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Synthesis and antiaggregant properties of new analogues of polyunsaturated fatty acid metabolites with naphthalene or quinoline cores

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Abstract—New bicyclic analogues of polyunsaturated fatty acid metabolites have been prepared using short and efficient routes. Preliminary studies of their activity as inhibitors of platelet aggregation are reported. © 2002 Elsevier Science Ltd. All rights reserved.

Polyunsaturated fatty acid metabolites have key regulatory functions in living systems and many of them have been associated with various diseases. For instance the 12(*S*) - hydroxy - 5(*Z*),8(*Z*),10(*E*),14(*Z*)eicosatetraenoic acid (12-HETE) has been implicated in many pathologies including inflammation, cardiovascular problems, cancer and diabetes.[1] Since 12-HETE is relatively labile, it is important to design more stable analogues: monoaromatic derivatives, joining carbon atoms C_7 and C_{11}, have been prepared previously and have shown useful biological properties as inhibitors of blood platelet aggregation.[2]

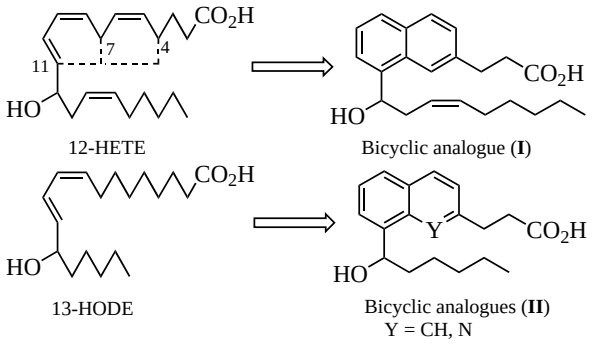

Figure 1.

Therefore, it appeared very attractive to add an extra ring joining the carbon atoms C_4 to C_7 and then giving the analogue (**I**) with a naphthalene core (Fig. 1).

The 13-HODE is an important metabolite of linoleic acid which has been involved in various pathologies.[3] It has been demonstrated that both enantiomers of 13-HODE are good antagonists of TXA_2-induced platelet aggregation.[4] Therefore, it appeared also interesting to introduce on the lipophilic side of the molecule a saturated C_5 chain, similar to that of 13-HODE. This led to the second family of analogues (**II**). In this case, they have been prepared both in the naphthalene and quinoline series.

For the first target molecule, 1-formyl 7-bromonaphthalene **3** was selected as a key intermediate since it has in proper position the aldehyde to introduce the lipophilic side chain and the bromine to anchor the acidic side chain via a Heck-type coupling (Scheme 1). Furthermore, this intermediate is easily accessible in two steps (bromination then oxidation, 64% overall yield) from the known naphthalene derivative **1**.[5] The lipophilic side chain was introduced in two separate steps: first a two carbon extension and, after functional group manipulation, a Wittig reaction in order to afford the last six carbon unit. Addition of lithioacetate on **3**, followed by protection of the secondary alcohol, led to the ester **4** which is then reduced to the alcohol **5** (79% yield from **3**). At this stage, the Heck coupling

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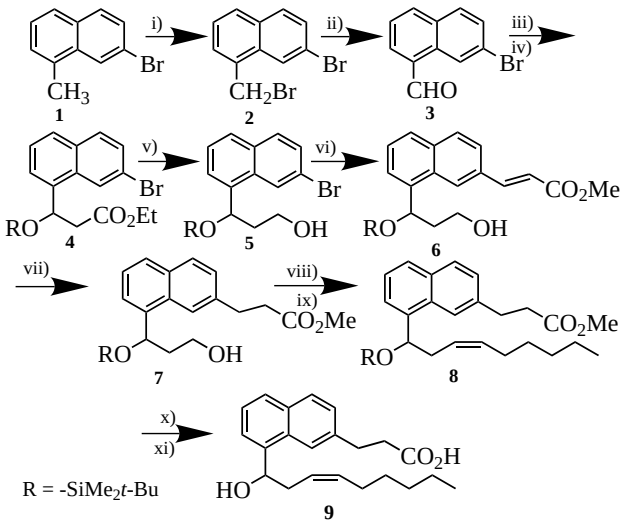
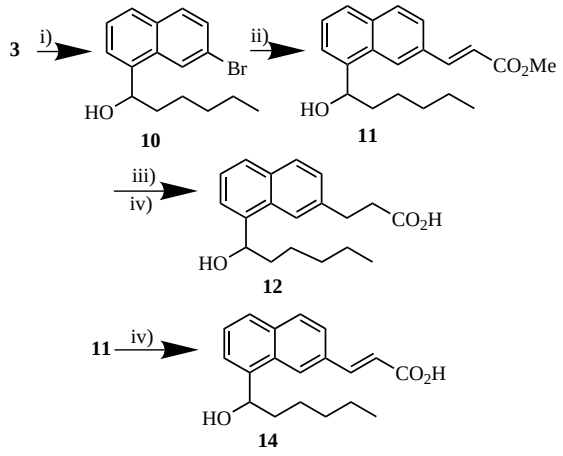


