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Synthesis and SAR study of modulators inhibiting tRXRα-dependent AKT activation

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Abstract

RXRα represents an intriguing and unique target for pharmacologic interventions. We recently showed that Sulindac and a designed analog could bind to RXRα and modulate its biological activity, including inhibition of the interaction of an N-terminally truncated RXRα (tRXRα) with the p85α regulatory subunit of phosphatidylinositol-3-OH kinase (PI3K). Here we report the synthesis, testing and SAR of a series of novel analogs of Sulindac as potential modulators for inhibiting tRXRα-dependent AKT activation. A new compound **30** was identified to have improved biological activity.

Keywords

RXRα; αtRXR modulator; AKT activation; Sulindac analogs

1. Introduction

Retinoid X receptor-α (RXRα) is a unique member of the nuclear receptor (NR) superfamily, playing an important role in many biological processes ranging from apoptosis, cell differentiation and growth to lipid metabolism [1–3]. RXRα acts primarily as a ligand-dependent transcription factor through forming homodimer with itself or heterodimer with other members of the NR family. Structurally RXRα shares a modular organization with other nuclear receptors, consisting of three main functional domains: an N-terminal region where the ligand-independent transcriptional activation function (AF-1) is located, a DNA-binding domain and a ligand-binding domain (LBD) [2]. The transcriptional activity is directly mediated by the LBD and thus the LBD has been the most studied domain. The LBD possesses a ligand-binding pocket (LBP) for the binding of small molecule ligands, a transactivation function domain termed AF-2 composed of Helix 12 (H12) of the LBD, a coregulator binding surface, and a dimerization surface. Numerous ligands targeting the

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LBP have been designed and reported [4, 5]. Natural RXRα ligand 9-*cis*-Retinoic Acid (9-*cis*-RA) and synthetic RXR ligands (rexinoids) have been effective in preventing tumorigenesis in animals [6] and RXRα has been a drug target for therapeutic applications, especially in the treatment of cancer [7]. Targretin, a synthetic RXR-selective retinoid, was approved for treating cutaneous T-cell lymphoma [8, 9], and it has also been explored for the treatment of other form of cancer such as lung cancer, breast cancer, and prostate cancer [10–12].

Sulindac, a nonsteroidal antiinflammatory drug (NSAID) drug, has been investigated as a cancer chemopreventive agent, because of its potent induction of apoptosis and inhibition of cancer cell growth [13–16]. It has been documented that the anti-cancer effect of Sulindac can be mediated through COX-2-independent mechanisms [14, 15, 17]. We recently reported that Sulindac induces apoptosis in several cancer cell lines and primary tumors by binding to an N-terminally-truncated RXRα (tRXRα) [18]. Tumor necrosis factor-α (TNFα) promoted tRXRα interaction with the p85α subunit of phosphatidylinositol-3-OH kinase (PI3K), activating PI3K/AKT signaling. When combined with TNFα, Sulindac inhibited TNFα-induced tRXRα/p85α interaction, leading to activation of the death receptor-mediated apoptotic pathway [18]. Furthermore, we showed, a designed Sulindac analog K-80003 (**2**) (Fig. 1) exhibits increased affinity to RXRα without COX inhibitory activity, and displays enhanced efficacy in inhibiting tRXRα-dependent AKT activation and tRXRα tumor growth in animals, demonstrating the feasibility of developing a new generation of RXRα-specific molecules for therapeutic application or mechanistic studies of RXRα. Here we present the synthesis, SAR studies and biological evaluation of a series of K-80003 derivatives and the discovery of a new scaffold **30**.

2. Results and discussion

Compared to Sulindac (**1,** Fig. 1), compound **2** displays an increased binding to RXRα and potency in inhibiting tRXRα-dependent AKT activation [18]. **1** and **2** differ in the replacement of the sulfide group in **1** by an isopropyl group in **2** at R^1 (Fig. 2). Thus, for the first round of SAR study we investigated the effects of various substituents of R^1 (Fig. 2) on the binding affinity to the RXRα LBD. Scheme 1 outlines the synthetic chemistry used for the preparation of this group of compounds (**3**–**14**) and the testing results are listed in Table 1. The designed compounds **3**–**14** provide an opportunity to study the effect of the size of the group and the influence of electron-deficient and electron-rich groups. It seems that the binding capability is sensitive to the size of R^1 group at position 4. Compound **3** with R^1 = H displayed weaker binding whereas compound **4** with R^1= CF3 exhibited slightly weaker binding and when R^1= $C(CH_3)_3$ the compound **5** showed no binding. Replacing R^1 of –$CH(CH_3)_2$ in **2** with either electron-donating (compounds **7** and **8**, **10**, **14**) diminished the compounds' binding. Electron-withdrawing group of -CN (compounds **9**) also abolished the binding. Similar trend was observed when the substitution was moved from position 4 to 3 (**11**–**13**, table 1).

Our previous molecular docking study showed that the carboxylate group of **2** formed charge-charge interaction with Arg316 in the ligand-binding pocket of RXRα in a similar fashion to the carboxylate group found in other RXRα ligands [18]. This binding model is consistent with the SAR study of R^2 group as shown in Table 2. Although extending the carboxylate group by one carbon (**15**) weakens the binding, replacing the carboxylate group with non-charged groups (**16**, **17** and **19**) resulted in the loss of the binding activity. Compounds **15**–**17** and **19** were synthesized according to Scheme 2.

A few substituents at R^3 and R^4 were also examined and the binding results are outlined in Table 3. It shows that R^3 can tolerate bulkier groups. For example, replacing methyl at R^3

with ethyl (**21**) or isobutyl group (**22**) did not affect the binding dramatically. However, R^4 is sensitive to different substituents. Except for the ethoxyl group, replacing floride by other groups including hydrogen, chloride, methyl (**23**–**26, 28, 29**) caused steep drop in binding. Compounds **21**–**29** were prepared according to the procedure outlined in Scheme 3.

Overall, the analogs synthesized for this SAR study didn't improve the binding activity compared to the original lead **2**. Therefore we decided to explore the *E*-isomer of **2**. Compound **30** (Figure 3) was prepared according to Scheme 4 and was found to exhibit slightly tighter binding with an IC_{50} of 1.6 μM. Compound **30** was then evaluated for the effect on RXRα transactivation activity by employing the Gal4 reporter assay. The LBD of RXRα was cloned as a Gal4 fusion and the resulting Gal4-RXRα/LBD chimera and Gal4 reporter system were used to evaluate the effect of compound **30**. Gal4-RXRα/LBD strongly activated the Gal4 reporter in the presence of 9-*cis*-RA, which was inhibited by BI-1003, a RXRα antagonist [19]. As shown in Fig. 4, treatment of cells with **2** or **30** resulted in inhibition of 9-*cis*-RA-induced reporter activity in a dose dependent manner. So, Like **2**, **30** acts as a RXRα antagonist, however **30** showed stronger antagonism activity.

30, being an E-isomer of **2**, displays a different shape from **2** due to the different orientation of the isopropyl benzene motif. With such a difference in shape, it would be expected intuitively that **30** would not be tolerated in the same pocket where **2** binds. Thus we were intrigued to understand how **2** and **30** bind to the same LBP. Docking study was performed to explore the potential binding modes of **2** and **30**. RXRα/antagonist complex structure 3A9E [20] from Protein Data Bank (PDB) was used and Glide docking program [21] from Schrodinger was applied. The docked binding mode of **2** suggested that **2** bound to the LBP of RXRα in a similar mode as previously proposed for Sulindac [18], in which the carboxylate interacts with Arg316 of RXRα and the isopropyl benzene portion of the compound interacts with hydrophobic side chains residing in H3, H5 and H7 (Fig. 5A). For **30**, it was found that **30** could be tolerated and docked into the same pocket (Fig. 5B). This is most likely explained by the large size and the hydrophobic nature of the LBP. However, the docked **30** adopts a different orientation from **2** and forms different interactions with the protein (Fig. 5C). In the docked mode, the carboxylate group of **30** is not close to Arg316 to make the same interaction as seen in **2**. Instead, **30** makes more extensive hydrophobic interactions with hydrophobic side chains in H3, H5, H7 and H11 (Fig. 5B). Recent crystal structures of RXRα in complex with antagonists have demonstrated the significance of the hydrophobic interactions that were found dominant in the ligand binding [22, 23]. Therefore in the case of **30**, it is conceivable that even though the acid group of **30** may not contribute as much to the binding as that of **2**, the hydrophobic interactions play a key role in the binding.

We further tested **30** in other biological assays for its effect on the apoptosis of cancer cells and its ability to inhibit the PI3K/AKT activation. In the MTT assay, **30** could dose-dependently induce growth inhibition in some cancer cell lines such as PC3 prostate cancer cells and ZR75-1 breast cancer cells (Figure 6A). In the induction of PARP cleavage, **30** was more effective than **1** or **2** (Figure 6B).

We previously demonstrated that inhibition of AKT activation by the Sulindac/TNFα combination was closely associated with its apoptotic effect [18]. We then investigated whether compound **30** could inhibit TNFα-induced AKT activation. In agreement with previous studies, treatment of A549 lung cancer cells with TNFα led to a strong AKT activation [18], which was inhibited by **1**, **2** or **30** (Figure 7A). Such effects were also observed in HCT-116 colon cancer cells and HepG2 liver cancer cells (data not shown). Consistently, compound **30** showed a better effect on the inhibition of TNFα-induced AKT activation. Knocking down tRXRα by siRNA significantly impaired the inhibitory effect of

30 on AKT activation (Figure 7B). These results indicated that inactivation of AKT by **30** was tRXRα-dependent.

We also examined whether **30** could enhance the TNFα-induced apoptosis. Figure 8 showed that **30** could significantly enhance the PARP cleavage in combination with TNFα, suggesting that **30** could activate TNFα-dependent apoptotic pathway. The observed synergistic effect of **30**/TNFα on the TNFα-induced apoptosis was stronger than that of **2**/TNFα or **1**/TNFα.

3. Chemistry

The synthesis started from the Perkin reaction of 4-fluorobenzaldehyde **31** with propionate anhydride [24], in which K_2CO_3 was used as a base to substitute hygroscopic sodium propionate, providing the desired product **32** in 83% yield (Scheme 1). Catalytic hydrogenation in the presence of Pd/C and under 10 atm of hydrogen gave carboxylic acid **33** in 90% yield. Polyphosphoric acid (PPA)-promoted intermolecular Friedel-Crafts acylation reaction produced indenone **34** in 74% yield. Treatment of indenone **34** with the enolate generated from ethyl acetate and LDA gave the corresponding β-hydroxy ester, which was treated with a mixture of HOAc and concentrated H_2SO_4 (*v/v* 10:1) to yield the indene **35** in 80% yield. Finally, two methods were used for the Claisen-Schmidt condensation reactions of compound **35** with differently substituted benzaldehydes to give compounds **3**~**14**, respectively. The electronic properties of the substituents on the aromatic aldehydes were found to have an impact on the reaction, and slightly different conditions should be used for the synthesis of a specific compound. The results of the reactions are summarized in Table 4.

4. Conclusion

In conclusion, we have described the synthesis and SAR studies on a series of novel analogs of Sulindac as potential modulators for inhibiting tRXRα-dependent AKT activation. Compound **30,** a geometric isomer of the original lead **2** and with better binding activity and improved biological effects, could bind to the LBP of RXRα in a different mode from **2,** which offers a new design strategy. **30** is a promising lead for further optimization studies and may find application as a small molecule probe in studying the mechanism of the tRXRα-dependent AKT signaling.

5. Experimental section

5.1. Chemistry

5.1.1. General methods—Melting points (M.p.) were determined on a Yanaco MP-500 micro melting point apparatus and were uncorrected. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet techniques. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or CD_3OD on a Bruker 400 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded by a Bruker Dalton ESquire 3000 plus liquid chromatography-mass spectrum (direct injection). Optical rotations were measured with a Perkin-Elmer 341 automatic polarimeter. Diastereoselectivities and enantioselectivities were determined by chiral HPLC analysis using a Shimadzu LC-10AT VP series and a Shimadzu SPD-M10Avp photo diode array detector (190–370 nm) with a Chiralcel OJ-H column using *n*-hexane/*i*-PrOH (98:2, *v/v*) as a mobile phase. Flash column chromatography was carried out with silica gel (300–400 mesh). THF was distilled over sodium benzophenone ketyl under N_2.

5.1.2. General Procedure A: the synthesis of acrylic acid from aromatic aldehyde—Appropriate anhydride (300 mmol, 1.6 equiv.) was added to potassium carbonate (224 mmol, 1.2 equiv.) at 0 °C. After stirring for 5 min to mix up, appropriate aromatic aldehyde (186 mmol, 1.0 equiv.) was added. The mixture was heated to reflux for 12 h. After cooling with an ice bath, to the reaction mixture was added water and solid Na_2CO_3 (30 g). After the resultant yellow precipitate was filtered, the reaction mixture was acidified to pH 6.0 using concentrated HCl to afford acrylic acid as a solid.

5.1.3. 3-(4-Fluorophenyl)-2-methylacrylic acid (32)—Compound **32** [24] was synthesized according to the general procedure A. Pale yellow crystals, yield: 83%. M.p. 155–158 °C (MeOH); IR (film): ν_{max} 3429, 3076, 2972, 1665, 1596, 1508, 1425, 1313, 1298, 1224 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.00 (d, J = 1.2 *H* Hz, 3H, C $_3$), 7.19–7.25 (m, 2H, Ar-*H*), 7.46–7.52 (m, 2H, 2H, Ar-*H*), 7.58 (s, 1H, vinyl-*H*), 12.50 (br s, 1H, COO*H*) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.2, 115.8 (d, $J_{C\text{-}F}$ = 21.0 Hz), 129.0, 132.2 (d, $J_{C\text{-}F}$ = 9.0 Hz), 132.46 (d, $J_{C\text{-}F}$ = 3.0 Hz), 136.9, 162.3 (d, $J_{C\text{-}F}$ = 245.0 Hz), 169.7 ppm; MS (ESI) *m/z* 179 ($M+H^+$).

5.1.4. General Procedure B: the synthesis of propanoic acid derivative from acrylic acid by Pd/C-catalyzed reduction—A mixture of acrylic acid (55 mmol, 1.0 equiv.) and Pd/C (10%) in methanol (70 mL) was hydrogenated under 10 atm of hydrogen for 24 h. The catalyst was filtered off and the filtrate concentrated to afford propanoic acid, which was used in the next step as it was. An analytical sample of compound was obtained by flash column chromato- graphy on silica gel.

5.1.5. 3-(4-Fluorophenyl)-2-methylpropanoic acid (33)—Compound **33** [24] was synthesized according to the general procedure B. Colorless oil, yield: 90%. IR (film): ν_{max} 3406, 2972, 2933, 1701, 1560, 1509, 1460, 1406, 1223 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (d, J = 6.7 Hz, 3H, C*H*$_3$), 2.60 (dd, J = 13.0, 7.9 Hz, 1H, C*H*$_2$CH), 2.66 (ddq, J = 7.9, 6.0, 6.7 Hz, C*H*CH$_3$), 2.99 (dd, J = 13.0, 6.0 Hz, 1H, *CH*$_2$CH), 6.90–7.00 (m, 2H, Ar-*H*), 7.06–7.14 (m, 2H, Ar-*H*), 9.80 (br s, 1H, COO*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 38.6, 41.8, 115.1 (d, $J_{C\text{-}F}$ = 21.0 Hz), 130.35 (d, $J_{C\text{-}F}$ = 8.0 Hz), 134.87 (d, $J_{C\text{-}F}$ = 3.0 Hz), 161.6 (d, $J_{C\text{-}F}$ = 243.0 Hz), 182.3 ppm; MS (ESI) *m/z* 181 ($M+H^+$).

5.1.6. General Procedure C: the synthesis of indenone from propanoic acid derivative by F-C acylation—A mixture of the crude propanoic acid derivative (42.0 mmol, 1.0 equiv.) and polyphosphoric acid (400 mmol, 9.5 equiv.) was stirred at 80 °C for 12 hours. The resulting mixture was poured into ice water and extracted with EtOAc (30 mL × 3). The combined extracts were washed with a saturated aqueous $NaHCO_3$ (10 mL × 3) to remove the starting acids, and then washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford indenone.

5.1.7. 6-Fluoro-2-methyl-2,3-dihydroinden-1-one (34)—Compound **34** [24] was synthesized according to the general procedure C, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:40). Pale yellow oil, yield: 74%. IR (film) ν_{max} 3064, 2968, 2932, 2873, 1716, 1611, 1509, 1486, 1444, 1264, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, J = 7.4 Hz, 3H, *CH*$_3$), 2.70 (dd, J = 16.7, 3.9 Hz, 1H, C*H*$_2$CH), 2.74–2.82 (m, 1H, C*H*CH$_3$), 3.37 (dd, J = 16.7, 7.6 Hz, 1H, C*H*$_2$CH), 7.26–7.33 (m, 1H, Ar-*H*), 7.36–7.44 (m, 2H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 34.4, 42.9, 109.7 (d, $J_{C\text{-}F}$ = 22.0 Hz), 122.3 (d, $J_{C\text{-}F}$ = 24.0 Hz), 127.85 (d, $J_{C\text{-}F}$ = 8.0 Hz), 138.1, 148.8, 162.3 (d, $J_{C\text{-}F}$ = 247.0 Hz), 208.4 ppm; MS (ESI) *m/z* 187 ($M+Na^+$).

5.1.8. General Procedure D: the synthesis of inden-3-yl acetate from indenone—To a solution of LDA or LHMDS (48.0 mmol, 2.0 equiv.) in anhydrous THF (100 mL) was added EtOAc (61.0 mmol, 2.5 equiv.) at −78 °C. The mixture was stirred at −78 °C for 30 min. To the resulting mixture was added dropwise a solution of indenone (24.0 mmol, 1.0 equiv.) in anhydrous THF (20 mL). The mixture was stirred at −78 °C for another 4 hr and then quenched with a saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. To the residue was added $HOAc/H_2SO_4$ (10/1, 40 mL). After stirring for 4 hr at room temperature, the mixture was extracted with EtOAc (15 mL × 3). The combined extracts were washed successively with water, saturated $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford inden-3-yl acetate.

