



Synthesis and anti-platelet evaluation of 2-benzoylaminobenzoate analogs

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Received 28 January 2008; revised 21 March 2008; accepted 22 March 2008

Available online 31 March 2008

Abstract—Fifty-two 2-benzoylaminobenzoate analogs were synthesized and subjected to anti-platelet aggregation assay using arachidonic acid (AA), collagen (Col), thrombin (Thr), and U46619 as inducers. The results revealed that most of 2-benzoylaminobenzoic acid derivatives showed a selectively inhibitory effect on AA-induced platelet aggregation. As a result of the 2-benzoylaminobenzoic acid derivatives (**18**, **44**, and **46**), there were no inhibitory effects on platelet aggregation induced by U46619, but these elicited an inhibitory effect on thromboxane B₂ formation at 1.0 μ M. These 2-benzoylaminobenzoate analogs were therefore proposed as cyclooxygenase inhibitors.

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1. Introduction

Arterial thromboembolic diseases such as acute coronary syndrome and ischemic stroke are caused by platelet aggregation, and are the major causes of death in the developed countries. Anti-platelet drugs (e.g., aspirin, ticlopidine) are used to protect against myocardial infarction, stroke, cardiovascular death, and other serious vascular events in patients with a history of previous vascular events or known risk factors for cardiovascular disease.¹ Current anti-platelet drugs have some restrictions in their mode of action and efficacy, and research and development of new generation anti-platelet agents continue.

We previously synthesized a series of derivatives of 2-benzoylaminobenzoic acid; we investigated their anti-platelet aggregation, as well as inhibition of superoxide anion generation and neutrophil elastase release of neutrophils.^{2,3} The results showed that most 2-benzoylaminobenzoic acid derivatives showed selective

inhibitory effects on arachidonic acid (AA)-induced platelet aggregation.^{2,3} We have designed and synthesized new substituted 2-benzoylaminobenzoate analogs in an attempt to obtain new anti-platelet aggregation agents. In particular, the synthetic structures that process in the (1) substitutions at the C-4 position; (2) length of carbon chain of the ester/amide at C-1; (3) straight-chain and branched-chain of the ester/amide at C-1; and (4) 2'- or 2',6'-disubstitution in the B ring⁴ were tested. Newly synthesized compounds were assayed for in vitro inhibitory effects on platelet aggregation induced by arachidonic acid (AA), collagen (Col), thrombin (Thr), and U46619 (Tables 1–4). To investigate the pharmacologic mechanism of 2-benzoylaminobenzoate analogs, the most potent compounds, including derivatives **18**, **44**, and **46**, were further assayed to test the inhibitory effect on thromboxane (Tx) B₂ formation. We describe the synthesis, bioactivity data, and structure–activity relationship (SAR) of anti-platelet aggregation related to 2-benzoylaminobenzoate analogs.

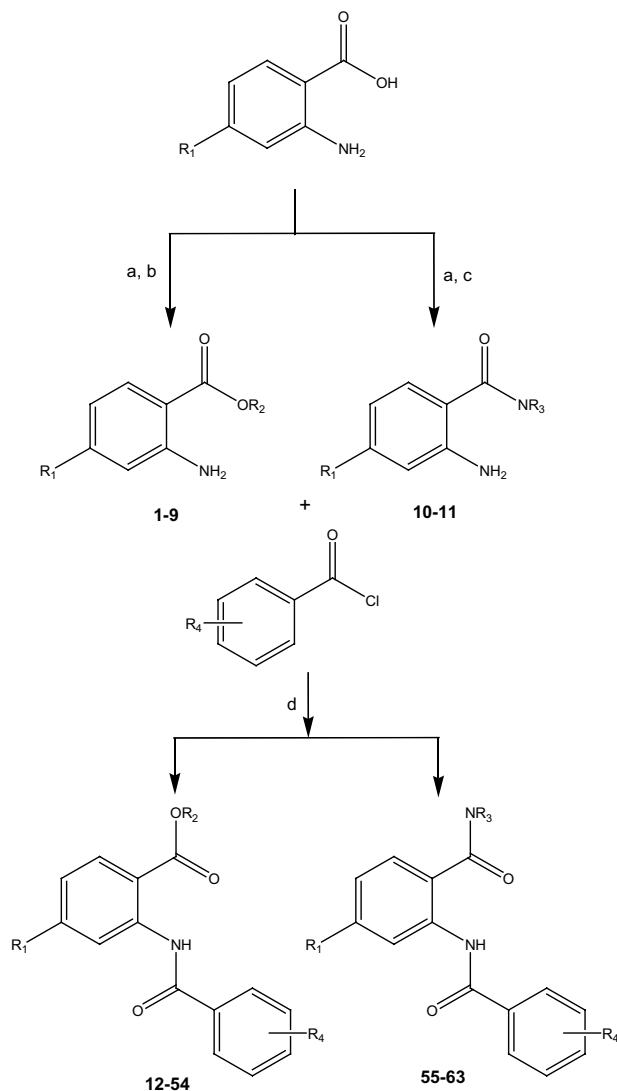
2. Results and discussion

2.1. Chemistry

Scheme 1 describes the synthesis of 52 new 2-benzoylaminobenzoate analogs (**12–63**) via an accomplished

