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Chiral separation of novel iminonaringenin derivatives

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Abstract

A series of 4-iminonaringenin derivatives **2-6** have been prepared in good overall yields from a condensation reaction between naringenin and primary amines. The structures of all products were confirmed by ultraviolet, infrared, proton nuclear magnetic resonance, and carbon-13 nuclear magnetic resonance spectroscopic techniques. These derivatives were analyzed by high-performance liquid chromatography using polysaccharide-based chiral stationary phases, namely, Chiralpak IB and Chiralcel OD, using various mobile phases. 2-Propanol showed a high enantioselectivity for naringin and its derivatives using achiral column containing immobilized polysaccharides (Chiralpak IB).

KEYWORDS

Chiralcel OD, Chiralpak IB, HPLC, *N*- 4-iminonaringenins, naringin, naringenin, polysaccharide-based chiral stationary phases

1 | INTRODUCTION

Flavonoids are polyphenolic compounds that are widely distributed in plants and preserve their health against infections and parasites.[1,2] They possess beneficial effects against several serious human diseases, such as AIDS, cancer, cardiovascular disease, and neurodegenerative disorders.[3-5] In vitro experimental studies show that flavonoids act as antioxidants, antimicrobials, antivirals, and anti-inflammatories.[6-9] Naringin, (*S*)-7-(((2*S*,3*R*,4*R*,5*S*,6*R*)-4,5-dihydroxy- 6-(hydroxymethyl)-3-(((2*S*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6 ethyl tetrahydro-2*H*-pyran-2-yl) oxy) tetrahydro-2*H*-pyran-2-yl)oxy)-5-hydroxy-2-(4-hydroxyphenyl) chroman-4-one, Figure 1, is the conjugate of naringenin with neohesperidose (rhamnosyl- α-1,2- glucose).[10] It is found in abundance in citrus, especially grape fruit, being partly responsible for its bitter taste. Naringenin shows various bioactivities potentially useful in promoting human health, being an antioxidant that acts as a reactive oxygen species scavenger, with neuroprotective properties.[11] It has anticancer effects[12,13] and has been investigated as a cancer preventive agent. Some naringin derivatives have also been investigated for their pharmacological properties; for instance, its oxime was screened for antioxidant activity by Ozyurek et al,[14,15] and several naringenin derivatives have been also studied in this regard.[16,17] It is relevant to note that naringin inhibits some drug-metabolizing cytochrome P450 enzymes, including CYP3A4 and CYP1A2, which may result in drug-drug interactions.[18] The ingestion of naringenin and related flavonoids can also affect the intestinal absorption of certain drugs, leading to either an increase or decrease in circulating drug levels. To avoid interference with drug absorption and metabolism, the

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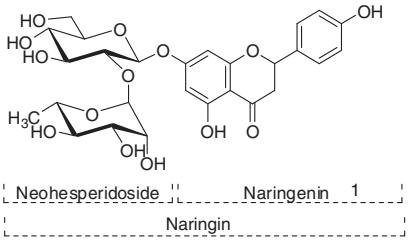

FIGURE 1 Structure of naringin

consumption of citrus (especially grapefruit) and other juices with medications is advised against. All these pharmacological properties are due to naringenin, which is generated by the liver enzyme naringinase by successively hydrolyzing its 2 glycoside bonds. This enzyme occurs widely in nature and is of potential industrial interest for citrus juice debittering and other applications.[19]

Because of the presence of a stereogenic center at their C2 position, flavanones can exist in enantiomeric forms. For many years, the research in our laboratory has been directed towards the synthesis and chiral separation of flavanone derivatives.[20-22] In the case of naringin, owing to the presence of additional stereo centers at the neohesperidoside moiety, the 2 possible species are diastereomers (epimers), but naringenin exists as 2 enantiomers. It is worth mentioning at this point that epimerization processes at the naringinand naringenin C-2 stereo center are well known,[23] and in fact, the commercially available materials consist of mixtures of both possible isomers at this stereo center. Interestingly, both enantiomers of naringenin have shown divergent biological properties,[24,25] which make their separation particularly important.