Scheme 1. *Reagents and conditions*: (i) NBS (1 equiv.), AIBN (cat.), CCl_4 (reflux, 30 min), 73%; (ii) Na (1.4 equiv.), 2-nitropropane (1.4 equiv.), MeOH (rt, 20 h), 88%; (iii) LDA, AcOEt (1.8 equiv.), THF (–80°C, 30 min), 94%; (iv) imidazole (2.5 equiv.), *t*-$BuMe_2SiCl$ (1.2 equiv.), DMF (rt, 15 h), 94%; (v) DIBAL-H (2 equiv.), Et_2O (–80°C, 2 h), 90%; (vi) Ph_3P (0.04 equiv.), $Pd(OAc)_2$ (cat), TMEDA, methyl acrylate (2.2 equiv.) (125°C, 2 h), 85%; (vii) H_2–Pd/C, AcOEt (rt), 88%; (viii) Swern oxidation; (ix) $Ph_3P^+(CH_2)_5CH_3Br^-$ (3 equiv.), *n*-BuLi (3 equiv.), HMPA/THF (–80°C, 4 h), 53%; (x) *n*-$Bu_4N^+F^-$ (1.3 equiv.), THF (from 0°C to rt, 15 h), quantitative; (xi) LiOH, THF/H_2O (rt, 15 h), acetic acid, 93%.

worked well to give the derivative **6** which was hydrogenated to the alcohol **7** (75% yield from **5**). The intermediate aldehyde obtained by Swern oxidation of the latter derivative was used in situ for the Wittig reaction leading to **8**. The final steps, deprotection and saponification, led to the target molecule **9** (11 steps and 19% overall yield from **1**).

A similar strategy was followed for the synthesis of the second analogue **14**, bearing a C_5 saturated lipophilic side chain. This chain was introduced by the addition of the *n*-pentyl Grignard reagent on **3**, leading to **10**. The Heck coupling to **10** proceeded also in good yield as well as the next steps towards target molecule **12** (four steps, 54% overall yield from **3**). For comparison of the biological properties, the corresponding unsaturated derivative **14** was also prepared by saponification of **11** (Scheme 2).

For the quinoline analogues, the 8-bromoquinaldine **15** was selected as starting material since it is easily accessible in one step and 47% yield from commercially available derivatives.[6] Metallation with *sec*-BuLi, followed by trapping with *n*-hexanal gave alcohol **16**. After protection as the TBDPS ether, SeO_2 oxidation led in 91% yield to the key intermediate **18**. Then the target molecule **20** was easily obtained by a Horner–Wadworth–Emmons reaction followed by a catalytic hydrogenation and deprotection (seven steps and 21% overall yield from **15**). The unsaturated analogue **21** was also

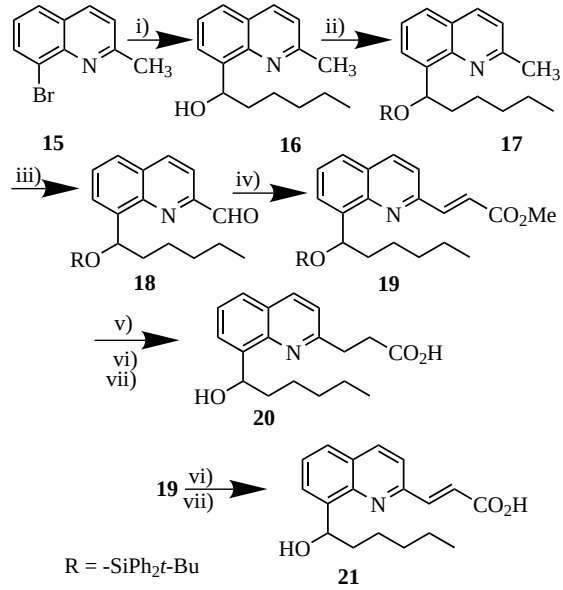


Scheme 2. *Reagents and conditions*: (i) *n*-$C_5H_{11}MgBr$ (1.7 equiv.), THF (–70°C, 30 min), 67%; (ii) Ph_3P (0.02 equiv.), $Pd(OAc)_2$ (0.01 equiv.), TMEDA, methyl acrylate (1.6 equiv.), (125°C, 2 h), 90%; (iii) H_2–Pd/C, AcOEt (rt), 96%. (iv) LiOH, THF/H_2O (rt, 15 h), acetic acid, 94%.

prepared by deprotection and saponification of the intermediate **19** (Scheme 3).