5.1.9. Ethyl 2-(5-fluoro-2-methyl-1H-inden-3-yl)acetate (35)—Compound **35** [24] was synthesized according to the general procedure D, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:50). Colorless oil, yield: 80%. IR (film) ν_{max} 2981, 2911, 1736, 1614, 1590, 1473, 1368, 1329, 1308, 1256, 1154, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.12 (s, 3H, $C{=}CCH_3$), 3.29 (s, 2H, $ArCH_2C{=}C$), 3.48 (s, 2H, CH_2COOEt), 4.14 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 6.77–6.83 (m, 1H, Ar-*H*), 6.94–6.99 (m, 1H, Ar-*H*), 7.23–7.27 (m, 1H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.15, 14.26, 31.5, 42.1, 60.9, 105.8 (d, $J_{C\text{-}F}$ = 23.0 Hz), 110.3 (d, $J_{C\text{-}F}$ = 23.0 Hz), 123.7 (d, $J_{C\text{-}F}$ = 9.0 Hz), 129.6, 137.19 (d, $J_{C\text{-}F}$ = 2.0 Hz) 144.5, 147.87 (d, $J_{C\text{-}F}$ = 9.0 Hz), 162.4 (d, $J_{C\text{-}F}$ = 239.0 Hz), 170.7 ppm; MS (ESI) *m/z* 257 ($M+Na^+$).

5.1.10. General Procedure E: the synthesis of indene derivative from appropriate inden-3-yl acetate—To a solution of indene-3-yl acetate **35** (1.3 mmol, 1.0 equiv.) in MeOH (4.0 mL) was added 2.5 N NaOMe (4.0 mmol, 3.0 equiv.) at room temperature to get an orange mixture. After stirring for 30 min, to the mixture was added appropriate aromatic aldehyde (1.3~2.0 mmol, 1.0~1.5 equiv.). The resulting mixture was refluxed at 80 °C for 4 h. After concentrated under reduced pressure, the residue was acidified with a 1N HCl solution to pH 4.0~6.0. After stirring for another 0.5 hr at room temperature, the mixture was extracted with EtOAc (15 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to afford indene derivative. An analytical sample of compound was obtained by recrystallization.

5.1.11. (Z)-2-(1-Benzylidene-5-fluoro-2-methyl-1H-inden-3-yl) acetic acid (3)—Compound **3** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:3). Yellow solid, yield: 77%. M.p. 175–176 °C (hexane/EtOAc); IR (film): ν_{max} 3430, 3021, 2918, 1705, 1604, 1467, 1415, 1302, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 3H, $C{=}CCH_3$), 3.50 (s, 2H, CH_2COOH), 6.43–6.50 (m, 1H, Ar-*H*), 6.75–6.84 (m, 1H, Ar-*H*), 7.13 (s, 1H, vinyl-*H*), 7.25–7.43 (m, 6H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 31.4, 105.7 (d, $J_{C\text{-}F}$ = 24.0 Hz), 110.6 (d, $J_{C\text{-}F}$ = 22.0 Hz), 123.8 (d, $J_{C\text{-}F}$ = 9.0 Hz), 128.0, 128.2, 128.5 (2C), 129.2 (2C), 129.4, 129.8, 130.1, 130.7, 136.5, 138.8, 140.2, 146.2 (d, $J_{C\text{-}F}$ = 8.0 Hz), 163.1 (d, $J_{C\text{-}F}$ = 245.0 Hz), 176.6 ppm; MS (ESI) *m/z* 317.1 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{19}H_{15}FNaO_2^+$ [$M+Na^+$]: 317.0948; found: 317.0951.

5.1.12. (Z)-2-(5-Fluoro-2-methyl-1-(4-trifluoromethylbenzylidene)-1H-inden-3-yl)acetic acid (4)—Compound **4** was synthesized according to the general procedure E,

and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:3). Yellow solid, yield: 62%. M.p. 188–189 °C (hexane/EtOAc); IR (film): ν_{max} 3435, 2918, 1708, 1604, 1467, 1321, 1165, 1122, 1065, 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 3H, C=CC*H*$_3$), 3.60 (s, 2H, C*H*$_2$COOH), 6.54–6.61 (m, 1H, Ar-*H*), 6.86–6.91 (m, 1H, Ar-*H*), 7.08–7.14 (m, 1H, Ar-*H*), 7.18 (s, 1H, vinyl-*H*), 7.57–7.63 (m, 2H, Ar-*H*), 7.67–7.74 (m, 2H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 31.3, 106.1 (d, $J_{C\text{-}F}$ = 23.0 Hz), 110.9 (d, $J_{C\text{-}F}$ = 22.0 Hz), 122.7, 123.7 (d, $J_{C\text{-}F}$ = 9.0 Hz), 125.46, 125.49, 128.3, 129.4, 129.5, 131.1, 138.6, 140.3, 141.6, 146.4 (d, $J_{C\text{-}F}$ = 8.0 Hz), 163.4 (d, $J_{C\text{-}F}$ = 245.0 Hz), 176.0 ppm; MS (ESI) *m/z* 385.1 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{20}H_{14}F_4NaO_2^+$ [$M+Na^+$]: 385.0822; found: 385.0819.

5.1.13. (Z)-2-(1-(4-tert-Butylbenzylidene)-5-fluoro-2-methyl-1H-inden-3-yl)acetic acid (5)—Compound **5** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:3). Yellow solid, yield: 72%. M.p. 187–188 °C (hexane/EtOAc); IR (film): ν_{max} 3420, 2964, 1708, 1604, 1503, 1464, 1412, 1363, 1266, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H, C(C*H*$_3$)$_3$), 2.20 (s, 3H, C=CC*H*$_3$), 3.60 (s, 2H, C*H*$_2$COOH), 6.56–6.64 (m, 1H, Ar-*H*), 6.86–6.93 (m, 1H, Ar-*H*), 7.20 (s, 1H, vinyl-*H*), 7.38–7.52 (m, 5H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 31.3, 31.4, 34.8, 105.6 (d, $J_{C\text{-}F}$ = 24.0 Hz), 110.6 (d, $J_{C\text{-}F}$ = 22.0 Hz), 123.8 (d, $J_{C\text{-}F}$ = 9.0 Hz), 125.4 (2C), 129.2 (2C), 129.7, 129.8, 130.9, 133.4, 139.0, 139.7, 146.2 (d, $J_{C\text{-}F}$ = 9.0 Hz), 151.6, 163.1 (d, $J_{C\text{-}F}$ = 244.0 Hz), 176.3 ppm; MS (ESI) *m/z* 373.2 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{23}H_{23}FNaO_2^+$ [$M+Na^+$]: 373.1574; found: 373.1571.

5.1.14. (Z)-2-(5-Fluoro-2-methyl-1-(4-(pyridin-2-yl)benzylidene)-1H-inden-3-yl)acetic acid (6)—To a solution of indene **35** (150 mg, 0.64 mmol) in toluene (4.0 mL) was added DBU (0.9 mL, 6.4 mmol) at room temperature. After stirring for 30 min at 80 °C, to the mixture was added the solution of aromatic aldehyde (168 mg, 0.96 mmol) in toluene (2.0 mL). The resulting mixture was heated at 80 °C for 36 h, then quenched with a saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Then to the residue in MeOH (3 mL) was added 2N NaOH (2 mL). The mixture was stirring for 2 hr at 65 °C. After concentrated under reduced pressure, the residue was acidified with a 1N HCl solution to pH 6.0~7.0. The residue was purified by flash chromatography on silica gel (eluent: ^1H NMR (400 MHz, DMSO-d_6) δ 2.18 (s, 3H, C=CC*H*$_3$), 3.59 (s, 2H, C*H*$_2$COOH), 6.70–6.77 (m, 1H, Ar-*H*), 7.00–7.05 (m, 1H, Ar-*H*), 7.31–7.36 (m, 1H, Ar-*H*), 7.36–7.40 (m, 1H, Ar-*H*), 7.40 (s, 1H, vinyl-*H*), 7.64–7.70 (m, 2H, Ar-*H*), 7.89–7.95 (m, 1H, Ar-*H*), 8.04–8.08 (m, 1H, Ar-*H*), 8.20–8.25 (m, 2H, Ar-*H*), 8.68–8.72 (m, 1H, Ar-*H*), 12.45 (br s, 1H, COO*H*) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.3, 31.1, 105.9 (d, $J_{C\text{-}F}$ = 24.0 Hz), 110.3 (d, $J_{C\text{-}F}$ = 23.0 Hz), 120.3, 122.9, 123.2 (d, $J_{C\text{-}F}$ = 9.0 Hz), 126.6 (2C), 129.6, 129.7, 130.4 (2C), 132.1, 136.8, 137.3, 138.0, 138.4, 139.8, 146.96 (d, $J_{C\text{-}F}$ = 8.0 Hz), 149.6, 155.3, 162.42 (d, $J_{C\text{-}F}$ = 242.0 Hz), 171.6 ppm; MS (ESI) *m/z* 372.1 ($M+H^+$, 100%); HRMS (ESI) calcd for $C_{24}H_{19}FNO_2^+$ [$M+H^+$]: 372.1394; found: 372.1395.

5.1.15. (Z)-2-(5-Fluoro-1-(4-methoxybenzylidene)- 2-methyl-1H-inden-3-yl)acetic acid (7)—Compound **7** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:4). Yellow solid, yield: 78%. M.p. 182–183 °C (hexane/EtOAc); IR (film): ν_{max} 3418, 2927, 2833, 1708, 1601, 1507, 1464, 1296, 1250, 1171, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H, C=CC*H*$_3$), 3.60 (s, 2H, C*H*$_2$COOH), 3.89 (s, 3H, OC*H*$_3$), 6.55–6.63 (m, 1H, Ar-*H*), 6.85–6.91 (m, 1H, Ar-*H*), 6.92–6.99 (m, 2H, Ar-*H*), 7.18 (s, 1H, vinyl-

H), 7.36–7.43 (m, 1H, Ar-*H*), 7.44–7.50 (m, 2H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.6, 31.3, 55.3, 105.6 (d, $J_{C\text{-}F}$ = 24.0 Hz), 110.5 (d, $J_{C\text{-}F}$ = 22.0 Hz), 113.9 (2C), 123.6 (d, $J_{C\text{-}F}$ = 9.0 Hz), 128.7, 129.5, 129.8, 130.8, 130.9 (2C), 139.0, 139.2, 146.1 (d, $J_{C\text{-}F}$ = 9.0 Hz), 159.7, 163.0 (d, $J_{C\text{-}F}$ = 245.0 Hz), 175.6 ppm; MS (ESI) *m/z* 347.1 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{20}H_{17}FNaO_3^+$ [$M+Na^+$]: 347.1054; found: 347.1060.

5.1.16. (Z)-2-(1-(4-Ethoxybenzylidene)-5-fluoro-2-methyl-1H-inden-3-yl)acetic acid (8)—Compound **8** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:4). Yellow solid, yield: 66%. M.p. 186–187 °C (hexane/EtOAc); IR (film): ν_{max} 3410, 2976, 2921, 1705, 1601, 1507, 1464, 1296, 1247, 1168, 1043 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (t, *J* = 7.0 Hz, 3H, OCH $_2$C*H*$_3$), 2.21 (s, 3H, C=CC*H*$_3$), 3.59 (s, 2H, C*H*$_2$COOH), 4.11 (q, *J* = 7.0 Hz, 2H, OC*H*$_2$CH$_3$), 6.56–6.63 (m, 1H, Ar-*H*), 6.86–6.99 (m, 3H, Ar-*H*), 7.18 (s, 1H, vinyl-*H*), 7.40–7.49 (m, 3H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.6, 14.8, 31.4, 63.5, 105.5 (d, $J_{C\text{-}F}$ = 23.0 Hz), 110.5 (d, $J_{C\text{-}F}$ = 22.0 Hz), 114.4 (2C), 123.5 (d, $J_{C\text{-}F}$ = 9.0 Hz), 128.5, 129.4, 129.8, 130.88, 130.94 (2C), 139.0, 139.1, 146.1 (d, $J_{C\text{-}F}$ = 9.0 Hz), 159.1, 163.0 (d, $J_{C\text{-}F}$ = 244.0 Hz), 176.9 ppm; MS (ESI) *m/z* 361.1 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{21}H_{19}FNaO_3^+$ [$M+Na^+$]: 361.1210; found: 361.1212.

5.1.17. (Z)-2-(1-(4-Cyanobenzylidene)-5-fluoro-2-methyl-1H-inden-3-yl)acetic acid (9)—Compound **9** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:4). Yellow solid, yield: 73%. M.p. 199–201 °C (hexane/EtOAc); IR (film): ν_{max} 3434, 2915, 2223, 1705, 1601, 1467, 1496, 1314, 1266, 1226, 1165, 1131, 1113, 1016 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H, C=CC*H*$_3$), 3.60 (s, 2H, C*H*$_2$COOH), 6.53–6.60 (m, 1H, Ar-*H*), 6.85–6.90 (m, 1H, Ar-*H*), 7.04–7.10 (m, 1H, Ar-*H*), 7.12 (s, 1H, vinyl-*H*), 7.59–7.62 (m, 2H, Ar-*H*), 7.70–7.75 (m, 2H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 31.3, 106.3 (d, $J_{C\text{-}F}$ = 24.0 Hz), 111.0 (d, $J_{C\text{-}F}$ = 22.0 Hz), 111.7, 118.6, 123.7 (d, $J_{C\text{-}F}$ = 9.0 Hz), 127.6, 129.2, 129.9 (2C), 131.5, 132.3 (2C), 138.5, 141.4, 142.1, 146.5 (d, $J_{C\text{-}F}$ = 8.0 Hz), 163.4 (d, $J_{C\text{-}F}$ = 246.0 Hz), 176.0 ppm; MS (ESI) *m/z* 342.1 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{20}H_{14}FNNaO_2^+$ [$M+Na^+$]: 342.0901; found: 342.0902.

5.1.18. (Z)-2-(1-(4-(Dimethylamino)benzylidene)-5-fluoro-2-methyl-1H-inden-3-yl)acetic acid (10)—Compound **10** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:4). Yellow solid, yield: 20%. M.p. 174–175 °C (hexane/EtOAc); IR (film): ν_{max} 3415, 2911, 1708, 1594, 1522, 1464, 1363, 1189, 1162, 1135, 1061 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 3H, C=CC*H*$_3$), 3.04 (s, 6H, N(C*H*$_3$)$_2$), 3.60 (s, 2H, C*H*$_2$COOH), 6.58–6.65 (m, 1H, Ar-*H*), 6.72–6.77 (m, 2H, Ar-*H*), 6.87–6.92 (m, 1H, Ar-*H*), 7.17 (s, 1H, vinyl-*H*), 7.45–7.51 (d, 2H, Ar-*H*), 7.64–7.70 (m, 1H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.7, 31.3, 40.3, 105.3 (d, $J_{C\text{-}F}$ = 23.0 Hz), 110.3 (d, $J_{C\text{-}F}$ = 23.0 Hz), 111.7 (2C), 123.4 (d, $J_{C\text{-}F}$ = 9.0 Hz), 123.8, 128.3, 130.0, 131.3 (2C), 132.1, 137.2, 139.2, 145.8 (d, $J_{C\text{-}F}$ = 10.0 Hz), 150.4, 162.8 (d, $J_{C\text{-}F}$ = 247 Hz), 175.8 ppm; MS (ESI) *m/z* 338.2 ($M+H^+$, 100%); HRMS (ESI) calcd for $C_{21}H_{21}FNO_2^+$ [$M+H^+$]: 338.1551; found: 338.1549.

5.1.19. (Z)-2-(5-Fluoro-2-methyl-1-(3-trifluoromethylbenzylidene)-1H-inden-3-yl)acetic acid (11)—Compound **11** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:4). Yellow solid, yield: 71%. M.p. 188–190 °C (hexane/EtOAc); IR (film): ν_{max} 3433, 2921, 1708, 1604, 1464, 1409, 1330, 1165, 1263, 1122, 1208, 1068 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 3H, C=CC*H*$_3$), 3.60 (s, 2H, C*H*$_2$COOH), 6.53–6.61 (m, 1H, Ar-*H*), 6.86–6.92 (m, 1H, Ar-*H*), 7.07–7.13 (m, 1H, Ar-*H*), 7.18 (s, 1H, vinyl-*H*), 7.53–7.59

(m, 1H, Ar-*H*), 7.62–7.72 (m, 2H, Ar-*H*), 7.74–7.79 (m, 1H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 31.4, 106.1 (d, $J_{C\text{-}F}$ = 24.0 Hz), 110.9 (d, $J_{C\text{-}F}$ = 23.0 Hz), 122.6, 123.6 (d, $J_{C\text{-}F}$ = 9.0 Hz), 124.8, 125.3, 126.12, 128.3, 129.0, 129.4, 131.0, 132.5, 137.3, 138.6, 141.5, 146.4 (d, $J_{C\text{-}F}$ = 9.0 Hz), 163.3 (d, $J_{C\text{-}F}$ = 245.0 Hz), 176.5 ppm; MS (ESI) *m/z* 385.1 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{20}H_{14}F_4NaO_2^+$ [$M+Na^+$]: 385.0822; found: 385.0825.

