Bioorganic & Medicinal Chemistry Letters 19 (2009) 4228–4231

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Application of a 3,3-diphenylpentane skeleton as a multi-template for creation of HMG-CoA reductase inhibitors

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ARTICLE INFO

Article history:
Received 8 May 2009
Revised 21 May 2009
Accepted 25 May 2009
Available online 29 May 2009

Keywords:
3,3-Diphenylpentane
DPP skeleton
HMG-CoA reductase
Statin

ABSTRACT

Based on our hypothesis that the 3,3-diphenylpentane (DPP) skeleton is useful as a multi-template for creation of various biologically active compounds and acts as a steroid skeleton substitute, we designed and synthesized novel HMG-CoA reductase inhibitors with a DPP skeleton. Among them, sodium (*E*,3*R*,5*S*)-7-(2-(4-fluorophenyl)-4-(3-phenylpentan-3-yl)phenyl)-3,5-dihydroxy-hept-6-enoate showed potent HMG-CoA reductase-inhibitory activity comparable with that of clinically useful mevastatin.

Biologically active compounds with a 3,3-diphenylpentane (DPP) skeleton include vitamin D_3 agonists, such as LG190178 (**1**) (Fig. 1).[1,2] We have been engaged in structural development studies of DPP-type vitamin D_3 agonists, and found that potent androgen antagonists, including DPP-0113 (**2**) (Fig. 1), can be created based on the DPP skeleton.[3,4] This led us hypothesize that the DPP skeleton can be employed as a steroid skeleton substitute, and we have verified this idea by creating progesterone antagonists, such as compound **3** (Fig. 1), farnesoid X receptor (FXR) agonists (whose cognate ligands include chenodeoxycholic acid), such as DPPF-01 (**4**) (Fig. 1), and peroxisome proliferator-activated nuclear receptor (PPAR) agonists, including DPPK-01 (**5**) (Fig. 1). Moreover, we showed that the DPP skeleton can be a superior scaffold for creating not only nuclear receptor ligands, but also steroid-metabolizing enzyme inhibitors, including potent inhibitors of 5α-reductase (whose cognate substrates include testosterone), such as compound **6** (Fig. 1).[5–7]

Furthermore, based on the idea that the number of protein fold structure types that comprise all the domains occurring in human proteins is quite limited (there may be only ca. 1000 fold structures) in spite of the huge number of human proteins (50,000–70,000 unique amino acid sequences),[8–10] we expected that the DPP skeleton would afford a superior scaffold to create various biologically active compounds.[11] Indeed, potent anti-bovine viral diarrhea viral (BVDV) agents, including compound DPP-0111 (**7**) (Fig. 1), have been created by using this approach, although steroidal anti-BVDV agents have not been reported as far as the authors know.[7,11,12] Overall, anyway, these results confirm the usefulness of the DPP skeleton as a multi-template for creation of various biologically active compounds, and therefore, we planned to apply the DPP skeleton as a scaffold for fragment-based drug design (FBDD) and as a structure for creation of a focused chemical library.

We chose 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase: HMGR) as the target molecule. HMGR is the rate-controlling enzyme in cholesterol biosynthesis, and is the target molecule of statins. An elevated level of low-density lipoprotein-cholesterol (LDL-C) is one of the key risk factors for atherosclerosis and coronary heart disease (CHD).[13,14] Statins, such as mevastatin (compactin, **8**), rosuvastatin (**9**), fluvastatin (**10**), atorvastatin (**11**) and pitavastatin (**12**) (Fig. 2), inhibit HMGR and reduce LDL-C levels in the bloodstream.[15–18] Many synthetic statins have been developed, and the structural requirements seem well established, that is, almost all of the synthetic statins, including rosuvastatin (**9**), fluvastatin (**10**), atorvastatin (**11**) and pitavastatin (**12**), possess (**A**) a 3-desmethylmevalonic acid moiety (MA part), (**B**) a 4-fluorophenyl group (FPh part) and (**C**) a bulky hydrophobic group such as an isopropyl group or a cyclopropyl group as pharmacophores. Therefore, we require a scaffold onto which functional groups **A**–**C** can be introduced for preparing novel HMGR inhibitors. In this connection, some steroids are known to inhibit HMGR,[19,20] and oxysterols possessing a hydroxyl group in the side chain tend to show potent inhibition. So far, cholest-5-ene-3β,25-diol (25-hydroxycholesterol, **13**) (Fig. 2), a direct metab-

