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Design and synthesis of 1-(4-benzoylphenyl)imidazole derivatives as new potent 20-HETE synthase inhibitors

Toshio Nakamura,* Takaaki Ishii, Noriyuki Miyata, Kazuo Taniguchi, Yasumitsu Tomishima, Tomokazu Ueki and Masakazu Sato*

Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd, 403, Yoshino-Cho 1-Chome, Kita-ku, Saitama-Shi, Saitama 331-9530, Japan

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Abstract—Structural modification of the novel 20-HETE synthase inhibitor **1** (IC_{50} 310 nM) is described. Introduction of a side chain with a carboxylic acid at the terminal position to **1** resulted in increased ability to inhibit human renal microsomal production of 20-HETE (**7c**: IC_{50} 7.9 nM), with good selectivity toward CYP2D6 and cyclooxygenases (COX)-1 and -2.

20-Hydroxy-5,8,11,14-eicosatetraenoic acid (20-HETE) is a major metabolite of arachidonic acid (AA) produced in the kidney.[1] Its biological properties have recently been extensively studied. The formation of 20-HETE from AA is catalyzed by cytochrome P450 (CYP) 4A isozymes (CYP4A1, 4A2, 4A3, and 4A8) in rat kidney[2] and cerebral artery,[3] and by CYP4A11 and 4F2 in human liver and kidney.[4] 20-HETE plays an important role in the regulation of vascular and tubular functions in kidneys and the regulation of vascular tone in the brain.[3,5–7] Therefore, 20-HETE is now considered to be a promising new target for the treatment of renal and cerebrovascular diseases. Several nonspecific 20-HETE synthase inhibitors such as 1-aminobenzotriazole (1-ABT),[8] and suicide-type inhibitors such as 17-octadecynoic acid (17-ODYA),[9] *N*-methylsulfonyl-12,12-dibromododec-11-enamide (DDMS), 12,12-dibromododec-11-enoic acid (DBDD),[10] and sodium 10-undecynyl sulfate (10-SUYS)[11] have been reported, however they received only limited therapeutic evaluation (Fig. 1).

We previously described the evaluation of *N*-hydroxyphenylformamidine derivative HET0016 (Fig. 1) as a selective 20-HETE synthase inhibitor.[12–15] We describe here an evaluation of phenylimidazole derivative **1**, which was obtained along with HET0016 by random screening of our in-house chemical library (Fig. 1). AA is metabolized to 20-HETE by oxidation of the ω-carbon atom with the oxygen atom coordinated to the heme iron atom of 20-HETE synthases. Accordingly, compound **1** should inhibit 20-HETE synthase activity through coordination of its imidazole ring to the active-site heme iron atom of the enzyme, as with well-known azole CYP inhibitors. On the other hand, AA has a characteristic carboxylic acid moiety opposite the hydrophobic terminal, which is recognized by 20-HETE synthase. Therefore, to improve the potency and selectivity of **1**, we examined the introduction of a carboxy moiety with a suitable linkage to the site opposite the imidazole ring of compound **1**.

Introduction of a carboxy side chain to the 4- and 6-positions of **1**, which may correspond to the expanded and folded conformations of AA,[16] was accomplished by Fries rearrangement of the *o*- and *p*-cresol 4-fluorobenzoate (**2** and **8**) followed by introduction of an imidazole ring and carboxyalkyl moiety (Schemes 1 and 2). Heating of **2** with powdered aluminum chloride without solvent[17] gave the benzophenone derivative **3**. Alkylation of **3** by ω-bromoalkanoates **4a**–**f** with potassium carbonate in dimethylformamide at 100 °C gave the corresponding esters **5a**–**f**. Subsequent treatment of **5a**–**f** with imidazole and sodium hydride in dimethylformamide at 100 °C gave the corresponding imidazole derivatives **6a**–**f**. The ester group of **6a**–**f** was hydrolyzed by 1 M sodium hydroxide solution in methanol at room temperature to give the carboxylic acids or sodium salts

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* Corresponding authors. Tel.: +81 48 669 3029; fax: +81 48 652 7254; e-mail: toshio.nakamura@po.rd.taisho.co.jp