5.1.20. (Z)-2-(5-Fluoro-1-(3-methoxybenzylidene)- 2-methyl-1H-inden-3-yl)acetic acid (12)—Compound **12** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:4). Yellow solid, yield: 70%. M.p. 132–133 °C (hexane/EtOAc); IR (film): ν_{max} 3418, 2936, 2833, 1708, 1598, 1464, 1424, 1275, 1159, 1049 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 3H, C=CC*H*$_3$), 3.59 (s, 2H, C*H*$_2$COOH), 3.82 (s, 3H, OC*H*$_3$), 6.53–6.61 (m, 1H, Ar-*H*), 6.86–6.91 (m, 1H, Ar-*H*), 6.91–6.96 (m, 1H, Ar-*H*), 7.01–7.10 (m, 2H, Ar-*H*), 7.20 (s, 1H, vinyl-*H*), 7.27–7.37 (m, 2H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 31.3, 55.3, 105.7 (d, $J_{C\text{-}F}$ = 23.0 Hz), 110.7 (d, $J_{C\text{-}F}$ = 23.0 Hz), 114.27, 114.30, 121.6, 124.0 (d, $J_{C\text{-}F}$ = 9.0 Hz), 129.6, 129.8, 130.2, 130.4, 137.9, 138.8, 140.4, 146.3 (d, $J_{C\text{-}F}$ = 9.0 Hz), 159.7, 163.2 (d, $J_{C\text{-}F}$ = 245.0 Hz), 175.9 ppm; MS (ESI) *m/z* 347.1 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{20}H_{17}FNaO_3^+$ [$M+Na^+$]: 347.1054; found: 347.1054.

5.1.21. (Z)-2-(1-(3-Cyanobenzylidene)-5-fluoro-2-methyl-1H-inden-3-yl)acetic acid (13)—Compound **13** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:4). Yellow solid, yield: 60%. M.p. 187–189 °C (hexane/EtOAc); IR (film): ν_{max} 3433, 2917, 2226, 1711, 1601, 1464, 1409, 1311, 1271, 1168, 1131, 1037 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H, C=CC*H*$_3$), 3.59 (s, 2H, C*H*$_2$COOH), 6.54–6.61 (m, 1H, Ar-*H*), 6.85–6.91 (m, 1H, Ar-*H*), 6.97–7.02 (m,1H, Ar-*H*), 7.09 (s, 1H, vinyl-*H*), 7.52–7.58 (m, 1H, Ar-*H*), 7.65–7.70 (m, 1H, Ar-*H*), 7.71–7.78 (m, 2H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 31.3, 106.3 (d, $J_{C\text{-}F}$ = 23.0 Hz), 111.0 (d, $J_{C\text{-}F}$ = 23.0 Hz), 112.9, 118.3, 123.5 (d, $J_{C\text{-}F}$ = 9.0 Hz), 127.0, 129.2, 129.4, 131.4, 131.6, 132.6, 133.5, 138.0, 138.4, 142.0, 146.5 (d, $J_{C\text{-}F}$ = 8.0 Hz), 163.4 (d, $J_{C\text{-}F}$ = 246.0 Hz), 175.6 ppm; MS (ESI) *m/z* 342.1 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{20}H_{14}FNNaO_2^+$ [$M+Na^+$]: 342.0901; found: 342.0899.

5.1.22. (Z)-2-(1-(4-Acetamidobenzylidene)-5-fluoro-2-methyl-1H-inden-3-yl)acetic acid (14)—Compound **14** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:4). Yellow solid, yield: 22%. M.p. 240–242 °C (hexane/EtOAc); IR (film): ν_{max} 3411, 3296, 2921, 1662, 1595, 1476, 1406, 1381, 1318, 1220, 1171, 1122, 1037 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.08 (s, 3H, COC*H*$_3$), 2.14 (s, 3H, C=CC*H*$_3$), 3.57 (s, 2H, C*H*$_2$COOH), 6.70–6.79 (m, 1H, Ar-*H*), 6.97–7.04 (m, 1H, Ar-*H*), 7.28 (s, 1H, vinyl-*H*), 7.32–7.37 (m, 1H, Ar-*H*), 7.45–7.53 (m, 2H, Ar-*H*), 7.65–7.73 (m, 2H, Ar-*H*), 10.13 (s, 1H, N*H*COCH$_3$), 12.40 (s, 1H, COO*H*) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.2, 24.0, 31.1, 105.7 (d, $J_{C\text{-}F}$ = 23.0 Hz), 110.1 (d, $J_{C\text{-}F}$ = 22.0 Hz), 118.6 (2C), 122.9 (d, $J_{C\text{-}F}$ = 9.0 Hz), 129.6, 130.0 (2C), 130.4, 130.9, 131.5, 137.9, 138.7, 139.5, 146.7 (d, $J_{C\text{-}F}$ = 9.0 Hz), 162.2 (d, $J_{C\text{-}F}$ = 241.0 Hz), 168.5, 171.6 ppm; MS (ESI) *m/z* 374.1 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{21}H_{18}FNNaO_3^+$ [$M+Na^+$]: 374.1163; found: 374.1162.

5.1.23. Methyl 3-(5-fluoro-2-methyl-1H-inden-3-yl)propanoate (38)—A solution of compound **34** (164.0 mg, 1.0 mmol), *iso*-propanol (0.38 mL, 5.0 mmol), and methyl acrylate (0.9 mL, 10 mmol) in THF (4 mL) was purged with argon for 20 min and cooled to 0 °C. A SmI_2 (3.0 mmol) solution in THF (30 mL) was added through transfer needle. After 5 min,

the reaction was quenched with saturated Na_2CO_3 (3 mL). The resulting mixture was extracted with Et_2O (5 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. To a solution of the residue in CH_3OH (4.0 mL) was added *p*-TsOH (*cat.*), then the mixture was refluxed for 3 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ (2.0 mL). The resulting mixture was extracted with EtOAc (5 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:10) to afford compound **38** (171 mg, 73%) as a colorless oil. IR (film): ν_{max} 2948, 1735, 1610, 1589, 1473, 1430, 1281, 1171, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.09 (s, 3H, C=CCH_3), 2.53 (t, J = 7.8 Hz, 2H, CH_2CH$_2$COOMe), 2.82 (t, J = 7.8 Hz, 2H, CH$_2$CH_2COOMe), 3.23 (s, 2H, ArCH_2C=C), 3.68 (s, 3H, COOCH_3), 6.76–6.82 (m, 1H, Ar-*H*), 6.89–6.93 (m, 1H, Ar-*H*), 7.23–7.28 (m, 1H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 20.6, 32.8, 42.0, 51.6, 105.2 (d, $J_{C\text{-}F}$ = 23.0 Hz), 110.0 (d, $J_{C\text{-}F}$ = 23.0 Hz), 123.75 (d, $J_{C\text{-}F}$ = 9.0 Hz), 134.85 (d, $J_{C\text{-}F}$ = 3.0 Hz), 137.56 (d, $J_{C\text{-}F}$ = 2.0 Hz), 142.3, 147.9 (d, $J_{C\text{-}F}$ = 9.0 Hz), 162.4 (d, $J_{C\text{-}F}$ = 240.0 Hz), 173.4 ppm; MS (ESI) *m/z* 257.1 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{14}H_{15}FNaO_2^+$ [$M+Na^+$]: 257.0948; found: 257.0946.

5.1.24. (Z)-3-(5-Fluoro-1-(4-isopropylbenzylidene)-2-methyl-1H-inden-3-yl)propanoic acid (15)—Compound **15** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:4). Yellow solid, yield: 86%. M.p. 130–131 °C (hexane/EtOAc); IR (film): ν_{max} 3426, 2961, 1711, 1601, 1464, 1412, 1290, 1193, 1138 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J = 6.9 Hz, 6H, CH(CH_3)$_2$), 2.18 (s, 3H, C=CCH_3), 2.62 (t, J = 7.8 Hz, 2H, CH_2CH$_2$COOH), 2.90 (t, J = 7.8 Hz, 2H, CH$_2$CH_2COOH), 2.97 (sept, J = 6.9 Hz, 1H, CH(CH$_3$)$_2$), 6.55–6.62 (m, 1H, Ar-*H*), 6.82–6.87 (m, 1H, Ar-*H*), 7.14 (s, 1H, vinyl-*H*), 7.27–7.31 (m, 2H, Ar-*H*), 7.35–7.40 (m, 1H, Ar-*H*), 7.42–7.46 (m, 2H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.3, 20.7, 23.9, 32.7, 34.0, 105.3 (d, $J_{C\text{-}F}$ = 23.0 Hz), 110.3 (d, $J_{C\text{-}F}$ = 23.0 Hz), 123.8 (d, $J_{C\text{-}F}$ = 9.0 Hz), 126.5, 129.4, 129.9, 130.24 (d, $J_{C\text{-}F}$ = 3.0 Hz), 134.0, 136.06 (d, $J_{C\text{-}F}$ = 2.0 Hz), 136.7, 140.0, 146.36 (d, $J_{C\text{-}F}$ = 8.0 Hz), 149.1, 163.1 (d, $J_{C\text{-}F}$ = 244.0 Hz), 178.3 ppm; MS (ESI) *m/z* 373.2 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{23}H_{23}FNaO_2^+$ [$M+Na^+$]: 373.1574; found: 373.1572.

5.1.25. 3-(5-Fluoro-2-methyl-1H-inden-3-yl)propanenitrile (39)—A solution of compound **34** (300.0 mg, 1.8 mmol), and *iso*-propanol (0.7 mL, 9.0 mmol), and acrylonitrile (1.2 mL, 18.0 mmol) in THF (4 mL) was purged with argon for 20 min and cooled to 0 °C. A SmI_2 (5.4 mmol) solution in THF (54 mL) was added through transfer needle. After 5 min, the reaction was quenched with saturated aqueous Na_2CO_3 (10 mL). The resulting mixture was extracted with Et_2O (15 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. To the residue was added HOAc/H_2SO_4 (10/1, 3.0 mL). After stirring for 4 hr at room temperature, the mixture was extracted with EtOAc (15 mL × 3). The combined extracts were washed successively with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:4) to afford compound **39** as a white solid (108 mg, 30%). M.p. 91–92 °C (hexane/EtOAc); IR (film): ν_{max} 2915, 2247, 1610, 1592, 1476, 1275, 1190, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H, C=CCH_3), 2.57 (t, J = 7.3 Hz, 2H, CH_2CH$_2$CN), 2.86 (t, J = 7.3 Hz, 2H, CH$_2$CH_2CN), 3.31 (s, 2H, CH_2C=C), 6.79–6.88 (m, 2H, Ar-*H*), 7.27–7.32 (m, 1H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 16.6, 21.3, 41.2, 104.8 (d, $J_{C\text{-}F}$ = 24.0 Hz), 110.5 (d, $J_{C\text{-}F}$ = 23.0 Hz), 119.2, 124.17 (d, $J_{C\text{-}F}$ = 9.0 Hz), 132.8, 137.5, 144.6, 146.9 (d, $J_{C\text{-}F}$ =

9.0 Hz), 162.4 (d, $J_{C\text{-}F}$ = 241.0 Hz) ppm; MS (ESI) *m/z* 224.1 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{13}H_{12}FNNa^+$ [$M+Na^+$]: 224.0846; found: 224.0848.

5.1.26. (Z)-3-(5-Fluoro-1-(4-isopropylbenzylidene)-2-methyl-1H-inden-3-yl)propanenitrile (16)—Compound **16** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:20). Yellow solid, yield: 53%. M.p. 108–109 °C (hexane/EtOAc); IR (film): ν_{max} 2957, 2927, 2866, 2247, 1598, 1464, 1199, 1162, 1138, 1055, 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, *J* = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.24 (s, 3H, $C{=}CCH_3$), 2.60 (t, *J* = 7.4 Hz, 2H, CH_2CH_2CN), 2.93 (t, *J* = 7.4 Hz, 2H, CH_2CH_2CN), 2.98 (sept, *J* = 6.9 Hz, 1H, $CH(CH_3)_2$), 6.58–6.65 (m, 1H, Ar-*H*), 6.75–6.80 (m, 1H, Ar-*H*), 7.21 (s, 1H, vinyl-*H*), 7.28–7.33 (m, 2H, Ar-*H*), 7.39–7.48 (m, 3H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 16.6, 21.6, 23.9, 34.0, 104.7 (d, $J_{C\text{-}F}$ = 23.0 Hz), 110.6 (d, $J_{C\text{-}F}$ = 22.0 Hz), 119.1, 124.0 (d, $J_{C\text{-}F}$ = 8.0 Hz), 126.5 (2C), 129.4 (2C), 130.2, 131.1, 133.68, 133.78, 138.2, 139.6, 145.47 (d, $J_{C\text{-}F}$ = 8.0 Hz), 149.3, 163.0 (d, $J_{C\text{-}F}$ = 244.0 Hz) ppm; MS (ESI) *m/z* 354.2 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{23}H_{22}FNNa^+$ [$M+Na^+$]: 354.1628; found: 354.1625.

5.1.27. 2-(5-Fluoro-1-(4-isopropylbenzylidene)-2-methyl-1H-inden-3-yl)acetamide (17 and 18)—A solution of compound **3** (*Z* : *E* = 2.5 : 1) (140.0 mg, 0.42 mmol), HOBt (72 mL, 0.53 mmol), and EDCI (101 mg, 0.53 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature under argon for 1 hr and cooled to 0 °C. Then to the solution was added $NH_3{\cdot}H_2O$ (0.1 mL), and stirred for 12 hr at room temperature. The reaction was quenched with 1.0 N citric acid, extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were washed with brine, saturated $NHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:1) to give compound (*Z*)-**17** as a yellow solid (82 mg, 58%), and compound (*E*)-**18** as a yellow solid (26 mg, 19%). The data for (*Z*)-**17**: M.p. 138–139 °C (hexane/EtOAc); IR (film) ν_{max} 3393, 3195, 2960, 2860, 1659, 1601, 1464, 1409, 1272, 1165, 1131, 1052, 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, *J* = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.21 (s, 3H, $C{=}CCH_3$), 2.98 (sept, *J* = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.51 (s, 2H, CH_2CO), 5.75 (s, 1H, $CONH_2$), 6.28 (s, 1H, $CONH_2$), 6.57–6.64 (m, 1H, Ar-*H*), 6.85–6.90 (m, 1H, Ar-*H*), 7.22 (s, 1H, vinyl-*H*), 7.28–7.32 (m, 2H, Ar-*H*), 7.40–7.48 (m, 3H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 23.8, 33.2, 33.9, 105.5 (d, $J_{C\text{-}F}$ = 24.0 Hz), 110.8 (d, $J_{C\text{-}F}$ = 23.0 Hz), 123.79 (d, $J_{C\text{-}F}$ = 9.0 Hz), 126.5 (2C), 129.3 (2C), 129.85, 129.87, 131.2, 133.5, 138.8, 139.5, 145.9 (d, $J_{C\text{-}F}$ = 8.0 Hz), 149.3, 163.0 (d, $J_{C\text{-}F}$ = 244.0 Hz), 172.4 ppm; MS (ESI) *m/z* 358.2 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{22}H_{22}FNNaO^+$ [$M+Na^+$]: 358.1578; found: 358.1572. The data for (*E*)-**18**: M.p. 169–170 °C (hexane/EtOAc); IR (film): ν_{max} 3393, 3192, 2961, 2918, 2872, 1656, 1607, 1461, 1397, 1257, 1147, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.29 (d, *J* = 6.9 Hz, 6H, $CH(CH_3)_2$), 1.90 (s, 3H, $C{=}CCH_3$), 2.96 (sept, *J* = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.50 (s, 2H, CH_2CO), 5.60 (s, 1H, $CONH_2$), 6.87 (s, 1H, $CONH_2$), 6.83–6.90 (m, 1H, Ar-*H*), 6.90–6.95 (m, 1H, Ar-*H*), 7.23–7.33 (m, 4H, Ar-*H*), 7.49–7.54 (m, 1H, Ar-*H*), 7.63 (s, 1H, vinyl-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 23.9, 33.2, 33.9, 105.4 (d, $J_{C\text{-}F}$ = 24.0 Hz), 111.3 (d, $J_{C\text{-}F}$ = 23.0 Hz), 119.5 (d, $J_{C\text{-}F}$ = 9.0 Hz), 126.2 (2C), 129.6 (2C), 130.3, 133.3, 133.5, 135.3, 136.2, 138.8, 143.07 (d, $J_{C\text{-}F}$ = 9.0 Hz), 149.2, 163.16 (d, $J_{C\text{-}F}$ = 243.0 Hz), 171.9 ppm; MS (ESI) *m/z* 358.2 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{22}H_{22}FNNaO^+$ [$M+Na^+$]: 358.1578; found: 358.1581.

5.1.28. 2-(5-Fluoro-1-(4-isopropylbenzylidene)-2-methyl-1H-inden-3-yl)-N-methylacetamide (19 and 20)—Following the procedure described for **17** and **18**, compounds **19** and **20** were synthesized respectively, and purified by flash column

chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:2). (*Z*)-**19** is a yellow solid (63%). The data for (*Z*)-**19**: M.p. 199–200 °C (hexane/EtOAc); IR (film): ν_{max} 3289, 2957, 2869, 1647, 1601, 1467, 1409, 1262, 1162, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.20 (s, 3H, $C{=}CCH_3$), 2.76 (d, J = 4.8 Hz, 3H, NCH_3), 2.97 (sept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.51 (s, 2H, CH_2CO), 5.85 (q, J = 4.8 Hz, 1H, CONH), 6.57–6.64 (m, 1H, Ar-*H*), 6.83–6.88 (m, 1H, Ar-*H*), 7.22 (s, 1H, vinyl-*H*), 7.27–7.32 (m, 2H, Ar-*H*), 7.40–7.48 (m, 3H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.5, 23.8, 26.4, 33.4, 33.9, 105.5 (d, $J_{C\text{-}F}$ = 23.0 Hz), 110.7 (d, $J_{C\text{-}F}$ = 22.0 Hz), 123.76 (d, $J_{C\text{-}F}$ = 9.0 Hz), 126.5 (2C), 129.3 (2C), 129.85, 129.87, 131.1 (2C), 133.5, 139.0, 139.5, 146.0 (d, $J_{C\text{-}F}$ = 9.0 Hz), 149.4, 163.0 (d, $J_{C\text{-}F}$ = 244.0 Hz), 169.9 ppm; MS (ESI) *m/z* 372.2 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{23}H_{24}FNNaO^+$ [$M+Na^+$]: 372.1734; found: 372.1733. (*E*)-**20** is a yellow solid (23%). The data for (*E*)-**20**: M.p. 135–136 °C (hexane/EtOAc); IR (film): ν_{max} 3296, 2957, 1644, 1598, 1470, 1409, 1202, 1150, 1049, 1013 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 1.89 (s, 3H, $C{=}CCH_3$), 2.75 (d, J = 4.8 Hz, 3H, NCH_3), 2.95 (sept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.51 (s, 2H, CH_2CO), 5.60 (q, J = 4.8 Hz, 1H, CONH), 6.84–6.92 (m, 2H, Ar-*H*), 7.23–7.33 (m, 4H, Ar-*H*), 7.50–7.56 (m, 1H, Ar-*H*), 7.63 (s, 1H, vinyl-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 23.9, 26.5, 33.5, 33.9, 105.5 (d, $J_{C\text{-}F}$ = 23.0 Hz), 111.35 (d, $J_{C\text{-}F}$ = 23.0 Hz), 119.5 (d, $J_{C\text{-}F}$ = 9.0 Hz), 126.2 (2C), 129.6 (2C), 130.2, 133.3, 133.5, 135.3, 136.4, 138.8, 143.18 (d, $J_{C\text{-}F}$ = 9.0 Hz), 149.2, 163.2 (d, $J_{C\text{-}F}$ = 244.0 Hz), 169.7 ppm; MS (ESI) *m/z* 372.2 ($M+Na^+$, 100%). HRMS (ESI) calcd for $C_{23}H_{24}FNNaO^+$ [$M+Na^+$]: 372.1734; found: 372.1732.