The aim of this work is to study the chiral separation of iminonaringenin diastereoisomer by high-performance liquid chromatography (HPLC) and to optimize the analytical conditions using polysaccharide-based chiral stationary phases (CSPs). These derivatives were synthesized in 1 step by reaction between naringenin and primary amines.

2 | MATERIALS AND METHODS

2.1 | Reagents and solvents

Naringenin was purchased from Sigma-Aldrich (Schnelldorf, Germany).

The primary amines used were propylamine, isobulylamine, *tert*-butylamine, 2-furfurylamine, and hexylamine, all of which were purchased from FlukaBuches.

2.2 | Synthesis of iminonaringenins 2-6

Naringenin (1 mmol) and the suitable primary amine (2 mmol) were refluxed in methanol (5 mL) for 24 hours. The mixture was cooled to room temperature, and, by adding 10 mL diethyl ether, a solid precipitated out, which was filtered and recrystallized from ethanol.

2.3 | Characterization data for compounds 2-6

2-(4-Hydroxy phenyl)-4-(propylimino) chromane-5,7-diol (2): yellow powder, yield 65%, mp 200°C to 202°C, UV_{max} (MeOH): 239 (band I); 315 (band II), IR (KBr, cm^{-1}): 3377 (OH, strong), 2967 (CH_3), 2962-2918 (CH_2), 1601 (CN), 1514 (C═C), 1066 (C—O), ^{1}H NMR (250 MHz, MeOD, δppm) 7.31 (2H, d, J = 7.5 Hz, H-2′, and H-6′), 6.29 (2H, d, J = 7.5 Hz, H-3′, and H-5′), 6.04 (1H, s, H-8), 5.0 (1H, dd, J = 7.5 and 2.5 Hz, H-2), 3.60 (2H, m, N—CH_2), 2.86 (1H, dd, J = 12.5 and 2.5 Hz, H3^b), 2.62 (1H, dd, J = 12.5 and 7.5 Hz, H3^a), 1.27 (2H, m, CH_2), 0, 71 (3H, m, CH_3). ^{13}C NMR (63 MHz, MeOD, ppm): 168.1 (C-4), 164.4 (C-7), 159.9 (C-5), 157.4 (C-4′), 156.7 (C-9), 128.7 (C-2′, C6′), 116.9 (C-3′,C5′), 95.1 (C-6), 94.2 (C-8), 76.7 (C-2), 59.8 (CH_2—N), 40.3 (C-3), 21.1 ($\underline{CH_2}$–CH_2—N), 11.3 (CH_3).

2-(4-Hydroxy phenyl)-4-(isobutylimino) chromane-5,7-diol (3): brown yellowish powder, yield 60%, mp 210°C to 212°C, UV_{max} (MeOH): 225 (band I); 310 (band II), IR (KBr, cm^{-1}): 3388 (OH, strong), 1607 (C═N), 1508 (C═C), 1126 (C—O).

^{1}H NMR (250 MHz, MeOD, δppm) 7.22 (2H, d, J = 7.5 Hz, H-2′, and H-6′), 6.72 (2H, d, J = 7.5 Hz, H-3′, and H-5′), 6.50 (2H, m, H-6, and H-8), 5.07 (1H, dd, J = 7.5 and 2.5 Hz, H-2), 3.06 (1H, d, N—CH), 2.85 (1H, dd, J = 2.5 and 12.5 Hz, H3^b), 2.61 (1H, dd, J = 7.5 and 12.5 Hz, H3^a), 1.32 (6H, m, $2CH_3$).

^{13}C NMR (63 MHz, MeOD, ppm): 168.1 (C-4,C-7), 163.6 (C-5), 160.0 (C-9), 158.2 (C-4′),129, 5 (C-1′),128.7 (C-2′,-C6′), 115.6 (C-3′,C5′), 95.0(C-6), 94.6 (C-8), 77.7 (C-2), 44.6 (CH-N), 39.6 (C3), 24.3 ($2CH_3$).

