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Synthesis of non-prenyl analogues of baccharin as selective and potent inhibitors for aldo-keto reductase 1C3

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ABSTRACT

Inhibitors of a human member (AKR1C3) of the aldo-keto reductase superfamily are regarded as promising therapeutics for the treatment of prostatic and breast cancers. Baccharin [3-prenyl-4-(dihydrocinnamoyloxy)cinnamic acid], a component of propolis, was shown to be both potent (K_i 56 nM) and highly isoform-selective inhibitor of AKR1C3. In this study, a series of derivatives of baccharin were synthesized by replacing the 3-prenyl moiety with aryl and alkyl ether moieties, and their inhibitory activities for the enzyme were evaluated. Among them, two benzyl ether derivatives, **6m** and **6n**, showed an equivalent inhibitory potency to baccharin. The molecular docking of **6m** in AKR1C3 has allowed the design and synthesis of (*E*)-3-{3-[(3-hydroxybenzyl)oxy]-4-[(3-phenylpropanoyl)oxy]phenyl}acrylic acid (**14**) with improved potency (K_i 6.4 nM) and selectivity comparable to baccharin. Additionally, **14** significantly decreased the cellular metabolism of androsterone and cytotoxic 4-oxo-2-nonenal by AKR1C3 at much lower concentrations than baccharin.

1. Introduction

Baccharin (Fig. 1) is a constituent in the ethanol extract of Brazilian propolis,[1] which is a natural resinous substance collected by honeybees and has been used in alternative medicine to treat inflammation, liver disorders, and stomach ulcers. Baccharin has several biological activities, such as growth suppressive and antiproliferative effects on cancer cell lines,[1–4] inhibition of hypoxia-inducible factor-1 expression,[5] and preventive effect on genotoxicity induced by methyl methanesulfonate and hydrogen peroxide.[6] In addition, we have recently found that baccharin is a selective and potent inhibitor of a human member of the aldo-keto reductase (AKR) superfamily, AKR1C3, and this correlates with the antiproliferative effect of baccharin against human prostatic cancer PC3 cells.[7]

AKR1C3 (17β-hydroxysteroid dehydrogenase type 5) plays a pivotal role in androgen biosynthesis especially in the prostate, where the enzyme catalyzes the NADPH-linked reduction of weak androgen precursors to testosterone and 5α-dihydrotestosterone.[8,9] The enzyme is one of the most highly upregulated enzymes in castrate-resistant prostate cancer, and is a target for drug development of the prostate cancer.[8–10] AKR1C3 is also responsible for estrogen synthesis by reducing estrone into 17β-estradiol,[11] and exhibits prostaglandin (PG) F synthase activity, which leads to decreases in the levels of antiproliferative PGD_2 and 15-deoxy-$\Delta^{12,14}$-PGJ_2.[11,12] Since AKR1C3 is also upregulated in breast cancer,[11] it is suggested to be implicated in the development and progression of both breast and prostatic cancers. Furthermore, AKR1C3 has been reported to be responsible for developing resistance of cancer cells to anticancer drugs such as human oxaliplatin,[13] cisplatin,[14] and anthracyclines.[15,16] Thus, this enzyme has been recognized as a potential therapeutic target for the treatment of the above types of cancers and chemoresistance.

Abbreviations: AKR, aldo-keto reductase; ONE, 4-oxo-2-nonenal; PG, prostaglandin.

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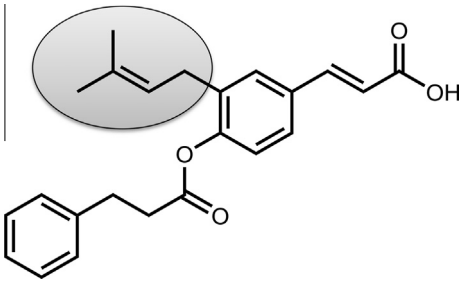


Figure 1. Structure of baccharin [3-prenyl-4-(dihydrocinnamoyloxy)cinnamic acid]. The prenyl moiety is circled.

AKR1C3 shares at least an 84% amino acid sequence identity with other human AKR1C isoforms (AKR1C1, AKR1C2 and AKR1C4) that play distinct roles in the metabolism of steroid hormones and bile acids such as 20- and/or 3-hydroxysteroid dehydrogenases.[11] The inhibitory selectivity to AKR1C3 over the other AKR1C isoforms is required for the development of drugs targeting this enzyme. During the past five years, many synthetic and natural compounds that show inhibitory effects on AKR1C3 have been reported, as reviewed by recent literature.[8,16,17] Among the synthetic inhibitors, 3-[3,4-dihydroisoquinolin-2(1*H*)-ylsulfonyl]benzoic acids,[18] *N*-phenylanthranilate derivatives,[19] 1-[4-(piperidin-1-ylsulfonyl) phenyl]pyrrolidin-2-ones,[20] morpholylureas,[21] indomethacin analogues[22] and *N*-(2-hydroxyphenyl)-2,4-dioxo-5-thiazolidineacetamide[23] show high inhibitory potency (IC_{50} values of less than 0.2 μM) and selectivity (more than 300-fold against the other three AKR1C isoforms). Out of the natural compounds, baccharin is the most potent and selective inhibitor showing an IC_{50} value of 0.11 μM and more than 900-fold selectivity to AKR1C3 over the other three AKR1C isoforms.[7] Due to its high inhibitory selectivity, baccharin represents a promising lead for the development of more potent and specific agents targeting AKR1C3. However, baccharin has a prenyl moiety that is difficult to be synthetically modified. In this study, we designed and synthesized non-prenyl derivatives based on the structural knowledge of the type of interactions between AKR1C3 and baccharin suggested by the previous molecular docking and site-directed mutagenesis studies.[7]

2. Results and discussion

2.1. Synthesis of non-prenyl derivatives of baccharin and their inhibitory potencies

In our earlier molecular docking of baccharin [3-prenyl-4-(dihydrocinnamoyloxy)cinnamic acid] in AKR1C3 and site-directed mutagenesis studies,[7] the following interactions were suggested to be important for tight binding. (1) The carbonyl group of the esterified dihydrocinnamoyloxy moiety is in close proximity to the enzyme's active site residues, Tyr55 and His117. (2) The carboxyl group of the cinnamic acid moiety forms a strong H-bond interaction with Ser118, in addition to hydrophobic/van der Waals interactions with Met120 and Phe311. In addition, the structure–inhibitory activity relationship of propolis-derived cinnamic acids suggests that the 3-prenyl moiety of baccharin is responsible for the selective binding to AKR1C3.[7] Since the modification of the prenyl substituent is synthetically difficult, we first synthesized derivatives having 3-aliphatic and aryl ethers from commercially available 3,4-dihydroxybenzaldehyde **1** instead of the 3-prenyl moiety (Scheme 1). The compounds (**3a**–**3p**) were synthesized by the alkylation of phenol (**2**).[24] The Horner–Wadsworth–Emmons reaction of **3a**–**3p** gave their unsaturated esters (**4a**–**4p**), which were converted to carboxylic acids (**5a**–**5p**) by hydrolysis followed by removal of MOM protecting group. The condensation of **5a**–**5p** with hydrocinnamoyl chloride gave esters (**6a**–**6z**). Compounds (**7w**–**7z**) were obtained by removal of THP protecting group of **6w**–**6z**.

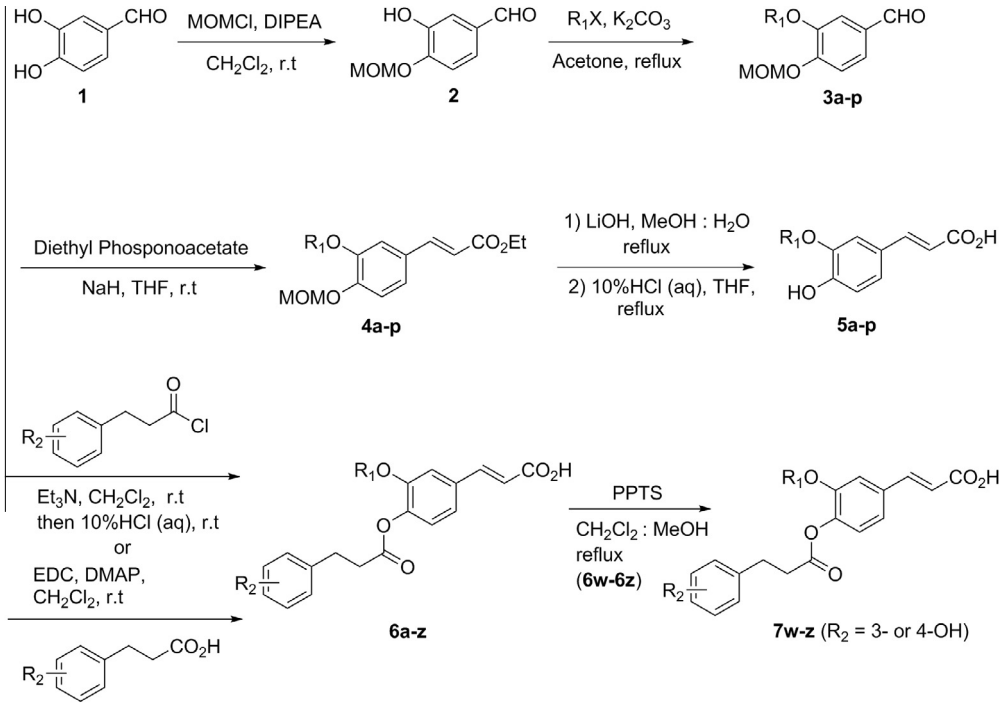
Within the synthesized compounds having a series of aliphatic ethers (Table 1) instead of the prenyl moiety of baccharin, the IC_{50} values for these ethers in the inhibition of AKR1C3 tended to decrease with increasing the aliphatic chain lengths, and **6j** having *n*-butyl ether showed the highest inhibitory potency. However, the compounds having benzyl ethers (**6f**, **6i** and **6m**–**6p**), except for **6h** having 4-chlorobenzyl ether and **6k** having phenethyl ether, exhibited more potent inhibition than **6j**. Among these benzyl ethers, **6m** with 4-methylbenzyl ether and **6n** with 3-fluorobenzyl ether were the most potent, although their IC_{50} values were the same as that for baccharin.

Compounds (**6q**–**6u** and **7w**–**7y**) are derivatives of **6m** and **6n**, which have fluoro or hydroxyl group on the phenyl rings in their dihydrocinnamoyloxy moieties, as shown in Table 2. These derivatives inhibited AKR1C3 less potently compared with the mother compounds (**6m** and **6n**). In addition, the compounds having the hydroxyphenyl rings (**7w**–**7y**) inhibited AKR1C4 (IC_{50} values for **7w**, **7x**, **7y** and **7z** were 1.7, 0.28, 0.72 and 2.9 μM, respectively), although the other synthesized compounds (**6a**–**6u**) did not show significant inhibition towards AKR1C4. Thus, the dihydrocinnamoyloxy moiety itself is the most suitable constituent for the selective and potent inhibition of AKR1C3.

2.2. Synthesis of baccharin derivatives based on its docked model

To design more potent and selective baccharin-based inhibitors, we constructed a model of docked **6m** in the AKR1C3–$NADP^+$ complex (Fig. 2A). In this model, the orientation of **6m** in the binding site and its interactions with amino acids resembled those in its previously reported baccharin-docked model.[7] However, the 4-methylbenzyl ether moiety of **6m** was bulky compared to the 3-prenyl moiety of baccharin, and its aromatic ring was in close proximity to the hydroxyl group of Tyr24, which also formed a H-bond interaction with the side chain of Arg226 that was positioned at a distance of 3.7 Å from the aromatic ring. This raised a possibility that an introduction of the hydroxyl group in the benzyl ether of **6m** at *m*-position (i.e., **14**) forms a new H-bond interaction with the phenolic side-chain of Tyr24. The suggested interaction (2.7 Å) was indeed predicted in a **14**-docked model (Fig. 2B), and its distance was shorter than the H-bond distance between Tyr24 and Arg226. To confirm the interaction of the 3-hydroxybenzyl ether moiety of **14** predicted from the docked model, we synthesized **14** and its methoxy derivative (**13b**) using the approach outlined in Scheme 2. Benzylation of dianion of **1** gave rise to benzyl ethers (**9a** and **9b**),[25] which were converted to unsaturated esters (**11a** and **11b**) after protection of phenols as THP ethers (**10a** and **10b**). Compound **13b** was synthesized via the carboxylic acid **12b** as described in Scheme 1. Compound **14** was obtained by deprotection of MOM group in **13b**.

Compound **14** with the 3-hydroxyl group on the phenyl ring in the benzyl ether moiety inhibited AKR1C3 approximately 5-fold more potently (IC_{50} 20 nM) than baccharin, and its inhibitory selectivity was compared with that of baccharin (Table 3). Although **14** showed a lower IC_{50} value towards AKR1C4 than baccharin, its selectivity towards AKR1C3 (IC_{50} ratios of other AKR1C isoforms/AKR1C3) was comparable to that of baccharin. In contrast to **14**, **13b**, methyl ether of **14**, significantly decreased the inhibition potency towards AKR1C3. The marked decline in inhibition by **13b** may be due to the alteration in orientation of its 3-methoxybenzyl ester moiety against Tyr24, Leu54 and Trp227, as well as the lack of the hydrogen bond interaction seen in the



a: R_1 = Et, R_2 = H **b:** R_1 = Me, R_2 = H **c:** R_1 = *i*-Bu, R_2 = H **d:** R_2 = *n*-Pr, R_2 = H **e:** R_1 = *i*-Pr, R_2 = H
f: R_1 = Benzyl, R_2 = H **g:** R_1 = 2-Methylallyl, R_2 = H **h:** R_1 = 4-Chlorobenzyl, R_2=H
i: R_1 = 4-Fluorobenzyl, R_2 = H **j:** R_1 = *n*-Bu, R_2 = H **k:** R_1 = Phenethyl, R_2= H **l:** R_1 = (*E*)-But-2-en-1-yl, R_2 = H
m: R_1 = 4-Methylbenzyl, R_2 = H **n:** R_1 = 3-Fluorobenzyl, R_2 = H **o:** R_1 = 2-Fluorobenzyl, R_2= H
p: R_1 = 3,5-di-Fluorobenzyl, R_2 = H **q:** R_1 = 3-Fluorobenzyl, R_2 = 3-Fluoro **r:** R_1 = 3-Fluorobenzyl, R_2 = 4-Fluoro
s: R_1 = 3-Fluorobenzyl, R_2 = 2,4,6-tri-Fluoro **t:** R_1 = 4-Methylbenzyl, R_2 = 3-Fluoro
u: R_1 = 4-Methylbenzyl, R_2 = 2,4,6-tri-Fluoro **v:** R_1 = 4-Methylbenzyl, R_2 = 4-Fluoro
w: R_1 = 3-Fluorobenzyl, R_2 = 4-(tetrahydro-2*H*-pyran-2-yl)oxy or 4-OH
x: R_1 = 3-Fluorobenzyl, R_2 = 3-(tetrahydro-2*H*-pyran-2-yl)oxy or 3-OH
y: R_1 = 4-Methylbenzyl, R_2 = 3-(tetrahydro-2*H*-pyran-2-yl)oxy or 3-OH
z: R_1 = 4-Methylbenzyl, R_2 = 4-(tetrahydro-2*H*-pyran-2-yl)oxy or 4-OH

Scheme 1. Synthesis of non-prenyl derivatives of baccharin (**6a**–**6v** and **7w**–**7z**).

