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N-Arylmethylaminoquercitols, a new series of effective antidiabetic agents having α-glucosidase inhibition and antioxidant activity

Wisuttaya Worawalai, Sumrit Wacharasindhu, Preecha Phuwapraisirisan *

Natural Products Research Unit, Department of Chemistry, Faculty of Science, Chulalongkorn University, Bangkok 10330, Thailand

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ABSTRACT

A new series of *N*-arylalkylaminoquercitols were synthesized by reductive amination of aminoquercitol bisacetonide **5** and a variety of aryl aldehydes. The targeted *N*-substituted aminoquercitols having phenolic moiety (**7a**–**7c**) displayed significantly enhanced α-glucosidase inhibition, which is 26–32 times more potent than that of the unmodified aminoquercitol **6**. In addition, compounds **7a**–**7c** also retained antioxidant activity with relatively more pronounced potency than their original phenolics. This recent finding suggests an approach to develop effective antidiabetic agents by incorporating antioxidative moiety into aminocyclitol core structure.

Patients with diabetes usually suffer from several complications such as neuropathy, blindness, nephropathy and cardiovascular diseases. Once prolonged hyperglycemia develops, the over excess of reactive radicals produced from autooxidation of glucose triggers the dysfunction of microvascular system.[1] Therefore, effective therapy for diabetes and its complications requires simultaneous suppression of both hyperglycemia and reactive radicals. This approach prompted us to synthesize a series of quercitylcinnamates (Scheme 1) as new antidiabetic agents having dual functions; lowering hyperglycemia by inhibiting α-glucosidase and scavenging reactive radicals.[2] The structure of quercitylcinnamate comprises (+)-*proto*-quercitol as a sugar mimic, which is connected by ester bond to a series of cinnamic acids as radical scavengers. We found that the installation of these cinnamic moieties can greatly attenuate glucose level by inhibiting α-glucosidase, in addition to their inherent antioxidation property. However, the vulnerability of ester bond between quercityl and cinnamate moieties under human condition possibly makes impractical for further applications.

To circumvent this problem, we turned our attempt to link quercitol and antioxidative phenolic moieties through C–N amine bond (Scheme 2), which is expected to be more resistant than ester linkage. In addition, the replacement of hydroxyl group in (+)-*proto*-quercitol by amino residue is expected to enhance α-glucosidase inhibition of the synthesized bioconjugates, possibly by tight binding with active site of the enzyme.[3] This postulation was also supported by previous reports of *N*-arylalkylaminocyclitols (Scheme 1) as potent glycosidase inhibitors.[4] Although a variety of aminocyclitols have been synthesized,[5] other related bioactivities have rarely been reported. Using the proposed strategy, we herein synthesize a new series of *N*-arylalkylaminoquercitols and evaluate their α-glucosidase inhibition and antioxidation activity.

(+)-*proto*-Quercitol (**1**) used as the starting material was obtained from the stems of *Arfeuillea arborescens*. The desired aminoquercitol bisacetonide **5** was synthesized from **1** by applying the methodology[6] previously described (Scheme 3). Initially, the hydroxyl groups in **1** were protected by $Me_2C(COMe)_2$ in the presence of *p*-TsOH, therefore exclusively yielding bisacetonide **2** (87%). The remaining hydroxyl group in **2** was thus converted to the more reactive mesyl group in **3** prior to azidation with NaN_3 to afford the azide **4** with inversion of configuration at C-1. This observation indicated that the replacement of mesyl group by azide ion (N_3^-) possibly proceeds by S_N2 fashion. Finally, the desired product **5** was obtained by azide reduction using $LiAlH_4$. The deprotected aminoquercitol **6** was also prepared from **5**, under acid condition, for bioactivity evaluation.

Having the desired aminoquercitol bisacetonide **5** in hand, a series of targeted bioconjugates were synthesized by reductive amination between **5** and aryl aldehydes (**a**–**c** and **e**–**h**, Fig. 1).[7] Reaction of **5** and 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (**a**), an antioxidant BHT-like motif, generated *N*-arylmethylaminoquercitol **7a**, after deprotection of bisacetonide (Table 1). Two

* Corresponding author. Tel.: +66 2 2187624; fax: +66 2 2187598.
E-mail address: preecha.p@chula.ac.th (P. Phuwapraisirisan).