2-(4-Hydroxyphenyl)-4-(*tert*-butylimino) chromane-5,7-diol (4): brown powder, yield 62%, mp 206°C to 208°C, UV_{max} (MeOH): 230 (band I); 300 (band II), IR (KBr, cm^{-1}): 3420 (OH, strong), 1569 (C═N), 1514 (C═C), 1181 (C—O). ^{1}H NMR (250 MHz, MeOH, δppm) 7.54 (2H, d, J = 7.2 Hz, H-2′, and H-6′), 6.34 (2H, d, J = 7.2 Hz, H-3′, and H-5′), 5.79 (2H, m, H-6, and H-8), 5.12 (1H, dd, J = 7.5 and 2.5 Hz, H-2), 2.95 (1H, dd, J = 12.5 and 2.5 Hz, H3^b), 2.64 (1H, dd, J = 12.5 and 7.5, H3^a), 1.30 (9H, s, $3CH_3$).

^{13}C NMR (63 MHz, MeOD, ppm): 164.2 (C-4), 164.1 (C-7), 162.7 (C-5), 160.0 (C-9), 157.4 (C-4′), 130.9 (C-1′),

127.9 (C-2′,-C6′), 126.8 (C-3′,C5′), 95.0 (C-6), 94.6 (C-8), 78.3 (C-2), 49, 9 (C-N), 40.7 (C3), 30.4 ($3CH_3$).

2-(4-Hydroxy phenyl)-4-(furfurylimino)chromane-5,7-diol (5): brown powder, yield 70%,mp 196°C to 198°C, UV_{max} (MeOH): 225 (band I); 320 (band II), IR (KBr, cm^{-1}): 3366 (OH, strong), 1607 (C═N), 1514 (C═C), 1170 (C—O).

^{1}H NMR (250 MHz, MeOD, δppm), 7.51 (1H, d, J = 7.5 Hz, H-3″), 7.31 (2H, d, J = 7.5 Hz, H-2′ and H-6′), 6.82 (2H, d, J = 4.61 Hz, H-3′, and H-5′), 6.48 (1H, m, H-4″), 6.28 (3H, m, H-6, 8, and 5″), 5.79 (1H, dd, J = 7.5 and 2.5 Hz, H-2), 4.81 (2H, s, N—CH_2), 2.90 (1H, dd, J = 15 and 2.5 Hz, H3^b), 2.73 (1H, dd, J = 15 and 7.5 Hz, H3^a).

^{13}C NMR (63 MHz, MeOD, ppm): 168.5 (C-4), 167,5 (C-7), 162.5 (C-5), 159.9 (C-9), 158.1 (C-4′), 152.1 (C-1″), 143.1 (C-3″), 129.7 (C-1′), 128.8 (C-2′ and 6′), 115.6 (C-3′ and 5′), 110.6 (C-4″),108.2 (C-10), 107.7 (C-5″), 95.3 (C-6), 94.8 (C-8), 77.7 (C-2), 44.2 (CH2—N), 39.1(C-3).

2-(4-Hydroxy phenyl)-4-(hexylimino) chromane-5,7-diol (6): yellow powder, yield 45%, mp 194°C to 196°C, UV_{max} (MeOH): 225 (band I); 315 (band II), IR (KBr, cm^{-1}): 3382 (OH, strong), 1596 (C═N), 1552 (C═C), 1125 (C—O).

^{1}H NMR (250 MHz, MeOD, δppm) 7.22 (2H, d, J = 7.5 Hz, H-2′, and H-6′), 6.71 (2H, d, J = 7.5 Hz, H-3′, and H-5′), 6.10 (1H, t, H-6), 5.76 (1H, dd, J = 7.5 and 2.5 Hz, H-2), 3.40 (2H, m, H1″), 3.20 (1H, dd, J = 15 and 2.5 Hz, H3^b) 2.68 (1H, dd, J = 7.5 and 15 Hz, H3^a), 1.63 (2H, m, H2″), 1.37 (2H, m, H5″), 1.29 (6H, m, H3″, 4″), 0.82 (3H, m, H6″).