Table 1
Effects of replacement of 3-prenyl moiety of baccharin with aliphatic and aromatic esters on inhibition of AKR1C3

Compound	R_1[a]	IC_{50} (μM)
Baccharin	Prenyl	0.11
6b	Me	4.5 ± 0.2
6a	Et	0.97 ± 0.09
6d	Propyl	2.2 ± 0.2
6e	*i*-Propyl	3.1 ± 0.1
6j	Butyl	0.42 ± 0.06
6c	*i*-Butyl	0.56 ± 0.02
6l	(*E*)-But-2-en-1-yl	1.1 ± 0.1
6g	2-Methylallyl	0.85 ± 0.05
6f	Benzyl	0.39 ± 0.01
6m	4-Methylbenzyl	0.11 ± 0.01
6o	2-Fluorobenzyl	0.32 ± 0.03
6n	3-Fluorobenzyl	0.11 ± 0.01
6i	4-Fluorobenzyl	0.22 ± 0.02
6p	3,5-Difluorobenzyl	0.36 ± 0.01
6h	4-Chlorobenzyl	0.89 ± 0.1
6k	Phenethyl	0.57 ± 0.08

[a] R_1 of compounds **6a**–**p** with R_2 = H in Scheme 1.

Table 2
Effect of introduction of fluoro and hydroxy groups in the dihydrocinnamoyloxy moieties of **6m** and **6n** on AKR1C3 inhibition

Compound	R2[a]	IC_{50} (μM)
6m *derivatives*		
6t	3-Fluoro	0.16 ± 0.01
6v	4-Fluoro	0.47 ± 0.01
6u	2,4,6-Trifluoro	0.54 ± 0.01
7z	4-Hydroxy	0.77 ± 0.01
7y	3-Hydroxy	0.91 ± 0.02
6n *derivatives*		
6q	3-Fluoro	0.40 ± 0.02
6r	4-Fluoro	0.54 ± 0.02
6s	2,4,6-Trifluoro	0.58 ± 0.04
7x	3-Hydroxy	0.80 ± 0.07
7w	4-Hydroxy	0.84 ± 0.02

[a] R_2 of **6m** with R_1 = 4-methylbenzyl ester and of **6n** with R_1 = 3-fluorobenzyl ester as shown in Scheme 1.

14-docked model. The inhibitory potency of **14** is slightly lower than the 3-[3,4-dihydroisoquinolin-2(1*H*)-ylsulfonyl]benzoic acids that are the most potent inhibitors known (IC_{50}, 6–13 nM),[18] but are comparable or superior to those of the other synthetic inhibitors (IC_{50}, 24–210 nM).[19–23] Compound **14** inhibited competitively with respect to the alcohol substrate in the *S*-1-tetralol oxidation by AKR1C3, showing its K_i value of 6.4 ± 0.5 nM, which is lower than that for baccharin (K_i 56 nM). The K_i value for **14** is

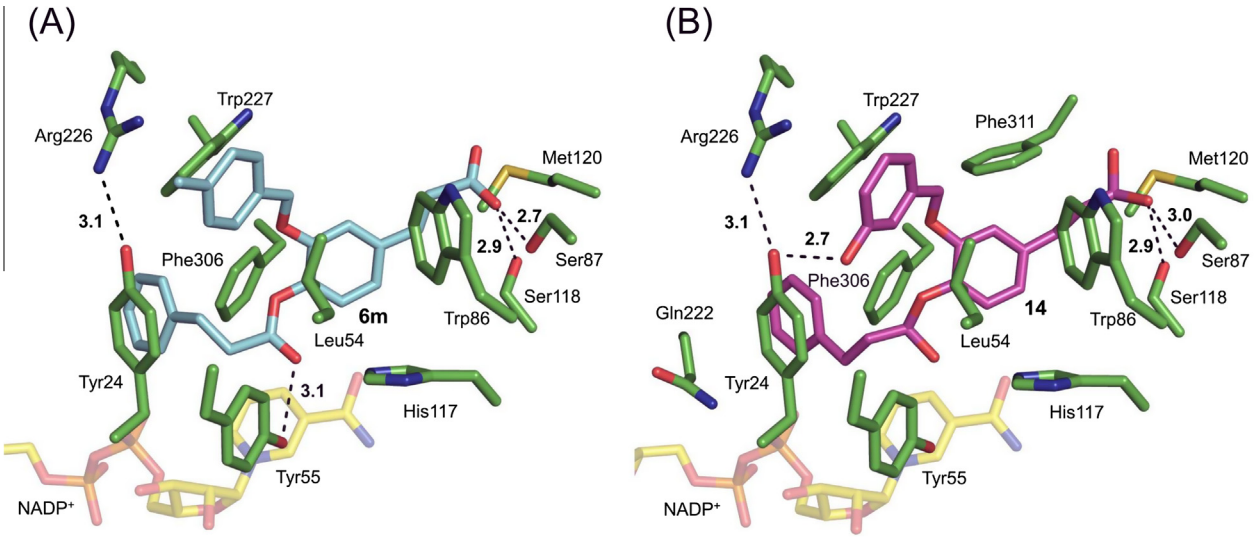
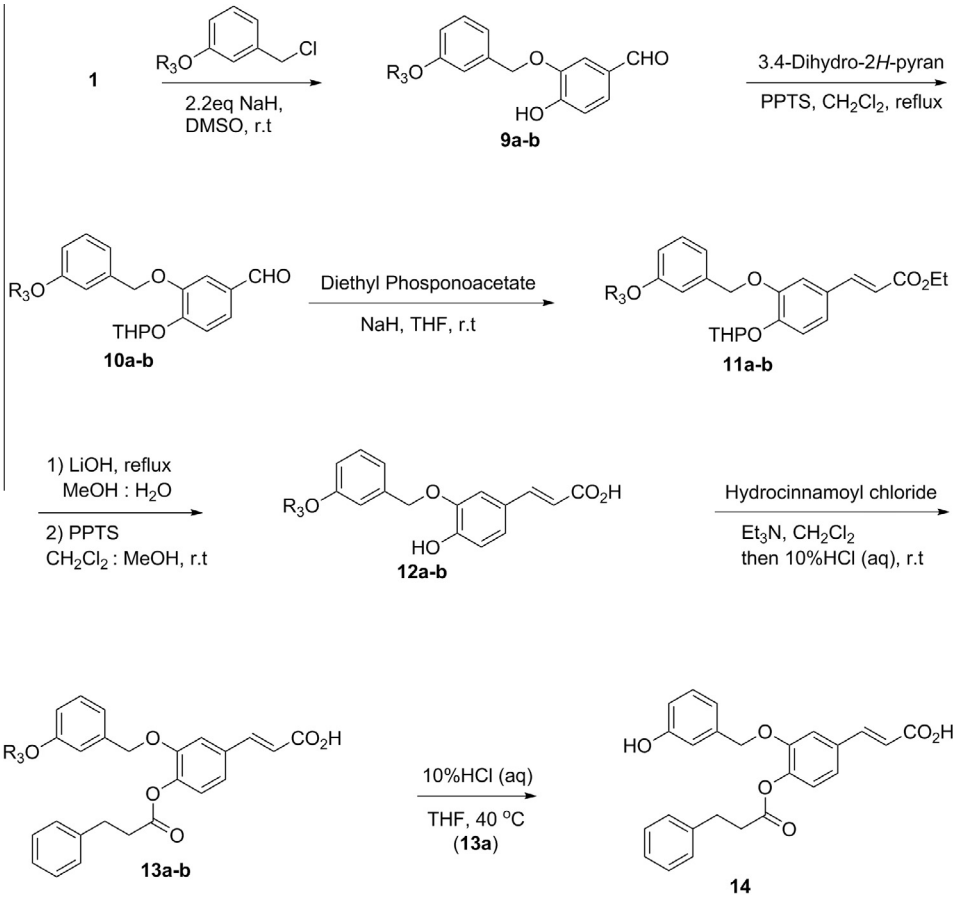


Figure 2. Models of docked compounds, **6m** (A) and **14** (B), in the AKR1C3–NADP$^+$ complex. In addition to the enzyme's residues within 3.5 Å from the inhibitors, Arg226 that forms a H-bond interaction with Tyr24 is depicted, although its distances from the benzyl ether moieties of **6m** and **14** are 3.8 and 3.6 Å, respectively. The possible H-bond interactions are illustrated as dotted lines with their distances given in Å.



Scheme 2. Synthesis of compounds **13b** and **14**.

Table 3
Inhibitory properties of **14** and **13b** on AKR1C3 and other human AKR1C isoforms

Compound	IC_{50} (μM) and inhibitory selectivity [a]			
	AKR1C3	AKR1C1	AKR1C2	AKR1C4
Baccharin	0.11	>100 (>909)	>100 (>909)	102 (927)
14	0.020 ± 0.004	81 ± 3 (4050)	>100 (>5000)	20 ± 3 (1000)
13b	0.96 ± 0.09	>100 (>104)	>100 (>104)	>100 (>104)

[a] Inhibitory selectivity is shown as an IC_{50} ratio of other enzyme/AKR1C3 in the parenthesis.

comparable to those for an estrogen spiro-δ-lactone, EM1404 (K_i 6.9 nM)[26] and tolfenamic acid (K_i 8 nM),[27] which were previously reported to show the lowest K_i values for AKR1C3.

2.3. Effect of compound 14 on cellular metabolism by AKR1C3

Compound **14** and baccharin were compared for their effects on cellular metabolism of androsterone (5α-androstan-3α-ol-17-one), which is rapidly reduced into 5α-androstane-3α,17β-diol by AKR1C3 highly expressed in A549 cells.[7] Compound **14** inhibited the androsterone metabolism more potently than baccharin, and was effective from 0.05 μM, showing an IC_{50} value of 8 μM, which was 20 μM for baccharin (Fig. 3A). We also compared the effects of **14** and baccharin on cellular metabolism of 4-oxo-2-nonenal (ONE) by AKR1C3 (Fig. 3B). ONE is highly cytotoxic towards cultured cells including bovine aortic endothelial cells,[28] and approximately 70% of the bovine aortic endothelial cells were killed by 24-h treatment of 15 μM ONE. Since ONE is efficiently metabolized by AKR1C3,[14] the cytotoxicity of ONE against the cells was significantly suppressed by the overexpression of AKR1C3. The suppressive effect of the AKR1C3 overexpression on the cytotoxicity by ONE was abrogated by the addition of **14** or baccharin in a dose dependent manner, in which **14** was effective at its lower concentrations than baccharin. The results clearly indicate that **14** was a more potent inhibitor than baccharin in cellular level.

3. Conclusion

In this study, a series of derivatives of baccharin, a selective AKR1C3 inhibitor, were synthesized by replacing the 3-prenyl moiety with aryl and alkyl ether moieties, and their inhibitory activities for the enzyme were evaluated. Two benzyl ether derivatives, **6m** and **6n**, showed an equivalent inhibitory potency to baccharin, although no improvement in the inhibitory potency was achieved by the introduction of fluoro- and hydroxyl groups in the dihydrocinnamoyloxy moieties of **6m** and **6n**. The molecular docking of **6m** in the crystal structure of AKR1C3 has allowed the design of a novel baccharin-based inhibitor (**14**) with improved potency (K_i 6.4 nM), which may be due to the introduction of a new interaction between the 3-hydroxyl group of the benzyl moiety of **14** and Tyr24 of the enzyme. The inhibitory selectivity of **14** for AKR1C3 over other human AKR1C isoforms was comparable or superior to that of baccharin. Moreover, **14** significantly decreased the cellular metabolism of androsterone and cytotoxic ONE by AKR1C3 at much lower concentrations than baccharin. Our synthesis and evaluation results of compound **14** are indicative of its efficacy as a potential candidate for both biological tools and the development of new therapeutics for cancers, in which AKR1C3 is overexpressed.

4. Experimental section

4.1. General procedure for alkylation of 2

To a stirred solution of **2**[24] (1 mmol) in acetone (4 mL) were added K_2CO_3 (2 mmol), and alkyl halide (3 mmol), and the resulting mixture was refluxed for 12 h. After cooling, the reaction mixture was filtered through celite. The filtrate was removed under reduced pressure, and the residue was chromatographed on silica gel (15 g, hexane/acetone = 30:1) to give the corresponding compound. Compounds **3a–f**[29] and **3j**[30] were known compounds.

4.1.1. 4-(Methoxymethoxy)-3-[(2-methylallyl)oxy]benzaldehyde (3g)

Yield: 56%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.87 (3H, s), 3.56 (3H, s), 4.61 (2H, s), 5.05 (1H, br s), 5.15 (1H, br s), 5.36 (2H, s), 7.29 (1H,

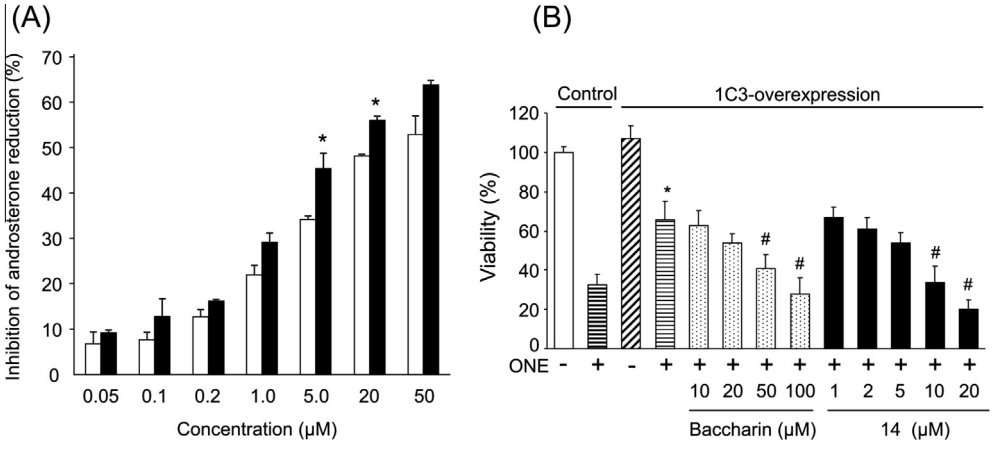


Figure 3. Inhibitory effects of compound **14** and baccharin on cellular metabolism of androsterone and ONE by AKR1C3. (A) Inhibition of reductive metabolism of androsterone in A549 cells by **14** and baccharin. The cells were incubated with 50 μM androsterone for 24 h in the presence of the indicated concentrations of **14** (■) and baccharin (□), and the substrate and its metabolite 5α-androstane-3α,17β-diol in the medium were determined by LC/MS. The inhibition percentages of the activity are expressed as the means ± SD (n = 3). *Significant difference from the cells treated with baccharin, $p < 0.05$. (B) Protective effect of AKR1C3 overexpression against ONE-induced cytotoxicity and its suppression by **14** and baccharin. The cells were transfected for 48 h with the expression vector alone (control) or the vector carrying AKR1C3 cDNA (1C3). The cells were pretreated for 2 h with the indicated concentrations of baccharin or **14** before treating for 24 h with 15 μM ONE (+), and their viability values represent the means ± SD (n = 3), in which that of the ONE-nontreated control cells (□) was taken as 100%. Cells: ONE-treated control and 1C3 cells (▤); ONE-nontreated 1C3 cells (▨); ONE-treated 1C3 cells pretreated with baccharin (▦); and ONE-treated 1C3 cells pretreated with **14** (■). *Significant difference from the ONE-treated control cells, $p < 0.05$. #Significant difference from the ONE-treated 1C3 cells, $p < 0.05$.

d, J = 7.0 Hz), 7.45 (1H, s), 7.46 (1H, d, J = 7.0 Hz), 9.88 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.2, 56.4, 72.4, 94.9, 111.7, 113.0, 115.2, 126.1, 130.9, 139.9, 149.2, 152.2, 190.9; IR (neat): 1690, 1506, 1263, 1128 cm^{-1}; MS (EI): m/z 236 (M^+); HRMS: Calcd for $C_{13}H_{16}O_4$ 236.1049, Found: 236.1048.