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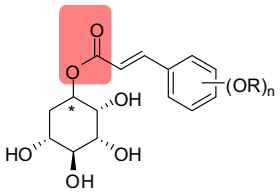
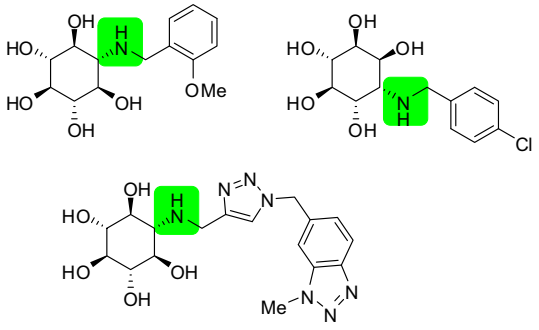
0960-894X/

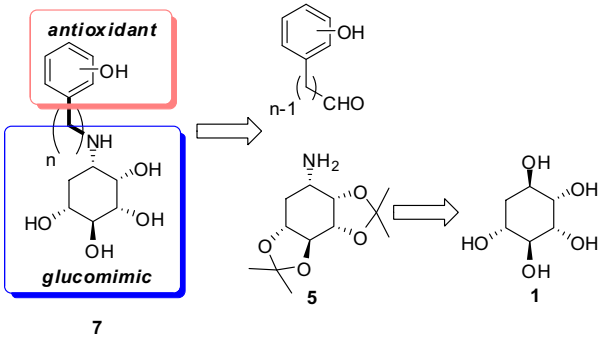
Our previous work: *quercityl cinnamates*



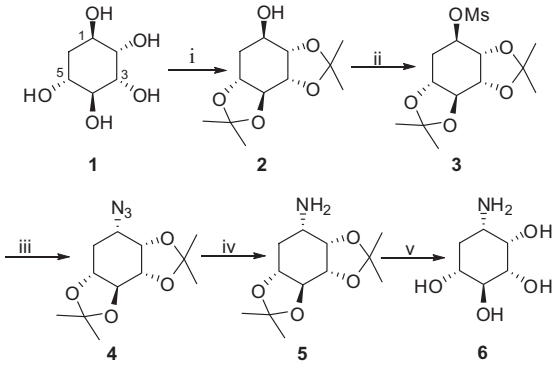
Other related works: *N-arylalkylaminocyclitols*



Scheme 1.



Scheme 2. Retrosynthesis of *N*-arylalkylaminoquercitols **7**.



Scheme 3. Reagents and conditions: (i) $Me_2C(OMe)_2$, DMF, *p*-TsOH, 87%; (ii) $MeSO_2Cl$, Et_3N, DMAP, 79%; (iii) NaN_3, DMF, 15-crown-5-ether, 100 °C, 75%; (iv) $LiAlH_4$, 81%; (v) TFA/MeOH, Dowex 50W-X8 (H^+), 69%.

related analogues (**7b** and **7c**) having phenolic moiety were also prepared using identical protocol.

To gain insight into the relationship between *N*-aryl moiety and inhibitory effect, other aryl (**e** and **f**) and heterocyclic (**g** and **h**) residues were also introduced into aminoquercitol bisacetonide

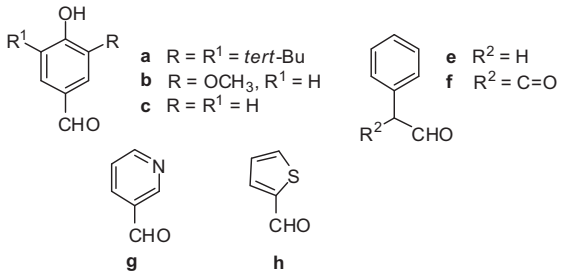
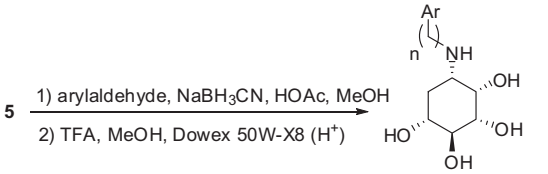


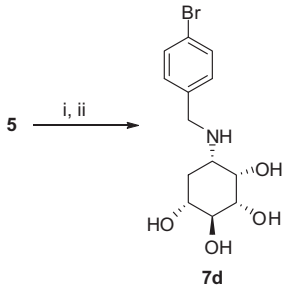
Figure 1. Aldehydes used in reductive amination with aminoquercitol bisacetonide (**5**).

