. Indole **13d** was synthesized by reduction of carbinol **22**, which was prepared from indole **21** and 4-ethylbenzaldehyde using Zhou's method.[25] Indazole **13e** was obtained by Negishi cross coupling reaction of 1-*tert*-buthoxycarbonyl-3-iodoindazole **23** with 4-ethylbenzylzinc bromide, followed by deprotection of **24**.[26]

Biological evaluations of heteroaromatic-N-glucosides **9a**–**9f** are presented in Table 1.[15] Pyrazole derivative **9a** exhibited weak hSGLT2 inhibitory activity (IC_{50} = 381 nM). Of the pyridones, **9b** showed moderate activity (IC_{50} = 163 nM), which was approximately 40-fold stronger than **9c** (IC_{50} = 6671 nM). The carbonyl group of **9c** is speculated to cause the undesired spatial orienta-



Scheme 3. Synthesis of aglycons **13a**–**13e**. Reagents and conditions: (a) malononitrile, K_2CO_3, *n*Bu_4NBr, toluene, rt (35%); (b) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux (69%); (c) H_3PO_2 aq, $NaNO_2$, 5 °C to rt (37%); (d) 4-ethylphenylmagnesium bromide, THF, 0 °C (**19b** 72%, **19c** 72%); (e) benzylalchol, NaH, DMF, rt (**20b** 77%, **20c** 41%); (f) $NH_2NH_2{\cdot}H_2O$, KOH, ethylene glycol, 190 °C (44%); (g) $NaBH_4$, EtOH, rt; (h) H_2, Pd/C, cHCl, MeOH, rt (27%, two steps); (i) 4-ethylbenzaldehyde, NaOH, MeOH, rt (70%); (j) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2,−78–0 °C (75%); (k) 4-ethylbenzylzinc bromide, $Pd_2(dba)_3$, tri(2-furyl)phosphine, DMF, THF, 0 °C to rt (70%); (l) NaOMe, MeOH, rt (61%).

Table 2
Pharmacokinetic parameters of **8a** and **9d** in SD rats

Compound	8a	9d
Dose (mg/kg; iv)	3	3
$t_{1/2}$ (h)	0.58	3.0
AUC_{0-inf} (μg h/mL)	0.41	8.7
CL_{tot} (L/h/kg)	7.4	0.35
Vd_{ss} (L/kg)	4.5	1.3
Dose (mg/kg; po)	10	10
$t_{1/2}$ (h)	0.43	2.9
t_{max} (h)	0.25	0.5
C_{max} (μg/mL)	0.43	2.0
AUC_{0-inf} (μg·h/mL)	0.23	17
F (%)	17	59

tion between the glucose moiety and the distal phenyl group. The N-glucoside **9d** possessing an indole core structure showed good hSGLT2 inhibitory activity (IC_{50} = 7.1 nM). The hSGLT1 inhibitory activity of **9d** was also evaluated, and IC_{50} was 1956 nM (hSGLT1/hSGLT2 ratio = 275). Thus, **9d** was found to be a potent and selective hSGLT2 inhibitor. As for indazoles, the 2-glucosylated isomer **9e** exhibited very weak activity (IC_{50} = 1098 nM), whereas its 1-isomer **9f** was moderately active (IC_{50} = 69 nM). Similar to the case of the C-glucoside hSGLT2 inhibitors,[7b] 1,3-orientation of the N-glucose moiety relative to the distal phenyl ring is considered to be preferable rather than 1,2-substitution. Next, the effect of indole-N-glucoside **9d** on UGE in SD rats was evaluated. As expected, **9d** demonstrated improved oral activity (UGE = 1830 mg/day), which is 20-fold as potent as that of **8a** (UGE = 93 mg/day), and furthermore, comparable to that of aryl-C-glucoside **3** (UGE = 1485 mg/day). As shown in Table 2, this large enhancement of in vivo potency of **9d** relative to **8a** was clearly supported by the pharmacokinetic results, wherein **9d** showed favorable profiles such as lower clearance, higher AUC, and better bioavailability. We attribute these enhanced in vivo profiles of **9d** in part to the inherent stability of the C–N glucosidic bond against hydrolysis, because **9d** was stable under acidic aqueous condition (0.5 N HCl, 37 °C) in our preliminary experiments (data not shown), and no aglycon **13d** was observed in the pharmacokinetic studies of **9d** in rats.

In summary, we synthesized a series of N-glucosides and evaluated their hSGLT2 inhibitory activities. The key concept of heteroaromatic-*N*-glucoside **9** was the combination of aryl-C-glucoside **7** and aniline-*N*-glucoside **8** to improve the stability of the C–N glucosidic bond. As a result, indole-N-glucoside **9d** was identified as a novel class of selective hSGLT2 inhibitor with favorable both in vitro and in vivo potencies. Encouraged by these findings, we started the more detailed SAR studies around **9d**. Further exploration will be reported in due course.