4.1.2. 3-[(4-Chlorobenzyl)oxy]-4-(methoxymethoxy)benzaldehyde (3h)

Yield: 99%; mp: 56–58 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.50 (3H, s), 5.15 (2H, s), 5.30 (2H, s), 7.35 (2H, d, J = 7.3 Hz), 7.27–7.43 (5H, m), 9.82 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.5, 70.1, 95.50, 111.9, 115.3, 126.7, 128.7, 128.8, 131.0, 134.8, 149.0, 152.4, 190.8; IR (KBr): 1684, 1508, 1265, 1128 cm^{-1}; MS (EI): m/z 306 (M^+); HRMS: Calcd for $C_{16}H_{15}ClO_4$ 306.0659, Found: 306.0656.

4.1.3. 3-[(4-Fluorobenzyl)oxy]-4-(methoxymethoxy)benzaldehyde (3i)

Yield: 99%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.52 (3H, s), 5.16 (2H, s), 5.32 (2H, s), 7.07 (2H, t, J = 8.3 Hz), 7.29 (1H, s), 7.41–7.47 (4H, m), 9.84 (1H, s), ^{13}C NMR (125 MHz, $CDCl_3$): 56.6, 70.3, 95.1, 112.1, 115.5, 115.7 (d, J = 22 Hz), 126.8, 129.4 (d, J = 7.2 Hz), 131.1, 132.2 (d, J = 3.7 Hz), 149.2. 152.6, 162.7 (d, J = 245 Hz), 191.0; IR (neat): 1688, 1595, 1506, 1263 cm^{-1}; MS (EI): m/z 290 (M^+); HRMS: Calcd for $C_{16}H_{15}FO_4$ 290.0954, Found: 290.0954.

4.1.4. 4-(Methoxymethoxy)-3-phenethoxybenzaldehyde (3k)

Yield: 75%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.18 (2H, t, J = 7.2 Hz), 3.50 (3H, s), 4.30 (2H, t, J = 7.2 Hz), 5.25 (2H, s), 7.23–7.26 (3H, m), 7.31–7.32 (3H, m), 7.41–7.43 (2H, m), 9.85 (1H, s), ^{13}C NMR (125 MHz, $CDCl_3$): δ 35.5, 56.4, 69.6, 95.0, 111.1, 115.5, 126.2, 126.6, 128.5, 129.0, 131.1, 137.7, 149.4, 152.2, 190.9; IR (neat): 1689, 1505, 1264, 1125 cm^{-1}; MS (EI): m/z 286 (M^+); HRMS: Calcd for $C_{17}H_{18}O_4$ 286.1205, Found: 286.1204.

4.1.5. 3-But-2-enyloxy-4-methoxymethoxybenzaldehyde (3l)

Yield: 61%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.76 (3H, d, J = 6.0 Hz), 3.52 (3H, s), 4.59 (2H, d, J = 6.0 Hz), 5.31 (2H, s), 5.77 (1H, m), 5.87 (1H, m), 7.26 (1H, s), 7.65 (1H, d, J = 8.0 Hz), 7.42–7.44 (1H, m), 9.86 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.6, 56.2, 69.3, 94.7, 111.1, 114.9, 125.2, 125.8, 130.8, 130.9, 149.0, 152.1, 190.7; IR (neat): 1689, 1506, 1261, 1127 cm^{-1}; MS (EI): m/z 236 (M^+); HRMS: Calcd for $C_{13}H_{16}O_4$ 236.1049, Found: 236.1047.

4.1.6. 4-(Methoxymethoxy)-3-[(4-methylbenzyl)oxy]benzaldehyde (3m)

Yield: 73%; mp: 71–72 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (3H, s), 3.52 (3H, s), 5.19 (2H, s), 5.31 (2H, s), 7.19 (2H, d, J = 7.8 Hz), 7.26 (1H, d, J = 7.7 Hz), 7.34 (2H, d, J = 7.8 Hz), 7.42 (1H, d, J = 7.7 Hz), 7.47 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.1, 56.4, 70.7, 94.9, 112.1, 115.4, 126.2, 127.5, 129.2, 131.0, 133.2, 149.3, 152.4, 190.9; IR (KBr): 1690, 1506, 1267, 1126 cm^{-1}; MS (EI): m/z 286 (M^+); HRMS: Calcd for $C_{17}H_{18}O_4$ 286.1205, Found: 286.1204.

4.1.7. 3-[(3-Fluorobenzyl)oxy]-4-(methoxymethoxy)benzaldehyde (3n)

Yield: 60%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.57 (3H, s), 5.24 (2H, s), 5.38 (2H, s), 7.05 (1H, m), 7.22 (1H, s), 7.25 (1H, d, J = 6.8 Hz), 7.32 (1H, d, J = 8.8 Hz), 7.36–7.39 (1H, m), 7.48 (1H, s), 7.50 (1H, dd, J = 4.6, 2.0 Hz), 9.88 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.5, 70.0, 95.0, 112.0, 114.1 (d, J = 22 Hz), 115.0 (d, J = 22 Hz), 115.3, 122.6 (d, J = 2.4 Hz), 126.6, 130.2 (d, J = 7.4 Hz), 131.0, 139.0 (d, J = 7.4 Hz), 149.0, 152.4, 163.0 (d, J = 247 Hz), 190.8; IR (neat): 1688, 1595, 1506, 1263 cm$^{-1;}$ MS (EI): m/z 290 (M^+); HRMS: Calcd for $C_{16}H_{15}O_4$ 290.0954, Found: 290.0954.

4.1.8. 3-[(2-Fluorobenzyl)oxy]-4-(methoxymethoxy)benzaldehyde (3o)

Yield: 55%; mp: 56–58 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.51 (3H, s), 5.25 (2H, s), 5.30 (2H, s), 7.16–7.26 (4H, m), 7.28–7.51 (3H, m), 9.85 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.5, 64.9, 95.0, 112.5, 115.4 (d, J = 21 Hz), 115.6, 123.6 (d, J = 21 Hz), 124.3 (d, J = 3.7 Hz), 126.45, 129.7 (d, J = 3.7 Hz), 130.0 (d, J = 8.6 Hz), 131.1, 149.1, 152.5, 160.5 (d, J = 248 Hz), 190.8; IR (KBr): 1690, 1508, 1263, 1128 cm^{-1}; MS (EI): m/z 290 (M^+); HRMS: Calcd for $C_{16}H_{15}FO_4$ 290.0954, Found: 290.0954.

4.1.9. 3-[(3,5-Difluorobenzyl)oxy]-4-(methoxymethoxy)benzaldehyde (3p)

Yield: 66%; mp: 79–81 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.54 (3H, s), 5.20 (2H, s), 5.32 (2H, s), 6.76 (1H, m), 6.99 (2H, J = 5.7 Hz), 7.29 (1H, d, J = 8.3 Hz), 7.42 (1H, d, J = 1.7 Hz), 7.47 (1H, dd, J = 6.3, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.6, 69.5, 95.0, 103.4 (t, J = 26 Hz), 109.7 (t, J = 6.1 Hz), 111.8, 115.3, 127.0, 140.4 (t, J = 9.2 Hz), 148.7, 152.5, 163.1 (d, J = 249 Hz), 163.2 (d, J = 249 Hz), 190.7; IR (KBr): 2831, 1690, 1601, 1269, 1126 cm^{-1}; MS (EI): m/z 308 (M^+); HRMS: Calcd for $C_{16}H_{14}F_2O_4$ 308.0860, Found: 308.0858.

4.2. General procedure for Horner–Wadsworth–Emmons reaction of 3

To a stirred suspension of NaH (1.2 mmol) in THF (4 mL) was added diethyl phosphonoacetate (1.2 mmol) at 0 °C, and the resulting solution was stirred for 30 min. A THF solution (1 mL × 2) of **3** (1 mmol) was added at 0 °C to the reaction mixture, and the resulting mixture was stirred for 12 h at room temperature. The reaction was quenched by H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (5 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (15 g, hexane/acetone = 100:1–80:1) to give the corresponding ester. Compounds **4b**[31] and **4f**[32] were known compounds. Compounds **4a**, **4c**, **4d**, and **4e** were converted to known **5a**, **5c**, **5d**, and **5e**, whose spectral data were identical with those of **5a**, **5c**, **5d**, and **5e**.

4.2.1. (*E*)-Ethyl 3-[4-(methoxymethoxy)-3-[(2-methylallyl)oxy)phenyl]acrylate (4g)

Yield: 73%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (3H, t, J = 7.2 Hz), 1.84 (3H, s), 3.52 (3H, s), 4.25 (2H, quint, J = 7.2 Hz), 4.54 (2H, s), 5.01 (1H, s), 5.11 (1H, s), 5.26 (2H, s), 6.27 (1H, d, J = 16.0 Hz), 7.07 (1H, br s), 7.09 (1H, d, J = 8.4 Hz), 7.12 (1H, d, J = 8.4 Hz), 7.60 (1H, d, J = 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 19.2, 56.2, 60.3, 72.6, 95.2, 122.7, 112.9, 116.4, 116.5, 122.2, 128.8, 140.4, 144.3, 148.7, 149.0, 167.1; IR (neat): 1707, 1508, 1254, 1157 cm^{-1}; MS (EI): m/z 306 (M^+); HRMS: Calcd for $C_{17}H_{22}O_5$ 306.1467, Found: 306.1468.

4.2.2. (*E*)-Ethyl 3-{3-[(4-chlorobenzyl)oxy]-4-(methoxymethoxy)phenyl}acrylate (4h)

Yield: 81%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (3H, t, J = 7.2 Hz), 3.62 (3H, s), 4.34 (2H, q, J = 7.2 Hz), 5.23 (2H, s), 5.35 (2H, s), 6.35 (1H, d, J = 16.0 Hz), 7.16 (1H, s), 7.19 (1H, dd, J = 8.3, 1.71 Hz), 7.44–7.49 (4H, m), 7.66 (1H, d, J = 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 56.3, 60.4, 70.3, 95.2, 113.3, 116.6, 116.7, 122.6, 128.6, 128.8, 128.9, 133.8, 135.2, 144.1, 148.8, 149.0, 167.0; IR (neat): 1705, 1508, 1256, 1157 cm^{-1}; MS (EI): m/z 376 (M^+); HRMS: Calcd for $C_{20}H_{21}ClO_5$ 376.1087, Found: 376.1087.

4.2.3. (*E*)-Ethyl 3-{3-[(4-fluorobenzyl)oxy]-4-(methoxymethoxy)phenyl}acrylate (4i)

Yield: 72%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (3H, t, J = 7.1 Hz), 3.51 (3H, s), 4.24 (2H, q, J = 7.1 Hz), 5.12 (2H, s), 5.25 (2H, s), 6.26 (1H, d, J = 15.9 Hz), 7.04–7.11 (4H, m), 7.14 (1H, d, J = 8.1 Hz), 7.41 (2H, dd, J = 5.4, 3.4 Hz), ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 56.3, 60.4, 70.4, 95.2, 113.3, 115.5 (d, J = 21 Hz), 116.6, 122.6, 128.9, 129.2 (d, J = 8.5 Hz), 132.4 (J = 2.5 Hz), 144.1, 148.8, 149.0, 162.5 (J = 246 Hz), 167.1; IR (neat): 1705, 1514, 1256, 1157 cm^{-1}; MS (EI): m/z 360 (M^+); HRMS: Calcd for $C_{20}H_{21}FO_5$ 360.1373, Found: 360.1375.

4.2.4. (*E*)-Ethyl 3-[3-butoxy-4-(methoxymethoxy)phenyl]acrylate (4j)

Yield: 93%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.978 (3H, t, J = 7.3 Hz), 1.33 (3H, t, J = 7.1 Hz), 1.52 (2H, sex, J = 7.3 Hz), 1.81 (2H, quint, J = 7.3 Hz), 3.51 (3H, s), 4.04 (2H, t, J = 7.3 Hz), 4.26 (2H, t, J = 7.1 Hz), 5.24 (2H, s), 6.31 (1H, d, J = 15.9 Hz), 7.04 (1H, d, J = 7.3 Hz), 7.05 (1H, s), 7.11 (1H, d, J = 8.8 Hz), 7.61 (1H, d, J = 15.9 Hz), ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.8, 14.3, 19.2, 31.2, 56.3, 60.4, 68.7, 95.3, 112.0, 116.5, 116.9, 122.0, 129.0, 144.4, 148.7, 149.6, 167.2; IR (neat): 1715, 1508, 1256, 1159 cm^{-1}; MS (EI): m/z 308 (M^+); HRMS: Calcd for $C_{17}H_{24}O_5$ 308.1624, Found: 308.1621.

4.2.5. (*E*)-Ethyl 3-[4-(methoxymethoxy)-3-phenethoxyphenyl]acrylate (4k)

Yield: 95%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (3H, t, J = 7.2 Hz), 3.16 (2H, t, J = 7.2 Hz), 3.51 (3H, s), 4.22–4.27 (4H, m), 5.20 (2H, s), 6.27 (1H, d, J = 15.9 Hz), 7.07 (1H, dd, J = 9.5, 1.7 Hz), 7.10 (1H, s), 7.11 (1H, d, J = 8.3 Hz), 7.30–7.35 (5H, m), 7.61 (1H, d, J = 15.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 35.7, 56.3, 60.4, 69.8, 95.3, 112.2, 116.6, 116.9, 122.3, 126.6, 128.5, 129.0, 137.9, 144.3, 148.7, 149.3, 167.1; IR (neat): 1707, 1508, 1256, 1159 cm^{-1}; MS (EI): m/z 356 (M^+); HRMS: Calcd for $C_{21}H_{24}O_5$ 356.1624, Found: 356.1623.