Table 1
Synthesis of arylalkylaminoquercitols (**7a**–**7c** and **7e**–**7h**)



Entry	Arylaldehyde	Product	% Yield[a]
1	**a**	**7a**	52
2	**b**	**7b**	50
3	**c**	**7c**	65
4	**e**	**7e**	34
5	**f**	**7f**	50
6	**g**	**7g**	85
7	**h**	**7h**	10

[a] Isolated yield calculated from two step reactions.



Scheme 4. Reagents and conditions: (i) 4-bromobenzyl bromide, TEA, DMF, 72%; (ii) 1.25 M HCl/MeOH, Dowex 50W-X8 (H^+), 29%.

5. The *N*-arylethylaminoquercitols (**7e**–**7f**) and *N*-arylmethylaminoquercitols (**7g**–**7h**) were successfully implemented in a good yield by reductive amination using $NaCNBH_3$. In addition, the *N*-(4-bromobenzyl)aminoquercitol (**7d**) was also synthesized by nucleophilic substitution of **5** and 4-bromobenzyl bromide (Scheme 4).

All *N*-arylalkylaminoquercitols **7a**–**7h** were evaluated for α-glucosidase inhibition[8] and radical scavenging[2] (Table 2). Of arylalkylaminoquercitols examined, **7a** (Fig. 2) displayed most potent inhibition against α-glucosidase with IC_{50} value of 89.1 μM. The slightly weaker inhibitions were also observed in **7b** (IC_{50} 94.4 μM) and **7c** (IC_{50} 110.6 μM), whose structure comprises phenolic moieties. Noticeably, the introduction of antioxidative phenolics to aminoquercitol core structure caused 26–32

Table 2
Glucosidase inhibition and radical scavenging of synthesized compounds

Compound	α-Glucosidase inhibition (IC_{50}, μM)	Radical scavenging (SC_{50}, mM)
6	2890	NA[a]
7a	89.1	0.4
7b	94.4	2.1
7c	110.6	16.2
7d	3145	NA
7e	1350	NA
7f	3010	NA
7g	NA[a]	NA
7h	NA	NA
Acarbose®	480	NA
a	NT[b]	1.4
b	NT	4.9
c	NT	NA

[a] Not active, inhibition against α-glucosidase less than 30% at concentration of 10 mg/mL or radical scavenging less than 20% at concentration of 5 mg/mL.
[b] Not tested.

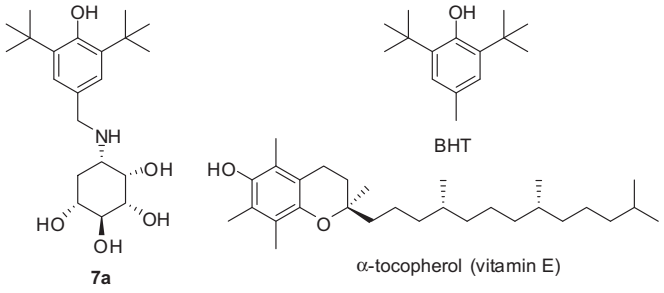


Figure 2.

times more improved inhibition than the unmodified starter (**6**). Conversely, the incorporation of heterocyclic and other aryl residues into aminoquercitol, led to very weak or no inhibitions in **7d**–**7h**.

On evaluation of radical scavenging activity, the phenolic-incorporated aminoquercitols **7a**–**7c** showed SC_{50} values in range of 0.4–16 mM whereas compounds **7d**–**7h** were not active. Interestingly, the scavenging activities of **7a**–**7c** were 2–3 times higher than those of their original phenolics (**a**–**c**).

Noticeably, α-glucosidase inhibitory potency of *N*-arylmethylaminoquercitols **7a**–**7c** is likely to be depend on antioxidative moieties introduced. This observation was supported by the most potent α-glucosidase inhibitor **7a**, whose structure comprises the most effective antioxidative motif **a** (SC_{50} 1.4 mM). In fact, the structure **a** is nearly identical to BHT (butylhydroxytoluene, Fig. 2), a well recognized antioxidant used in a wide variety of applications. Although various *N*-arylalkylaminocyclitols have been synthesized,[3,4,9] none of them has been examined for radical scavenging activity. The finding of enhanced α-glucosidase inhibition of *N*-arylmethylaminoquercitols **7a**–**7c** suggested a possible approach capable of improving this inhibition in other aminocyclitols by incorporating potent antioxidative motifs such as α-tocopherol (vitamin E, Fig. 2).