^{13}C NMR (63 MHz, MeOD, ppm): 167.9 (C-4 and C-7), 163.5 (C-5), 160.0 (C-9),158.2 (C-4′),129.7 (C-1′), 128.8 (C-2′&6′), 115.6 (C-3′ and 5′), 95.6 (C-6), 94.7 (C-8), 77.7 (C-2), 45.1 (C-1″), 39.7 (C-3), 31.3 (C-2″ and C-4″), 26.5 (C-3″), 22.5 (C-5″),14.3 (C-6″).

2.4 | Chromatographic separation

The enantiomeric separations were conducted on a SHIMADZU LC 20-A system equipped with a vacuum degasser, PerkinElmer (Norwalk, Connecticut), Shimadzu LC 20 AD (Kyoto, Japan) 200 LC pump, injector with 20 μL Rheodyne 1907 sample loop equipped with a UV detector Shimadzu SPD-20 A (Kyoto, Japan). All analytes were dissolved in methanol at concentrations in a 0.5 to 1 mg mL^{-1} range. Injection volume was 20 μL, and the UV detector was set at 280 nm. Chromatographic separa-

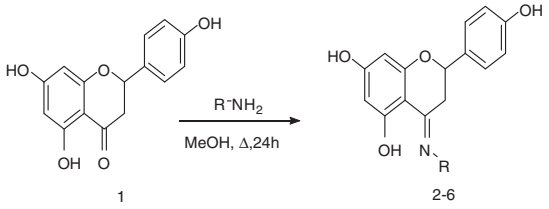

FIGURE 2 Synthesis of 4-iminonaringenins **2-6**

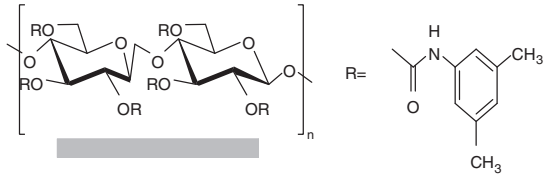

FIGURE 4 Chiralpak IB (cellulose tris-(3,5-dimethylphenylcarbamate)

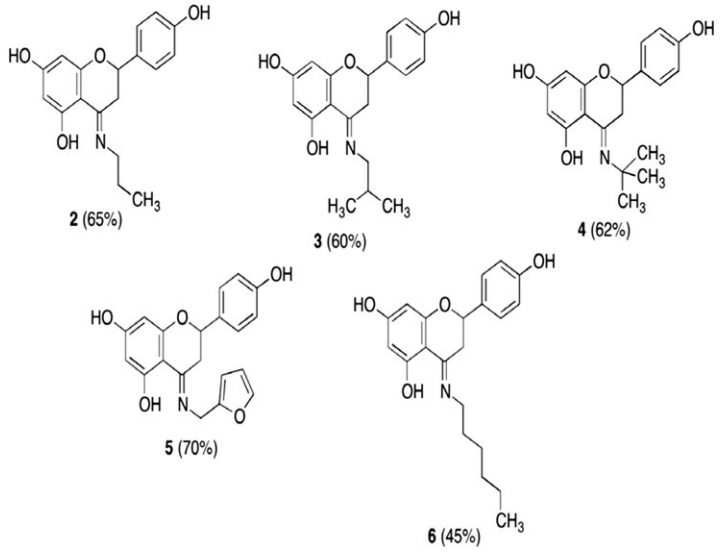

FIGURE 3 Structures and yields of 4-iminonaringenin derivatives **2-6**

tions were conducted at ambient temperature under isocratic mode at a flow rate of 0.2 to 0.4 mL min^{-1}, which may be changed in particular cases.