4.2.6. (*E*)-Ethyl 3-[3-((*E*)-but-2-en-1-yloxy)-4-(methoxymethoxy)phenyl]acrylate (4l)

Yield: 84%; mp: 88–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (3H, t, J = 7.1 Hz), 1.75 (3H, d, J = 5.7 Hz), 3.51 (3H, s), 4.25 (2H, q, J = 7.1 Hz), 4.55 (2H, d, J = 5.7 Hz), 5.25 (2H, s), 5.75 (1H, m), 5.87 (1H, m), 6.29 (1H, d, J = 16.0 Hz), 7.08 (1H, s), 7.14 (2H, d, J = 8.8 Hz); 7.61 (1H, d, J = 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 17.9, 56.3, 60.4, 69.7, 95.2, 112.5, 116.4, 116.4, 122.1, 125.7, 128.8, 130.9, 144.4, 148.9, 149.0, 167.2; IR (KBr): 1715, 1508, 1256, 1159 cm^{-1}; MS (EI): m/z 306 (M^+); HRMS: Calcd for $C_{17}H_{22}O_5$ 306.1467, Found: 306.1469.

4.2.7. (*E*)-Ethyl 3-{4-(methoxymethoxy)-3-[(4-methylbenzyl)oxy]phenyl}acrylate (4m)

Yield: 96%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (3H, t, J = 7.1 Hz), 2.36 (3H, s), 3.51 (3H, s), 4.24 (2H, q, J = 7.1 Hz), 5.13 (2H, s), 5.25 (2H, s), 6.25 (1H, d, J = 15.9 Hz), 7.08 (1H, d, J = 7.3 Hz), 7.09 (1H, s), 7.13 (1H, d, J = 8.8 Hz), 7.18 (2H, d, J = 7.8 Hz), 7.32 (2H, d, J = 7.8 Hz), 7.57 (1H, d, J = 15.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 21.1, 56.3, 60.3, 70.9, 95.2, 113.3, 116.5, 116.7, 122.3, 127.3, 128.8, 129.2, 133.6, 137.7, 144.3, 148.9, 149.1, 167.1; IR (neat): 1705, 1508, 1256, 1157 cm^{-1}; MS (EI): m/z 356 (M^+); HRMS: Calcd for $C_{21}H_{24}O_5$ 356.1624, Found: 356.1627.

4.2.8. (*E*)-Ethyl 3-{3-[(3-fluorobenzyl)oxy]-4-(methoxymethoxy)phenyl}acrylate (4n)

Yield: 87%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (3H, t, J = 7.1 Hz), 3.53 (3H, s), 4.25 (2H, t, J = 7.1 Hz), 5.16 (2H, s), 5.18 (2H, s), 6.25 (1H, d, J = 15.9 Hz), 7.02 (1H, t, J = 7.6 Hz), 7.07 (1H, dd, J = 6.3, 1.7 Hz), 7.10 (1H, s), 7.11 (1H, dd, J = 7.1, 2.0 Hz), 7.151–7.230 (2H, m), 7.40–7.38 (1H, m), 7.57 (1H, d, J = 15.9 Hz), ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 56.3, 60.3, 70.2, 95.2, 113.2, 114.0 (d, J = 22 Hz), 114.8 (d, J = 22 Hz), 116.55, 116.63, 122.5 (d, J = 2.4 Hz), 122.6, 128.8, 130.1 (d, J = 7.4 Hz), 139.3 (d, J = 7.4 Hz), 144.0, 148.7, 149.0, 163.0 (d, J = 247 Hz), 167.0; IR (neat): 1701, 1510, 1251, 1130 cm^{-1}; MS (EI): m/z 360 (M^+); HRMS: Calcd for $C_{20}H_{21}FO_5$ 360.1373, Found: 360.1374.

4.2.9. (*E*)-Ethyl 3-{3-[(2-fluorobenzyl)oxy]-4-(methoxymethoxy)phenyl}acrylate (4o)

Yield: 99%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (3H, t, J = 7.1 Hz), 3.51 (3H, s), 4.25 (2H, quin, J = 7.1 Hz), 5.23 (2H, s), 5.25 (2H, s), 6.28 (1H, d, J = 15.9 Hz), 7.10–7.16 (5H, m), 7.28 (1H, t, J = 8.1 Hz), 7.52 (1H, t, J = 8.1 Hz), 7.60 (1H, d, J = 15.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 56.3, 60.4, 64.8, 64.9, 95.3, 113.3, 115.4 (d, J = 21 Hz), 116.7 (d, J = 7.3 Hz), 122.7, 123.8 (d, J = 21 Hz), 124.3 (d, J = 3.7 Hz), 129.0, 129.6, 129.7, 129.8 (d, J = 7.3 Hz), 144.2, 148.8, 149.0, 160.4 (d, J = 247 Hz), 167.1; IR (neat): 1705, 1508, 1256, 1159 cm^{-1}; MS (EI): m/z 360 (M^+); HRMS: Calcd for $C_{20}H_{21}FO_5$ 360.1373, Found: 360.1372.

4.2.10. (*E*)-Ethyl-3-{3-[(3,5-difluorobenzyl)oxy]-4-(methoxymethoxy)phenyl}acrylate (4p)

Yield: 87%; mp: 78–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (3H, t, J = 7.1 Hz), 3.53 (3H, s), 4.25 (2H, quin, J = 7.1 Hz), 5.14 (2H, s), 5.28 (2H, s), 6.26 (1H, d, J = 16.0 Hz), 6.76 (1H, t, J = 8.8 Hz), 6.98 (2H, d, J = 6.1 Hz), 7.04 (1H, s), 7.15 (2H, quin, J = 8.8 Hz), 7.57 (1H, d, J = 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 56.4, 60.5, 69.8, 95.2, 103.4 (t, J = 28 Hz), 109.6 (d, J = 6.1 Hz), 109.7 (d, J = 6.1 Hz), 113.3, 116.5, 116.8, 122.9, 128.9, 140.8 (t, J = 9.8 Hz), 144.0, 148.5, 149.0, 163.2 (d, J = 249 Hz), 163.3 (d, J = 249 Hz), 167.0; IR (KBr): 1701, 1510, 1252, 1130 cm^{-1}; MS (EI): m/z 378 (M^+); HRMS: Calcd for $C_{20}H_{20}F_2O_5$ 378.1279, Found: 378.1275.

4.3. General procedure for the synthesis of carboxylic acids (5f–5p)

To a stirred solution of the ester (**4**, 1 mmol) in MeOH/H_2O (3:1) was added LiOH·H_2O (2 mmol), and the resulting mixture was refluxed for 2 h. After cooling, the reaction was quenched by 10% HCl. The aqueous mixture was extracted with EtOAc (5 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated. To the residue were added THF (4 mL), and 10% HCl (5 drop), and the resulting mixture was refluxed for 12 h. After cooling, the reaction mixture was saturated with NaCl, and the aqueous mixture was extracted with hot EtOAc (5 mL × 5). The organic extracts were combined, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel (15 g, CH_2Cl_2 only) to give the corresponding carboxylic acid. Compounds **5a**,[33] **5b**,[34] **5c**,[35] **5d**,[36] and **5e**[35] were known compounds.

4.3.1. (*E*)-3-[3-(Benzyloxy)-4-hydroxyphenyl]acrylic acid (5f)

Yield: 88%; mp: 180–184 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.13 (2H, s), 5.28 (2H, s), 6.24 (1H, d, J = 15.9 Hz), 6.93 (1H, d, J = 8.5 Hz), 7.10 (1H, d, J = 6.8 Hz), 7.11 (1H, s), 7.36–7.42 (5H, m), 7.65 (1H, d, J = 15.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 70.3, 113.5, 116.2, 116.4, 123.6, 126.2, 128.3, 128.9, 137.7, 145.0, 147.3, 147.6, 150.0, 168.5; IR (KBr): 3028, 1684, 1514, 1271, 1200 cm^{-1}, MS (EI): m/z 270 (M^+); HRMS: Calcd for $C_{16}H_{14}O_4$ 270.0892, Found: 270.0890.

4.3.2. (*E*)-3-{4-Hydroxy-3-[(2-methylallyl)oxy]phenyl}acrylic acid (5g)

Yield: 99%; mp: 145–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.77 (3H, s), 4.51 (2H, s), 4.93 (1H, s), 5.10 (1H, s), 6.31 (1H, d,

J = 15.8 Hz), 6.80 (1H, d, J = 8.3 Hz), 7.06 (1H, dd, J = 6.3, 2.0 Hz), 7.26 (1H, d, J = 2.3 Hz), 7.45 (d, J = 15.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 19.8, 72.1, 112.9, 113.3, 116.1, 116.3, 123.5, 126.2, 141.5, 145.0, 147.2, 149.8, 168.5; IR (KBr): 3524, 1693, 1516, 1277, 1165 cm^{-1}; MS (EI): m/z 234 (M^+); HRMS: Calcd for $C_{13}H_{14}O_4$ 234.0892, Found: 234.0981.

4.3.3. (*E*)-3-{3-[(4-Chlorobenzyl)oxy]-4-hydroxyphenyl}acrylic acid (5h)

Yield: 99%; mp: 188–190 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.16 (1H, s), 6.30 (1H, d, J = 16.0 Hz), 6.99 (1H, d, J = 8.5 Hz), 7.13 (1H, s), 7.17 (1H, d, J = 8.5 Hz), 7.35–7.49 (4H, m), 7.71 (1H, d, J = 16.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 69.0, 113.1, 115.8, 115.9, 123.3, 125.7, 128.4, 129.6, 132.4, 136.3, 144.4, 146.6, 149.5, 168.0; IR (KBr): 3065, 1684, 1514, 1269 cm^{-1}; MS (EI): m/z 304 (M^+); HRMS: Calcd for $C_{16}H_{13}ClO_4$ 304.0502, Found: 304.0502.

4.3.4. (*E*)-3-{3-[(4-Fluorobenzyl)oxy]-4-hydroxyphenyl}acrylic acid (5i)

Yield: 78%; mp: 216–218 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.11 (2H, s), 6.26 (1H, d, J = 16.0 Hz), 6.95 (1H, d, J = 8.1 Hz), 7.10 (4H, m), 7.41 (2H, dd, J = 5.1, 4.4 Hz), 7.68 (1H, d, J = 16.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 69.5, 113.6, 115.7 (d, J = 22 Hz), 116.2, 116.4, 123.7, 126.2, 130.5 (d, J = 8.5 Hz), 133.9 (d, J = 2.4 Hz), 144.9, 147.2, 150.0, 162.2 (d, J = 243 Hz), 168.5; IR (KBr): 2934, 1682, 1512, 1273, 1190 cm^{-1}, MS (EI): m/z 288 (M^+); HRMS: Calcd for $C_{16}H_{13}FO_4$ 288.0798, Found: 288.0796.

4.3.5. (*E*)-3-(3-Butoxy-4-hydroxyphenyl)acrylic acid (5j)

Yield: 99%; mp: 129–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (3H, t, J = 7.3 Hz), 1.51 (2H, sex, J = 7.3 Hz), 1.83 (2H, quin, J = 7.3 Hz), 4.09 (2H, t, J = 7.3 Hz), 5.92 (1H, s), 6.28 (1H, d, J = 15.9 Hz), 6.93 (1H, d, J = 8.1 Hz), 7.04 (1H, s), 7.08 (1H, dd, J = 6.1, 2.0 Hz), 7.69 (1H, d, J = 15.9 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.3, 19.2, 31.3, 68.5, 112.8, 114.8, 116.1, 123.2, 126.3, 145.1, 147.8, 149.8, 168.6; IR (KBr): 2939, 1690, 1516, 1269 cm^{-1}; MS (EI): m/z 236 (M^+); HRMS: Calcd for $C_{13}H_{16}O_4$ 236.1049, Found: 236.1049.

4.3.6. (*E*)-3-(4-Hydroxy-3-phenethoxyphenyl)acrylic acid (5k)

Yield: 92%, mp: 147–149 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.03 (2H, t, J = 7.2 Hz), 4.19 (2H, t, J = 7.2 Hz), 6.34 (1H, d, J = 16.0 Hz), 6.78 (1H, d, J = 8.3 Hz), 7.05 (1H, dd, J = 6.6, 1.7 Hz), 7.19 (1H, t, J = 7.2 Hz), 7.25–7.29 (3H, m), 7.32 (2H, d, J = 7.2 Hz), 7.47 (1H, d, J = 16.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 35.6, 69.6, 113.1, 116.16, 116.21, 123.5, 126.4, 126.8, 128.8, 129.6, 138.9, 145.0, 147.6, 149.8, 168.6; IR (KBr): 2974, 1693, 1516, 1165 cm^{-1}; MS (EI): m/z 284 (M^+); HRMS: Calcd for $C_{17}H_{16}O_4$ 284.1049, Found: 284.1051.

4.3.7. (*E*)-3-{3-[(*E*)-But-2-en-1-yloxy]-4-hydroxyphenyl}acrylic acid (5l)

Yield: 85%; mp: 151–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78 (3H, d, J = 5.6 Hz), 4.56 (2H, d, J = 5.6 Hz), 5.72 (1H, m), 5.87–5.95 (2H, m), 6.28 (1H, d, J = 16.1 Hz), 6.93 (1H, d, J = 8.3 Hz), 7.06 (1H, s), 7.10 (1H, dd, J = 6.3, 1.8 Hz), 7.69 (1H, d, J = 16.1 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 18.1, 69.3, 113.2, 116.1, 116.2, 123.3, 126.2, 127.2, 130.1, 145.0, 147.3, 149.9, 168.5; IR (KBr): 2924, 1684, 1512, 1267 cm^{-1}; MS (EI): m/z 234 (M^+); HRMS: Calcd for $C_{13}H_{14}O_4$ 234.0892, Found: 234.0892.

4.3.8. (*E*)-3-{4-Hydroxy-3-[(4-methylbenzyl)oxy]phenyl}acrylic acid (5m)

Yield: 90%; mp: 151–153 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (3H, s), 5.10 (2H, s), 6.25 (1H, d, J = 15.9 Hz), 6.94 (1H, d, J = 7.8 Hz), 7.11 (1H, d, J = 8.5 Hz), 7.12 (1H, s), 7.22 (2H, d, J = 7.9 Hz), 7.32 (2H, d, J = 7.9 Hz), 7.69 (1H, d, J = 15.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 70.7, 111.1, 114.4, 115.0, 123.7, 126.6, 128.1, 129.5, 146.1, 147.1, 147.5, 148.6, 148.8, 161.9, 182.6; IR (KBr): 3535, 2945, 1684, 1510, 1269 cm^{-1}; MS (EI): m/z 284 (M^+); HRMS: Calcd for $C_{17}H_{16}O_4$ 284.1049, Found: 284.1051.

4.3.9. (*E*)-3-{3-[(3-Fluorobenzyl)oxy]-4-hydroxyphenyl}acrylic acid (5n)

Yield: 95%; mp: 157–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12 (3H, s), 5.15 (2H, s), 6.25 (1H, d, J = 15.9 Hz), 6.97 (1H, d, J = 8.1 Hz), 7.09 (2H, s), 7.14 (2H, d, J = 8.1 Hz), 7.20 (1H, d, J = 8.1 Hz), 7.40 (1H, q, J = 5.9 Hz), 7.68 (1H, d, J = 15.7 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 69.5, 113.6, 114.7, 114.9 (d, J = 7.4 Hz), 115.2 (d, J = 19.0 Hz), 116.3 (d, J = 19 Hz), 121.3, 123.8, 124.0 (d, J = 2.5 Hz), 126.3, 130.9 (d, J = 7.4 Hz), 144.9, 147.1, 149.9, 163.8 (d, J = 243 Hz), 168.5; IR (KBr): 3535, 2928, 1684, 1514, 1273 cm^{-1}; MS (EI): m/z 288 (M^+); HRMS: Calcd for $C_{16}H_{13}FO_4$ 288.0798, Found: 288.0796.