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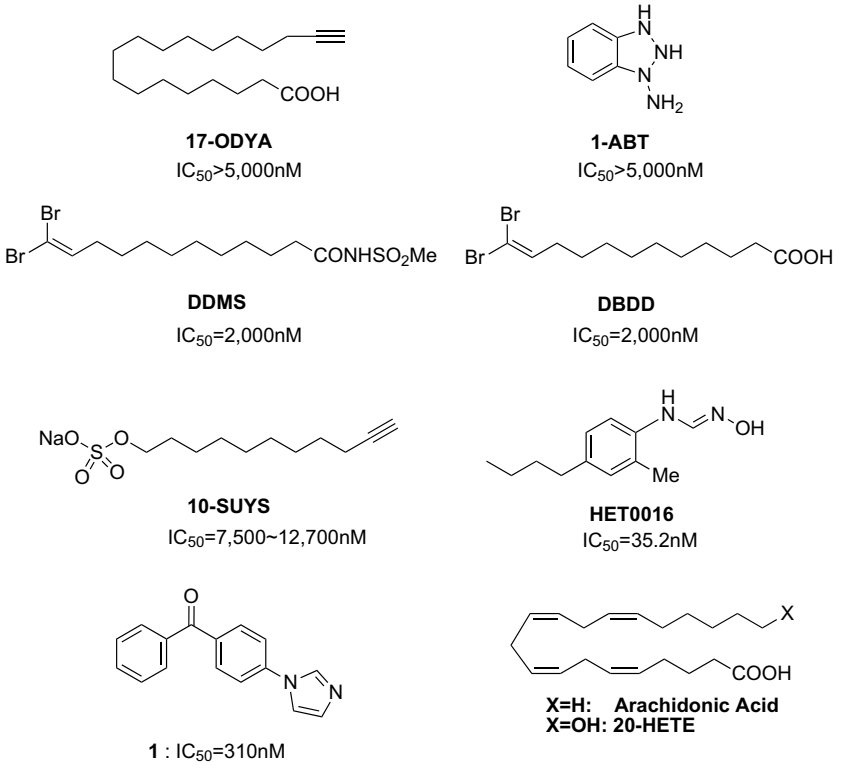
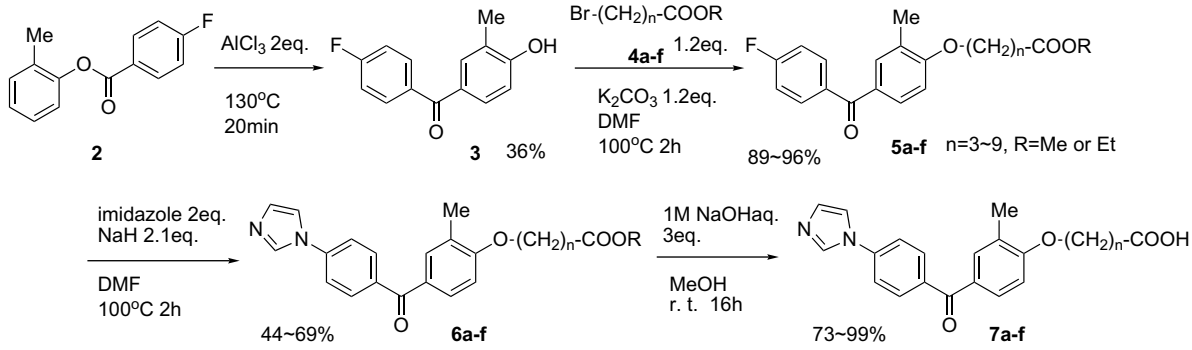
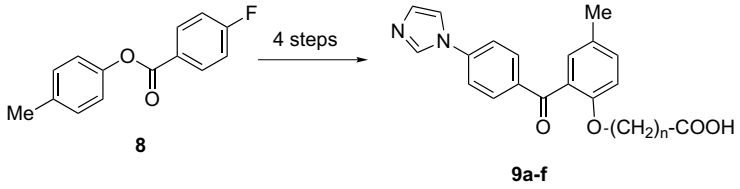


Figure 1. Structures of reported 20-HETE synthase inhibitors and compound **1**. IC_{50} values are for the production of 20-HETE from AA by rat renal microsome.



Scheme 1.

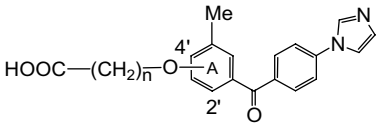


Scheme 2.

7a–**f**. Corresponding 2′-carboxyalkyl derivatives **9a**–**f** were prepared from *p*-cresol ester **8** in the same way.