Biological tests

In order to improve the solubility of these acids in water, we have prepared the corresponding sodium salts[7] and used the latter derivatives for the biological tests. Preliminary data on the in vitro biological activity of representative examples are summarized in Table 1 The anti-platelet activity of the compounds was mea-



Scheme 3. *Reagents and conditions*: (i) *sec*-BuLi (1.14 equiv.), THF (–80°C) then hexanal (2 equiv.), 47%; (ii) imidazole (2.5 equiv.), *t*-$BuPh_2SiCl$ (1.2 equiv.), DMF (rt, 15 h), 91%; (iii) SeO_2 (1.2 equiv.), H_2O, dioxane (reflux, 45 min), 91%; (iv) $(CH_3O)_2P(O)CH_2CO_2CH_3$ (1.4 equiv.), $LiOH{\cdot}H_2O$ (2.2 equiv.), THF (reflux, 1 h), 92%; (v) H_2–Pd/C, AcOEt (rt, 32 h), 96%; (vi) *n*-$Bu_4N^+F^-$ (1.3 equiv.), THF (from 0°C to rt, 15 h), 65%; (vii) LiOH, THF/H_2O (rt, 15 h, 95%).

Table 1. Biological activities of compounds

Inhibition of platelet aggregation (IC_{50}, μM)[a]		
Compounds	U 46619	Collagen
12	0.2	25
14	23	142
20	0.3	146
21	17	57
Bay u 3405	NT	0.26
12 (R) HETE	4	NT

[a] $n=2$–5 in all experiments; NT, not tested.

sured by studying their inhibitory effects on human and rabbit washed platelets (WP) respectively aggregated with U 46619 (0.2 μM), a stable mimetic analogue of thromboxane A_2 or with collagen (1 μg/ml), a physiological agonist that causes endogenous thromboxane A_2 synthesis. The IC_{50} values are expressed in μM.

All compounds described in Table 1 are antagonists of thromboxane (TP) receptors. The arachidonate metabolite, 12 (R) HETE, inhibits U 46619-induced platelet aggregation; Bay u 3405, a selective TP-receptor antagonist, is a potent inhibitor of platelet aggregation induced by collagen, illustrating that activation of the TP-receptors is implicated. For the naphthalene analogue, the best antagonist activity is obtained with **12** on U 46619- and collagen-induced platelet aggregation. However, the quinoline analogue, **20** shows an equipotent antagonist activity than **12** on U 46619-induced platelet aggregation, but is less active against collagen-induced platelet aggregation; the saturated lipophilic side chain influences the inhibitory activity of **20** in comparison with **21** on U 46619- but not on collagen-induced platelet aggregation. There is an apparent correlation between the order of potency with the naphthalene analogues against the two platelet activators, which does not exist with the quinoline analogues.

In conclusion, we have reported short and versatile sequences towards novel analogues of polyunsaturated fatty acid metabolites with naphthalene or quinoline cores. Some of these derivatives are good inhibitors of platelet aggregation.