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doi:10.1016/j.bmcl.2009.05.100

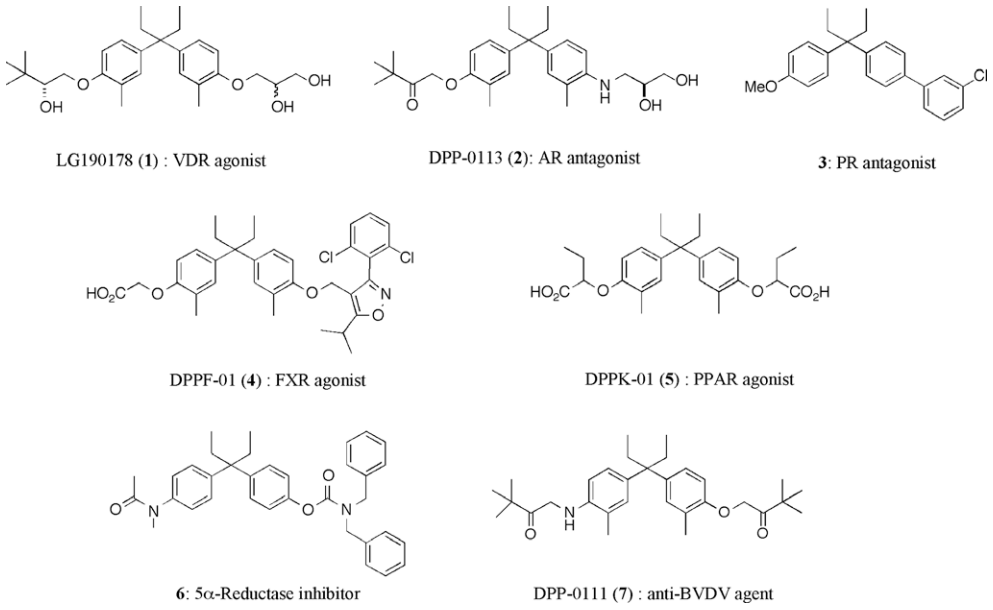


Figure 1. Typical biologically active compounds based on a 3,3-diphenylpentane skeleton.