5.1.29. 2-(4-FluorIbenzylidene)butanoic acid (40)—Compound **40** was synthesized according to the general procedure A. White solid, yield: 50%. M.p. 113–114 °C (hexane/EtOAc); IR (film): ν_{max} 3425, 2957, 1668, 1595, 1506, 1424, 1308, 1257, 1223, 1162, 1141 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, J = 7.4 Hz, 3H, CH_2CH_3), 2.56 (q, J = 7.4 Hz, 2H, CH_2CH_3), 7.06–7.15 (m, 2H, Ar-*H*), 7.35–7.45 (m, 2H, Ar-*H*), 7.76 (s, 1H, vinyl-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 20.5, 115.66 (d, $J_{C\text{-}F}$ = 22.0 Hz), 131.3 (d, $J_{C\text{-}F}$ = 8.0 Hz), 131.5 (d, $J_{C\text{-}F}$ = 4.0 Hz), 133.7, 139.6, 162.8 (d, $J_{C\text{-}F}$ = 249.0 Hz), 174.0 ppm; MS (ESI) *m/z* 193.1 ($M-H^+$); HRMS (ESI) calcd for $C_{11}H_{10}FO_2^-$ [$M-H^+$]: 193.0670; found: 193.0667.

5.1.30. 2-(4-FluorIbenzyl)butanoic acid (41)—Compound **41** was synthesized according to the general procedure B. Colorless oil, yield: 90%. IR (film): ν_{max} 3415, 2969, 1705, 1598, 1509, 1458, 1415, 1229, 1149 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.52–1.72 (m, 2H, CH_2CH_3), 2.52–2.63 (m, 1H, CH_2CH), 2.73 (dd, J = 13.8, 6.6 Hz, 1H, CH_2CH), 2.93 (dd, J = 13.8, 8.2 Hz, 1H, CH_2CH), 6.92–7.00 (m, 2H, Ar-*H*), 6.09–7.17 (m, 2H, Ar-*H*), 10.40 (br s, 1H, COOH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 24.8, 36.9, 49.1, 115.2 (d, $J_{C\text{-}F}$ = 21.0 Hz) (2C), 130.26 (d, $J_{C\text{-}F}$ = 8.0 Hz) (2C), 134.78 (d, $J_{C\text{-}F}$ = 3.0 Hz), 162.6 (d, $J_{C\text{-}F}$ = 243.0 Hz), 181.7 ppm; MS (ESI) *m/z* 195.1 ($M-H^+$); HRMS (ESI) calcd for $C_{11}H_{12}FO_2^-$ [$M-H^+$]: 195.0827; found: 195.0824.

5.1.31. 2-Ethyl-6-fluoro-2,3-dihydro-1H-inden-1-one (42)—Compound **42** was synthesized according to the general procedure C, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:40). Colorless oil, yield: 85%. IR (film): ν_{max} 2967, 2930, 2872, 1717, 1613, 1482, 1439, 1287, 1263, 1229, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.48–1.61 (m, 1H, CH_2CH_3), 1.90–2.01 (m, 1H, CH_2CH_3), 2.62–2.70 (m, 1H, CH_2CH), 2.78 (dd, J = 17.0, 3.7 Hz, 1H, CH_2CH), 3.28 (dd, J = 17.0, 7.8 Hz, 1H, CH_2CH), 7.25–7.32 (m, 1H, Ar-*H*), 7.34–7.38 (m, 1H, Ar-*H*), 7.39–7.44 (m, 1H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5, 24.4, 31.7, 49.6, 109.5 (d, $J_{C\text{-}F}$ = 22.0 Hz), 122.2 (d, $J_{C\text{-}F}$ = 23.0 Hz), 127.85 (d, $J_{C\text{-}F}$ = 8.0 Hz), 138.6 (d, $J_{C\text{-}F}$ = 7.0 Hz), 149.1, 162.25 (d, $J_{C\text{-}F}$ = 246.0 Hz), 207.9 ppm; MS (ESI)

m/z 201.1 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{11}H_{11}FNaO^+$ [$M+Na^+$]: 201.0686; found: 201.0688.

5.1.32. Ethyl-2-(2-ethyl-5-fluoro-1H-inden-3-yl)acetate (43)—Compound **43** was synthesized according to the general procedure D, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:50). Colorless oil, yield: 67%. IR (film): ν_{max} 2970, 2930, 1735, 1613, 1592, 1473, 1372, 1321, 1260, 1150, 1089, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (t, J = 7.6 Hz, 3H, CH_2CH_3), 1.25 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.53 (q, J = 7.6 Hz, 2H, CH_2CH_3), 3.32 (s, 2H, $ArCH_2C{=}C$), 3.50 (s, 2H, CH_2CO), 4.14 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 6.78–6.85 (m, 1H, Ar-*H*), 6.97–7.04 (m, 1H, Ar-*H*), 7.26–7.31 (m, 1H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.1, 21.9, 31.5, 39.3, 60.9, 105.9 (d, $J_{C\text{-}F}$ = 24.0 Hz), 110.4 (d, $J_{C\text{-}F}$ = 23.0 Hz), 123.84 (d, $J_{C\text{-}F}$ = 9.0 Hz), 128.8, 137.24 (d, $J_{C\text{-}F}$ = 2.0 Hz), 147.86 (d, $J_{C\text{-}F}$ = 9.0 Hz), 150.5, 162.4 (d, $J_{C\text{-}F}$ = 240.0 Hz), 170.7 ppm; MS (ESI) *m/z* 271.1 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{15}H_{17}FNaO_2^+$ [$M+Na^+$]: 271.1105; found: 271.1104.

5.1.33. (Z)-2-(2-Ethyl-5-fluoro-1-(4-isopropylbenzylidene)-1H-inden-3-yl)acetic acid (21)—Compound **21** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:4). Yellow solid, yield: 45%. M.p. 160–161 °C (hexane/EtOAc); IR (film): ν_{max} 3426, 2967, 2939, 2866, 1707, 1598, 1464, 1412, 1299, 1174, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, J = 7.6 Hz, 3H, CH_2CH_3), 1.32 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.65 (q, J = 7.6 Hz, 2H, CH_2CH_3), 2.98 (sept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.60 (s, 2H, CH_2CO), 6.56–6.63 (m, 1H, Ar-*H*), 6.89–6.94 (m, 1H, Ar-*H*), 7.22 (s, 1H, vinyl-*H*), 7.27–7.32 (m, 2H, Ar-*H*), 7.38–7.43 (m, 1H, Ar-*H*), 7.44–7.49 (m, 2H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.6, 18.3, 23.9, 31.3, 34.0, 105.8 (d, $J_{C\text{-}F}$ = 23.0 Hz), 110.7 (d, $J_{C\text{-}F}$ = 22.0 Hz), 123.96 (d, $J_{C\text{-}F}$ = 9.0 Hz), 126.5 (2C), 129.0, 129.5 (2C), 129.9, 130.9, 133.8, 138.1, 145.0, 146.1 (d, $J_{C\text{-}F}$ = 9.0 Hz), 149.3, 163.1 (d, $J_{C\text{-}F}$ = 244.0 Hz), 176.4 ppm; MS (ESI) *m/z* 373.2 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{23}H_{23}FNaO_2^+$ [$M+Na^+$]: 373.1574; found: 373.1574.

5.1.34. 6-Fluoro-2-isobutyl-2,3-dihydro-1H-inden-1-one (44)—To the solution of 6-fluoro-1-indanone **34** (600 mg, 4.0 mmol), KOH (336 mg, 6.0 mmol), and Pd/C (60 mg, 10 %) in EtOH (40 mL), was added *i*-PrCHO (0.55 mL, 6.0 mmol) at 0 °C. After stirring for 1 hr at room temperature, the catalyst was filtered off and the mixture was acidified with a 6N HCl solution to pH 7.0, concentrated, extracted with EtOAc (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentration under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether) to afford compound **44** as white solid (511 mg, 62%). M.p. 42–43 °C (hexane/EtOAc); IR (film): ν_{max} 2961, 2930, 2872, 1717, 1607, 1488, 1436, 1281, 1260, 1162, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (dd, J = 6.2, 1.3 Hz, 6H, $CH(CH_3)_2$), 1.24–1.37 (m, 1H, $CH_2CH(CH_3)_2$), 1.70–1.87 (m, 2H, $CH(CH_3)_2$ and $CH_2CH(CH_3)_2$), 2.71–2.80 (m, 2H, $ArCH_2CH$ and $ArCH_2CH$), 3.30 (dd, J = 17.6, 8.6 Hz, 1H, $ArCH_2CH$), 7.26–7.32 (m, 1H, Ar-*H*), 7.36–7.38 (m, 2H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 23.4, 26.5, 32.8, 40.6, 46.9, 109.6 (d, $J_{C\text{-}F}$ = 22.0 Hz), 122.2 (d, $J_{C\text{-}F}$ = 24.0 Hz), 127.8 (d, $J_{C\text{-}F}$ = 7.0 Hz), 138.4 (d, $J_{C\text{-}F}$ = 7.0 Hz), 148.93 (d, $J_{C\text{-}F}$ = 2.0 Hz), 162.29 (d, $J_{C\text{-}F}$ = 247.0 Hz), 208.26 (d, $J_{C\text{-}F}$ = 3.0 Hz) ppm; MS (ESI) *m/z* 229.1 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{13}H_{15}FNaO^+$ [$M+Na^+$]: 229.0999; found: 229.0996.

5.1.35. Ethyl-2-(5-fluoro-2-isobutyl-1H-inden-3-yl) acetate (45)—Compound **45** was synthesized according to the general procedure D, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:50). Yellow oil, yield: 57%. IR (film): ν_{max} 2957, 1738, 1610, 1586, 1476, 1366, 1263, 1153, 1031 cm^{-1}; ^1H

NMR (400 MHz, $CDCl_3$) δ 0.94 (d, J = 6.6 Hz, 6H, CH(CH_3)$_2$), 1.24 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.85–2.00 (m, 1H, $CH(CH_3)_2$), 2.38 (d, J = 7.4 Hz, 2H, CH_2CH), 3.31 (s, 2H, $ArCH_2C$=C), 3.51 (s, 2H, CH_2COOEt), 4.14 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 6.78–6.85 (m, 1H, Ar-*H*), 6.98–7.04 (m, 1H, Ar-*H*), 7.25–7.30 (m, 1H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 28.9, 31.6, 38.1, 40.2, 60.8, 106.0 (d, $J_{C\text{-}F}$ = 23.0 Hz), 110.4 (d, $J_{C\text{-}F}$ = 22.0 Hz), 123.7 (d, $J_{C\text{-}F}$ = 9.0 Hz), 130.32, 130.35, 137.3, 147.79 (d, $J_{C\text{-}F}$ = 8.0 Hz), 148.3, 162.4 (d, $J_{C\text{-}F}$ = 240.0 Hz), 170.7 ppm; MS (ESI) *m/z* 299.1 (M+Na^+, 100%); HRMS (ESI) calcd for $C_{17}H_{21}FNaO_2^+$ [M+Na^+]: 299.1418; found: 299.1419.

5.1.36. (Z)-2-(5-Fluoro-2-isobutyl-1-(4-isopropylbenzylidene)-1H-inden-3-yl) acetic acid (22)—Compound **22** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:10). Yellow solid, yield: 75%. M.p. 135–136 °C (hexane/EtOAc); IR (film): ν_{max} 3425, 2957, 2927, 2866, 1714, 1604, 1467, 1412, 1278, 1165, 1049 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (d, J = 6.6 Hz, 6H, CH(CH_3)$_2$), 1.32 (d, J = 6.9 Hz, 6H, PhCH(CH_3)$_2$), 1.88–2.01 (m, 1H, $CH(CH_3)_2$), 2.51 (d, J = 7.3 Hz, 2H, CH_2CH), 2.98 (sept, J = 6.9 Hz, 1H, PhC*H*(CH_3)$_2$), 3.63 (s, 2H, CH_2CO), 6.57–6.64 (m, 1H, Ar-*H*), 6.88–6.94 (m, 1H, Ar-*H*), 7.20 (s, 1H, vinyl-*H*), 7.27–7.33 (m, 2H, Ar-*H*), 7.36–7.42 (m, 1H, Ar-*H*), 7.43–7.48 (m, 2H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8 (2C), 23.9 (2C), 30.4, 31.6, 34.0, 34.2, 105.85 (d, $J_{C\text{-}F}$ = 23.0 Hz), 110.66 (d, $J_{C\text{-}F}$ = 23.0 Hz), 123.85 (d, $J_{C\text{-}F}$ = 9.0 Hz), 126.5 (2C), 129.4 (2C), 129.9, 130.4, 131.4, 133.8, 139.0, 142.4, 145.97 (d, $J_{C\text{-}F}$ = 9.0 Hz), 149.3, 163.0 (d, $J_{C\text{-}F}$ = 244.0 Hz), 176.5 ppm; MS (ESI) *m/z* 401.2 (M+Na^+, 100%); HRMS (ESI) calcd for $C_{25}H_{27}FNaO_2^+$ [M+Na^+]: 401.1887; found: 401.1887.

5.1.37. 12-Methyl-3-phenylacrylic acid (47a)—Compound **47a** [25] was synthesized according to the general procedure A. Yellow solid, yield: 40%. M.p. 80–82 °C (hexane/EtOAc); IR (film): ν_{max} 3415, 3425, 3040, 1662 (CO), 1609, 1443, 1407,1260 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3H, CH=CC H_3), 7.30–7.45 (m, 5H, Ar-*H*), 7.85 (s, 1H, C*H*=CCH_3) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 1 3.7, 127.6, 128.4, 128.7, 129.8, 135.6, 141.1, 174.3 ppm; MS (ESI) *m/z* 163 (M+H^+).

5.1.38. 2-Benzylpropanoic acid (48a)—Compound **48a** [25] was synthesized according to the general procedure B. Colorless oil, yield: 100%. IR (film): ν_{max} 3401, 2977, 2664, 1705, 1455, 1292, 1240 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, J = 6.9 Hz, 3H, $CHCH_3$), 2.66 (dd, J = 13.3, 8.0 Hz, 1H, CH_2CH), 2.71–2.81 (ddq, J = 8.0, 6.3, 6.9 Hz, 1H, $CHCH_3$), 3.07 (dd, J = 13.3, 6.3 Hz, 1H, CH_2CH), 7.16–7.31 (m, 5H, Ar-*H*), 11.03 (br s, 1H, COO*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 39.3, 41.3, 126.4, 128.4, 129.0, 139.0, 182.6 ppm; MS (ESI) *m/z* 165 (M+H^+).

6.1.39. 2,3-Dihydro-2-methylinden-1-one (49a)—Compound **49a** [26] was synthesized according to the general procedure C, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:40). Yellow oil, yield: 83%. IR (film): ν_{max} 3072, 2929, 1709, 1605, 1462, 1288, 1201 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J = 7.3 Hz, 3H, $CHCH_3$), 2.66–2.76 (m, 2H, CH_2CH+CH_2CH), 3.40 (dd, J = 17.9, 8.8 Hz, 1H, CH_2CH), 7.33–7.78 (m, 4H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 34.9, 41.9, 123.9, 126.5, 127.3, 134.6, 136.3, 153.4, 209.4 ppm; MS (ESI) *m/z* 169 (M+Na^+).

5.1.40. Ethyl 2-(2-methyl-1H-inden-3-yl) acetate (50a)—Compound **50a** [26] was synthesized according to the general procedure D, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:50). Yellow oil, yield: 72%. IR (film): ν_{max} 2976, 2903, 1732, 1610, 1470, 1394, 1366, 1308, 1257, 1156,

1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.14 (s, 3H, C=CCH_3), 3.35 (s, 2H, ArCH_2C=C), 3.54 (s, 2H, CH_2COOEt), 4.15 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 7.11–7.16 (m, 1H, Ar-*H*), 7.24–7.32 (m, 2H, Ar-*H*), 7.36–7.40 (m, 1H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.13, 14.16, 31.6, 42.7, 60.7, 118.4, 123.1, 123.9, 126.1, 129.8, 141.95, 142.0, 145.9, 171.0 ppm; MS (ESI) *m/z* 239.1 ($M+Na^+$, 100%).