Introduction of a ω-carboxyalkoxy moiety with 3–9 methylene groups to the 4′-position of compound **1** (**7a**–**f**) enhanced the 20-HETE synthase inhibitory activity 4- to 40-fold (Table 1). However, introduction of the same moieties at the 2′-position (**9a**–**f**) resulted in a great loss of activity (1/8 to less than 1/30). These results suggest that the region around the 2′-position of compound **1** is spatially limited in the coordination to 20-HETE synthase. The length of the carboxyalkoxy moiety of

Table 1. Inhibitory activities of **7a**–**f** and **9a**–**f** toward 20-HETE synthase



No.	*n*	IC_{50} (nM)[a]	
		7	**9**
a	3	13[b]	>10,000
b	4	12	8384
c	5	7.9[b]	3290
d	6	22	2461
e	7	44	4797
f	9	73[b]	6743

[a] IC_{50} value for the production of 20-HETE from AA by human renal microsome ($n = 2$).
[b] Sodium salt.

7a–**f** was clearly correlated with the activity. A sequential increase in the number of methylene groups from 3 to 5 gradually enhanced the activity. The optimal compound **7c** ($n = 5$) showed an IC_{50} value of 7.9 nM, which is about 2-fold more potent than **7a** ($n = 3$). An increase in the number of methylene groups in **7c** was sensitively associated with the loss of activity. Compound **7d** ($n = 6$, $IC_{50} = 22$ nM) was about three times weaker than **7c**, and **7f** ($n = 9$) was about ten times weaker than **7c**.

Superimposition of the crystal structure of the optimal compound **7c**[18] with the predicted crystal structure of AA[16] was performed using the Molecular Operating Environment (MOE 2004. 03) method.[19] Their 3-D structures nearly overlapped (Fig. 2). The carboxy moiety of AA and that of **7c** were consistent with each other. The imidazole ring of **7c** and the C_{20} carbon atom of AA, which is the position oxidized by 20-HETE synthase, were also well accorded. These results suggest that AA might be located in the active site of 20-HETE synthase with a expanded conformation rather than a folded conformation, which is thought to be more stable in solution.[16] Selectivity for drug-metabolizing enzymes (CYP2D6 was inhibited 50.7% by **7c** and 71.1% by **1** at 1 μM) was also improved by the introduction of a carboxyalkoxy moiety, and **7c** did not inhibit the activities of cyclooxygenases-1 and -2 (COX-1 and COX-2), even at higher concentrations (100 μM). These results indicate that **7c** is a potent and selective inhibitor of the formation of 20-HETE from AA.

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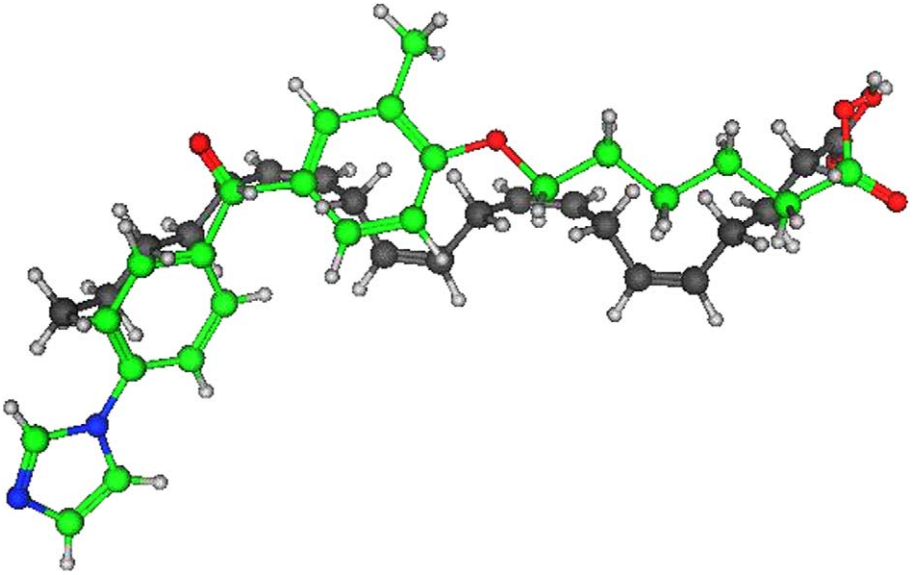

Figure 2. Superposition of a predicted crystal structure of AA and the crystal structure of **7c**. The superimposition of arachidonic acid (gray) and **7c** (green) was studied using the Molecular Operating Environment (MOE 2004.03) method.

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