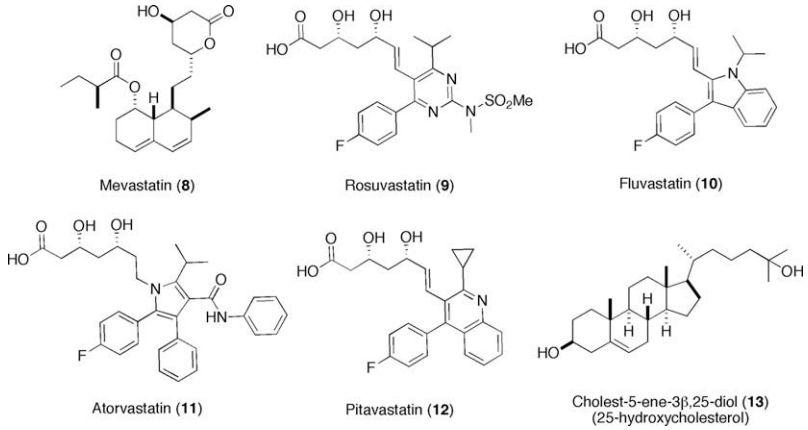


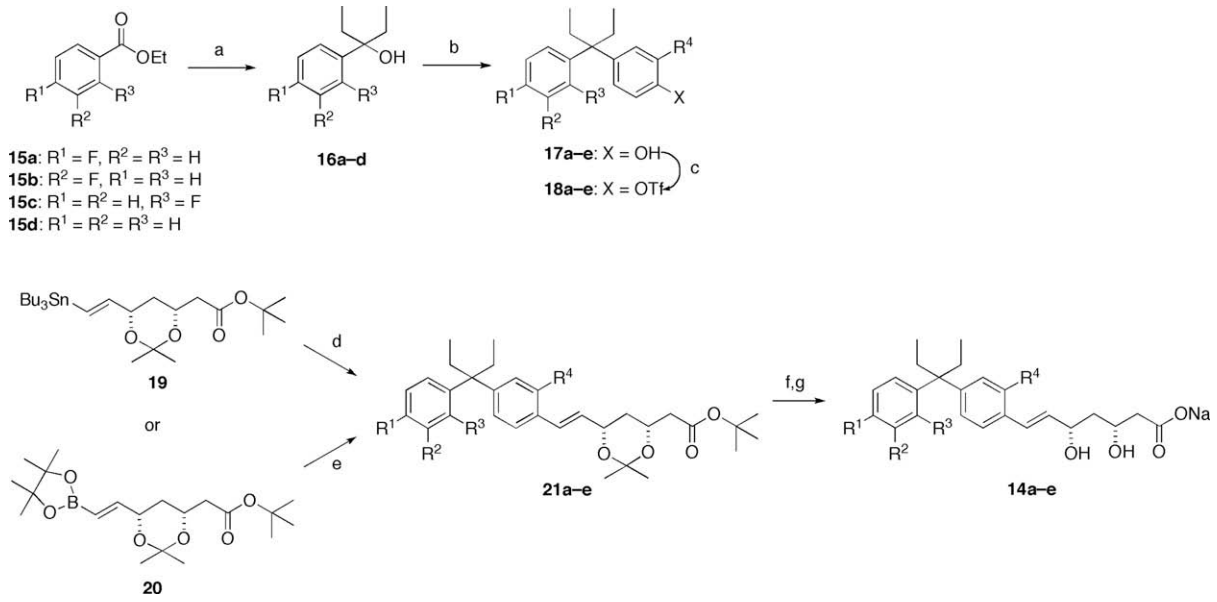
Figure 2. Statin-type and oxysterol-type HMGR inhibitors.

olite of cholesterol in the liver, is the most potent inhibitor among reported oxysterols. Since the DPP skeleton is considered to act as a steroid substitute and a multi-template as mentioned above, we decided to use the DPP skeleton as a scaffold upon which to display the moieties **A**, **B** and **C**, with the aim of creating novel HMGR inhibitors.

We first planned to use one of the phenyl rings of the DPP skeleton as the FPh part by introducing fluorine, and also planned to introduce the MA part into the other phenyl ring of the DPP skeleton, that is, compounds **14a–e**, to create candidate DPP-type HMGR inhibitors. Compounds **14a–e** were prepared according to Scheme 1. Starting from ethyl fluorobenzoate **15a–d**, the diethyl moiety and phenol group were introduced, and then the phenolic hydroxyl group of **17a–e** was converted to triflate (**18a–e**). A desmethylmevalonic acid moiety, as the organotin derivative **19** (Stille coupling) or the boronate ester **20** (Suzuki coupling), was coupled with triflates **18a–e** to afford **21a–e**. Finally, deprotection of acetal and *tert*-butyl ester by means of acidic and basic hydrolysis afforded **14a–e** as sodium salts.[21–25]

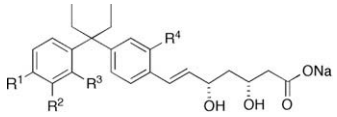
The inhibitory potency of the prepared compounds toward rat HGMR was evaluated by the method described previously.[26] Briefly, DL-[3-^{14}C]HMG-CoA (3.7 MBq in method A or 0.37 MBq in method B) and 10 mg protein of microsomal fraction was incubated at 37 °C for 30 min. The reaction was terminated by addition of 2 M HCl aq and the metabolites were converted to mevalonolactone. The metabolite mixture was separated by means of thin layer chromatography (Merck 20 TLC plates Silica Gel 60 F_{254}) with acetone/benzene (1:1 v/v). The radioactivity of each spot on the plate was measured with a bioimaging analyzer (FLA-7000, Fuji Film, Japan).