5.1.41. (Z)-2-(1-(4-Isopropylbenzylidene)-2-methyl-1H-inden-3-yl) acetic acid (23)—Compound **23** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:10). Yellow solid, yield: 78%. M.p. 133–134 °C (hexane/EtOAc); IR (film): ν_{max} 3420, 2964, 1705, 1601, 1452, 1409, 1299, 1217, 1162, 1052, 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.20 (s, 3H, C=CCH_3), 2.97 (sept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.63 (s, 2H, CH_2COOH), 6.89–6.95 (m, 1H, Ar-*H*), 7.14–7.19 (m, 2H, Ar-*H*), 7.21 (s, 1H, vinyl-*H*), 7.27–7.31 (m, 2H, Ar-*H*), 7.45–7.51 (m, 2H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.4, 23.9, 31.3, 34.0, 117.9, 122.8, 124.5, 126.4, 127.7, 129.4, 130.6, 131.0, 134.1, 136.9, 140.7, 143.8, 149.1, 176.1 ppm; MS (ESI) *m/z* 341.1 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{22}H_{22}NaO_2^+$ [$M+Na^+$]: 341.1512; found: 341.1512.

5.1.42. 2-Methyl-3-p-tolylacrylic acid (47b)—Compound **47b** was synthesized according to the general procedure A. White solid, yield: 30%. M.p. 163–164 °C (hexane/EtOAc); IR (film): ν_{max} 3410, 2924, 1662, 1601, 1412, 1318, 1263, 1208, 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H, C=CCH_3), 2.39 (s, 3H, Ar-CH_3), 7.19–7.40 (m, 4H, Ar-*H*), 7.82 (s, 1H, vinyl-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 21.4, 126.6, 129.2, 130.0, 132.8, 139.0, 141.2, 174.4 ppm; MS (ESI) *m/z* 175.1 ($M-H^+$); HRMS (ESI) calcd for $C_{11}H_{11}O_2^-$ [$M-H^+$]: 175.0765; found: 175.0762.

5.1.43. 2-Methyl-3-p-tolylpropanoic acid (48b)—Compound **48b** was synthesized according to the general procedure B. Colorless oil yield: 98%. IR (film): ν_{max} 3400, 2979, 1702, 1516, 1461, 1412, 1290, 1241, 1198, 1119, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, J = 6.9 Hz, 3H, $CHCH_3$), 2.33 (s, 3H, Ar-CH_3), 2.65 (dd, J = 13.4, 8.0 Hz, 1H, $CHCH_2$), 2.74 (ddq, J = 8.0, 6.4, 6.9 Hz, 1H, $CHCH_3$), 3.04 (dd, J = 13.4, 6.4 1H, $CHCH_2$), 7.06–7.13 (m, 4H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 21.0, 38.9, 41.3, 128.9, 129.1, 135.87, 135.92, 182.7 ppm; MS (ESI) *m/z* 177.1 ($M-H^+$); HRMS (ESI) calcd for $C_{11}H_{13}O_2^-$ [$M-H^+$]: 177.0921; found: 177.0919.

5.1.44. 2,6-Dimethyl-2,3-dihydro-1H-inden-1-one (49b)—Compound **49b** was synthesized according to the general procedure C, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:40). Yellow oil yield: 87%. IR (film): ν_{max} 2960, 2924, 2869, 1710, 1610, 1494, 1281, 1150, 1116, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, J = 7.3 Hz, 3H, $CHCH_3$), 2.40 (s, 3H, Ar-CH_3), 2.67 (dd, J = 17.0, 3.9 Hz, 1H, $CHCH_2$), 2.67–2.75 (m, 1H, $CHCH_3$), 3.34 (dd, J = 17.0, 7.9 Hz, 1H, $CHCH_2$), 7.30–7.35 (m, 1H, Ar-*H*), 7.38–7.42 (m, 1H, Ar-*H*), 7.54–7.57 (m, 1H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 21.1, 34.6, 42.3, 123.9, 126.2, 135.9, 136.5, 137.2, 150.8, 209.6 ppm; MS (ESI) *m/z* 183.1 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{11}H_{12}NaO^+$ [$M+Na^+$]: 183.0780; found: 183.0772.

5.1.45. Ethyl 2-(2,5-dimethyl-1H-inden-3-yl) acetate (50b)—Compound **50b** was synthesized according to the general procedure D, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:50). Colorless oil yield: 79%. IR (film) ν_{max} 2982, 2915, 1735, 1616, 1479, 1366, 1253, 1153, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.12 (s, 3H, C=CCH_3), 2.39 (s, 3H, Ar-CH_3), 3.30 (s, 2H, CH_2C=C), 3.52 (s, 2H, CH_2COOEt), 4.15 (q, J = 7.1 Hz, 2H,

OCH_2CH$_3$), 6.92–6.97 (m, 1H, Ar-*H*), 7.09–7.13 (m, 1H, Ar-*H*), 7.23–7.27 (m, 1H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (2C), 21.5, 31.6, 42.3, 60.7, 119.2, 122.8, 124.6, 129.7, 135.7, 139.1, 142.2, 146.1, 171.1 ppm; MS (ESI) *m/z* 253.1 (M+Na$^+$, 100%); HRMS (ESI) calcd for $C_{15}H_{18}NaO_2^+$ [M+Na$^+$]: 253.1199; found: 253.1199.

5.1.46. (Z)-2-(1-(4-iso-Propylbenzylidene)-2,5-dimethyl-1H-inden-3-yl) acetic acid (24)—Compound **24** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:10). Yellow solid, yield: 70%. M.p. 143–144 °C (hexane/EtOAc); IR (film): ν_{max} 3416, 2961, 2924, 1705, 1607, 1467, 1415, 1311, 1159, 1046 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, *J* = 6.9 Hz, 6H, CH(CH_3)$_2$), 2.19 (s, 3H, C=CCH_3), 2.33 (s, 3H, Ar-CH_3), 2.97 (sept, *J* = 6.9 Hz, 1H, C*H*(CH$_3$)$_2$), 3.61 (s, 2H, CH_2COOH), 6.71–6.76 (m, 1H, Ar-*H*), 6.97–7.02 (m, 1H, Ar-*H*), 7.14 (s, 1H, vinyl-*H*), 7.27 (m, 2H, Ar-*H*), 7.34–7.39 (m, 1H, Ar-*H*), 7.44–7.50 (m, 2H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 21.7, 23.9, 31.3, 34.0, 118.8, 122.6, 125.1, 126.4, 129.5, 130.0, 130.4, 131.5, 134.3, 137.2, 137.7, 140.6, 144.1, 148.9, 176.3 ppm; MS (ESI) *m/z* 355.2 (M+Na$^+$, 100%); HRMS (ESI) calcd for $C_{23}H_{24}NaO_2^+$ [M+Na$^+$]: 355.1699; found: 355.1664.

5.1.47. 3-(4-Methoxyphenyl)-2-methylacrylic acid (47c)—Compound **47c** [25] was synthesized according to the general procedure A. White solid, yield: 32%. M.p. 154–155 °C (hexane/EtOAc); IR (film): ν_{max} 3390, 2945, 2836. 1662, 1598, 1513, 1424, 1281, 1257, 1177, 1037 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H, C=CCH_3), 3.85 (s, 3H, OCH_3), 6.90–7.00 (m, 2H, Ar-*H*), 7.40–7.48 (m, 2H, Ar-*H*), 7.79 (s, 1H, vinyl-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 55.3, 113.9, 125.1, 128.2, 131.7, 140.8, 160.0, 174.5 ppm; MS (ESI) *m/z* 215.1 (M+Na$^+$, 100%).

5.1.48. 3-(4-Methoxyphenyl)-2-methylpropanoic acid (48c)—Compound **48c** [25] was synthesized according to the general procedure B. Colorless oil, yield: 99%. IR (film): ν_{max} 3380, 2933, 1711, 1613, 1513, 1461, 1247, 1299, 1183, 1116, 1037 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, *J* = 6.9 Hz, 3H, CHCH_3), 2.63 (dd, *J* = 13.4, 7.9 Hz, 1H, CHCH_2), 2.72 (ddq, *J* = 7.9, 6.3, 6.9 Hz, 1H, C*H*CH$_3$), 3.02 (dd, *J* = 13.4, 6.3 1H, CHCH_2), 3.79 (s, 3H, OCH_3), 6.81–6.87 (m, 2H, Ar-*H*), 7.08–7.14 (m, 2H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 38.4, 41.5, 55.2, 113.8, 129.9, 131.1, 158.1, 182.6 ppm; MS (ESI) *m/z* 217.1 (M+Na$^+$, 100%).

5.1.49. 6-Methoxy-2-methyl-2,3-dihydro-1H-inden-1-one (49c)—Compound **49c** [27] was synthesized according to the general procedure C, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:40). Colorless oil, yield: 50%. IR (film): ν_{max} 2961, 2927, 1708, 1619, 1488, 1436, 1278, 1244, 1171, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, *J* = 7.4 Hz, 3H, CHCH_3), 2.64 (dd, *J* = 16.6, 3.6 Hz, 1H, CHCH_2), 2.68–2.78 (m, 1H, C*H*CH$_3$), 3.32 (dd, *J* = 16.6, 7.6 Hz, 1H, CHCH_2), 3.83 (s, 3H, OCH_3), 7.15–7.20 (m, 2H, Ar-*H*), 7.31–7.35 (m, 1H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 34.3, 42.8, 55.6, 105.1, 124.1, 127.2, 137.4, 146.2, 159.4, 209.5 ppm; MS (ESI) *m/z* 199.1 (M+Na$^+$, 100%).

5.1.50. Ethyl 2-(5-methoxy-2-methyl-1H-inden-3-yl) acetate (50c)—Compound **50c** [27] was synthesized according to the general procedure D, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:50). White solid, yield: 75%. M.p. 36–37 °C (hexane/EtOAc); IR (film): ν_{max} 2985, 2933, 2908, 1729, 1619, 1583, 1479, 1284, 1244, 1202, 1153, 1092, 1040 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3), 2.12 (s, 3H, C=CCH_3), 2.29 (s, 2H, ArCH_2C=C), 3.50 (s, 2H, CH_2COOEt), 3.83 (s, 3H, OCH_3), 4.14 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 6.66–6.71

(m, 1H, Ar-*H*), 6.85–6.88 (m, 1H, Ar-*H*), 7.22–7.26 (m, 1H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.19, 14.27, 31.6, 42.0, 55.5, 60.8, 104.5, 109.4, 123.5, 129.7, 134.1, 143.6, 147.4, 158.9, 171.0 ppm; MS (ESI) *m/z* 269.1 ($M+Na^+$, 100%).

5.1.51. (Z)-2-(1-(4-Isopropylbenzylidene)-5-methyl-2-methyl-1H-inden-3-yl) acetic acid (25)—Compound **25** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:10). Yellow solid, yield: 76%. M.p. 117–119 °C (hexane/EtOAc); IR (film) ν_{max} 3411, 2957, 1705, 1598, 1473, 1214, 1162, 1037 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, *J* = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.19 (s, 3H, $C=CCH_3$), 2.97 (sept, *J* = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.60 (s, 2H, CH_2COOH), 3.79 (s, 3H, OCH_3), 6.41–6.47 (m, 1H, Ar-*H*), 6.74–6.77 (m, 1H, Ar-*H*), 7.10 (s, 1H, vinyl-*H*), 7.26–7.29 (m, 2H, Ar-*H*), 7.37–7.41 (m, 1H, Ar-*H*), 7.44–7.49 (m, 2H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.6, 23.9, 31.3, 34.0, 55.4, 104.7, 108.9, 123.6, 126.4, 126.9, 129.1, 129.5, 130.1, 134.3, 138.4, 140.2, 145.8, 148.9, 160.0, 175.7 ppm; MS (ESI) *m/z* 371.2 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{23}H_{24}NaO_3^+$ [$M+Na^+$]: 371.1618; found: 371.1620.

5.1.52. 3-(4-Ethylphenyl)-2-methylacrylic acid (47d)—Compound **47d** was synthesized according to the general procedure A. White solid, yield: 41%. M.p. 126–127 °C (hexane/EtOAc); IR (film): ν_{max} 3411, 2957, 1671, 1607, 1424, 1314, 1269, 1180, 1132 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 2.18 (s, 3H, $C=CCH_3$), 2.70 (q, *J* = 7.6 Hz, 2H, CH_2CH_3), 7.23–7.30 (m, 2H, Ar-*H*), 7.37–7.44 (m, 2H, Ar-*H*), 7.85 (s, 1H, vinyl-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 15.3, 28.7, 126.6, 128.0, 130.1, 133.0, 141.2, 145.2, 174.6 ppm; MS (ESI) *m/z* 189.1 ($M-H^+$); HRMS (ESI) calcd for $C_{12}H_{13}O_2^-$ [$M-H^+$]: 189.0921; found: 189.0919.

5.1.53. 3-(4-Ethylphenyl)-2-methylpropanoic acid (48d)—Compound **48d** was synthesized according to the general procedure B. Colorless oil, yield: 100%. IR (film): ν_{max} 3401, 2967, 2933, 1708, 1595, 1516, 1464, 1418, 1293, 1238, 1196, 1122 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, *J* = 6.9 Hz, 3H, $CHCH_3$), 1.23 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 2.63 (q, *J* = 7.6 Hz, 2H, CH_2CH_3), 2.65 (dd, *J* = 13.4, 8.2 Hz, 1H, $CHCH_2$), 2.74 (ddq, *J* = 8.2, 6.3, 6.9 Hz, 1H, $CHCH_3$), 3.06 (dd, *J* = 13.4, 6.3 1H, $CHCH_2$), 7.08–7.16 (m, 4H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 16.5, 28.4, 38.9, 41.3, 127.9, 128.9, 136.2, 142.3, 182.4 ppm; MS (ESI) *m/z* 191.1 ($M-H^+$); HRMS (ESI) calcd for $C_{12}H_{15}O_2^-$ [$M-H^+$]: 191.1078; found: 191.1074.

5.1.54. 6-Ethyl-2-methyl-2,3-dihydro-1H-inden-1-one (49d)—Compound **49d** [28] was synthesized according to the general procedure C, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:40). Yellow oil, yield: 91%. IR (film): ν_{max} 2967, 2930, 2872, 1711, 1613, 1494, 1452, 1275, 1153, 1122 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 1.30 (d, *J* = 7.3 Hz, 3H, $CHCH_3$), 2.64–2.76 (m, 4H, $CHCH_3$, $CHCH_2$, CH_2CH_3), 3.35 (dd, *J* = 17.2, 8.0 Hz, 1H, $CHCH_2$), 7.33–7.39 (m, 1H, Ar-*H*), 7.40–7.46 (m, 1H, Ar-*H*), 7.56–7.61 (s, 1H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.5, 16.3, 28.5, 34.6, 42.3, 122.6, 126.3, 135.0, 136.5, 143.7, 151.1, 209.6 ppm; MS (ESI) *m/z* 197.1 ($M+Na^+$, 100%).

5.1.55. Ethyl 2-(5-ethyl-2-methyl-1H-inden-3-yl) acetate (50d)—Compound **50d** was synthesized according to the general procedure D, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:50). Colorless oil, yield: 84%. IR (film): ν_{max} 2957, 2924, 1732, 1613, 1479, 1366, 1305, 1263, 1144, 1034 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.26 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 2.12 (s, 3H, $C=CCH_3$), 2.69 (q, *J* = 7.6 Hz, 2H, CH_2CH_3), 3.30 (s, 2H,

ArCH_2C=C), 3.52 (s, 2H, CH_2COOEt), 4.15 (q, J = 7.1 Hz, 2H, OCH_2CH$_3$), 6.94–7.00 (m, 1H, Ar-H), 7.11–7.16 (m, 1H, Ar-H), 7.26–7.30 (m, 1H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (2C), 16.2, 29.1, 31.7, 42.4, 60.7, 118.0, 123.0, 123.6, 129.8, 139.4, 142.2, 142.4, 146.2, 171.1 ppm; MS (ESI) *m/z* 267.1 (M+Na$^+$, 100%); HRMS (ESI) calcd for $C_{16}H_{20}NaO_2^+$ [M+Na$^+$]: 267.1356; found: 267.1352.

5.1.56. (Z)-2-(5-Ethyl-1-(4-isopropylbenzylidene)-2-methyl-1H-inden-3-yl) acetic acid (26)—Compound **26** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:10). Yellow solid, yield: 76%. M.p. 111–112 °C (hexane/EtOAc); IR (film): ν_{max} 3413, 2957, 2933, 2872, 1705, 1604, 1506, 1467, 1409, 1293, 1055 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J = 7.6 Hz, 3H, CH$_2$CH_3), 1.32 (d, J = 6.9 Hz, 6H, CH(CH_3)$_2$), 2.20 (s, 3H, C=CCH_3), 2.64 (q, J = 7.6 Hz, 2H, CH_2CH$_3$), 2.98 (sept, J = 6.9 Hz, 1H, CH(CH$_3$)$_2$), 3.63 (s, 2H, CH_2COOH), 6.75–6.80 (m, 1H, Ar-H), 7.01–7.06 (m, 1H, Ar-H), 7.16 (s, 1H, vinyl-H), 7.27–7.31 (m, 2H, Ar-H), 7.38–7.43 (m, 1H, Ar-H), 7.46–7.51 (m, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.5, 15.7, 23.9, 29.1, 31.4, 34.0, 117.6, 122.7, 124.0, 126.4, 129.5, 130.0, 130.5, 131.7, 134.3, 137.2, 140.7, 144.1, 144.2, 148.9, 176.9 ppm; MS (ESI) *m/z* 369.2 (M+Na$^+$, 100%); HRMS (ESI) calcd for $C_{24}H_{26}NaO_2^+$ [M+Na$^+$]: 369.1825; found: 369.1818.

5.1.57. 3-(4-Ethoxyphenyl)-2-methylacrylic acid (47e)—Compound **47e** was synthesized according to the general procedure A. White solid, yield: 30%. M.p. 166–167 °C (hexane/EtOAc); IR (film): ν_{max} 3385, 2930, 1671, 1601, 1509, 1424, 1256, 1180, 1122, 1043 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3), 2.16 (d, J = 1.3 Hz, 3H, C=CCH_3), 4.07 (q, J = 7.0 Hz, 2H, OCH_2CH$_3$), 6.91–6.95 (m, 2H, Ar-H), 7.39–7.45 (m, 2H, Ar-H), 7.78 (q, J = 1.3 Hz, 1H, vinyl-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 14.8, 63.5, 114.4, 124.9, 128.1, 131.8, 140.8, 159.4, 174.0 ppm; MS (ESI) *m/z* 205.1 ([M−H$^+$); HRMS (ESI) calcd for $C_{12}H_{13}O_3^-$[M−H$^+$]: 205.0870; found: 205.0866.