4.3.10. (*E*)-3-{3-[(2-Fluorobenzyl)oxy]-4-hydroxyphenyl}acrylic acid (5o)

Yield: 86%; mp: 172–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.20 (2H, s), 5.28 (2H, s), 5.92 (1H, br), 6.26 (1H, d, J = 15.9 Hz), 6.94 (1H, d, J = 8.1 Hz), 7.11–7.20 (5H, m), 7.36 (1H, t, J = 7.1 Hz), 7.42 (1H, t, J = 7.1 Hz), 7.66 (1H, d, J = 15.9 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 64.6, 113.5, 115.8 (d, J = 21 Hz), 116.4 (d, J = 21 Hz), 123.8, 124.5 (d, J = 8.6 Hz), 125.0 (d, J = 2.5 Hz), 126.3, 130.8 (d, J = 8.6 Hz), 131.3, 131.3, 144.9, 147.3, 149.9, 160.9 (d, J = 246 Hz), 168.5; IR (KBr): 3425, 2968, 1686, 1516, 1274, 1180 cm^{-1}; MS (EI): m/z 288 (M^+); HRMS: Calcd for $C_{16}H_{13}FO_4$ 288.0798, Found: 288.0796.

4.3.11. (*E*)-3-{3-[(3,5-Difluorobenzyl)oxy]-4-hydroxyphenyl}acrylic acid (5p)

Yield: 82%; mp: 207–209 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.14 (1H, s), 6.25 (1H, d, J = 15.9 Hz), 6.83 (1H, t, J = 8.3 Hz), 6.98–7.00 (3H, m), 7.05 (1H, s), 7.15 (1H, d, J = 8.3 Hz), 7.66 (1H, d, J = 15.9 Hz), ^{13}C NMR (125 MHz, DMSO-d_6): δ 69.1, 103.6 (t, J = 26 Hz), 110.8 (d, J = 6.1 Hz), 111. (d, J = 6.1 Hz), 113.7, 116.4, 116.7, 124.1, 126.5, 142.5 (t, J = 9.2 Hz), 144.9, 146.4, 146.9, 150.0, 162.9 (d, J = 247 Hz), 163.0 (d, J = 247 Hz), 168.6; IR (KBr): 3543, 1684, 1516, 1277 cm^{-1}; MS (EI): m/z 378 (M^+); HRMS: Calcd for $C_{16}H_{12}F_2O_4$ 306.0704, Found: 306.0701.

4.4. General procedure for condensation reaction of 5

Method A: ***6a–6p:*** To a stirred solution of carboxylic acid (**5**, 1 mmol) in CH_2Cl_2 (8 mL) were added Et_3N (6 mmol), and hydrocinnamoyl chloride (2 mmol) at 0 °C, and the resulting mixture was stirred for 12 h at room temperature. 10% HCl (aq) was added to the reaction mixture, and the resulting mixture was stirred for 30 min. The aqueous mixture was extracted with EtOAc (5 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel (15 g, hexane/acetone = 20:1–5:1) to give corresponding ester.

Method B: ***6q–6z:*** To a stirred solution of carboxylic acid in CH_2Cl_2 (8 mL) were added EDC·HCl (1.2 equiv), DMAP (0.1 equiv), and compound **5** (1 mmol). The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (15 g, hexane/acetone = 10:1–3:1) to give corresponding ester.

4.4.1. (*E*)-3-{3-Ethoxy-4-[(3-phenylpropanoyl)oxy]phenyl}acrylic acid (6a)

Yield: 47%; mp: 145–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (3H, t, J = 7.0 Hz), 2.89 (2H, t, J = 7.8 Hz), 3.08 (2H, t, J = 7.8 Hz), 4.05 (2H, q, J = 7.0 Hz), 6.35 (1H, d, J = 15.9 Hz), 6.98 (1H, d, J = 7.8 Hz),

7.08–7.09 (3H, m), 7.20–7.32 (4H, m), 7.69 (1H, d, J = 15.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.6, 31.0, 35.5, 64.4, 112.4, 117.4, 121.5, 123.2, 126.4, 128.3, 128.6, 132.8, 140.2, 142.0, 146.4, 150.8, 170.7, 172.1; IR (KBr): 2978, 1761, 1674, 1263, 1124 cm^{-1}; MS (EI): m/z 340 (M^+); HRMS: Calcd for $C_{20}H_{20}O_5$ 340.1311, Found: 340.1309.

4.4.2. (*E*)-3-{3-Methoxy-4-[(3-phenylpropanoyl)oxy]phenyl}acrylic acid (6b)

Yield: 41%; mp: 163–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.91 (2H, t, J = 7.6 Hz), 3.07 (2H, t, J = 7.6 Hz), 3.81 (3H, s), 6.37 (1H, d, J = 16.0 Hz), 6.97 (1H, d, J = 8.1 Hz), 7.09 (1H, s), 7.10 (1H, d, J = 8.1 Hz), 7.22–7.31 (5H, m), 7.70 (1H, d, J = 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.8, 35.5, 55.9, 111.4, 117.4, 121.6, 123.3, 126.4, 128.4, 128.5, 132.9, 140.1, 141.8, 146.3, 151.4, 170.7, 172.1; IR (KBr): 2936, 1674, 1508, 1265, 1126 cm^{-1}; MS (EI): m/z 326 (M^+); HRMS: Calcd for $C_{19}H_{18}O_5$ 326.1154, Found: 326.1156.

4.4.3. (*E*)-3-{3-Isobutoxy-4-[(3-phenylpropanoyl)oxy]phenyl}acrylic acid (6c)

Yield: 42%; mp: 116–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (6H, d, J = 7.8 Hz), 2.03 (1H, m); 2.89 (2H, t, J = 7.6 Hz), 3.07 (2H, t, J = 7.6 Hz), 3.74 (2H, d, J = 7.6 Hz), 6.36 (1H, d, J = 15.8 Hz), 6.98 (1H, d, J = 7.8 Hz), 7.08 (1H, s), 7.10 (1H, d, J = 7.8 Hz), 7.24–7.31 (5H, m), 7.70 (1H, d, J = 15.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.1, 28.2, 30.9, 35.6, 74.9, 112.1, 117.3, 121.4, 123.1, 126.4, 128.3, 128.6, 132.8, 140.2, 141.9, 146.3, 150.9, 170.6, 172.0; IR (KBr): 2965, 1762, 1691, 1265, 1123 cm^{-1} MS (EI): m/z 368 (M^+); HRMS: Calcd for $C_{22}H_{24}O_5$ 368.1624, Found: 368.1624.

4.4.4. (*E*)-3-{3-Propoxy-4-[(3-phenylpropanoyl)oxy]phenyl}acrylic acid (6d)

Yield: 42%, mp: 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (3H, t, J = 6.3 Hz), 1.77 (2H, quin, J = 6.3 Hz), 2.91 (2H, t, J = 7.9 Hz), 3.09 (2H, t, J = 7.9 Hz), 3.96 (2H, t, J = 6.3 Hz), 6.38 (1H, d, J = 15.8 Hz), 7.00 (1H, d, J = 7.7 Hz), 7.11 (1H, s), 7.12 (1H, d, J = 7.7 Hz), 7.23–7.28 (3H, m), 7.32 (2H, t, J = 7.7 Hz), 7.71 (1H, d, J = 15.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.4, 22.4, 31.0, 35.5, 70.2, 112.3, 117.5, 121.4, 123.1, 126.4, 128.3, 128.5, 132.9, 140.2, 142.0, 146.2, 150.9, 170.6, 172.0; IR (KBr): 2966, 1763, 1690, 1263, 1124 cm^{-1}; MS (EI): m/z 354 (M^+); HRMS: Calcd for $C_{21}H_{22}O_5$ 354.1467, Found: 354.1467.

4.4.5. (*E*)-3-{3-Isopropoxy-4-[(3-phenylpropanoyl)oxy]phenyl}acrylic acid (6e)

Yield: 63%; mp: 141–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (6H, d, J = 6.1 Hz), 2.88 (2H, t, J = 7.8 Hz), 3.07 (2H, t, J = 7.8 Hz), 4.54 (1H, sept, J = 6.1 Hz), 6.35 (1H,d, J = 16.0 Hz), 6.98 (1H, d, J = 8.5 Hz), 7.10–7.16 (2H, m), 7.20–7.32 (5H, m), 7.69 (1H, d, J = 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.9, 30.88, 30.93, 35.6, 71.3, 114.0, 117.4, 121.2, 123.4, 126.4, 128.3, 128.5, 132.8, 140.2, 142.8, 146.3, 149.7, 170.6, 172.1; IR (KBr): 2960, 1684, 1506, 1269, 1128 cm^{-1}; MS (EI): m/z 354 (M^+); HRMS: Calcd for $C_{21}H_{22}O_5$ 354.1467, Found: 354.1464.

4.4.6. (*E*)-3-{3-(Benzyloxy)-4-[(3-phenylpropanoyl)oxy]phenyl}acrylic acid (6f)

Yield: 62%; mp: 138–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.73 (2H, t, J = 7.8 Hz), 2.87 (2H, t, J = 7.8 Hz), 4.96 (2H, s), 6.21 (1H, d, J = 16.0 Hz), 6.89 (1H, d, J = 8.6 Hz), 7.01 (2H, d, J = 8.6 Hz), 7.09 (3H, t, J = 7.4 Hz), 7.12–7.17 (2H, m), 7.20–7.26 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.9, 35.6, 70.8, 113.0, 117.6, 121.8, 123.3, 126.4, 127.4, 128.2, 128.3, 128.5, 128.6, 132.9, 136.1, 140.1, 142.2, 146.0, 150.5, 170.8, 171.5; IR (KBr): 2926, 1761, 1690, 1508, 1261, 1123 cm^{-1}; MS (EI): m/z 402 (M^+); HRMS: Calcd for $C_{25}H_{22}O_5$ 402.1467, Found 402.1465.

4.4.7. (*E*)-3-{3-[(2-Methylallyl)oxy]-4-[(3-phenylpropanoyl)oxy]phenyl}acrylic acid (6g)

Yield: 65%; mp: 110–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.79 (3H, s), 2.92 (2H, t, J = 7.7 Hz), 3.09 (2H, t, J = 7.7 Hz), 4.46 (2H, s), 5.00 (1H, s), 5.07 (1H, s), 6.36 (1H, d, J = 15.9 Hz), 7.01 (1H, d, J = 8.3 Hz), 7.10 (1H, s), 7.13 (1H, d, J = 8.3 Hz), 7.24–7.34 (5H, m), 7.69 (1H, d, J = 15.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.2, 30.9, 35.5, 72.3, 112.8, 113.1, 117.4, 121.6, 123.3, 126.4, 128.4, 128.6, 132.8, 139.7, 140.1, 142.0, 146.3, 150.5, 170.6, 171.7; IR (KBr): 2928, 1763, 1692, 1132 cm^{-1}; MS (EI): 366 m/z (M^+); HRMS: Calcd for $C_{22}H_{22}O_5$ 366.1467, Found: 366.1465.

4.4.8. (*E*)-3-{3-[(4-Chlorobenzyl)oxy]-4-[(3-phenylpropanoyl)oxy]phenyl}acrylic acid (6h)

Yield: 47%; mp: 158–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.87 (2H, t, J = 8.1 Hz), 3.00 (2H, t, J = 8.1 Hz), 5.05 (2H, s), 6.34 (1H, d, J = 15.9 Hz), 7.03 (1H, d, J = 8.1 Hz), 7.12 (1H, s), 7.15–7.36 (10H, m), 7.68 (1H, d, J = 15.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.8, 35.5, 69.9, 112.9, 117.5, 122.0, 123.4, 126.4, 128.3, 128.5, 128.7, 128.8, 132.8, 134.0, 134.5, 140.0, 142.2, 146.1, 150.3, 170.7, 172.2; IR (KBr): 2928, 1763, 1692, 1259, 1121 cm^{-1}; MS (EI): m/z 436 (M^+); HRMS: Calcd for $C_{25}H_{21}ClO_5$ 436.1078, Found: 436.1073.

4.4.9. (*E*)-3-{3-[(4-Fluorobenzyl)oxy]-4-[(3-phenylpropanoyl)oxy]phenyl}acrylic acid (6i)

Yield: 22%; mp: 130–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.84 (2H, t, J = 7.8 Hz), 3.00 (2H, t, J = 7.8 Hz), 5.05 (2H, s), 6.35 (1H, d, J = 16.0 Hz), 7.05 (4H, dd, J = 8.1, 8.30 Hz), 7.14–7.31 (6H, m), 7.35 (2H, dd, J = 5.4, 2.9 Hz), 7.69 (1H, d, J = 16.0 Hz), ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.9, 35.6, 70.1, 112.9, 115.6 (d, J = 22 Hz), 117.5, 122.0, 123.4, 126.4, 128.3, 128.6, 129.3 (d, J = 8.6 Hz), 131.9 (d, J = 2.5 Hz), 132.9, 140.1, 142.2, 146.1, 150.4, 162.6 (d, J = 245 Hz), 170.7, 171.6; IR (KBr): 2926, 1761, 1512, 1261, 1121 cm^{-1}; MS (EI): m/z 420 (M^+); HRMS: Calcd for $C_{25}H_{21}FO_5$ 420.1373, Found: 420.1375.

4.4.10. (*E*)-3-{3-Butoxy-4-[(3-phenylpropanoyl)oxy]phenyl}acrylic acid (6j)

Yield: 41%; mp: 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (3H, t, J = 7.3 Hz), 1.49 (2H, sex, J = 7.3 Hz), 1.77 (2H, quin, J = 7.3 Hz), 2.94 (2H, t, J = 7.9 Hz), 3.13 (2H, t, J = 7.9 Hz), 4.04 (2H, t, J = 7.3 Hz), 6.42 (1H, d, J = 15.9 Hz), 7.04 (1H, d, J = 8.5 Hz), 7.14 (1H, s), 7.15 (1H, d, J = 7.1 Hz), 7.26–7.38 (5H, m), 7.75 (1H, d, J = 15.9 Hz), ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 19.2, 31.2, 35.7, 68.6, 112.3, 117.4, 121.1, 123.3, 126.5, 128.5, 128.7, 140.2, 140.3, 146.4, 164.2, 165.6, 170.7, 171.7; IR (KBr): 2932, 1761, 1690, 1263, 1126 cm^{-1}; MS (EI): m/z 368 (M^+); HRMS: Calcd for $C_{22}H_{24}O_5$ 368.1624, Found: 368.1621.