Keywords: 2-Benzoylaminobenzoate analogs; Anti-platelet aggregation; Cyclooxygenase; Structure–activity relationships (SAR).

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Scheme 1. The straightforward synthesis of 52 new 2-benzoylaminobenzoate analogs (**12–63**). Reagents: (a) SO_2Cl_2 , DCM; (b) R_2OH ; (c) R_3NH_2 ; (d) DCM.

previously described pathway.^{2,3} Initially, 4-substituted benzoic ester/amide derivatives **1–11** were obtained by a simple method. These derivatives were then added with the corresponding substituted benzoyl chlorides.^{2,3} The mixtures were stirred at room temperature for 16 h to give compounds **12–63**. The products (**22–63**) were new compounds and fully characterized using spectroscopic data as shown in Section 4.

2.2. Anti-platelet activity

All synthesized 2-benzoylaminobenzoic acid analogs (**12–63**) were subjected to anti-platelet aggregation assay with AA, Col, Thr, and U46619 (a thromboxane receptor inhibitor) as inducers. The results showed that all synthesized agents did not produce an inhibitory effect on platelet aggregation assay when Thr and U46619 were used as inducers. Tables 1–3 list the IC_{50} values obtained with these compounds, as well as the positive controls, aspirin, and indomethacin. Compounds **18**, **34**, **44**, **45**, and **46** exhibited more potent inhibitory ef-

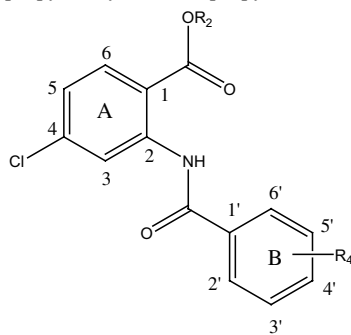
fects on AA-induced platelet aggregation (ca. 200-fold) than aspirin, with IC_{50} values of 0.7, 0.9, 0.7, 0.9, and 0.5 μM , respectively. Compounds **18**, **44**, **45**, **46**, **60**, **61**, and **62** showed more potent inhibitory effects on Col-induced platelet aggregation, with IC_{50} values of 2.3, 1.6, 1.2, 1.0, 2.2, 1.1, and 1.0 μM , respectively.

Anti-platelet aggregation assay data and SAR analysis confirmed that activity depended on the substituents on 2'- or 2',6'-disubstitution in the B ring, the length of carbon chain of ester/amide at C-1, as well as the straight-chain and branched-chain of the ester/amide at C-1. Conversely, in our previous research,^{2,3} we proposed that a chloro-substituent at C-4 is required for the anti-platelet activity of 2-benzoylaminobenzoic acids. However, changing the chloro-substituent into its isosteres⁴ (e.g., fluoro- and methyl groups) or replacement by an electron-donating (nitro) group were slightly enhanced the anti-platelet aggregation activity (Table 1). Most ethyl and propyl ester derivatives (**12–21**) were more active toward anti-platelet aggregation with AA as inducers than the corresponding isopropyl (**52–54**) esters (Table 1). Anti-platelet aggregation activities vanished when the isopropyl ester was substituted at C-1, indicating that the size of R_2 and R_3 enhanced bioactivity. Additionally, 2',6'-difluoro derivatives (**44–47**) were more potent than the 2'-fluoro-substituted (**12,17**, and **22**) and 2',6'-dichloro derivatives (**48–51**; Table 1).⁵ However, the monosubstituted (2'-Cl) derivatives were more potent than the 2',6'-dichloro derivatives (**48–51**; Table 1), suggesting that the bulky group substituted at 2' and 6' blocks the activity. We therefore propose that the amide between A and B rings is required for anti-platelet aggregation. Furthermore, amide analogs enhanced the selectivity (AA vs Col) of platelet aggregation inhibitory effects (Tables 1–3), indicating that the amide at the C-1 position was necessary for inhibiting platelet aggregation induced by collagen.