5.1.58. 3-(4-Ethoxyphenyl)-2-methylpropanoic acid (48e)—Compound **48e** was synthesized according to the general procedure B. White solid, yield: 98%. M.p. 56–57 °C (hexane/EtOAc); IR (film) ν_{max} 3378, 2973, 2933, 1705, 1610, 1509, 1378, 1244, 1177, 1119, 1046 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, J = 6.9 Hz, 3H, CHCH_3), 1.41 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3), 2.62 (dd, J = 13.4, 7.9 Hz, 1H, CHCH_2), 2.72 (ddq, J = 7.9, 6.4, 6.9 Hz, 1H, CHCH$_3$), 3.02 (dd, J = 13.4, 6.4, 1H, CHCH_2), 4.02 (q, J = 7.0 Hz, 2H, OCH_2CH$_3$), 6.80–6.87 (m, 2H, Ar-H), 7.06–7.13 (m, 2H, Ar-H), 10.33 (br s, 1H, COOH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 16.4, 38.5, 41.5, 63.3, 114.4, 129.9, 130.9, 157.5, 182.6 ppm; MS (ESI) *m/z* 207.1 (M−H$^+$); HRMS (ESI) calcd for $C_{12}H_{15}O_3^-$ [M −H$^+$]: 207.1027; found: 207.1023.

5.1.59. 6-Ethoxy-2-methyl-2,3-dihydro-1H-inden-1-one (49e)—Compound **49e** was synthesized according to the general procedure C, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:40). White solid, yield: 50%. M.p. 49–50 °C (hexane/EtOAc); IR (film): ν_{max} 2969, 2927, 1705, 1616, 1491, 1446, 1278, 1241, 1174, 1116, 1040 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, J = 7.4 Hz, 3H, CHCH_3), 1.41 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3), 2.64 (dd, J = 16.6, 3.6 Hz, 1H, CHCH_2), 2.67–2.78 (m, 1H, CHCH$_3$), 3.31 (dd, J = 16.6, 7.6 Hz, 1H, CHCH_2), 4.05 (q, J = 7.0 Hz, 2H, OCH_2CH$_3$), 7.14–7.19 (m, 2H, Ar-H), 7.29–7.34 (m, 1H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 16.3, 34.2, 42.7, 63.8, 105.7, 124.5, 127.2, 137.4, 146.1, 158.7, 209.5 ppm; MS (ESI) *m/z* 213.1 (M+Na$^+$, 100%); HRMS (ESI) calcd for $C_{12}H_{14}NaO_2^+$[M +Na$^+$]: 213.0886; found: 213.0886.

5.1.60. Ethyl 2-(5-ethoxy-2-methyl-1H-inden-3-yl) acetate (50e)—Compound **50e** was synthesized according to the general procedure D, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:50). White solid, yield: 82%. M.p. 37–38 °C (hexane/EtOAc); IR (film): ν_{max} 2979, 2909, 1732, 1607, 1467, 1394, 1259, 1208, 1153, 1086, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.42 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 2.12 (s, 3H, $C{=}CCH_3$), 3.27 (s, 2H, $ArCH_2C{=}C$), 3.49 (s, 2H, CH_2COOEt), 4.05 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 4.14 (q, J = 7.1 Hz, 2H, $COOCH_2CH_3$), 6.65–6.69 (m, 1H, Ar-*H*), 6.84–6.87 (m, 1H, Ar-*H*), 7.21–7.24 (m, 1H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.19, 14.27, 14.9, 31.6, 42.0, 60.7, 63.6, 105.3, 110.1, 123.5, 129.8, 134.1, 143.5, 147.3, 158.2, 171.0 ppm; MS (ESI) *m/z* 283.1 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{16}H_{20}NaO_3^+$ [$M+Na^+$]: 283.1305; found: 283.1303.

5.1.61. (Z)-2-(5-Ethoxy-(4-isopropylbenzylidene)-2-methyl-1H-inden-3-yl) acetic acid (27)—Compound **27** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:10). Yellow solid, yield: 67%. M.p. 146–147 °C (hexane/EtOAc); IR (film) ν_{max} 3410, 2957, 2930, 1705, 1610, 1464, 1385, 1211, 1156, 1119, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 1.39 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 2.19 (s, 3H, $C{=}CCH_3$), 2.97 (sept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.59 (s, 2H, CH_2COOH), 4.02 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 6.40–6.46 (m, 1H, Ar-*H*), 6.72–6.78 (m, 1H, Ar-*H*), 7.09 (s, 1H, vinyl-*H*), 7.24–7.30 (m, 2H, Ar-*H*), 7.36–7.40 (m, 1H, Ar-*H*), 7.43–7.49 (m, 2H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 14.8, 23.9, 31.3, 34.0, 63.5, 105.3, 109.5, 123.6, 126.4, 126.7, 128.9, 129.5, 130.1, 134.3, 138.3, 140.2, 145.7, 148.8, 159.3, 176.1 ppm; MS (ESI) *m/z* 385.2 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{24}H_{26}NaO_3^+$ [$M+Na^+$]: 385.1774; found: 385.1777.

5.1.62. 3-(4-iso-Propylphenyl)-2-methylacrylic acid (47f)—Compound **47f** was synthesized according to the general procedure A. White solid, yield: 30%. M.p. 86–87 °C (hexane/EtOAc); IR (film) ν_{max} 3380, 2961, 1677, 1619, 1421, 1360, 1272, 1217, 1122, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.17 (d, J = 1.3 Hz, 3H, $C{=}CCH_3$), 2.95 (sept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 7.26–7.31 (m, 2H, Ar-*H*), 7.38–7.43 (m, 2H, Ar-*H*), 7.83 (q, J = 1.3 Hz, 1H, vinyl-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.8, 23.8, 34.0, 126.6, 130.1, 130.4, 133.1, 141.1, 149.8, 174.4 ppm; MS (ESI) *m/z* 203.1 ($M-H^+$); HRMS (ESI) calcd for $C_{13}H_{15}O_2^-$[$M-H^+$]: 203.1078; found: 203.1075.

5.1.63. 3-(4-iso-Propylphenyl)-2-methylpanoic acid (48f)—Compound **48f** was synthesized according to the general procedure B. Colorless oil, yield: 97%. IR (film): ν_{max} 3365, 2957, 1705, 1513, 1461, 1418, 1284, 1238, 1193, 1116, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, J = 6.9 Hz, 3H, $CHCH_3$), 1.25 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.64 (dd, J = 13.4, 7.1 Hz, 1H, $CHCH_2$), 2.76 (ddq, J = 7.1, 6.2, 6.9 Hz, 1H, $CHCH_3$), 2.89 (sept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.08 (dd, J = 13.4, 6.2, 1H, $CHCH_2$), 7.10–7.19 (m, 4H, Ar-*H*), 9.70 (br s, 1H, COO*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 24.0, 33.7, 38.9, 41.2, 126.4, 128.9, 136.3, 146.9, 182.6 ppm; MS (ESI) *m/z* 205.1 ($M-H^+$); HRMS (ESI) calcd for $C_{13}H_{17}O_2^-$ [$M-H^+$]: 205.1234; found: 205.1230.

5.1.64. 6-iso-Propyl-2-methyl-2,3-dihydro-1H-inden-1-one (49f)—Compound **49f** was synthesized according to the general procedure C, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:40). Yellow oil, yield: 87%. IR (film): ν_{max} 2960, 2927, 2866, 1708, 1622, 1494, 1436, 1259, 1174, 1119 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 1.30 (d, J = 7.3 Hz, 3H, $CHCH_3$), 2.64–2.76 (m, 2H, $CHCH_2$, $CHCH_3$), 2.97 (sept, J = 6.9 Hz, 1H,

C*H*(CH_3)$_2$), 3.35 (dd, *J* = 17.0, 7.9 Hz, 1H, CHC*H*$_2$), 7.34–7.39 (m, 1H, Ar-*H*), 7.45–7.49 (m, 1H, Ar-*H*), 7.61–7.64 (m, 1H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 23.9, 33.9, 34.6, 42.3, 121.1, 126.3, 133.8, 136.5, 148.5, 151.3, 209.7 ppm; MS (ESI) *m/z* 211.1 (M+Na^+, 100%). HRMS (ESI) calcd for $C_{13}H_{16}NaO^+$ [M+Na^+]: 211.1093; found: 211.1095.

5.1.65. Ethyl 2-(5-isopropyl-2-methyl-1H-inden-3-yl) acetate (50f)—Compound **50f** was synthesized according to the general procedure D, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:50). Colorless oil, yield: 82%. IR (film): ν_{max} 2954, 1741, 1610, 1482, 1366, 1302, 1253, 1156, 1031 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.32 (d, *J* = 6.8 Hz, 6H, $CH(CH_3)_2$), 2.16 (s, 3H, C=CCH_3), 2.99 (sept, *J* = 6.8 Hz, 1H, C*H*(CH_3)$_2$), 3.33 (s, 2H, ArCH_2C=C), 3.57 (s, 2H, CH_2COOEt), 4.18 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 7.02–7.07 (m, 1H, Ar-*H*), 7.18–7.24 (m, 1H, Ar-*H*), 7.30–7.36 (m, 1H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 24.3 (2C), 31.7, 34.3, 42.3, 60.7, 116.5, 122.1, 122.9, 129.8, 139.6, 142.2, 146.1, 147.0, 171.1 ppm; MS (ESI) *m/z* 281.2 (M+Na^+, 100%); HRMS (ESI) calcd for $C_{17}H_{22}NaO_2^+$ [M+Na^+]: 281.1512; found: 281.1517.

5.1.66. (Z)-2-(5-iso-Propyl-1-(4-isopropylbenzylidene)-2-methyl-1H-inden-3-yl) acetic acid (28)—Compound **28** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:10). Yellow solid, yield: 78%. M.p. 125–126 °C (hexane/EtOAc); IR (film) ν_{max} 3405, 2954, 1714, 1607, 1507, 1467, 1406, 1299, 1213, 1052, 1013 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, *J* = 6.9 Hz, 6H, $CH(CH_3)_2$), 1.32 (d, *J* = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.19 (s, 3H, C=CCH_3), 2.89 (sept, *J* = 6.9 Hz, 1H, C*H*(CH_3)$_2$), 2.97 (sept, *J* = 6.9 Hz, 1H, C*H*(CH_3)$_2$), 3.63 (s, 2H, CH_2COOH), 6.78–6.83 (m, 1H, Ar-*H*), 7.03–7.08 (m, 1H, Ar-*H*), 7.15 (s, 1H, vinyl-*H*), 7.26–7.31 (m, 2H, Ar-*H*), 7.38–7.42 (m, 1H, Ar-*H*), 7.45–7.50 (m, 2H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 23.9, 24.0, 31.4, 34.0, 34.3, 116.3, 122.4, 122.7, 126.4, 129.4, 130.0, 130.6, 131.9, 134.3, 137.1, 140.7, 144.1, 148.88, 148.92, 176.6 ppm; MS (ESI) *m/z* 383.2 (M+Na^+, 100%). HRMS (ESI) calcd for $C_{25}H_{28}NaO_2^+$ [M +Na^+]: 383.1982; found: 383.1982.

5.1.67. 3-(4-Chlorophenyl)-2-methylacrylic acid (47g)—Compound **47g** [25] was synthesized according to the general procedure A. White solid, yield: 55%. M.p. 164–165 °C (hexane/EtOAc); IR (film): ν_{max} 3360, 2957, 2826, 1671, 1491, 1446, 1424, 1308, 1287, 1263, 1214, 1132, 1092, 1012 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13 (d, *J* = 1.4 Hz, C=CCH_3), 7.35–7.41 (m, 4H, Ar-*H*), 7.79 (q, *J* = 1.4 Hz, 1H, vinyl-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 128.1, 128.7, 131.1, 134.0, 134.7, 139.7, 173.7 ppm; MS (ESI) *m/z* 197.0 (M+Na^+, 100%).

5.1.68. 3-(4-Chlorophenyl)-2-methylpropanoic acid (48g)—A mixture of the acrylic acid **47g** (1.5 g, 7.63 mmol) and 10 % Pd/C (150 mg) in EtOAc (30 mL) was hydrogenated under 3 atm of hydrogen for 12 h. The catalyst was filtered off and the filtrate concentrated to afford compound **48g** as a white solid (1.46 g, 96%). M.p. 52–53 °C (hexane/EtOAc); IR (film): ν_{max} 3351, 2976, 2933, 1698, 1494, 1461, 1406, 1296, 1232, 1196, 1089, 1019 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.8 Hz, 3H, C*H*CH_3), 2.66 (dd, *J* = 13.3, 7.6 Hz, 1H, CHC*H*$_2$), 2.74 (ddq, *J* = 7.6, 6.5, 6.8 Hz, 1H, C*H*CH_3), 3.02 (dd, *J* = 13.3, 6.5, 1H, CHC*H*$_2$), 7.09–7.14 (m, 2H, Ar-*H*), 7.24–7.28 (m, 2H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.5, 38.6, 41.1, 128.5, 130.3, 132.3, 137.4, 182.2 ppm; MS (ESI) *m/z* 221.0 (M+Na^+, 100%).

5.1.69. 6-Chloro-2-methyl-2,3-dihydro-1H-inden-1-one (49g)—Compound **49g** was synthesized according to the general procedure C, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:40). White solid, yield: 78%. M.p. 62–64 °C (hexane/EtOAc); IR (film): ν_{max} 3079, 2967, 1930, 1774, 1704, 1604, 1455, 1433, 1256, 1235, 1193, 1104, 1064 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, J = 7.3 Hz, 3H, CHCH_3), 2.68 (dd, J = 16.8, 3.9 Hz, 1H, CHCH_2), 2.71–2.79 (m, 1H, CHCH$_3$), 3.36 (dd, J = 16.8, 7.6, 1H, CHCH_2), 7.35–7.40 (m, 1H, Ar-H), 7.50–7.55 (m, 1H, Ar-H), 7.67–7.71 (m, 1H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 34.5, 42.6, 123.8, 127.8, 133.7, 134.7, 137.9, 151.5, 208.0 ppm; MS (ESI) m/z 203.0 ($M+Na^+$, 100%).

5.1.70. Ethyl 2-(5-chloro-2-methyl-1H-inden-3-yl) acetate (50g)—Compound **50g** was synthesized according to the general procedure D, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:50). Colorless oil, yield: 67%. IR (film): ν_{max} 2976, 2906, 1732, 1601, 1464, 1363, 1305, 1256, 1156, 1098, 1074, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 2.14 (s, 3H, C=CCH_3), 3.32 (s, 2H, ArCH_2C=C), 3.50 (s, 2H, CH_2COOEt), 4.17 (q, J = 7.1 Hz, 2H, OCH_2CH$_3$), 7.08–7.13 (m, 1H, Ar-H), 7.24–7.29 (m, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.15, 14.2, 31.4, 42.3, 60.9, 118.8, 123.7, 124.0, 129.4, 132.2, 140.2, 144.1, 147.7, 170.7 ppm; MS (ESI) m/z 273.1 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{14}H_{15}ClNaO_2^+$ [$M+Na^+$]: 273.0653; found: 273.0659.

5.1.71. (Z)-2-(5-Chloro-1-(4-isopropylbenzylidene)-2-methyl-1H-inden-3-yl) acetic acid (29)—Compound **29** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:10). Yellow solid, yield: 77%. M.p. 182–183 °C (hexane/EtOAc); IR (film): ν_{max} 3392, 2961, 2930, 1705, 1595, 1452, 1412, 1308, 1217, 1086, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J = 6.9 Hz, 6H, CH(CH_3)$_2$), 2.21 (s, 3H, C=CCH_3), 2.97 (sept, J = 6.9 Hz, 1H, CH(CH$_3$)$_2$), 3.60 (s, 2H, CH_2COOH), 6.86–6.90 (m, 1H, Ar-H), 7.14–7.16 (m, 1H, Ar-H), 7.23 (s, 1H, vinyl-H), 7.27–7.31 (m, 2H, Ar-H), 7.35–7.39 (m, 1H, Ar-H), 7.42–7.47 (m, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 23.9, 31.2, 34.0, 118.3, 123.6, 124.1, 126.6, 129.4, 129.7, 131.9, 132.3, 133.5, 133.7, 138.6, 139.7, 145.6, 149.4, 176.0 ppm; MS (ESI) m/z 375.1 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{22}H_{21}ClNaO_2^+$ [$M+Na^+$]: 375.1122; found: 375.1125.

5.1.72. Ethyl 2-(5-Fluoro-1H-inden-3-yl)acetate (52)—Compound **52** was synthesized according to the general procedure D, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:50). Colorless oil, yield: 55%. IR (film): ν_{max} 3054, 2982, 2931, 1704, 1636, 1486, 1446, 1369, 1345, 1288, 1276 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H, CH$_2$CH_3), 3.35 (s, 2H, CH_2CO), 3.56 (m, 2H, CH_2CH), 4.19 (q, J = 7.2 Hz, 2H, CH_2CH$_3$), 6.52 (s, 1H, C=CH), 6.87–6.94 (m, 1H, Ar-H), 7.03–7.09 (m, 1H, Ar-H), 7.33–7.39 (m, 1H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 34.1, 37.4, 61.0, 106.5 (d, $J_{C\text{-}F}$ = 24.0 Hz), 111.5 (d, $J_{C\text{-}F}$ = 23.0 Hz), 124.4 (d, $J_{C\text{-}F}$ = 9.0 Hz), 134.1, 136.36 (d, $J_{C\text{-}F}$ = 3.0 Hz), 139.24 (d, $J_{C\text{-}F}$ = 2.0 Hz), 146.34 (d, $J_{C\text{-}F}$ = 8.0 Hz), 162.3 (d, $J_{C\text{-}F}$ = 241.0 Hz), 170.7 ppm; MS (ESI) m/z 243.1 ($M+Na^+$); Anal. Calcd for $C_{13}H_{13}FO_2$: C, 70.90; H, 5.95. Found: C, 71.30; H, 6.23.