In screening using method A, **14a** showed no apparent HMGR-inhibitory activity even at 100 mM under the experimental conditions used (Table 1). However, compound **14b** containing an isopropyl group at the R^4 position showed slight inhibitory activity with IC_{50} values of 26 and 2.2 mM in methods A and B, respectively. This one order of magnitude difference in the IC_{50} values can be attributed to the difference of substrate concentration between methods A and B. Possibly because **14b** is a competitive inhibitor, the measured IC_{50} values are dependent on the concentrations of the substrate and enzyme. The appearance of HMGR-inhibitory activity in **14b** but not in **14a** suggests that a bulky hydrophobic moiety be required as a substituent group R^4 for the activity. Next, the effect of the position of the fluoro group on the terminal phenyl ring on the activity was investigated. Compared with the *para*-fluoro derivative **14b**, the *meta*-fluoro derivative



Scheme 1. Reagents and conditions: (a) EtMgBr, THF, 16 h, 61–95%; (b) 2-R^4-phenol, H_2SO_4 aq, 1 h; (c) Tf_2O, DIPEA, CH_2Cl_2, 0 °C, 4 h, 59–87% (two steps); (d) **18a–b**, $PdCl_2(PPh_3)_2$, PPh_3, LiCl, DMF, 80 °C, 6 h; (e) **18c–e**, $Pd(PPh_3)_4$, K_3PO_4, DMF–H_2O, 65 °C, 6 h; (f) HCl aq, THF, 14–34% (two steps); (g) NaOH aq, THF, 38–97%.

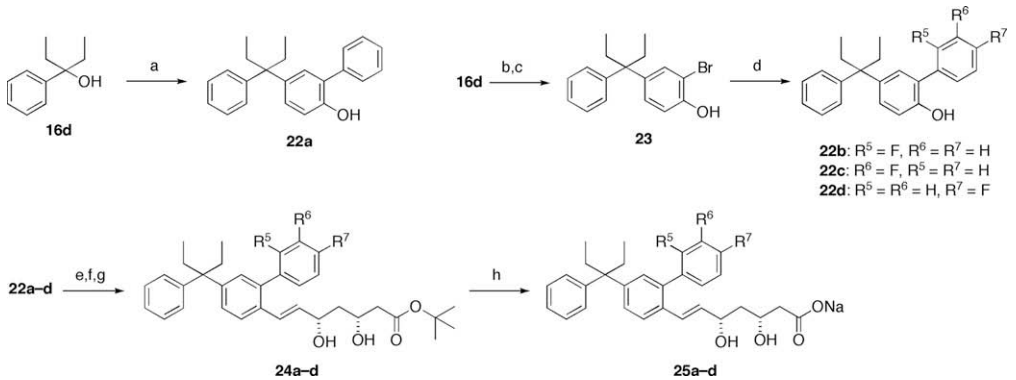
Table 1
SAR for HMGR inhibition (1)



Compound	R^1	R^2	R^3	R^4	IC_{50} (μM) Method A	IC_{50} (μM) Method B
14a	F	H	H	H	Inactive	
14b	F	H	H	*i*-Pr	26	2.2
14c	H	F	H	*i*-Pr	92	
14d	H	H	F	*i*-Pr		7.4
14e	H	H	H	*i*-Pr		1.8
Mevastatin (**8**)						0.04
Fluvastatin (**10**)						0.003

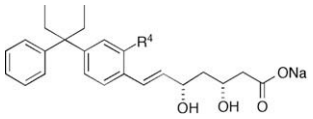
14c and *ortho*-fluoro derivative **14d** showed less potent inhibition. However, the non-substituted derivative **14e** possessed similar activity to **14b**, suggesting that the effect of *para*-fluoro substitution is negligible, that is, the *para*-fluorophenyl moiety does not function as a FPh part.

Therefore, we next introduced the FPh part at another position. Based on the structure of **14e** and other synthetic statins, we designed compounds possessing another phenyl group **25a**[27] and fluorophenyl group **25b–d**,[28–30] and synthesized them by methods similar to that used for the preparation of **14e** (Scheme 2).