2.5 | Chiral stationary phases

Two polysaccharide CSPs were evaluated in this study, namely, cellulose derivatives: Chiralcel OD and Chiralpak IB purchased from Chiral Technologies Europe (Illkirch, France). HPLC-grade solvents used were 2-propanol, methanol, and ethanol.

3 | RESULTS AND DISCUSSION

3.1 | Synthesis of 4-iminonaringin derivatives

The synthesis of 4-iminonaringenin derivatives (compounds **2**-**6**) was achieved directly from naringenin **1**, which was treated with various primary amines in refluxing methanol without the addition of any external catalyst as shown in Figure 2. The reaction yields ranged 45% to 70% as shown in Figure 3. The structures of the synthesized compounds were confirmed by the analysis

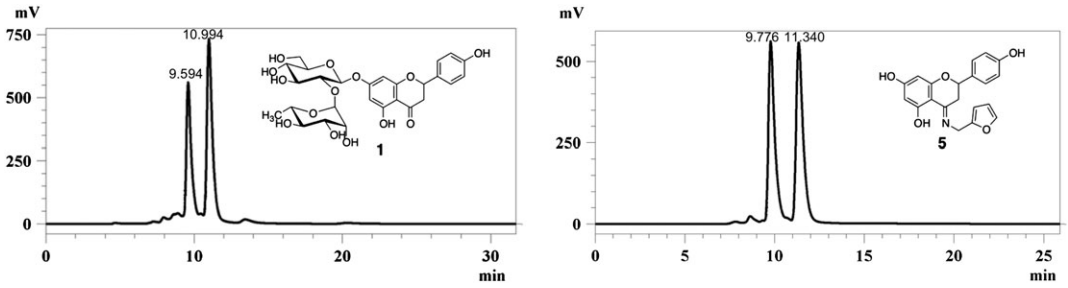

FIGURE 5 Chromatograms of enantiomeric separation of compounds **1** and **5** under polar organic phase mode using 100% EtOH in Chiralpak IB, temperature 25°C, and UV detector set at 280 nm.