5.1.73. (E)-2-(5-Fluoro-1-(4-isopropylbenzylidene)-1H-inden-3-yl)acetic acid (30)—Compound **30** was synthesized according to the general procedure E, and purified by flash column chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1:10). Yellow solid, yield: 78%. M.p. 128–129 °C (hexane/EtOAc); IR (film): ν_{max} 3426, 2960, 1708, 1604, 1513, 1461, 1418, 1247, 1159, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, J = 6.9 Hz, 6H, CH(CH_3)$_2$), 2.96 (sept, J = 6.9 Hz, 1H, CH(CH$_3$)$_2$), 3.69 (s, 2H,

C*H*$_2$COO), 6.90–6.98 (m, 1H, Ar-*H*), 7.01–7.06 (m, 1H, Ar-*H*), 7.09 (s, 1H, CH_2C=C*H*), 7.27–7.32 (m, 2H, Ar-*H*), 7.40 (s, 1H, vinyl-*H*), 7.50–7.55 (m, 2H, Ar-*H*), 7.59–7.64 (m, 1H, Ar-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 33.8, 34.0, 106.5 (d, $J_{C\text{-}F}$ = 23.0 Hz), 111.96 (d, $J_{C\text{-}F}$ = 23.0 Hz), 119.97 (d, $J_{C\text{-}F}$ = 9.0 Hz), 126.9 (2C), 127.0, 129.2, 130.2 (2C), 133.6, 134.2, 137.0, 137.6, 142.96 (d, $J_{C\text{-}F}$ = 9.0 Hz), 149.7, 162.9 (d, $J_{C\text{-}F}$ = 243.0 Hz), 176.1 ppm; MS (ESI) *m/z* 345.1 ($M+Na^+$, 100%); HRMS (ESI) calcd for $C_{21}H_{19}FNaO_2^+$ [$M+Na^+$]: 345.1261; found: 345.1262.

5.2. Biological assays

5.2.1. Ligand-binding Competition Assay—The GST-tagged human RXRα-LBD (223–462) was incubated with unlabeled 9-*cis*-RA or different concentrations of compounds in 200 μL binding buffer [0.15 M KCl, 10 mMTris·HCl (pH7.4), 8% glycerol, and 0.5% CHAPS detergent] at 4°C for 1 h. [^{3}H]-9-*cis*-RA was added to the final concentration of 7.5 nM and final volume of 300 μL and incubated overnight at 4°C. The RXRα-LBD was captured by Glutathione sepharose beads. Bound [^{3}H]-9-*cis*-RA was quantitated by liquid scintillation counting [29, 30].

5.2.2. Cell Culture and Transfection—HeLa cervix cancer, HCT-116 colon cancer and A549 lung cancer cells were cultured in Dulbecco modified Eagle's medium supplemented with 10% fetal bovine serum (FBS). PC3 prostate cancer and ZR-75-1 breast cancer cells were grown in RPMI1640 medium containing 10% FBS. The cells were maintained at 5% CO_2 at 37°C.

5.2.3. MTT assay—Cells cultured in 96-well dishes were treated with various concentrations of compound **30** for 24 hr. The cells were then incubated with 2 mg/mL MTT for 4 hr at 37°C and dissolved by addition of 150 μL DMSO each well. Absorbance was measured at 570 nm [30].

5.2.4 Western Blotting—Cells were lysed and equal proteins were electrophoresed on 10% SDS-PAGE gels and transferred onto PVDF membranes (Millipore). The membranes were blocked in 5% skimmed milk in TBST [50 mmol/L Tris-HCl (pH7.4),150 mmol/L NaCl and 0.1% Tween20] for 1 hr, then incubated with primary antibodies and secondary antibodies and detected using ECL system(Thermo). The dilutions of the primary antibodies were anti-RXRα(N197, Santa Cruz) in 1:1000, anti-PARP(H-250, Santa Cruz) in 1:3000, anti-p-AKT (D9E, Cell Signaling Technology) in 1:1000, anti-AKT1/2/3 (H-136, Santa Cruz) in 1:1000, anti-β-actin (Sigma) in 1:5000.

5.2.5. Transient transfection and reporter assay—HCT-116 colon cancer cells were transfected with pG5 luciferase reporter vector (50 ng/well) and pGAL-4-RXRα-LBD expression vector (50ng/well) for 24hr. Cells were incubated with varied concentrations of compounds for another 12 hr. Luciferase activities were measured using the Dual-Luciferase Assay System Kit (Promega).

5.2.6. RXRα siRNA and transfection—RXRα siRNA used in the experiments were obtained from Dharmacon Research, Inc. A 2.5-μl aliquot of 20 μmol of siRNA/well was transfected into cells grown in 12-well plates by using oligofectamine reagent (Invitrogen) according to the manufacturer's recommendations. Two days after transfection, the cells were harvested for Western blotting [18].

5.3. Ligand Docking

Schrodinger's (Portland, OR) (www.schrodinger.com) GLIDE[21], a grid-based docking program, was used for docking studies of the small molecule ligands to the protein. The

crystal structure of RXRα LBD in complex with antagonist LG100754 (Protein Data Bank code 3A9E) was used. The GLIDE GScore was used as docking score to rank the docking results. Visual inspection was done to pick the docked pose from the ranked results. Schrödinger's Maestro 6.5 was used to prepare Figure 5.

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Abbreviations

RXRα	retinoid X receptor alpha
tRXRα	N-terminally-truncated retinoid X receptor alpha
PI3K	phosphatidylinositol-3-OH kinase
NR	nuclear receptor
LBD	ligand-binding domain
LBP	ligand-binding pocket
NSAID	nonsteroidal antiinflammatory drug
TNFα	Tumor necrosis factor-α
LDA	lithium diisopropylamide
TMS	tetramethylsilane
LHMDS	bis(trimethylsilyl)amine lithium
THF	tetrahydrofuran
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
***p*-TsOH**	*p*-toluenesulfonic acid
HOBt	*N*-Hydroxybenzotriazole
EDCI	1-Ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride
SAR	structure–activity relationship

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Highlights

- 28 new Sulindac analogs as modulators of tRXRa-dependent AKT activation were synthesized.
- Binding assay was used to test the 28 compounds for SAR study.
- A new scaffold was found with improved biological properties.

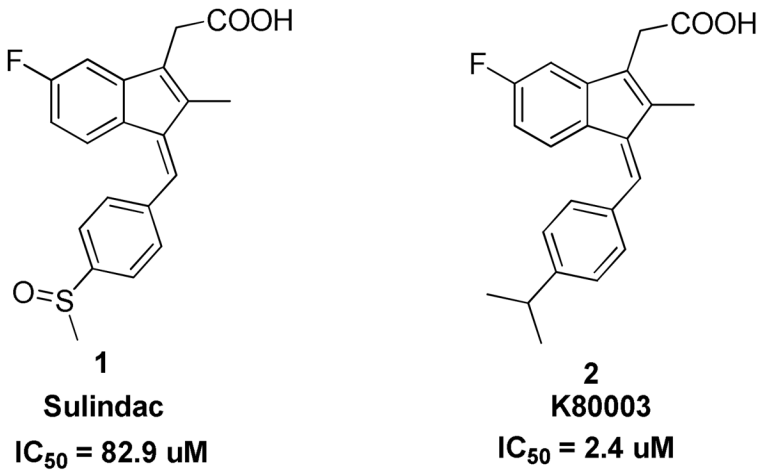


Figure 1.
Structure and RXRα binding activity of Sulindac and K-80003

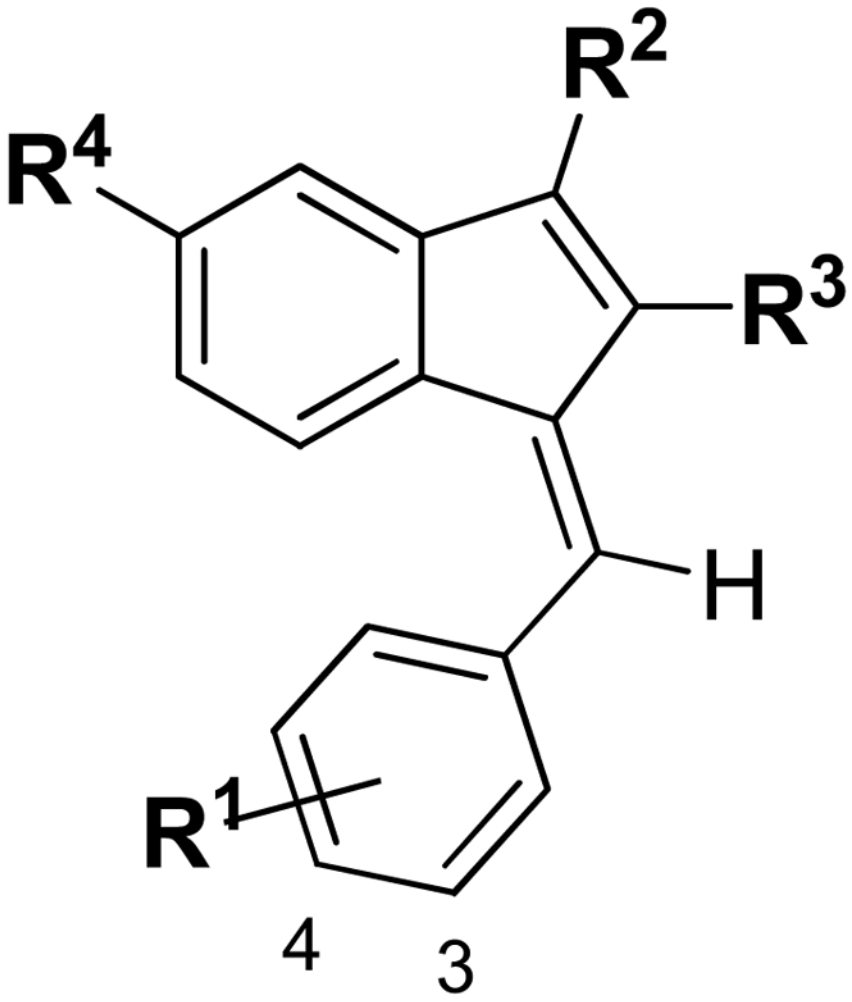


Figure 2.
Scaffold for the SAR study

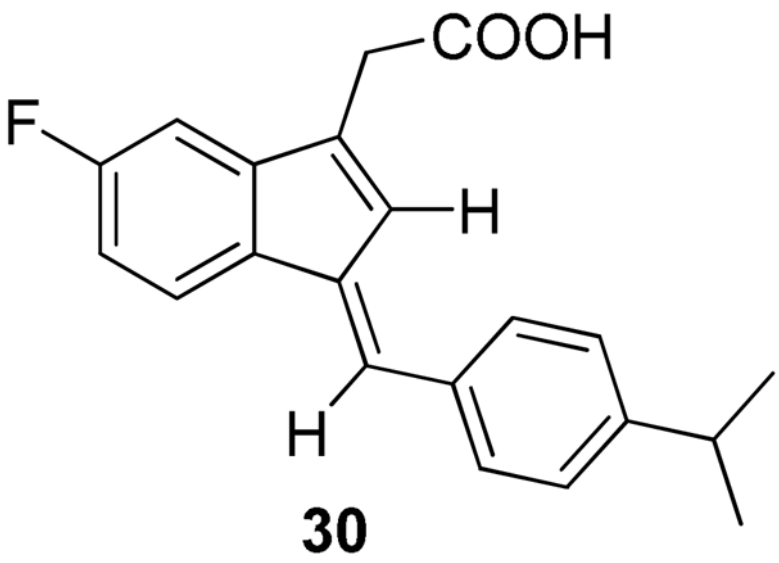


Figure 3.
Structure of *E*-isomer **30**

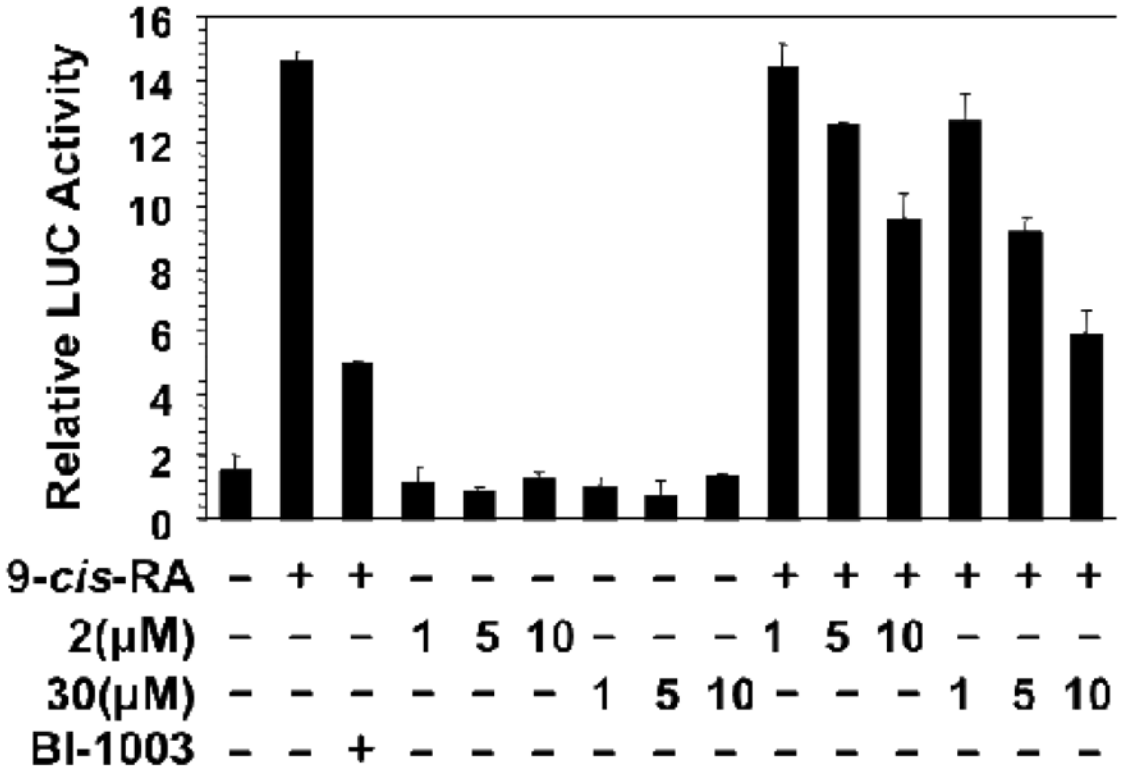


Figure 4.

Inhibition of Gal4-RXRα-LBD activit by **30**. HCT116 cells transfected with pG5 luciferase reporter vector and pGAL4-RXRα-LBD expression vector (50ng/well) were incubated with or without 9-*cis*-RA (10^{-7} M) in the presence or absence of the indicated concentrations of **2** or **30** for 12 hr. Luciferase activities were measured using the Dual-Luciferase Assay System Kit. For comparison, the effect of BI-1003 (1 μM) was shown.

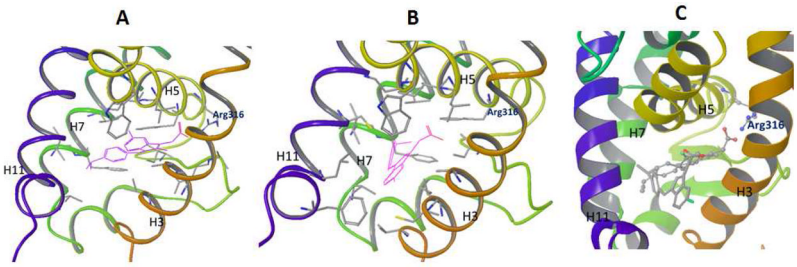


Figure 5.

Docking study of **2** and **30.** (A) Proposed binding mode of 2 by docking. **2** is shown in magenta and the side chains in the LBP that could interact favorably with the ligand are displayed. (B) Proposed binding mode of **30** by docking. **30** is shown in magenta and the side chains in the LBP that could interact favorably with the ligand are displayed. (C) Relative orientation of the docked **2** (in ball and stick) and **30** (in tube) in the LBP.

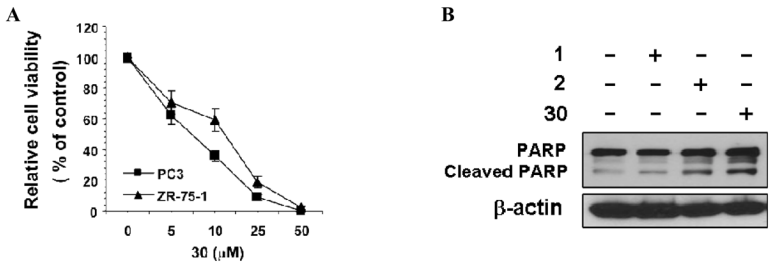


Figure 6.

Compound **30** induces cancer cell apoptosis. (A) Growth inhibition by **30**. PC3 and ZR-75-1 breast cancer cells were treated with the indicated concentration of **30** for 24 hr. Cell viability was determined by the MTT colorimetric assay. (B) Induction of PARP cleavage by **1**, **2** or **30**. ZR-75-1 cells were treated with vehicle or 30 μM compound as indicated for 6 hr. PARP cleavage was analyzed.

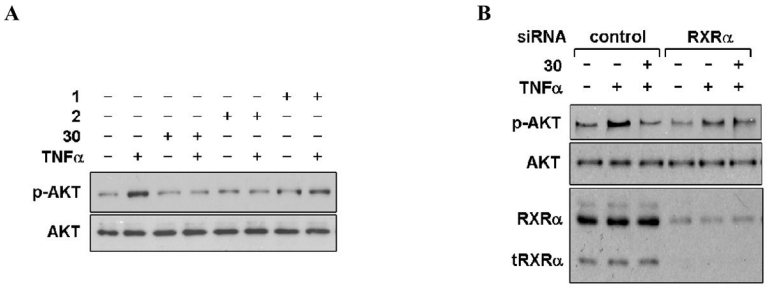


Figure 7.