Scheme 2. Reagents and conditions: (a) 2-phenylphenol, H_2SO_4 aq, 1 h, quant; (b) phenol, H_2SO_4 aq, 1 h, 90%; (c) NBS, CH_3CN, 61%; (d) phenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, DME–H_2O, reflux, 7 h, 70–82%; (e) Tf_2O, DIPEA, CH_2Cl_2, 0 °C, 4 h; (f) **20**, $Pd(PPh_3)_4$, K_3PO_4, DMF–H_2O, 65 °C, 6 h; (g) HCl aq, THF, 13–23% (three steps); (h) NaOH aq, THF, 41–56%.

Table 2
SAR for HMGR inhibition (2)



Compound	R^4	IC_{50} (μM) Method B
14e	*i*-Pr	1.8
25a	Ph	0.85
25b	2-F-Ph	0.82
25c	3-F-Ph	1.2
25d	4-F-Ph	0.15

As shown in Table 2, all the compounds thus prepared (**25a**–**d**) showed more potent HMGR-inhibitory activity than **14e**. Especially, the *para*-fluorophenyl group-bearing analog **25d** showed the most potent activity, having an IC_{50} value of 0.15 mM (measured by method B), among the compounds prepared. Introduction of a fluoro group at the *para*-position seems to be quite effective, that is, the *para*-fluoro analog shows an almost one order of magnitude lower IC_{50} value compared to the *ortho*- and *meta*-fluoro regioisomers (IC_{50} values of 0.82–1.2 mM measured by method B). Introduction of a fluoro group at only the *para*-position of **25a** (i.e., **25d**) resulted in an increase of the activity. Introduction at the *ortho*-position (**25b**) had almost no effect on the activity, and introduction at the *meta*-position (**25c**) resulted in a decrease of the activity.

In conclusion, we obtained the potent HMGR inhibitor **25d** with an IC_{50} value comparable to that of mevastatin **8** (the relative potency of **25d** vs mevastatin (**8**) is approximately 0.3), by employing the DPP skeleton as a scaffold upon which to array the pharmacophore structures known to be required for statins (i.e., the MA part and FPh part). Although the structure of **25d** is not outside the general range of structures of known synthetic statins, our results suggest that the DPP skeleton is indeed useful as a core scaffold for fragment-based drug design and creation of focused chemical libraries, and also as a multi-template for creation of analogs of steroidal bioactive compounds. These results further support the validity of the multi-template hypothesis[6,12,31] as a technique for the design of novel biologically active compounds.

Acknowledgements

We thank Kaneka Corporation for a generous gift of *tert*-butyl (3*R*,5*S*)-6-hydroxy-3,5-*O*-isopropylidene-3,5-dihydroxyhexanoate. The work described in this paper was partially supported by Grants-in-Aid for Scientific Research from The Ministry of Education, Culture, Sports, Science and Technology, Japan, and the Japan Society for the Promotion of Science.