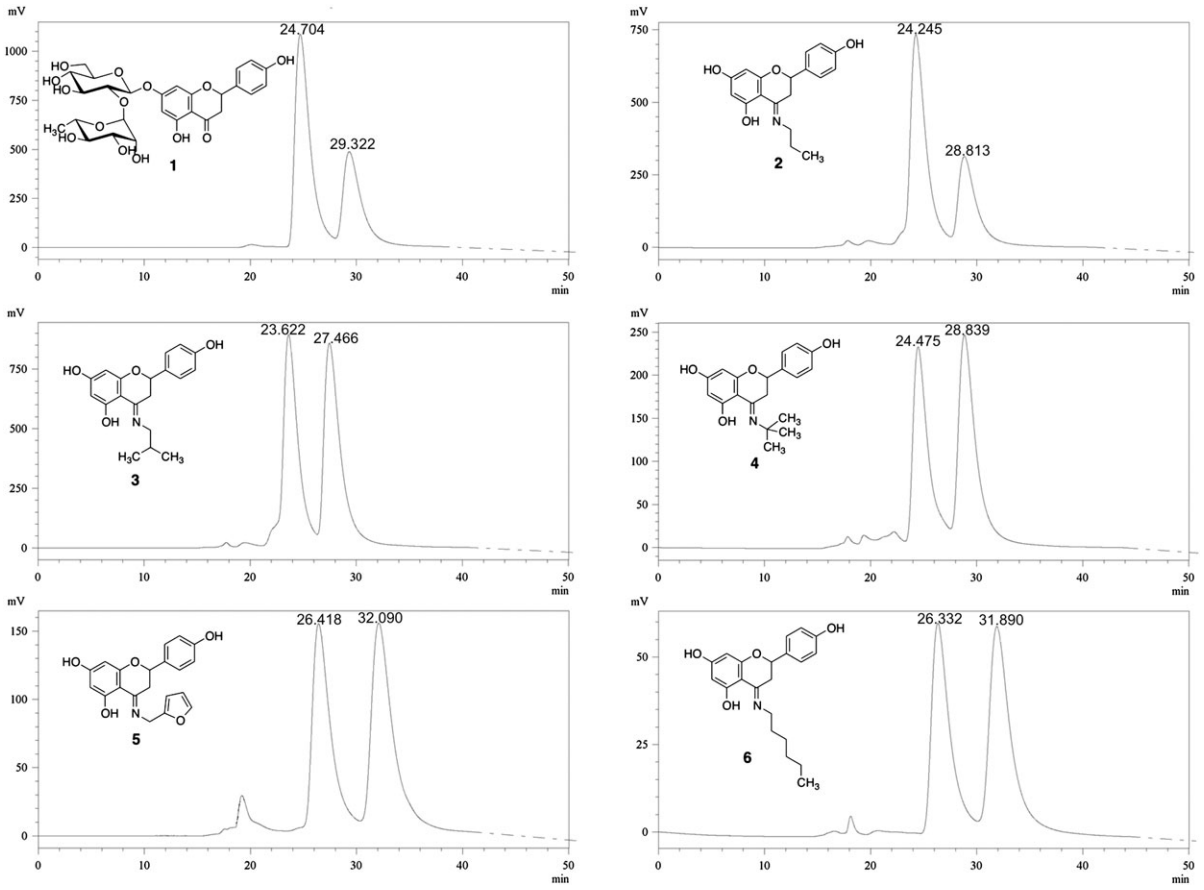

FIGURE 6 Chromatograms showing the enantiomeric separation of compounds **1**, **2**, **3**, **4**, **5**, and **6** under polar organic phase mode using 100% 2-propanol in Chiralpak IB, temperature 25°C, and UV detector set at 280 nm

TABLE 1 Chromatographic data for the separation of 4–iminonaringenins derivatives by Chiral HPLC

CSP	Eluent, % of alcohol	Product	Flow Rate, mL/min	t_1	t_2	k_1	k_2	Rs	α
Chiralpak IB	2–Propanol	1		24.70	29.32	5.17	6.32	2.77	1.22
		2		24.24	28.81	5.06	6.02	3.00	1.19
		3		23.62	27.46	4.90	5.86	2.30	1.20
		4	0.2	24.47	28.83	5.11	6.62	2.84	1.29
		5		26.42	32.09	5.60	7.02	2.83	1.25
		6		26.33	31.89	5.58	6.97	2.78	1.24
	EtOH	1		9.59	10.99	1.39	1.74	2	1.25
		2		–	–	–	–	–	–
		3		–	–	–	–	–	–
		4	0.4	–	–	–	–	–	–
		5		9.77	11.34	1.44	1.83	1.57	1.27
		6		–	–	–	–	–	–
	MeOH	1		8.59	9.01	1.14	1.25	0.84	1.09
		2		–	–	–	–	–	–
		3		–	–	–	–	–	–
		4	0.4	8.59	9.03	1.14	1.25	0.88	1.09
		5		–	–	–	–	–	–
		6		–	–	–	–	–	–
Chiralcelk OD	2–Propanol	1		22.62	37.89	4.65	8.47	2.34	1.82
		2		–	–	–	–	–	–
		3		–	–	–	–	–	–
		4	0.2	–	–	–	–	–	–
		5		24.09	–	5.02	–	–	–
		6		–	–	–	–	–	–
	EtOH	1		12.96	13.94	2.24	2.48	0.65	1.10
		2		7.50	–	0.87	–	–	–
		3		13.23	13.96	2.30	2.49	0.36	1.08
		4	0.4	12.63	13.88	2.15	2.47	0.62	1.14
		5		7.15	7.46	0.78	0.86	0.62	1.10
		6		–	–	–	–	–	–
	MeOH	1		7.39	13.91	0.84	2.47	0.68	1.88
		2		–	–	–	–	–	–
		3		–	–	–	–	–	–
		4	0.4	–	–	–	–	–	–
		5		–	–	–	–	–	–
		6		–	–	–	–	–	–

Abbreviations: HPLC, high–performance liquid chromatography; CSP, chiral stationary phase.

of their spectral data, including UV/IR (the spectra of all products did not show any absorption due to the presence of C═O).