Inhibition of tRXRα-dependent AKT activation by compound **30**. (A) Synergistic inhibition of AKT activation by Sulindac and its analogs. A549 cells were pretreated with 30 μM, **1, 2** or **30** for 1 hr before exposed to TNFα (10 ng/mL) for 30 min. Phosphorylated AKT and total AKT were analyzed by immunoblotting. (B) **30** inhibits AKT activation dependent on RXRα expression. HeLa cells transfected with scramble or RXRα siRNA were pretreated with 20 μM **30** for 1 hr before exposed to TNFα (10 ng/mL) for 30 min. The effect of RXRα siRNA and **30** on the inhibition of TNFα-induced AKT activation was analyzed by immunoblotting.

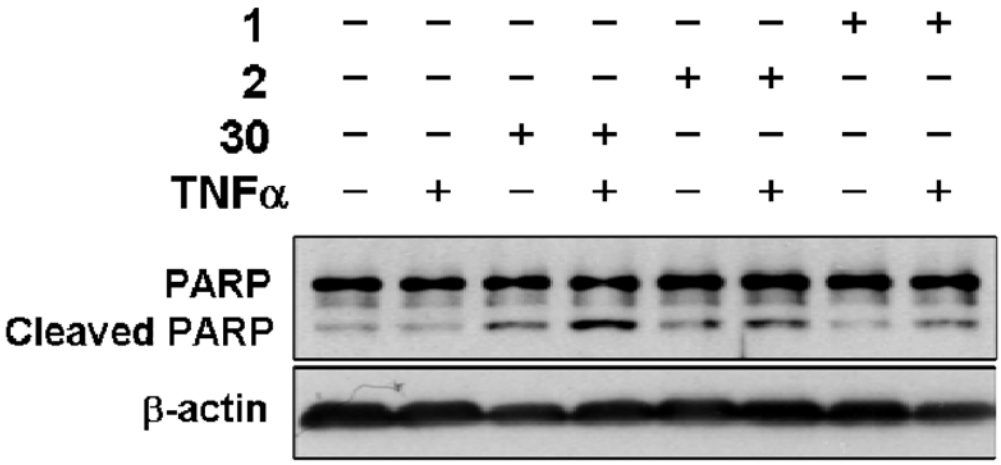
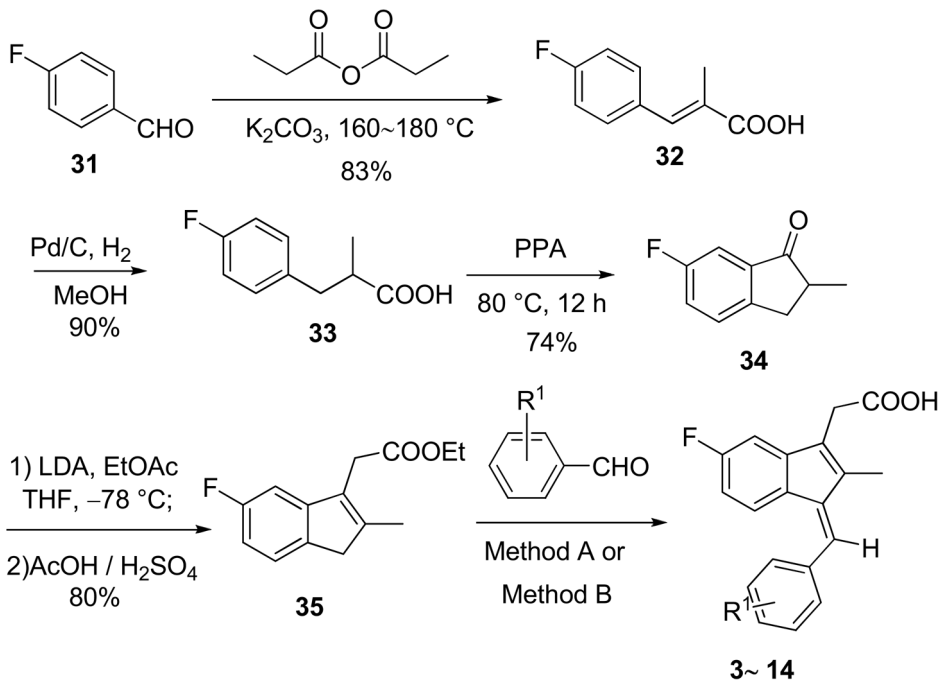
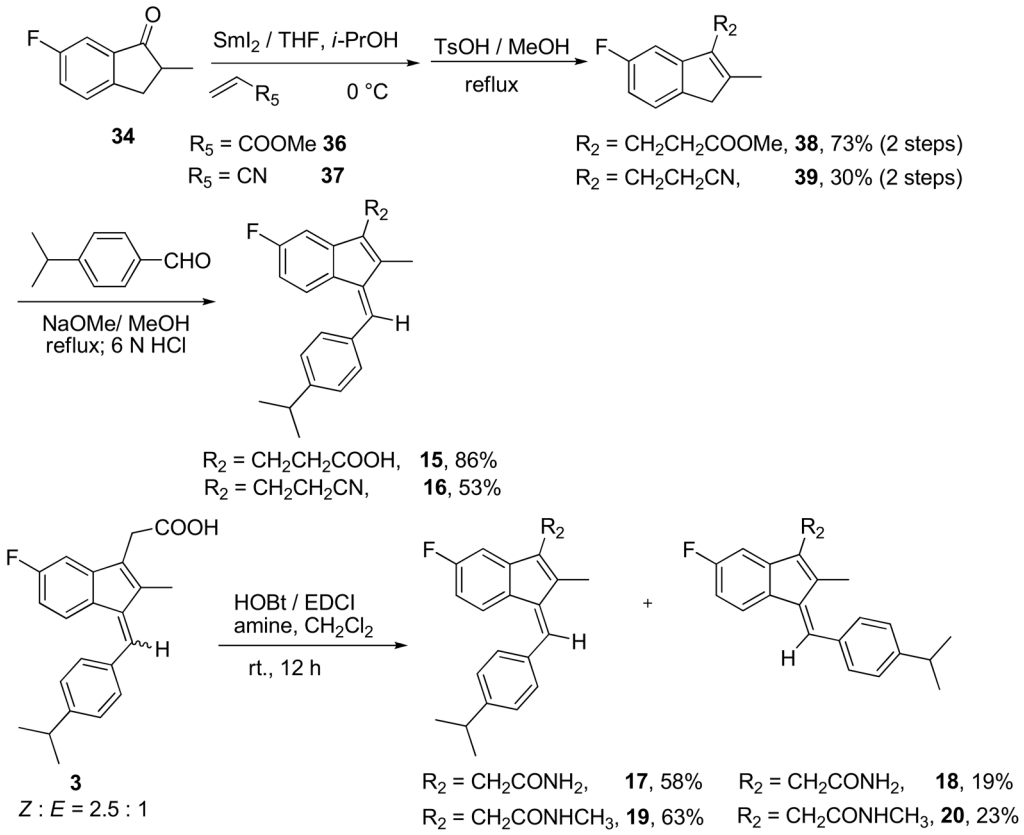


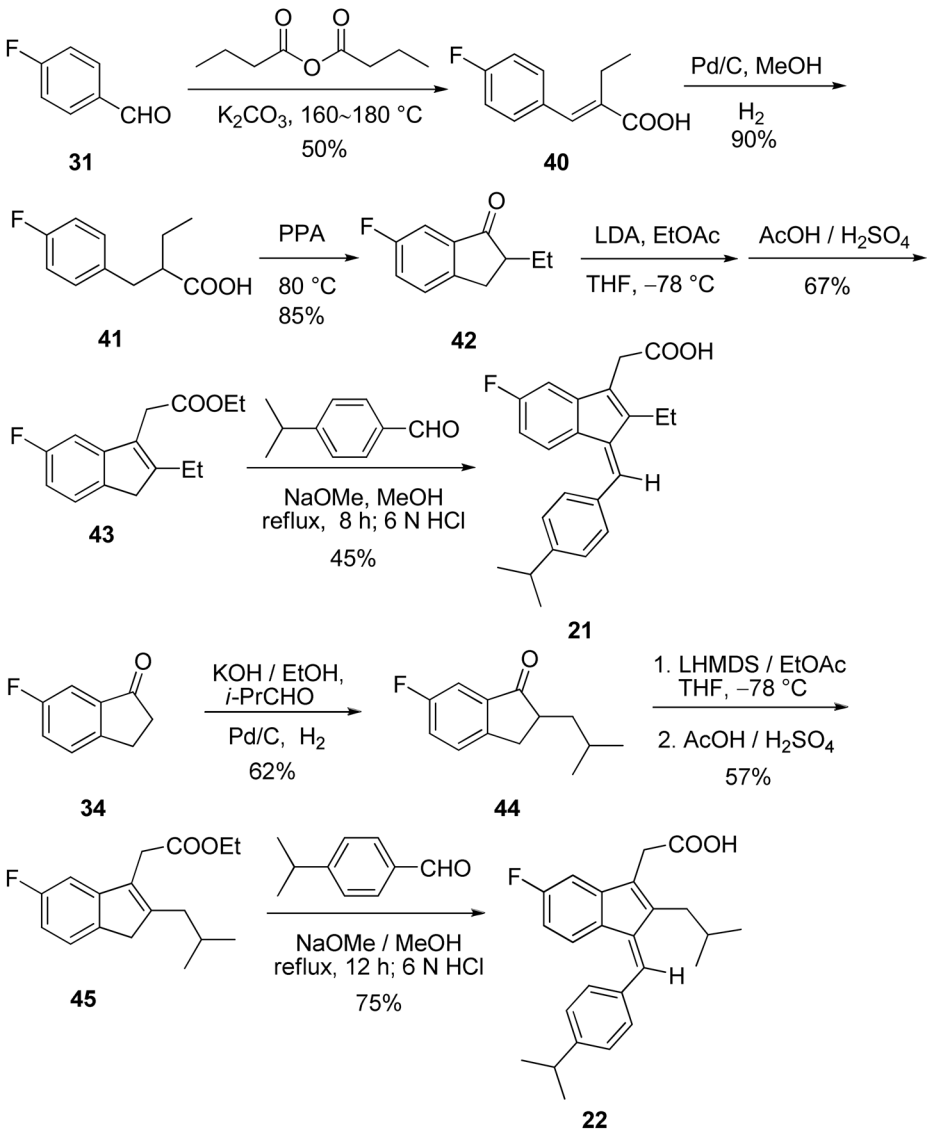
Figure 8.
Synergistic induction of apoptosis by compound/TNFα combination. HCT116 cells treated with 40 μM, **1, 2** or **30** in the presence or absence of TNFα for 4 hr were analyzed by immunoblotting.

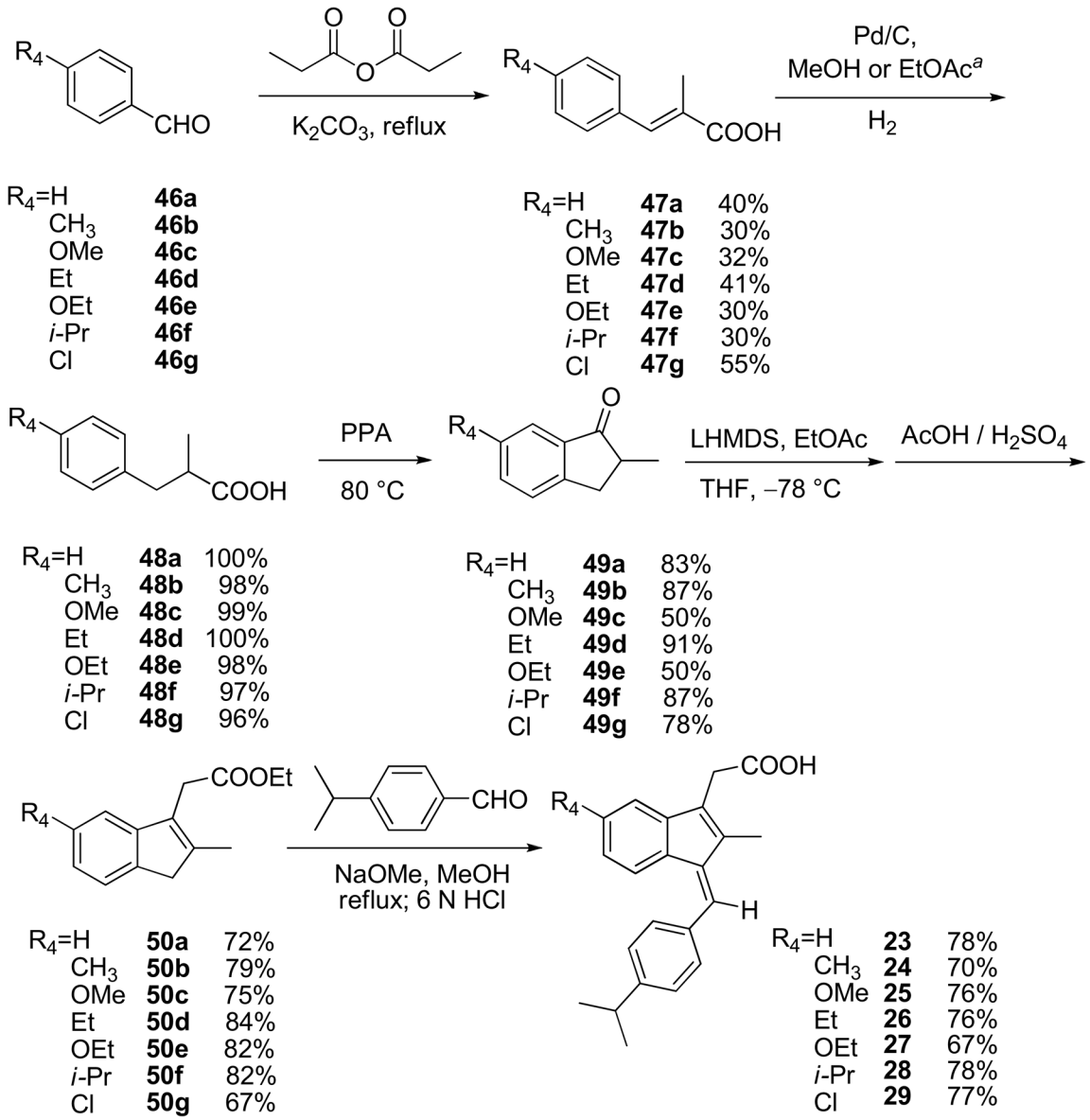


Scheme 1.
Synthesis of compounds **3**~**14**

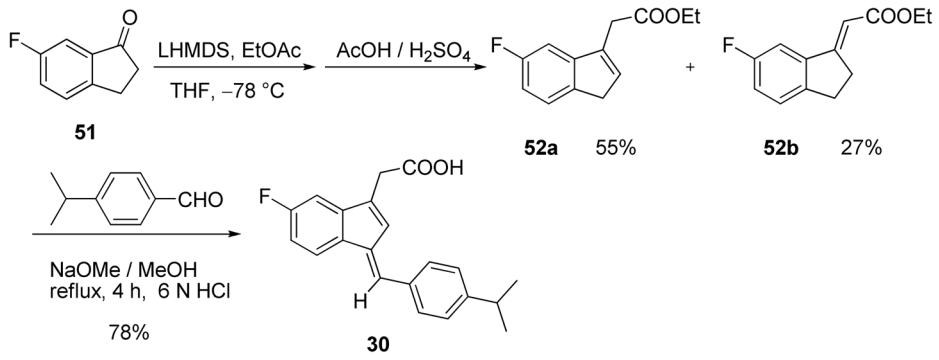


Scheme 2.
Synthesis of compounds **15**~**20**





Scheme 3.
Synthesis of compounds **21**~**29**



Scheme 4.
Synthesis of compounds **30**

Table 1

Summary of the binding data for the R^1 derivatives

Compound	R^1 (R^2= CH_2COOH; R^3= CH_3; R^4= F)	RXRα Binding IC_{50} (μM)
3	H	10.65
4	4-CF_3	4.73
5	4-$C(CH_3)_3$	≥100
6		≥100
7	4-OCH_3	≥100
8	4-OCH_2CH_3	≥100
9	4-CN	≥100
10	4-$N(CH_3)_2$	≥100
11	3-CF_3	8.27
12	3-OCH_3	≥100
13	3-CN	≥100
14	4-$NHC(O)CH_3$	≥100

Table 2

Summary of the binding data for the R^2 derivatives

Compound	R^2 (R^1= $CH(CH_3)_2$; R^3= CH_3; R^4= F)	RXRα Binding IC_{50} (μM)
15	CH_2CH_2COOH	5.71
16	CH_2CH_2CN	≥100
17	CH_2CONH_2	≥100
18	$CH_2C(O)NHCH_3$	≥100

Table 3

Summary of the binding data for the R^3/R^4 derivatives

Compound	R^3 (R^1=$CH(CH_3)_2$ R^2= CH_2COOH)	R^4 (R^1= $CH(CH_3)_2$ R^2= CH_2COOH)	RXRα Binding IC_{50} (μM)
21	CH_2CH_3	F	6.29
22	$CH_2CH(CH_3)_2$	F	3.15
23	CH_3	H	≥100
24	CH_3	CH_3	≥100
25	CH_3	OCH_3	≥100
26	CH_3	CH_2CH_3	≥100
27	CH_3	OCH_2CH_3	3.08
28	CH_3	$CH(CH_3)_2$	≥100
29	CH_3	Cl	≥100

Table 4

Results of the Claisen-Schmidt reactions

Compound	R^1	Yield (%)	Compound	R^1	Yield (%)
3	H	77	**4**	4-CF_3	62
5	4-$(CH_3)_3C$	72	**6**		33
7	4-CH_3O	78	**8**	4-CH_3CH_2O	66
9[i]	4-CN	73	**10**	4-$(CH_3)_2N$	20
11	3-CF_3	71	**12**	3-CH_3O	70
13	3-CN	60	**14**	4-CH_3CONH	22