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21. *(E,3R,5S)-7-(4-(3-(4-Fluorophenyl)pentan-3-yl)phenyl)-3,5-dihydroxyhept-6-enoic acid* (**14a**). ^{1}H NMR (500 MHz, DMSO) δ 7.30 (d, J = 8.1 Hz, 2H), 7.15 (dd, J = 8.5, 5.6 Hz, 2H), 7.08–7.04 (m, 4H), 6.45 (d, J = 15.9 Hz, 1H), 6.17 (dd, J = 15.9, 6.4 Hz, 1H), 4.26 (q, J = 6.4 Hz, 1H), 3.84–3.80 (m, 1H), 2.21–2.18 (m, 1H), 2.07–2.02 (m, 5H), 1.63–1.58 (m, 1H), 1.48–1.44 (m, 1H), 0.61 (t, J = 7.3 Hz, 6H); HRMS (FAB, *m/z*, M^+) calcd for $C_{24}H_{29}FO_4$, 400.2050; found 400.2033.
22. *(E,3R,5S)-7-(4-(3-(4-Fluorophenyl)pentan-3-yl)-2-isopropylphenyl)-3,5-dihydroxyhept-6-enoic acid* (**14b**). ^{1}H NMR (500 MHz, DMSO) δ 7.28 (d, J = 8.6 Hz, 1H), 7.15 (dd, J = 9.0, 5.6 Hz, 2H), 7.07 (t, J = 9.0 Hz, 2H), 7.01 (d, J = 1.7 Hz, 1H), 6.86 (dd, J = 8.6, 1.7 Hz, 1H), 6.79 (d, J = 15.8 Hz, 1H), 6.00 (dd, J = 15.8, 6.2 Hz, 1H), 4.31–4.26 (m, 1H), 3.92–3.88 (m, 1H), 3.20 (sept, J = 6.8 Hz, 1H), 2.28 (dd, J = 14.5, 4.7 Hz, 1H), 2.16–2.13 (m, 1H), 2.04 (q, J = 7.3 Hz, 4H), 1.66–1.60 (m, 1H), 1.54–1.49 (m, 1H), 1.10 (d, J = 6.8 Hz, 6H), 0.55 (t, J = 7.3 Hz, 6H); HRMS (FAB, *m/z*, $[M+Na]^+$) calcd for $C_{27}H_{35}FNaO_4$, 465.2417; found 465.2433.
23. *Sodium (E,3R,5S)-7-(4-(3-(3-fluorophenyl)pentan-3-yl)-2-isopropylphenyl)-3,5-dihydroxyhept-6-enoate* (**14c**). ^{1}H NMR (500 MHz, DMSO) δ 7.31–7.27 (m, 2H), 7.02 (d, J = 1.2 Hz, 1H), 6.99–6.91 (m, 3H), 6.86 (dd, J = 7.9, 1.2 Hz, 1H), 6.77 (d, J = 15.9 Hz, 1H), 6.01 (dd, J = 15.9, 6.1 Hz, 1H), 4.28 (q, J = 6.7 Hz, 1H), 3.81–3.76 (m, 1H), 3.18 (sept, J = 6.7 Hz, 1H), 2.07–2.03 (m, 5H), 1.95–1.91 (m, 1H), 1.62–1.56 (m, 1H), 1.48–1.43 (m, 1H), 1.10 (d, J = 6.7 Hz, 6H), 0.55 (t, J = 7.3 Hz, 6H); MS (FAB, $[M-Na+H]^+$) *m/z* 443.
24. *Sodium (E,3R,5S)-7-(4-(3-(2-fluorophenyl)pentan-3-yl)-2-isopropylphenyl)-3,5-dihydroxyhept-6-enoate* (**14d**). ^{1}H NMR (500 MHz, DMSO) δ 7.50 (t, J = 7.9 Hz, 1H), 7.29–7.24 (m, 2H), 7.20 (t, J = 7.3 Hz, 1H), 6.98–6.94 (m, 2H), 6.81 (d, J = 7.9 Hz, 1H), 6.77 (d, J = 15.9 Hz, 1H), 6.00 (dd, J = 15.9, 6.1 Hz, 1H), 4.28 (q, J = 6.7 Hz, 1H), 3.83–3.80 (m, 1H), 3.16 (sept, J = 6.7 Hz, 1H), 2.15–2.10 (m, 3H), 2.06–1.97 (m, 3H), 1.63–1.57 (m, 1H), 1.50–1.45 (m, 1H), 1.06 (d, J = 6.7 Hz, 6H), 0.54 (t, J = 7.3 Hz, 6H); HRMS (FAB, *m/z*, $[M+H]^+$) calcd for $C_{27}H_{35}FNaO_4$, 465.2417; found 465.2421.