In summary, we have synthesized a new series of *N*-arylalkylaminoquercitols (**7a**–**7h**) by reductive amination of aminoquercitol bisacetonide **5** and arylaldehydes (**a**–**h**). The incorporation of phenolic moieties (**a**–**c**) into aminoquercitol core structure not only markedly improved α-glucosidase inhibition but also enhanced radical scavenging activity. Their unique dual functions would make them more intriguing for diabetes therapy as they concomitantly suppress hyperglycemia and prevent the onset of complications triggered by over excess of reactive radicals.

Acknowledgments

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Supplementary data

Supplementary data (^1H and ^{13}C NMR spectra of compounds **7a**–**7h**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.04.033.

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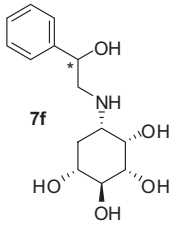
7. *General procedure for reductive amination and deprotection of bisacetonide:* To a solution of aminoquercitol bisacetonide **5** (1 equiv) in methanol (1.0 mL/0.1 mmol of **5**) under an atmosphere of N_2 was added sodium cyanoborohydride (2 equiv), acetic acid (4 μL/0.05 mmol of **5**) and aldehyde **a** (1.5 equiv). After stirring at ambient temperature for 24 h, the reaction mixture was quenched with water, concentrated and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford crude product, which was subsequently purified by silica gel or Sephadex LH-20 column chromatography to afford the bisacetonide.
To a solution of the bisacetonide in 5% TFA–MeOH was stirred at room temperature for 2 h. The reaction mixture was evaporated to dryness, dissolved in H_2O, loaded onto Dowex 50W-X8 (H^+) column, which was initially eluted with H_2O followed by 50% NH_4OH. Fractions eluted with 50% NH_4OH were lyophilized to give **7a**. Other *N*-arylalkylaminoquercitols (**7b**–**7c** and **7e**–**7h**) were also synthesized using the aforementioned protocol.
N-(3,5-Di-tert-butyl-4-hydroxybenzyl)-epi-aminoquercitol (**7a**): Yellow oil. ^1H NMR (CD_3OD, 400 MHz) δ 7.05 (br s, 2H), 4.00 (s, 1H), 3.66 (d, J = 12.0 Hz, 1H), 3.56 (d, J = 12.0 Hz, 1H), 3.43 (dd, J = 8.0, 8.0 Hz, 1H), 3.26 (m, 1H), 3.15 (dd, J = 12.0, 4.0 Hz, 1H), 2.59 (br d, J = 12.0 Hz, 1H), 1.86 (m, 1H), 1.56 (m, 1H), 1.32 (br s, 18H); ^{13}C NMR (CD_3OD, 100 MHz) δ 154.6, 139.4, 130.8, 126.3, 76.4, 75.1, 72.0, 70.8, 55.0, 51.5, 35.6, 34.1, 30.8, 30.8; HRMS m/z 382.2582 $[M+H]^+$ (calcd for $C_{21}H_{36}NO_5$, 382.2593).
N-(4-Hydroxy-3-methoxybenzyl)-epi-aminoquercitol (**7b**): Pale yellow oil. ^1H NMR (CD_3OD, 400 MHz) δ 7.03 (br s, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 4.14 (br s, 1H), 3.97 (m, 1H), 3.90 (m, 1H), 3.86 (s, 3H), 3.55 (t, J = 10.0 Hz, 1H), 3.38 (m, 1H), 3.29 (m, 1H), 2.97 (br d, J = 12.0 Hz, 1H), 2.01 (m, 1H), 1.78 (m, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 149.3, 148.0, 127.6, 123.4, 116.5, 114.0, 76.0, 74.5, 71.5, 69.9, 56.6, 55.3, 50.4, 32.6; HRMS m/z 300.1440 $[M+H]^+$ (calcd for $C_{14}H_{22}NO_6$, 300.1447).
N-(4-Hydroxybenzyl)-epi-aminoquercitol (**7c**): White solid. ^1H NMR (D_2O, 400 MHz) δ 7.01 (d, J = 8.0 Hz, 2H), 6.61 (d, J = 8.0 Hz, 2H), 3.93 (br s, 1H), 3.61–3.71 (m, 2H), 3.13–3.32 (m, 3H), 2.77 (br d, J = 12.0 Hz, 1H), 1.80 (br s, 1H), 1.43 (m, 1H); ^{13}C NMR (D_2O, 100 MHz) δ 156.6, 130.9, 126.3, 116.0, 74.2, 72.5, 69.7, 68.7, 52.9, 48.5, 30.9; HRMS m/z 270.1339 $[M+H]^+$ (calcd for $C_{13}H_{20}NO_5$, 270.1341).