4.4.11. (*E*)-3-{3-Phenethoxy-4-[(3-phenylpropanoyl)oxy]phenyl}acrylic acid (6k)

Yield: 40%; mp: 82–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.83 (2H, t, J = 7.4 Hz), 3.02 (4H, t, J = 7.4 Hz), 4.20 (2H, t, J = 7.4 Hz), 6.31 (1H, d, J = 15.9 Hz), 6.97 (1H, d, J = 8.1 Hz), 7.07 (1H, s), 7.08 (1H, d, J = 8.1 Hz), 7.26–7.30 (5H, m), 7.66 (1H, d, J = 15.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.8, 35.4, 35.5, 69.3, 112.4, 117.4, 121.7, 123.3, 126.4, 126.6, 128.4, 128.5, 128.6, 128.9, 132.8, 137.6, 140.2, 142.0, 146.3, 150.7, 170.6, 172.0; IR (KBr): 2924, 1763, 1692, 1261, 1124 cm^{-1}; MS (EI): m/z 416 (M^+); HRMS: Calcd for $C_{26}H_{24}O_5$ 416.1624, Found: 416.1628.

4.4.12. (*E*)-3-{3-[(*E*)-But-2-en-1-yloxy]-4-[(3-phenylpropanoyl)oxy]phenyl}acrylic acid (6l)

Yield: 41%; mp: 100–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74 (3H, d, J = 5.9 Hz), 2.92 (2H, t, J = 7.9 Hz), 3.09 (2H, t, J = 7.9 Hz), 4.49 (2H, d, J = 5.9 Hz), 5.61–5.69 (1H, m), 5.81–5.86 (1H, m),

6.36 (1H, d, J = 16.1 Hz), 7.00 (1H, d, J = 8.1 Hz), 7.12 (1H, s), 7.13 (1H, dd, J = 5.4, 2.3 Hz), 7.22–7.34 (5H, m), 7.71 (1H, d, J = 16.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.9, 30.9, 35.6, 69.6, 113.1, 117.3, 121.6, 123.3, 125.4, 126.4, 128.4, 128.6, 130.7, 140.2, 142.2, 146.4, 150.6, 170.7, 171.2; IR (KBr): 2926, 1761, 1690, 1124 cm^{-1}; MS (EI): m/z 366 (M^+); HRMS: Calcd for $C_{22}H_{22}O_5$ 366.1467, Found: 366.1464.

4.4.13. (*E*)-3-{3-[(4-Methylbenzyl)oxy]-4-[(3-phenylpropanoyl)oxy]phenyl}acrylic acid (6m)

Yield: 41%; mp: 148–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (3H, s), 2.84 (2H, t, J = 7.8 Hz), 2.98 (2H, t, J = 7.8 Hz), 5.05 (2H, s), 6.34 (1H, d, J = 16.0 Hz),7.02 (1H, d, J = 7.8 Hz), 7.14 (1H, d, J = 7.8 Hz), 7.12 (1H, s), 7.17–7.29 (9H, m), 7.68 (1H, d, J = 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.8, 30.9, 35.6, 70.7, 113.0, 117.4, 121.8,123.2, 126.3, 127.5, 128.3, 128.5, 129.3, 132.8, 133.0, 138.0, 140.2, 142.3, 146.3, 150.6, 170.7, 172.1; IR (KBr): 2924, 1759, 1686, 1259, 1130 cm^{-1}; MS (EI): m/z 356 (M^+); HRMS: Calcd for $C_{26}H_{24}O_5$ 416.1624, Found: 416.1620.

4.4.14. (*E*)-3-{3-[(3-Fluorobenzyl)oxy]-4-[(3-phenylpropanoyl)oxy]phenyl}acrylic acid (6n)

Yield: 56%; mp: 115–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.84 (2H, t, J = 8.3 Hz), 2.95 (2H, t, J = 8.3 Hz), 5.02 (2H, s), 6.28 (1H, d, J = 15.9 Hz), 6.97 (2H, d, J = 8.1 Hz), 7.05 (1H, s), 7.08 (2H, d, J = 7.6 Hz), 7.15–7.23 (7H, m), 7.60 (1H, d, J = 15.9 Hz), ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.9, 35.6, 69.9, 112.9, 114.3 (d, J = 21 Hz), 115.1 (d, J = 21 Hz), 117.6, 122.1, 122.6 (d, J = 2.4 Hz), 123.4, 126.4, 128.3, 128.5, 130.2 (d, J = 7.4 Hz), 132.9, 138.7 (d, J = 7.4 Hz), 140.1, 142.2, 146.1, 150.3, 163.0 (d, J = 247 Hz), 170.7, 171.7; IR (KBr): 2924, 1767, 1693, 1261, 1121 cm^{-1}; MS (EI): m/z 420 (M^+); HRMS: Calcd for $C_{25}H_{21}FO_5$ 420.1373, Found: 420.1370.

4.4.15. (*E*)-3-{3-[(2-Fluorobenzyl)oxy]-4-[(3-phenylpropanoyl)oxy]phenyl}acrylic acid (6o)

Yield: 21%; mp: 143–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.87 (2H, t, J = 7.7 Hz), 3.01 (2H, t, J = 7.7 Hz), 5.17 (2H, s), 6.37 (1H, d, J = 15.9 Hz) (2H, d, J = 8.1 Hz), 7.08–7.31 (9H, m), 7.40 (1H, t, J = 7.3 Hz),7.70 (1H, d, J = 15.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.9, 35.6, 64.5, 113.1, 115.4 (d, J = 21 Hz), 117.6, 122.1, 123.3 (d, J = 21 Hz), 124.4 (d, J = 3.7 Hz), 126.4, 128.3, 128.5, 129.6 (d, J = 3.7 Hz), 130.04 (d, J = 8.6 Hz), 132.9, 140.1, 142.3, 146.0, 146.1, 150.3, 160.5 (d, J = 248 Hz), 190.8; IR (KBr): 2932, 1763, 1690, 1263, 1124 cm^{-1}; MS (EI): m/z 420 (M^+); HRMS: Calcd for $C_{25}H_{21}FO_5$ 420.1373, Found: 420.1376.

4.4.16. (*E*)-3-{3-[(3,5-Difluorobenzyl)oxy]-4-[(3-phenylpropanoyl)oxy]phenyl}acrylic acid (6p)

Yield: 33%; mp: 119–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.91 (2H, t, J = 7.1 Hz), 3.05 (2H, t, J = 7.1 Hz), 5.06 (2H, s), 6.35 (1H, d, J = 16.1 Hz), 6.78 (1H, t, J = 8.9 Hz), 6.92 (2H, d, J = 5.6 Hz), 7.04 (1H, d, J = 8.1 Hz), 7.08 (1H, d, J = 2.0 Hz), 7.18–7.32 (6H, m), 7.69 (1H, d, J = 16.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 31.0, 35.7, 69.5, 103.7 (t, J = 26 Hz), 109.8 (d, J = 6.1 Hz), 109.9 (d, J = 6.1 Hz), 113.0, 117.7, 122.4, 123.7, 126.5, 128.4, 128.7, 133.1, 140.1 (t, J = 9.8 Hz), 142.21, 146.1, 150.2, 160.2, 163.2 (d, J = 248 Hz), 163.4 (d, J = 248 Hz), 170.7, 171.7; IR (KBr): 2926, 1695, 1632, 1261, 1121 cm^{-1}; MS (EI): m/z 438 (M^+); HRMS: Calcd for $C_{25}H_{20}F_2O_5$ 438.1279, Found: 438.1283.

4.4.17. (*E*)-3-{3-[(3-Fluorobenzyl)oxy]-4-[(3-(3-fluorophenyl)propanoyl)oxy]phenyl}acrylic acid (6q)

Yield: 63%, mp: 152–153 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.88 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.5 Hz), 5.09 (2H, s), 6.35 (1H, d, J = 15.8 Hz), 6.88–7.03 (4H, m), 7.05 (1H, d, J = 8.0 Hz), 7.10–7.25 (5H, m), 7.34 (1H, quin, J = 8.0 Hz), 7.70 (1H, d, J = 15.8 Hz), ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.5, 30.9, 35.2, 69.9, 112.9, 113.3 (d, J = 21 Hz), 114.1 (d, J = 21 Hz), 115.2 (d, J = 21 Hz), 115.3 (d, J = 21 Hz), 117.4, 122.1, 122.61 (d, J = 2.4 Hz), 123.4, 123.9 (d, J = 2.4 Hz), 130.0 (d, J = 8.6 Hz), 130.3 (d, J = 8.6 Hz), 133.0, 138.7 (d, J = 7.3 Hz), 142.1, 142.6 (d, J = 7.3 Hz), 146.0, 150.3, 162.9 (J = 247 Hz), 163.0 (J = 247 Hz), 170.4, 170.7; IR (KBr): 2862, 1765, 1682, 1261, 1121 cm^{-1}; MS (EI): m/z 438 (M^+); HRMS: Calcd for $C_{25}H_{20}F_2O_5$ 438.1279, Found: 438.1283.

4.4.18. (*E*)-3-{3-[(3-Fluorobenzyl)oxy]-4-[(3-(4-fluorophenyl)propanoyl)oxy]phenyl}acrylic acid (6r)

Yield: 50%; mp: 154–155 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.86 (2H, t, J = 8.0 Hz), 2.99 (2H, t, J = 8.0 Hz), 5.08 (2H, s), 6.35 (1H, d, J = 16.0 Hz), 6.96 (2H, t, J = 7.9 Hz), 7.04 (2H, d, J = 7.9 Hz), 7.12–7.19 (6H, m), 7.34 (1H, quin, J = 7.9 Hz), 7.69 (1H, d, J = 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.1, 35.7, 70.0, 106.4, 113.0, 114.2 (d, J = 21 Hz), 115.2, 115.4 (d, J = 21 Hz), 115.8, 117.7, 122.2, 122.7 (d, J = 2.5 Hz), 122.8, 123.5, 129.9 (d, J = 8,6 Hz), 130.4 (d, J = 8.6 Hz), 133.1, 135.8 (d, J = 3.7 Hz), 138.8 (d, J = 7.3 Hz), 142.2, 146.2, 150.4, 157.4 (d, J = 7.3 Hz), 159.7 (d, J = 247 Hz), 160.7 (d, J = 247 Hz), 168.2, 170.6; IR (KBr): 2928, 1763, 1630, 1259, 1119 cm^{-1}; MS (EI): m/z 438 (M^+); HRMS: Calcd for $C_{25}H_{20}F_2O_5$ 438.1279, Found: 438.1278.

4.4.19. (*E*)-3-{3-[(3-Fluorobenzyl)oxy]-4-[(3-(2,4,6-trifluorophenyl)propanoyl)oxy]phenyl}acrylic acid (6s)

Yield: 59%; mp: 178–180 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.83 (2H, t, J = 7.2 Hz), 2.91 (2H, t, J = 7.2 Hz), 5.19 (2H, s), 6.56 (1H, d, J = 16.0 Hz), 7.11–7.17 (5H, m), 7.20 (1H, d, J = 7.8 Hz), 7.28 (1H, dd, J = 6.9, 1.1 Hz), 7.41 (1H, quin, J = 7.8 Hz), 7.53 (1H, d, J = 16.0 Hz), 7.56 (1H, s); ^{13}C NMR (125 MHz, DMSO-d_6): δ 17.7, 33.1, 69.5, 101.0 (t, J = 28 Hz), 113.5, 114.3 (d, J = 23 Hz), 115.2 (d, J = 23 Hz), 120.2, 122.5, 123.6, 131.0 (d, J = 8.6 Hz), 133.9, 140.1 (d, J = 7.4 Hz), 141.5, 143.7, 150.3, 160.1, 161.4 (d, J = 245 Hz), 162.7 (d, J = 245 Hz), 168.1, 170.2; IR (KBr): 2926, 1771, 1684, 1252, 1117 cm^{-1}; MS (EI): m/z 474 (M^+); HRMS: Calcd for $C_{25}H_{18}F_4O_5$ 474.1090, Found: 474.1087.

4.4.20. (*E*)-3-{4-[(3-(3-Fluorophenyl)propanoyl)oxy]-3-[(4-methylbenzyl)oxy]phenyl}acrylic acid (6t)

Yield: 48%, mp: 171–173 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (3H, s), 2.83 (2H, t, J = 8.0 Hz), 2.96 (2H, t, J = 8.0 Hz), 5.07 (2H, s), 6.35 (1H, d, J = 16.1 Hz), 6.91 (1H, d, J = 8.0 Hz), 6.96 (1H, d, J = 8.0 Hz), 7.02 (2H, d, J = 8.0 Hz), 7.16–7.28 (7H, m), 7.70 (1H, d, J = 16.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.3, 30.7, 35.3, 70.9, 89.7, 113.1, 113.4 (d, J = 21 Hz), 115.4 (d, J = 21 Hz), 117.5, 121.9, 123.3, 124.0 (d, J = 2.5 Hz), 127.7, 129.4, 130.1 (d, J = 8.5 Hz), 133.1 (d, J = 8.5 Hz), 138.2, 142.3, 142.8, 146.4, 150.7, 163.0 (J = 247 Hz), 170.6, 171.8; IR (KBr): 2924, 1763, 1693, 1259, 1121 cm^{-1}; MS (EI): m/z 434 (M^+); HRMS: Calcd for $C_{26}H_{23}FO_5$ 434.1520, Found: 434.1528.

4.4.21. (*E*)-3-{3-[(4-Methylbenzyl)oxy]-4-[(3-(2,4,6-trifluorophenyl)propanoyl)oxy]phenyl}acrylic acid (6u)

Yield: 84%; mp: 159–161 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (3H, s), 2.81 (2H, t, J = 7.8 Hz), 3.00 (2H, t, J = 7.8 Hz), 5.06 (2H, s), 6.35 (1H, d, J = 16.0 Hz), 6.64 (2H, t, J = 8.1 Hz), 7.06 (1H, d, J = 8.5 Hz), 7.14–7.26 (6H, m), 7.69 (1H, d, J = 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.7, 21.3, 33.3, 70.9, 100.0 (d, J = 8.6 Hz), 100.2 (d, J = 4.9 Hz), 100.4 (d, J = 26 Hz), 113.1, 117.4, 121.9, 123.3, 127.5, 129.4, 133.1 (d, J = 15 Hz), 138.1, 142.3, 146.4, 150.7, 170.1, 171.6; IR (KBr): 2926, 1767, 1630, 1258, 1115 cm^{-1}; MS (EI): m/z 470 (M^+); HRMS: Calcd for $C_{26}H_{21}F_3O_5$ 470.1341, Found: 470.1342.

4.4.22. (*E*)-3-{4-[(3-(4-Fluorophenyl)propanoyl)oxy]-3-[(4-methylbenzyl)oxy]phenyl}acrylic acid (6v)

Yield: 67%; mp: 168–170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (3H, s), 2.82 (2H, t, J = 7.6 Hz), 2.95 (2H, t, J = 7.6 Hz), 5.05 (2H, s), 6.35 (1H, d, J = 15.9 Hz), 6.95 (2H, t, J = 8.7 Hz), 7.02 (1H, d, J = 7.6 Hz), 7.12–7.19 (8H, m), 7.69 (1H, d, J = 15.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.2, 30.0, 35.6, 70.8, 113.0, 115.3 (d, J = 21 Hz), 117.4, 121.8, 123.2, 127.6, 129.3, 129.8 (d, J = 8.6 Hz), 132.8, 133.0, 135.8 (d, J = 3.6 Hz), 138.0, 142.2, 146.3, 150.6, 161.5 (d, J = 245 Hz), 170.6, 171.9; IR (KBr): 2924, 1763, 1630, 1512, 1119 cm^{-1}; MS (EI): m/z 434 (M^+); HRMS: Calcd for $C_{26}H_{23}FO_5$ 434.1530, Found: 434.1526.