25. *Sodium (E,3R,5S)-7-(4-(3-phenylpentan-3-yl)-2-isopropylphenyl)-3,5-dihydroxyhept-6-enoate* (**14e**). ^{1}H NMR (500 MHz, DMSO) δ 7.28–7.24 (m, 3H), 7.15–7.13 (m, 3H), 7.02 (s, 1H), 6.85 (d, J = 9.8 Hz, 1H), 6.76 (d, J = 15.9 Hz, 1H), 6.00 (dd, J = 15.9, 5.5 Hz, 1H), 5.02 (br, 1H), 4.28 (q, J = 6.1 Hz, 1H), 3.75–3.70 (m, 1H), 3.20–3.15 (m, 1H), 2.05 (q, J = 7.3 Hz, 4H), 2.01 (dd, J = 15.6, 3.1 Hz, 1H), 1.81 (dd, J = 15.6, 8.5 Hz, 1H), 1.59–1.53 (m, 1H), 1.40 (dt, J = 14.0, 6.1 Hz, 1H), 1.09 (d, J = 6.7 Hz, 6H), 0.55 (t, J = 7.3 Hz, 6H); HRMS (FAB, *m/z*, $[M-Na+H]^+$) calcd for $C_{27}H_{36}O_4$, 424.2614; found 424.2600.
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27. *Sodium (E,3R,5S)-7-(2-phenyl-4-(3-phenylpentan-3-yl)phenyl)-3,5-dihydroxyhept-6-enoate* (**25a**). ^{1}H NMR (500 MHz, DMSO) δ 7.52 (d, J = 8.5 Hz, 1H), 7.41 (t, J = 7.3 Hz, 2H), 7.35–7.12 (m, 6H), 7.08 (dd, J = 7.9, 1.8 Hz, 1H), 7.00 (d, J = 1.8 Hz, 1H), 6.41 (d, J = 15.9 Hz, 1H), 6.12 (dd, J = 15.9, 6.1 Hz, 1H), 5.02 (br, 1H), 4.15 (q, J = 6.7 Hz, 1H), 3.79–3.72 (m, 1H), 2.09 (q, J = 7.3 Hz, 4H), 1.76–1.73 (m, 2H), 1.60–1.43 (m, 2H), 0.58 (t, J = 7.3 Hz, 6H); HRMS (FAB, *m/z*, $[M-Na+H]^+$) calcd for $C_{30}H_{34}O_4$, 458.2457; found 458.2430.
28. *Sodium (E,3R,5S)-7-(2-(2-fluorophenyl)-4-(3-phenylpentan-3-yl)phenyl)-3,5-dihydroxy-hept-6-enoate* (**25b**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 8.5 Hz, 1H), 7.24–7.07 (m, 10H), 7.03 (t, J = 8.5 Hz, 1H), 6.37 (d, J = 15.7 Hz, 1H), 6.03 (dd, J = 15.7, 7.0 Hz, 1H), 4.33 (m, 1H), 4.18 (m, 1H), 2.38 (m, 2H), 2.09 (q, J = 7.3 Hz, 4H), 1.67 (m, 1H), 1.51 (m, 1H), 0.62 (t, J = 7.3 Hz, 6H); HRMS (FAB, *m/z*, $[M+H]^+$) calcd for $C_{30}H_{33}FNaO_4$, 499.2261; found 499.2282.
29. *Sodium (E,3R,5S)-7-(2-(3-fluorophenyl)-4-(3-phenylpentan-3-yl)phenyl)-3,5-dihydroxy-hept-6-enoate* (**25c**). ^{1}H NMR (500 MHz, $CDCl_3$) *d* 7.25–6.94 (m, 12H), 6.50 (d, J = 15.9 Hz, 1H), 6.09 (m, 1H), 4.41 (m, 1H), 4.28 (m, 1H), 2.47 (m, 2H), 2.11 (q, J = 7.3 Hz, 4H), 1.73 (m, 1H), 1.60 (m, 1H), 0.58 (t, J = 7.3 Hz, 6H); HRMS (FAB, *m/z*, $[M+H]^+$) calcd for $C_{30}H_{33}FNaO_4$, 499.2261; found 499.2231.
30. *Sodium (E,3R,5S)-7-(2-(4-fluorophenyl)-4-(3-phenylpentan-3-yl)phenyl)-3,5-dihydroxy-hept-6-enoate* (**25d**). ^{1}H NMR (500 MHz, DMSO) δ 7.45 (d, J = 9.2 Hz, 1H), 7.25–7.14 (m, 6H), 7.09–7.04 (m, 5H), 6.50 (d, J = 15.9 Hz, 1H), 6.07 (dd, J = 15.9, 6.7 Hz, 1H), 4.47–4.43 (m, 1H), 4.29–4.25 (m, 1H), 2.11 (q, J = 7.3 Hz, 4H), 1.78–1.73 (m, 2H), 1.65–1.61 (m, 2H), 0.63 (t, J = 7.3 Hz, 6H); HRMS (FAB, *m/z*, $[M-Na+H]^+$) calcd for $C_{30}H_{33}FO_4$, 476.2363; found 476.2365.
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