N-(4-Bromobenzyl)-epi-aminoquercitol (**7d**): White solid. ^{1}H NMR (D_2O+2 drops of CD_3OD, 400 MHz) δ 7.36 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 3.94 (br s, 1H), 3.63–3.74 (m, 2H), 3.21–3.34 (m, 2H), 3.15 (m, 1H), 2.70 (br d, J = 11.6 Hz, 1H), 1.81 (m, 1H), 1.42 (q, J = 12.0 Hz, 1H); ^{13}C NMR (D_2O+2 drops MeOD, 100 MHz) δ 135.3, 131.8, 130.8, 121.5, 74.2, 72.5, 69.8, 68.9, 53.1, 48.5, 31.3; HRMS m/z 332.0498, 334.0479 $[M+H]^+$ (calcd for $C_{13}H_{19}{}^{79}BrNO_4$, 332.0497 and $C_{13}H_{19}{}^{81}BrNO_4$, 334.0477).

N-Phenylethyl-epi-aminoquercitol (**7e**): Colorless oil. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.12–7.23 (m, 5H), 3.97 (br s, 1H), 3.43 (dd, J = 9.2, 9.2 Hz, 1H), 3.31 (m, 1H), 3.19 (m, 1H), 2.78–2.99 (m, 5H), 1.89 (m, 1H), 1.61 (q, J = 12.0 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 139.6, 129.8, 129.7, 127.8, 76.0, 74.5, 71.5, 70.1, 56.0, 48.3, 35.3, 32.7; HRMS m/z 268.1543 $[M+H]^+$ (calcd for $C_{14}H_{22}NO_4$, 268.1549).

N-(Phenylhydroxyethyl)-epi-aminoquercitol (**7f**): Yellow oil. ^{1}H NMR (D_2O, 400 MHz) δ 7.25–7.32 (m, 5H), 4.89 (dd, J = 12.0, 4.0 Hz, 1H), 4.08 (br d, J = 12.0 Hz, 1H), 3.11–3.44 (m, 6H), 2.03 (m, 1H), 1.71 (m, 1H); ^{13}C NMR (D_2O, 100 MHz) δ 139.6, 129.1, 129.1, 126.1, 73.8, 71.9, 69.1, 67.6, 67.4, 54.8, 50.9, 29.4; HRMS m/z 284.1497 $[M+H]^+$ (calcd for $C_{14}H_{22}NO_5$, 284.1498). Note that the ketone group in phenylglyoxal (**f**) was also reduced to chiral secondary alcohol by $NaCNBH_3$, upon reductive amination with aminoquercitol bisacetonide **5**. Thus, the actual structure of **7f** was shown below. Note that only single isomer of **7f** was obtained after purification by cationic exchange resin. An attempt to determine the configuration of newly generated chiral center was not carried out because **7f** showed very weak α-glucosidase inhibition and no radical scavenging activity.



7f

N-(3-Methylpyridyl)-epi-aminoquercitol (**7g**): Pale yellow oil. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.64 (br s, 1H), 8.55 (d, J = 4.0 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.51 (dd, J = 8.0, 4.0 Hz, 1H), 4.11–4.23 (m, 3H), 3.57 (t, J = 8.0 Hz, 1H), 3.47 (m, 1H), 3.37 (m, 1H), 3.18 (br d, J = 12.0 Hz, 1H), 2.10 (m, 1H), 1.84 (m, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 149.6, 148.8, 138.3, 130.8, 124.2, 74.3, 72.7, 69.7, 68.2, 54.6, 46.2, 30.7; HRMS m/z 255.1339 $[M+H]^+$ (calcd for $C_{12}H_{19}N_2O_4$, 255.1345).

N-(2-Methylthiophenyl)-epi-aminoquercitol (**7h**): White solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.20 (br s, 1H), 6.86–6.91 (m, 2H), 3.88–3.97 (m, 3H), 3.42 (dd, J = 9.2, 9.2 Hz, 1H), 3.25 (m, 1H), 3.12 (br d, J = 9.6 Hz, 1H), 2.58 (br d, J = 12.0 Hz, 1H), 1.83 (br d, J = 9.6 Hz, 1H), 1.53 (q, J = 12.0 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 143.8, 127.8, 126.9, 125.8, 76.3, 75.0, 72.0, 71.0, 54.6, 45.5, 34.2; HRMS m/z 260.0951 $[M+H]^+$ (calcd for $C_{11}H_{18}NO_4S$, 260.0957).

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