4.4.23. (*E*)-3-{3-[(3-Fluorobenzyl)oxy]-4-{3-{4-[(tetrahydro-2*H*-pyran-2-yl)oxy]phenyl}propanoyloxyphenyl}acrylic acid (6w)

Yield: 43%; mp: 152–154 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.52–2.01 (6H, m), 2.85 (2H, t, J = 7.8 Hz), 2.97 (2H, t, J = 7.8 Hz), 3.58–3.60 (1H, m), 3.89–3.92 (1H, m), 5.10 (2H, s), 5.37 (1H, t, J = 3.0 Hz), 6.35 (1H, d, J = 16.0 Hz), 6.97 (2H, d, J = 8.3 Hz), 7.04 (2H, d, J = 8.3 Hz), 7.12–7.18 (6H, m), 7.32–7.37 (1H, m), 7.69 (1H, d, J = 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.8, 25.2, 29.7, 30.0, 35.8, 62.1, 70.0, 96.5, 113.0, 114.1 (d, J = 22 Hz), 115.1 (d, J = 22 Hz), 116.6, 117.3 (d, J = 2.5 Hz), 122.0, 122.6, 123.5, 129.2, 129.6, 130.2 (d, J = 7.3 Hz), 132.9, 138.8 (d, J = 7.3 Hz), 142.2, 146.0, 150.3, 162.9 (d, J = 248 Hz), 170.7, 173.2, IR (KBr): 2926, 1741, 1685, 1263, 1137 cm^{-1}; MS (EI): m/z 436 (M^+−84); HRMS: Calcd for $C_{25}H_{21}FO_6$ 436.1322, Found: 436.1324.

4.4.24. (*E*)-3-{3-[(3-Fluorobenzyl)oxy]-4-[(3-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)propanoyl)oxy]phenyl}acrylic acid (6x)

Yield: 42%; mp: 117–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26–2.05 (6H, m), 2.88 (2H, t, J = 7.7 Hz), 2.98 (2H, t, J = 7.7 Hz), 3.60 (1H, d, J = 11.5 Hz), 3.89 (1H, t, J = 8.8 Hz), 5.09 (2H, s), 5.41 (1H, m), 6.34 (1H, d, J = 15.9 Hz), 6.79 (1H, d, J = 7.9 Hz), 6.65 (1H, d, J = 7.9 Hz), 6.92 (1H, s), 7.01 (1H, d, J = 8.3 Hz), 7.06 (1H, d, J = 8.3 Hz), 7.12–7.22 (5H, m), 7.34 (1H, quin, J = 7.9 Hz), 7.69 (1H, d, J = 15.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.73, 25.16, 30.33, 30.83, 35.44, 62.00, 69.84, 96.24, 112.91, 114.1 (d, J = 22 Hz), 114.31, 115.1 (d, J = 22 Hz), 116.52, 117.55, 121.54, 122.00, 122.6 (d, J = 2.4 Hz), 123.39, 129.43, 130.2 (d, J = 7.4 Hz), 132.86, 138.7 (d, J = 7.4 Hz), 141.53, 142.14, 146.02, 150.25, 157.17, 163.1 (d, J = 246 Hz), 170.66, 171.82; IR (KBr): 2945, 1693, 1258, 1123 cm^{-1}; MS (EI): m/z 436 (M^+−84); HRMS: Calcd for $C_{25}H_{21}FO_6$ 436.1322, Found: 436.1322.

4.4.25. (*E*)-3-{3-[(4-Methylbenzyl)oxy]-4-[(3-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)propanoyl)oxy]phenyl}acrylic acid (6y)

Yield: 27%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26–2.35 (6H, m), 2.83 (2H, t, J = 7.8 Hz), 2.94 (2H, t, J = 7.8 Hz), 3.60 (1H, d, J = 11.2 Hz), 3.91 (1H, t, J = 9.0 Hz), 5.06 (2H, s), 5.41 (1H, m), 6.34 (1H, d, J = 15.9 Hz), 6.67 (1H, s), 6.82 (1H, d, J = 7.8 Hz), 6.91 (1H, s), 6.92 (1H, d, J = 7.8 Hz), 7.04 (1H, d, J = 7.8 Hz), 7.13–7.22 (6H, m), 7.68 (1H, d, J = 15.9 Hz); ^{13}C NMR (100 MHz,$CDCl_3$): δ 18.73, 21.14, 25.16, 30.34, 30.85, 35.45, 61.99, 70.71, 96.24, 112.99, 114.19, 116.56, 117.37, 121.53, 121.73, 123.21, 129.26, 129.39, 132.78, 133.04, 137.94, 141.64, 142.27, 146.22, 150.55, 157.16, 170.74, 171.86; IR (neat): 1684, 1506, 1259, 1121 cm^{-1}; MS (EI): m/z 432 (M^+-84); HRMS: Calcd for $C_{26}H_{24}O_6$ 432.1573, Found: 432.1570.

4.4.26. (*E*)-3-{3-[(4-Methylbenzyl)oxy]-4-[(3-(4-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)propanoyl)oxy]phenyl}acrylic acid (6z)

Yield: 61%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (3H, s), 2.81 (2H, t, J = 8.3 Hz), 2.93 (2H, t, J = 8.3 Hz), 3.59 (1H, d, J = 11.7 Hz), 3.91 (1H, t, J = 6.3 Hz), 5.05 (2H, s), 5.37 (1H, m), 6.34 (1H, d, J = 16.1 Hz), 6.97 (1H, d, J = 8.1 Hz), 7.02 (1H, d, J = 8.1 Hz), 7.08–7.31 (9H, m), 7.69 (1H, d, J = 16.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.79, 21.72, 25.19, 30.10, 30.56, 35.81, 62.03, 70.75, 96.45, 113.02, 115.34, 116.55, 117.39, 121.74, 123.24, 127.52, 129.18, 129.28, 129.37, 129.49, 132.82, 133.07, 137.97, 142.28, 146.16, 150.59, 154.29, 155.54, 170.87, 171.53; IR (neat): 1684, 1508, 1121 cm^{-1}; MS (EI): m/z 432 (M^+−84); HRMS: Calcd for $C_{26}H_{24}O_6$ 432.1573, Found: 432.1570.

4.5. General procedure for deprotection of the tetrahydro-2*H*-pyran-2-yl moiety

To a stirred solution of ester (**6w**–**6z**, 1 mmol) in CH_2Cl_2/MeOH (3:1) were added PPTS (0.3 mmol), and the resulting mixture was refluxed for 12 h. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (15 g, CH_2Cl_2/MeOH = 80:1–70:1) to give corresponding compound.

4.5.1. (*E*)-3-{3-[(3-Fluorobenzyl)oxy]-4-[(3-(4-hydroxyphenyl)propanoyl)oxy]phenyl}acrylic acid (7w)

Yield: 95%; mp: 155–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.84 (2H, t, J = 7.7 Hz), 2.96 (2H, t, J = 7.7 Hz), 5.09 (2H, s), 6.34 (1H, d, J = 16.1 Hz), 6.75 (2H, d, J = 8.3 Hz), 7.04 (2H, d, J = 8.3 Hz), 7.08–7.18 (6H, m), 7.34 (1H, quin, J = 7.8 Hz), 7.68 (1H, d, J = 16.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.0, 31.9, 35.7, 69.4, 113.5, 114.4 (d, J = 21 Hz), 115.2 (d, J = 21 Hz), 115.6, 120.1, 122.5, 123.7, 129.6, 131.0 (d, J = 7.4 Hz), 133.7, 140.1 (d, J = 7.4 Hz), 141.7, 143.7, 150.3, 156.2, 162.7 (J = 243 Hz), 168.1, 171.0; IR (KBr): 3400, 2930, 1692, 1516, 1261, 1123 cm^{-1}; MS (EI): m/z 436 (M^+); HRMS: Calcd for $C_{25}H_{21}FO_6$ 436.1322, Found: 436.1325.

4.5.2. (*E*)-3-{3-[(3-Fluorobenzyl)oxy]-4-[(3-(3-hydroxyphenyl)propanoyl)oxy]phenyl}acrylic acid (7x)

Yield: 73%; mp: 176–178 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.87 (2H, t, J = 7.8 Hz), 2.98 (2H, t, J = 7.8 Hz), 5.09 (1H, s), 6.34 (1H, d, J = 15.9 Hz), 6.68 (1H, d, J = 8.1 Hz), 6.71 (1H, s), 6.79 (1H, d, J = 8.1 Hz), 7.05 (2H, d, J = 8.1 Hz), 7.12–7.18 (5H, m), 7.34 (1H, quin, J = 8.1 Hz), 7.68 (1H, d, J = 15.9 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 30.7, 35.2, 69.4, 113.6 (d, J = 22 Hz), 114.4 (d, J = 22 Hz), 115.1, 115.7, 119.3, 120.2, 122.4, 123.7, 129.8, 130.2 (d, J = 3.7 Hz), 131.0 (d, J = 7.4 Hz), 133.7, 140.1 (d, J = 7.4 Hz), 141.7, 142.0, 143.7, 150.3, 157.9, 159.0, 162.7 (d, J = 245 Hz), 168.1, 170.9; IR (KBr): 3649, 1684, 1508, 1261, 1123 cm^{-1}; MS (EI): m/z 436 (M^+); HRMS: Calcd for $C_{25}H_{21}FO_6$ 436.1322, Found: 436.1322.

4.5.3. (*E*)-3-{4-[(3-(3-Hydroxyphenyl)propanoyl)oxy]-3-[(4-methylbenzyl)oxy]phenyl}acrylic acid (7y)

Yield: 53%; mp: 172–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.83 (2H, t, J = 7.6 Hz), 2.94 (2H, t, J = 7.6 Hz), 5.06 (2H, s), 6.24 (1H, d, J = 16.0 Hz), 6.67 (1H, s), 6.68 (1H, d, J = 7.3 Hz), 6.76 (1H, d, J = 7.3 Hz), 7.03 (1H, d, J = 7.3 Hz), 7.13–7.20 (7H, m), 7.68 (1H, d, J = 16.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): 21.3, 30.7, 31.2, 35.2, 70.3, 113.6, 113.7, 115.7, 119.3, 120.1, 122.2, 123.6, 128.1, 129.5, 129.8, 133.7, 134.1, 137.7, 141.8, 142.0, 143.8, 150.6, 157.9, 168.1, 170.9; IR (KBr): 3400, 2923, 1686, 1261, 1123 cm^{-1}; MS (EI): m/z 432 (M^+); HRMS: Calcd for $C_{26}H_{24}O_6$ 432.1573, Found: 432.1570.

4.5.4. (*E*)-3-{[4-(3-(4-Hydroxyphenyl)propanoyl)oxy]-3-[(4-methylbenzyl)oxy]phenyl}acrylic acid (7z)

Yield: 43%; mp: 155–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.80 (2H, t, J = 8.3 Hz), 2.92 (2H, t, J = 8.3 Hz), 5.05, (2H, s), 6.34 (1H, d, J = 16.1 Hz), 6.74 (2H, d, J = 8.5 Hz), 7.02 (1H, d, J = 8.3 Hz), 7.06 (2H, d, J = 8.3 Hz), 7.13–7.28 (6H, m), 7.68 (1H, d, J = 16.1 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 21.3, 29.9, 35.7, 70.3, 113.6, 115.6,

120.1, 123.6, 128.1, 129.5, 129.6, 130.7, 133.6, 134.1, 137.7, 141.7, 143.7, 150.6, 168.1, 171.0; IR (KBr): 2926, 1685, 1516, 1264, 1121 cm^{-1}; MS (EI): *m*/*z* 432 (M^+); HRMS: Calcd for $C_{26}H_{24}O_6$ 432.1573, Found: 432.1569.

4.6. General procedure for benzylation

To a stirred solution of **1** (1 mmol) in DMSO (8 mL) was added NaH (2.2 mmol) at 0 °C, and the reaction mixture was stirred for 30 min. Benzyl chloride (1 mmol) was added to the reaction mixture, and the resulting mixture was stirred for 12 h at room temperature. The reaction was quenched by 10% HCl (pH ≈ 4), and the aqueous mixture was extracted with EtOAc (5 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel (15 g, hexane/acetone = 10:1–50:1) to give corresponding benzyl ether.

4.6.1. 4-Hydroxy-3-[3-(methoxymethoxy)benzyloxy]benzaldehyde (9a)

Yield: 92%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.49 (3H, s), 5.16 (2H, s), 5.21 (2H, s), 6.22 (1H, br), 7.06 (2H, d, *J* = 8.3 Hz), 7.11 (1H, s), 7.34 (1H, t, *J* = 7.9 Hz), 7.44 (1H, t, *J* = 6.8, 1.3 Hz), 7.49 (1H, d, *J* = 1.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.0, 71.0, 94.3, 110.3, 114.7, 115.8, 116.4, 121.4, 127.6, 129.8, 129.9, 137.0, 146.3, 151.8, 157.5, 190.8; IR (neat): 1684, 1508, 1288, 1151 cm^{-1}; MS (EI): *m*/*z* 288 (M^+); HRMS: Calcd for $C_{16}H_{16}O_5$ 288.0998, Found: 288.0999.

4.6.2. 4-Hydroxy-3-[(3-methoxybenzyl)oxy]benzaldehyde (9b)

Yield: 92%; mp: 92–93 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.83 (3H, s), 5.15 (2H, s), 6.22 (1H, br), 6.92 (H, dd, *J* = 5.7, 2.6 Hz), 6.93 (1H, s), 7.01 (1H, d, *J* = 7.5 Hz), 7.06 (1H, d, *J* = 8.0 Hz), 7.34 (1H, t, *J* = 8.0 Hz), 7.45 (1H, dd, *J* = 6.3, 1.7 Hz), 7.50 (1H, d, *J* = 1.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.2, 71.0, 110.3, 113.5, 113.9, 114.7, 120.1, 127.5, 129.7, 129.8, 136.9, 146.3, 151.9, 159.8, 190.8; IR (KBr): 3368, 1686, 1597, 1292, 1271 cm^{-1}; MS (EI): *m*/*z* 258 (M^+); HRMS: Calcd for $C_{15}H_{14}O_4$ 258.0892, Found: 258.0892.

4.7. General procedure for protection of 9

To a stirred solution of **9** (1 mmol) in CH_2Cl_2 (4 mL) were added 3.4-dihydro-2*H*-pyran (1.1 mmol), and PPTS (0.2 mmol), and the resulting mixture was refluxed for 12 h. After cooling, the reaction was quenched by satd $NaHCO_3$ (aq), and the aqueous mixture was extracted with CH_2Cl_2 (5 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel (15 g, hexane/acetone = 40:1–20:1) to give corresponding compound.