2-Benzoylaminobenzoic acids inhibited AA-, but not U46619-induced platelet aggregation, this suggests that 2-benzoylaminobenzoic acids inhibit AA conversion to TxA_2 rather than blocking the TxA_2 receptor. Therefore, compounds **18**, **44**, and **46** were further examined for their inhibitory effect on AA-induced TxB_2 formation (Table 4).⁶ The results showed compounds **18**, **44**, and **46** inhibited TxB_2 formation at 1.0 μM , suggesting that 2-benzoylaminobenzoic acid analogs caused anti-platelet aggregation effect via arachidonic pathway.

3. Conclusion

The bioassay results of these compounds show dramatic relationships between structure and anti-platelet aggregation effects. Compounds **18**, **44**, and **46** exhibited inhibitory effects 200-times more potent than aspirin on platelet aggregation and TxB_2 formation induced by AA. These data suggest that the anti-platelet aggregation of 2-benzoyl-4-chloroaminobenzoic acid analogs via inhibiting arachidonic pathway. Additionally, these could be developed as new lead compounds for anti-platelet aggregation agents.

Table 1. Anti-platelet aggregation potencies of ethyl, propyl, butyl, and *iso*-propyl ester derivatives of 2-benzoylamino-4-chlorobenzoate

Compound	Substituents		Anti-platelet aggregation, IC ₅₀ ^{a,b} (μM)			
	R ₂	R ₄	AA (150 μM)	Thr (0.1 U/ml)	Col (10 μg/ml)	U46619
Aspirin ^c			149.8 ± 0.7 ^{a,b}	>100	153.2 ± 12.0 ^{a,b}	>100
Indomethacin ^c			0.12 ± 0.0	>100	0.4 ± 0.0	>100
12 ^d	Ethyl	2'-F	3.8 ± 1.1	>100	20.1 ± 6.8	>100
13 ^d	Ethyl	2'-Cl	1.0 ± 0.2	>100	7.6 ± 0.5	>100
14 ^d	Ethyl	2'-Br	3.6 ± 0.0	>100	13.9 ± 1.3	>100
15 ^d	Ethyl	2'-CH ₃	4.9 ± 1.1	>100	15.9 ± 0.7	>100
16 ^d	Ethyl	2'-OCH ₃	4.9 ± 1.1	>100	46.4 ± 0.5	>100
17 ^d	Propyl	2'-F	1.6 ± 0.0	>100	11.6 ± 1.6	>100
18 ^d	Propyl	2'-Cl	0.7 ± 0.2	>100	2.3 ± 1.2	>100
19 ^d	Propyl	2'-Br	3.5 ± 0.0	>100	9.5 ± 1.8	>100
20 ^d	Propyl	2'-CH ₃	2.2 ± 0.5	>100	8.3 ± 0.2	>100
21 ^d	Propyl	2'-OCH ₃	23.4 ± 6.2	>100	>100	>100
22	Butyl	2'-F	3.0 ± 0.6	>100	32.1 ± 2.1	>100
23	Butyl	2'-Cl	2.1 ± 0.5	>100	19.5 ± 3.8	>100
24	Butyl	2'-Br	7.1 ± 0.1	>100	50.4 ± 16.7	>100
25	Butyl	2'-CH ₃	4.7 ± 1.0	>100	76.2 ± 11.7	>100
26	Butyl	2'-OCH ₃	>100	>100	>100	>100
44	Methyl	2',6'-di-F	0.7 ± 0.2	>100	35.8 ± 4.7	>100
45	Ethyl	2',6'-di-F	0.9 ± 0.2	>100	1.6 ± 0.1	>100
46	Propyl	2',6'-di-F	0.5 ± 0.1	48.8 ± 14.3	1.2 ± 0.2	>100
47	Butyl	2',6'-di-F	1.5 ± 0.0	>100	21.8 ± 6.4	>100
48	Methyl	2',6'-di-Cl	12.6 ± 2.1	>100	3.4 ± 0.8	>100
49	Ethyl	2',6'-di-Cl	68.3 ± 14.3	>100	32.3 ± 0.5	>100
50	Propyl	2',6'-di-Cl	38.4 ± 12.7	>100	29.7 ± 2.1	>100
51	Butyl	2',6'-di-Cl	>100	>100	>100	>100
52	<i>iso</i> -Propyl	2'-F	>100	>100	36.7 ± 0.6	>100
53	<i>iso</i> -Propyl	2'-Cl	82.2 ± 8.9	>100	8.51 ± 0.5	>100
54	<i>iso</i> -Propyl	2',6'-di-F	>100	>100	28.8 ± 1.4	>100

^a Platelets were pre-incubated with DMSO (0.5%, control) or test compounds at 37 °C for 3 min before the addition of the inducers.