3.2 | Enantioseparation of the 4-iminonaringenin derivatives

The chromatographic conditions were optimized to achieve the best separation of the 4-iminonaringin enantiomers under polar organic phase and normal phase modes using cellulose tris (3,5-dimethylphenylcarbamate) coated on 10 μm silica-gel (Chiralcel OD) and cellulose tris (3,5-dimethyl phenylcarbamate) immobilized on 5 μm silica-gel (Chiralpak IB), whose structure is shown in Figure 4. HPLC enantioseparation of naringenin has been previously reported on polysaccharide CSPs,[26] but its imino derivatives are unexplored in this regard. Polysaccharide-based (cellulose and amylose) CSPs have proved to be very efficient materials in HPLC (in both normal and reversed and polar organic phase modes) for the resolution of chiral drugs. The chiral discrimination power of these polysaccharide phases stems from complex interactive forces (which have not been fully elucidated yet) with the solutes. In summary, a combination of hydrophobic interactions, hydrogen bonding, dipole-dipole interactions, and charge transfer (π-π) formation is believed to explain the chiral recognition mechanisms.[27-30] The difference in the chiral recognition ability between the amylose and the cellulose may be due the difference in the polysaccharide configuration. Amylose possesses a more helical configuration than cellulose that is more rigid and linear in nature.

The chiral separation of the 4-iminonaringenin derivatives was assayed in normal and organic polar phase modes. However, in normal phase mode, no separation was obtained using mobile phases consisting of hexane-EtOH: 95-5, 50:50 *v*/v for the compounds under study. However, under organic polar phase mode using 100% alcohol, efficient enantioseparations were achieved. In the first experiment, naringenin was resolved on Chiralpak IB and Chiralcel OD using a mobile phase consisting of neat MeOH albeit with a low resolution (R = 0.8 under Chiralpak IB and R = 0.68 under Chiralcel OD).

Our next studies showed that compound **5** and naringenin could be separated in a mobile phase consisting of 100% EtOH under Chiralpak IB with good selectivity factors, α = 1.27 and 1.25, respectively (Figure 5). However, no separation was achieved on Chiralpak IB and for compounds **2**, **4,** and **6** when using a 100% MeOH or 100% EtOH as mobile phases.

The use of 2-propanol led to the best selectivity values for the resolution for all 4-iminonaringenin enantiomers. Baseline separation Rs > 1.5 was always achieved on cellulose-based CSPs for the reference naringenin **1** and all products **2**-**6** (Figure 6). The resolution value ranged from 2.3 to 3.0. The best separation was observed on the Chiralpak IB column using 2-propanol for compound **2**, for which Rs = 3. All experiments were performed at 25°C.

The selection of organic solvent as the mobile phase in polar organic phase mode is important to achieve successful enantioseparation as well and the type of CSPs selected. The effect of mobile phase-composition temperature and flow rate on resolution Rs and selectivity α was examined. The optimal conditions were found to involve the use of a mobile phase of 100% 2-propanol at a flow rate of 0.2 mL/min on a Chiralpak IB column maintained at ambient temperature (Figure 6). The associated chromatographic parameters are collected in Table 1.

4 | CONCLUSION

This study describes the synthesis of various 4-iminonaringenin derivatives and discusses their enantioseparation using 2 polysaccharide-based CSPs, namely, Chiralpak IB and Chiralcel OD. The best resolution for naringenin and 4-iminonaringenins was achieved when using immobilized type Chiralpak IB columns under polar organic phase mode using 100% 2-propanol as the mobile phase.

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