4.7.1. 3-{[3-(Methoxymethoxy)benzyl]oxy}-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]benzaldehyde (10a)

Yield: 61%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60–2.06 (6H, m), 3.64 (1H, d, *J* = 11.0 Hz), 3.90 (1H, t, *J* = 8.1 Hz), 5.16 (2H, s), 5.19 (2H, s), 5.60 (1H, t, *J* = 5.6 Hz), 6.99 (1H, dd, *J* = 4.9, 2.7 Hz), 7.10 (1H, d, *J* = 7.6 Hz), 7.18 (1H, s), 7.27–7.32 (2H, m), 7.45 (1H, dd, *J* = 6.3, 2.0 Hz), 7.49 (1H, d, *J* = 7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.1, 24.8, 29.8, 54.8, 61.6, 70.4, 96.5, 97.1, 112.1, 112.5, 113.2, 115.8, 118.9, 126.2, 129.5, 130.5, 138.7, 149.1, 152.2, 159.5, 190.6; IR (neat): 1689, 1514, 1267, 1153 cm^{-1}; MS (EI): *m*/*z* 288 (M^+−84); HRMS: Calcd for $C_{16}H_{16}O_5$ 288.0998, Found: 288.1000.

4.7.2. 3-[(3-Methoxybenzyl)oxy]-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]benzaldehyde (10b)

Yield: 63%; mp: 73–77 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.55–2.17 (6H, m), 3.64 (1H, d, *J* = 7.1 Hz), 3.82 (3H, s), 3.90 (1H, t, *J* = 8.0 Hz), 5.17 (2H, s), 5.61 (1H, t, *J* = 6.1 Hz), 6.86 (1H, dd, *J* = 5.7, 2.6 Hz), 7.03 (1H, d, *J* = 6.3 Hz), 7.05 (1H, s), 7.27 (1H, m), 7.30 (1H, t, *J* = 7.5 Hz), 7.45 (1H, dd, *J* = 6.3, 2.0 Hz), 7.50 (1H, d, *J* = 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.1, 24.8, 29.8, 54.8, 61.6, 70.2, 96.5, 112.1, 112.5, 113.2, 115.8, 118.9, 126.2, 129.3, 130.5, 138.1, 149.1, 152.2, 159.5, 190.6; IR (KBr): 1684, 1508, 1273, 1123 cm^{-1}; MS (EI): *m*/*z* 258 (M^+−84); HRMS: Calcd for $C_{15}H_{14}O_4$ 258.0892, Found: 258.0892.

4.8. General procedure for Horner–Wadsworth–Emmons reaction of 10

Compounds **10a** and **10b** were esterified as described for the synthesis of **4**.

4.8.1. (*E*)-Ethyl-3-{3-[(3-(methoxymethoxy)benzyl)oxy]-4-[(tetrahydro-2*H*-pyran-2-yl)-oxy]phenyl}acrylate (11a)

Yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (3H, t, *J* = 7.1 Hz), 1.63–1.96 (6H, m), 3.47 (3H, s), 3.61 (1H, d, *J* = 11.1 Hz), 3.95 (1H, t, *J* = 7.8 Hz), 4.24 (2H, quint, *J* = 7.1 Hz), 5.11 (2H, s), 5.18 (2H, s), 5.51 (1H, t, *J* = 5.9 Hz), 6.27 (1H, d, *J* = 15.9 Hz), 6.98 (1H, dd, *J* = 5.6, 2.7 Hz), 7.08–7.16 (5H, m), 7.30 (1H, t, *J* = 7.8 Hz), 7.58 (1H, d, *J* = 15.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.8, 18.3, 25.0, 30.0, 55.8, 60.2, 61.8, 70.9, 94.2, 96.9, 114.0, 114.8, 115.6, 116.2, 117.3, 122.7, 128.5, 129.4, 138.6, 144.2, 149.0, 149.1, 157.3, 167.0; IR (neat): 1684, 1508, 1121 cm^{-1}; MS (EI): *m*/*z* 358 (M^+−84); HRMS: Calcd for $C_{20}H_{20}O_6$ 358.1416, Found: 358.1419.

4.8.2. (*E*)-Ethyl-3-{3-[(3-methoxybenzyl)oxy]-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]phenyl}acrylate (11b)

Yield: 96%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (3H, t, *J* = 7.2 Hz), 1.56–2.17 (6H, m), 3.59–3.63 (1H, m), 3.82 (3H, s), 3.94 (1H, t, *J* = 8.0 Hz), 4.24 (2H, quin, *J* = 7.2 Hz), 5.12 (2H, s), 5.51 (1H, m), 6.28 (1H, d, *J* = 15.9 Hz), 6.85 (1H, dd, *J* = 6.3, 2.3 Hz), 7.02 (1H, d, *J* = 7.8 Hz), 7.05 (1H, s), 7.10–7.16 (3H, m), 7.29 (1H, t, *J* = 7.8 Hz), 7.59 (1H, d, *J* = 15.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 18.3, 25.0, 30.0, 54.9, 60.1, 61.7, 70.8, 96.8, 112.2, 113.2, 113.8, 116.2, 117.7, 119.0, 122.6, 128.5, 129.3, 138.5, 144.2, 148.9, 149.1, 159.6, 166.9; IR (neat): 1707, 1508, 1258, 1165 cm^{-1}; MS (EI): *m*/*z* 328 (M^+−84); HRMS: Calcd for $C_{19}H_{20}O_5$ 328.1311, Found: 328.1309.

4.9. General procedure for hydrolysis and deprotection of 11

To a stirred solution of **11** (1 mmol) in MeOH/H_2O (3:1) was added LiOH·H_2O (2 mmol), and the resulting mixture was refluxed for 2 h. After cooling, the reaction was quenched by 10% HCl (aq), and the aqueous mixture was extracted with EtOAc (5 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated. To the residue were added CH_2Cl_2/MeOH (3:1) and PPTS (0.3 mmol), and the resulting mixture was stirred for 12 h at room temperature. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (15 g, CH_2Cl_2/MeOH = 80:1–70:1) to give corresponding compound.

4.9.1. (*E*)-3-{4-Hydroxy-3-[(3-(methoxymethoxy)benzyl)oxy]phenyl}acrylic acid (12a)

Yield: 99%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.51 (3H, s), 5.12 (2H, s), 5.20 (2H, s), 6.26 (1H, d, *J* = 15.9 Hz), 6.95 (1H, d, *J* = 8.1 Hz), 7.05–7.14 (5H, m), 7.34 (1H, t, *J* = 8.1 Hz), 7.67 (1H, d, *J* = 15.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.0, 71.0, 94.3, 111.3, 114.7, 115.1, 115.6, 116.4, 121.2, 123.7, 126.6, 129.9, 137.3, 146.0, 146.9, 148.6, 157.5, 172.3; IR (neat): 2361, 1684, 1508, 1271 cm^{-1}; MS (EI): *m*/*z* 330 (M^+); HRMS: Calcd for $C_{18}H_{18}O_6$ 330.1103, Found: 330.1106.

4.9.2. (*E*)-3-{4-Hydroxy-3-[(3-methoxybenzyl)oxy]phenyl}acrylic acid (12b)

Yield: 89%; mp: 167–169 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.83 (3H, s), 5.13 (2H, s), 6.26 (1H, d, J = 15.9 Hz), 6.91–6.97 (3H, m); 7.01 (1H, d, J = 8.0 Hz), 7.12 (2H, m), 7.34 (1H, t, J = 7.7 Hz), 7.67 (1H, d, J = 15.9 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.6, 70.2, 113.5, 113.7, 113.8, 116.2, 116.4, 120.4, 123.7, 126.3, 130.0, 139.3, 145.0, 147.3, 150.0, 159.9, 168.6; IR (KBr): 2939, 1684, 1514, 1271 cm^{-1}; MS (EI): m/z 300 (M^+); HRMS: Calcd for $C_{17}H_{16}O_5$ 300.0998, Found: 300.1000.

4.10. General procedure for the synthesis of 13

Compounds **13a** and **13b** were synthesized as described for the synthesis of **6a**–**6z**.

4.10.1. (*E*)-3-{3-{[3-(Methoxymethoxy)benzyl]oxy}-4-[(3-phenylpropanoyl)oxy]phenyl}acrylic acid (13a)

Yield: 93%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.88 (2H, t, J = 8.0 Hz), 3.02 (2H, t, J = 8.0 Hz), 3.44 (3H, s), 5.01 (2H, s), 5.16 (2H, s), 6.34 (1H, d, J = 16.0 Hz), 6.99–7.29 (12H, m), 7.68 (1H, d, J = 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.8, 35.5, 56.0, 70.5, 94.3, 113.0, 115.0, 115.9, 117.4, 120.6, 121.9, 123.3, 126.3, 128.3, 128.5, 129.7, 132.8, 137.7, 140.1, 142.2, 146.2, 150.5, 157.5, 170.7, 171.7; IR (neat): 2927, 1762, 1685, 1259, 1121 cm^{-1}; MS (EI): m/z 462 (M^+); HRMS: Calcd for $C_{27}H_{26}O_7$ 462.1679, Found: 462.1677.

4.10.2. (*E*)-3-{3-[(3-Methoxybenzyl)oxy]-4-[(3-phenylpropanoyl)oxy]phenyl}acrylic acid (13b)

Yield: 54%; mp: 97–99 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.79 (2H, t, J = 7.4 Hz), 3.02 (2H, t, J = 7.4 Hz), 3.80 (3H, s), 5.08 (2H, s), 6.34 (1H, d, J = 15.9 Hz), 6.86 (1H, dd, J = 5.3, 2.3 Hz), 6.95 (1H, s), 6.96 (1H, d, J = 8.0 Hz), 7.03 (1H, d, J = 8.0 Hz), 7.14–7.18 (2H, m), 7.20–7.24 (3H, m), 7.28–7.31 (3H, m), 7.68 (1H, d, J = 15.9 Hz), ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.9, 35.6, 55.2, 70.6, 112.8, 113.0, 113.6, 117.3, 119.3, 121.8, 123.3, 126.4, 128.3, 128.5, 129.7, 132.9, 137.7, 140.2, 142.2, 146.2, 150.5, 159.9, 170.7, 171.4; IR (KBr): 2934, 1763, 1690, 1265, 1122 cm^{-1}; MS (EI): m/z 432 (M^+); HRMS: Calcd for $C_{26}H_{24}O_6$ 423.1573, Found: 432.1572.

4.11. Synthesis of 14

To a stirred solution of the ester (**13b**, 1.85 mmol) in THF (5 mL) was added 10% HCl (aq, 15 drops), and the resulting mixture was heated to 40 °C for 16 h. After cooling, the reaction was quenched by H_2O. The aqueous mixture was extracted with EtOAc (5 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel (15 g, hexane/acetone = 8:1–2:1) to give **14**.

4.11.1. (*E*)-3-{3-[(3-Hydroxybenzyl)oxy]-4-[(3-phenylpropanoyl)oxy]phenyl}acrylic acid (14)

Yield: 52%; mp: 150–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.89 (2H, t, J = 7.6 Hz), 3.03 (2H, t, J = 7.6 Hz), 5.05 (2H, s), 6.31 (1H, d, J = 15.7 Hz), 6.78 (1H, dd, J = 6.1, 1.9 Hz), 6.83 (1H, s), 6.91 (1H, d, J = 7.8 Hz), 7.01 (1H, d, J = 8.1 Hz), 7.09 (1H, s), 7.12 (1H, d, J = 8.1 Hz), 7.19–7.31 (6H, m), 7.66 (1H, d, J = 15.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 31.0, 35.7, 70.4, 113.1, 114.1, 115.3, 115.7, 119.2, 121.9, 123.3, 126.5, 128.4, 128.6, 133.0, 140.2, 142.2, 146.2, 150.5, 156.2, 171.3, 171.4; IR (KBr): 3030, 1686, 1508, 1263, 1121 cm^{-1}; MS (EI): m/z 418 (M^+); HRMS: Calcd for $C_{25}H_{22}O_6$ 418.1416, Found: 418.1413.

4.12. Biological assays

4.12.1. Materials

Baccharin was gifted by API Co. Ltd (Gifu, Japan). ONE and steroids were obtained from Cayman Chemical (Ann Arbor, MI, United States) and Steraloids (Newport, RI, United States), respectively. Human A549 cells were obtained from the American Type Culture Collection (Manassas, VA, United States), and bovine aortic endothelial cells were generous gifts from Taisho Pharmaceutical Co. (Saitama, Japan).

4.12.2. Preparation of recombinant enzymes

Recombinant AKR1C1,[37] AKR1C2,[38] AKR1C3,[39] and AKR1C4[37] were prepared and purified to homogeneity, as described previously.

4.12.3. Assay of enzyme activity

The dehydrogenase activities of the AKR1C isoforms were determined at 25 °C by measuring the rate of change in NADPH fluorescence (at 455 nm with an excitation wavelength of 340 nm).[7] The IC_{50} values for inhibitors were determined in the reaction mixture that consisted of 0.1 M potassium phosphate, pH 7.4, 0.25 mM $NADP^+$, *S*-1-tetralol (0.1 mM for AKR1C1 and 1 mM for other AKR1C isoforms), and enzyme, in a total volume of 2.0 mL. Kinetic studies in the presence of inhibitors were carried out in the $NADP^+$-linked *S*-1-tetralol oxidation over a range of five substrate concentrations (0.33–2 mM) at a saturating concentration (0.25 mM) of $NADP^+$. The IC_{50} and K_i values are expressed as the means ± SD of at least three determinations.

4.12.4. Molecular modeling

Atomic coordinates for the AKR1C3–$NADP^+$–flufenamic acid complex (PDB code: 1S2C)[40] were obtained from the RCSB Protein Data Bank. The structure was prepared using the Maestro (Schrödinger, LLC) software package Version 8.5, as described previously.[41] The ligand (**6m** or **14**) was subjected to a full minimization using the program LigPrep prior to the docking. The docking calculations for the ligands were performed using the program Glide 5.0[42] on a Linux workstation (for **6m**-docked model) and Molegro Virtual Docker 5.5 (for **14**-docked model) under the conditions described previously.[43] Among the poses generated, the poses showing a distance of less than 3.5 Å between the docked molecules and the catalytically important residues, Tyr55 and His117, were selected initially. Finally, we selected the pose, in which the ligand positioned in the substrate binding site of the enzyme most similarly to baccharin in the previously reported model, which is supported by the site-directed mutagenesis results.[7] The figure showing the docked model was generated using *PyMOL* (DeLano Scientific).

4.12.5. Cell culture experiments

The cells were cultured in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum, 100 U/mL penicillin, and 100 μg/mL streptomycin at 37 °C in a humidified incubator containing 5% CO_2. The analysis of the metabolism of androsterone in A549 cells was carried out as described previously.[7] The transfection of the pGW1 plasmids harboring the cDNA for AKR1C3 into bovine aortic endothelial cells,[7,14] and the overexpression of the enzyme was confirmed by Western blotting using the antibody against AKR1C3, in contrast to no immunopositive band in the extract of the control cells transfected with the vector alone.[14] Following the treatment of 15 μM ONE for 24 h, the cell viability was measured by a tetrazolium dye-based cytotoxicity assay using 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2*H*-tetrazolium monosodium salt,[44] and expressed as % of control culture

conditions. Data are expressed as means ± SD of at least three independent experiments. Statistical evaluation of the data was performed by using the unpaired Student's *t*-test and ANOVA followed by Fisher's test. A p value <0.05 was considered statistically significant.

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