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3. See for instance: (a) Babubri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron* **2000**, *56*, 327–331; (b) Prakesch, M.; Gree, D.; Gree, R. *J. Org. Chem.* **2001**, *66*, 3146–3151 and references cited therein.
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7. All new compounds have spectral and analytical data in agreement with the indicated structures. We thank Drs. J. P. Volland and M. Amm (IdRS) for the microanalyses. Spectral and analytical data for the final products submitted to biological tests, as their sodium salts. Compound **12**: IR (NaCl, film, ν cm^{-1}): 3402 (OH), 1567 (C=O); ^1H NMR (90 MHz, CD_3OD): δ 7.94–7.23 (m, 6 H, arom.), 5.44 (t, 1 H, CHOH, $J=6.1$), 3.12–3.01 (m, 2 H, CH_2-CH_2-CO_2Na), 2.70–2.48 (m, 2 H, CH_2-CH_2-CO_2Na), 2.05–1.71 (m, 2 H, CH_2-CHOH), 1.67–1.11 (m, 6 H, $CH_2(CH_2)_3CH_3$), 0.88 (t, 3 H, CH_2CH_3, $J=5.7$); ^{13}C NMR (22.5 MHz, D_2O): δ 181.8 (CO_2Na), 140.3, 139.8, 133.1, 131.6 (4 C quat. arom.), 129.7, 128.3, 127.5, 125.3, 124.2, 122.5 (6 CH arom.), 71.3 (CHOH), 39.6 (CH_2CHOH), 38.1, 33.4, 32.1 ($CH_2CH_2CO_2Na$, $CH_2CH_2CH_3$), 25.9 ($CH_2(CH_2)_2CH_3$), 22.9 (CH_2CH_3), 14.2 (CH_3). Anal. calcd for $C_{19}H_{23}NaO_3$: C, 70.79; H, 7.19. Found: C, 71.41; H, 7.45%. Compound **14**: IR (NaCl, film, ν cm^{-1}): 3388 (OH), 1637 (C=C), 1560 (C=O); ^1H NMR (90 MHz, CD_3OD): δ 8.19 (s, 1 H, arom.), 7.94–7.29 (m, 5 H arom. and CH=$CHCO_2Na$), 6.65 (d, 1 H, CH=$CHCO_2Na$, $J=15.8$), 5.45 (t, 1 H, CHOH, $J=6.0$), 2.0–1.7 (m, 2 H, CH_2-CHOH), 1.63–1.26 (m, 6 H, $CH_2(CH_2)_3CH_3$), 0.88 (t, 3 H, CH_2CH_3, $J=5.9$); ^{13}C NMR (22.5 MHz, CD_3OD): δ 175.4 (CO_2Na), 142.8, 141.4 (C quat. and CH=$CHCO_2Na$), 135.6, 134.6, 131.9, 130.4, 128.3, 127.1, 126.7, 125.3, 124.6, 124.1 (9 CH arom. and CH=$CHCO_2Na$), 71.5 (CHOH), 39.8 (CH_2CHOH), 32.9 ($CH_2CH_2CH_3$), 26.9 ($CH_2(CH_2)_2CH_3$), 23.7 (CH_2CH_3), 14.3 (CH_3). Anal. calcd for $C_{19}H_{21}NaO_3$: C, 71.23; H, 6.61. Found: C, 71.70; H, 6.96%. Compound **20**: white powder, mp 105–108°C; IR (NaCl, film, ν cm^{-1}): 3388 (OH), 1581 (C=O); ^1H NMR (90 MHz, CD_3OD): δ 8.14 (d, 1 H, arom., $J=8.5$), 7.8–7.3 (m, 4 H, arom.), 5.5 (t, 1 H, CHOH, $J=6.6$), 3.4–3.18 (m, 2 H, $CH_2CH_2CO_2Na$), 2.9–2.62 (m, 2 H, $CH_2CH_2CO_2Na$), 2–1.8 (m, 2 H, CH_2-CHOH), 1.6–1.11 (m, 6 H, $CH_2(CH_2)_3CH_3$), 0.86 (t, 3 H, CH_2CH_3, $J=6.4$); ^{13}C NMR (22.5 MHz, D_2O): δ 180.5 (CO_2Na), 161.2, 145.8, 140.3, 138.0, 127.7, 127.5, 126.0, 122.3 (arom.), 73.8 (CHOH), 39.1 (CH_2CHOH), 36.1 (CH_2CO_2Na), 35.1 ($CH_2CH_2CO_2Na$), 32.2 ($CH_2CH_2CH_3$), 26.1 ($CH_2(CH_2)_2CH_3$), 22.9 (CH_2CH_3), 14.3 (CH_3). Anal. calcd for $C_{18}H_{22}NNaO_3$: C, 66.86; H, 6.86; N, 4.33. Found: C, 67.44; H, 7.10; N, 4.44%. Compound **21**: white powder, 165°C (dec.); IR (NaCl, film, ν cm^{-1}): 3402 (OH), 1651 (C=C), 1567 (C=O); ^1H NMR (90 MHz, CD_3OD): δ 8.23 (d, 1 H, arom., $J=8.5$), 7.84–7.39 (m, 4 H arom. and CH=$CHCO_2Na$), 7.04 (d, 1 H, CH=$CHCO_2Na$, $J=16.0$), 5.70 (t, 1 H, CHOH, $J=6.1$), 2.09–1.72 (m, 2 H, CH_2-CHOH), 1.61–1.11 (m, 6 H, $CH_2(CH_2)_3CH_3$), 0.86 (t, 3 H, CH_2CH_3, $J=6.2$); ^{13}C NMR (22.5 MHz, CD_3OD): δ 174.9 (CO_2Na), 154.9, 146.8, 143.6, 140.2, 138.3, 132.6, 129.2, 127.8, 127.7, 127.5, 120.8, (9 CH arom. and CH=$CHCO_2Na$), 72.6 (CHOH), 40.2 (CH_2CHOH), 32.9 ($CH_2CH_2CH_3$), 26.8 ($CH_2(CH_2)_2CH_3$), 23.6 (CH_2CH_3), 14.4 (CH_3). Anal. calcd for $C_{18}H_{20}NNaO_3$: C, 67.28; H, 6.27; N, 4.36. Found: C, 67.13; H, 6.36; N, 4.49%.