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13. Reactions without any additives in refluxing MeOH were sluggish and finally led to a complex mixture. There is a patent literature, in which ammonium sulfate is used as an additive; see Tam, T. F.; Karimian, K.; Leung-Toung, R. C. S. H.; Zhao, Y.; Wodzinska, J. M.; Li, W.; Lowrie, J. N. *Eur. Pat. Appl.* EP1348710, **2003**; *Chem. Abstr.* **2003**, *139*, 276904.
14. The anomeric stereochemistry in **8a** is β-configuration, which was confirmed by the coupling constant (J = 8.4 Hz) between anomeric C–H and adjacent C–H in ^{1}H NMR studies (D_2O exchange in DMSO-d_6).
15. (a) Sodium-dependent glucose uptake in CHO cells expressing hSGLT1 and hSGLT2; parental CHOK cells expressing hSGLT2 and hSGLT1 were used in these experiments. For the uptake assay, cells were seeded into 24-well plates, and were post-confluent on the day of assay. Cells were rinsed one time with 400 μL Assay Buffer (137 mM NaCl, 5 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 50 mM HEPES, 20 mM Tris Base, pH 7.4), and were pre-incubated with the solutions of compounds (250 μL) for 10 min at 37 °C. The transport reaction was initiated by addition of 50 μL AMG/^{14}C-AMG solution (16.7 μ Ci; final concentration, 0.3 mM for CHOK-hSGLT1 and 0.5 mM for CHOK-hSGLT2, respectively), and incubated for 120 min at 37 °C. After the incubation, the AMG uptake was halted by aspiration of the incubation mixture followed by immediate washing three times with PBS. The cells were solubilized in 0.3 N NaOH of 300 μL and the radioactivity associated with the cells was monitored by a liquid scintillation counter (Quantasmart™ (Packard, Boston, MA, USA)). Inhibitory concentration of 50% (IC_{50}) was calculated by nonlinear least squares analysis using a four-parameter logistic model (Prism version 4; GraphPad Software, San Diego, CA, USA); see Dudash, J., Jr.; Zhang, X.; Zeck, R. E., Johnson, S. G.; Cox, G. G.; Conway, B. R.; Rybczynski, P. J.; Demarest, K. T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5121; (b) Rat UGE Study; male SD rats aged 4-5 weeks were obtained from Japan SLC (Shizuoka, Japan) and were used for experiments at 6 weeks of age after acclimation period. The animals were divided into experimental groups matched for body weight (n = 3). The compounds were prepared in vehicles as suspension or solution. UGE studies were performed after two-day acclimation period in metabolic cages. The compounds or vehicle were orally administered at a dose of 30 mg/kg in 0.2% CMC/0.2% Tween 80. Urine samples were collected for 24 h using metabolic cages to measure urinary glucose excretion. Urine glucose contents were determined by an enzymatic assay kit (UGLU-L, Serotec, Hokkaido, Japan). All animals were allowed free access to a standard pellet diet (CRF1; Oriental Yeast Co., Ltd, Tokyo, Japan) and tap water..
16. Pigman et al. reported that glucosylaniline underwent hydrolysis or isomerization in aqueous solutions; see Pigman, W.; Cleveland, E. A.; Couch, D. H.; Cleveland, J. H. *J. Am. Chem. Soc.* **1976**, *1951*, 73. Although **8a** was hydrolyzed under acidic aqueous condition, it remained stable under the assay condition of hSGLT inhibitory activities (pH 7.4; see Ref. 15a).
17. The stereochemistry of **9a**–**9f** at the anomeric center was determined as β-configuration by the coupling constant between anomeric C–H and adjacent C–H in ^{1}H NMR studies (J = 8.8–9.3 Hz in DMSO-d_6).
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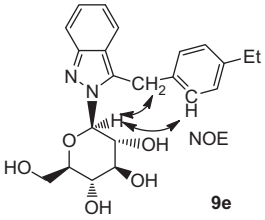
19. In the cases of pyridones **15b** and **15c**, N-glucosylated products were obtained. These N-glucosides were confirmed by the presence of carbonyl absorptions in the IR spectrum of the corresponding deacetylated compounds **9b** and **9c** (1667 cm^{-1} and 1650 cm^{-1}, respectively).
20. *Synthesis of 3-(4-ethylphenylmethyl)-1-(β-D-Glucopyranosyl)indole* ***9d*** *from* ***13d***: To a solution of **13d** (920 mg, 3.9 mmol) in MeCN (30 mL) was added BSA (>75%, 1.6 mL, ca. 4.7 mmol) and the mixture was stirred at 60 °C for 3 h under argon atmosphere. After being cooled to ambient temperature, the solvent was removed by evaporation and the resulting residue was dissolved in dichloroethane (35 mL). Then, **14** (2.5 g, 6.4 mmol) and TMSOTf (1.1 mL, 6.1 mmol) were added to the solution, and the reaction mixture was stirred at 80 °C for an hour followed by at 60 °C for 12 h under argon atmosphere. After being cooled to ambient temperature, the reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution and extracted with AcOEt. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and purified by silica gel column chromatography (hexane: AcOEt = 98: 2–50:50) to give **15d** (315 mg, 17%) as a powder. NaOMe (28% MeOH solution, 5 drops) was added to a stirred solution of **15d** (300 mg, 0.53 mmol) in MeOH (10 mL)–THF (5 mL) at room temperature. After 30 min, the reaction mixture was concentrated under reduced pressure, and purified by silica gel column chromatography ($CHCl_3$: MeOH = 100: 0–86: 14) to give **9d** (145 mg, 48%) as a

powder. APCI-Mass *m*/*z* 415 (M+NH_4). ^{1}H NMR (DMSO-d_6) δ 1.14 (t, *J* = 7.5 Hz, 3H), 2.54 (q, *J* = 7.5 Hz, 2H), 3.20–3.48 (m, 4H), 3.63–3.73 (m, 2H), 3.97 (s, 2H), 4.51 (t, *J* = 5.5 Hz, 1H), 5.07 (d, *J* = 5.1 Hz, 1H), 5.15 (d, *J* = 5.0 Hz, 1H), 5.16 (d, *J* = 5.9 Hz, 1H), 5.36 (d, *J* = 9.0 Hz, 1H), 6.99 (t, *J* = 7.3 Hz, 1H), 7.08–7.12 (m, 3H), 7.21 (d, *J* = 7.9 Hz, 2H), 7.24 (s, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H).

21. In the ^{1}H NMR studies of **9e**, NOEs were observed as shown below.



9e

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