^b The IC₅₀ values are presented as means ± SEM (*n* = 3).

^c Aspirin and indomethacin, two cyclooxygenase inhibitors, were used as positive controls in platelet aggregation assay.

^d The biological data of compounds **12–21** were reported in the literature.¹

4. Experimental

4.1. General

The NMR spectra using C₅D₅N and CDCl₃ as solvents were obtained on a Varian NMR spectrometer (Unity Plus 400 and Unity INOVA-500). Chemical shifts were internally referenced to the solvent signals in CDCl₃ (¹H, δ 7.26; ¹³C: δ 77.0). Low-resolution EI-MS were recorded on a Quattro GC/MS spectrometer having a direct inlet system, high-resolution ESI-MS spectra on a Bruker Daltonics APEX II 30e spectrometer.

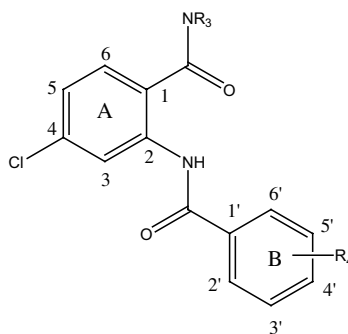
4.2. General procedure for the synthesis of compounds 1–11

To a DCM solution of compounds **1–11** (1.0 mmol) were added the suitable alcohols or amines. The

reaction mixture was stirred and at reflux for 8.0 h. The solvent was evaporated at reduced pressure. The residue was purified by flash column chromatography (Si-Gel) using *n*-hexane to afford the products.

4.3. General procedure for the synthesis of compounds 22–63

To compounds **1–11** (1.0 mmol) dissolved in DCM were added the suitable benzoyl chlorides. The reaction mixture was stirred at room temperature for 16 h. The solvent was evaporated at reduced pressure. The residue was purified by column chromatography (Si-Gel) using CHCl₃/hexane (2:7) mixture to afford the products.

Table 2. Anti-platelet aggregation effects of amide derivatives of 2-benzoylamino-4-chlorobenzoate

Compound	Substituents		Anti-platelet aggregation, IC ₅₀ ^{a,b} (μM)			
	R ₃	R ₄	AA (150 μM)	Thr (0.1 U/ml)	Col (10 μg/ml)	U46619
Aspirin ^c			149.8 ± 0.7 ^{a,b}	>100	153.2 ± 12.0 ^{a,b}	>100
Indomethacin ^c			0.12 ± 0.0	>100	0.4 ± 0.0	>100
55	Propyl	2'-F	1.9 ± 0.4	>100	8.7 ± 1.0	>100
56	Propyl	2'-Cl	3.4 ± 1.2	>100	4.1 ± 0.1	>100
57	Propyl	2'-Br	1.5 ± 0.6	>100	3.4 ± 2.1	>100
58	Propyl	2'-CH ₃	8.4 ± 2.5	>100	10.3 ± 0.8	>100
59	Propyl	2'-OCH ₃	6.0 ± 1.0	>100	11.1 ± 2.5	>100
60	Propyl	2',6'-di-F	2.9 ± 0.4	>100	1.0 ± 0.2	>100
61	Butyl	2'-F	3.5 ± 0.1	>100	2.2 ± 0.2	>100
62	Butyl	2'-Cl	3.4 ± 0.0	>100	1.1 ± 0.1	>100
63	Butyl	2',6'-di-F	3.5 ± 0.0	>100	1.0 ± 0.2	>100

^a Platelets were pre-incubated with DMSO (0.5%, control) or test compounds at 37 °C for 3 min before the addition of the inducers.

^b The IC₅₀ values are presented as means ± SEM (*n* = 3).

^c Aspirin and indomethacin, two cyclooxygenase inhibitors, were used as positive controls in platelet aggregation assay.

4.4. Butyl 4-chloro-2-(2-fluorobenzamido)benzoate (22)

Yield (62%) from **3** and 2-fluorobenzoyl chlorides; EI-MS (*m/z*, %): 351(8), 349(25) [M]⁺, 250(23), 249(63), 124(74), 123(100); ¹H NMR (CDCl₃) δ 11.96 (1H, br, NH), 9.01 (1H, d, *J* = 2.0 Hz, H-3), 8.05 (1H, td, *J* = 8.0, 2.0 Hz, H-6'), 7.99 (1H, d, *J* = 8.8 Hz, H-6), 7.51 (1H, m, H-4'), 7.28 (1H, td, *J* = 8.0, 1.2 Hz, H-5'), 7.19 (1H, ddd, *J* = 10.4, 8.0, 1.2 Hz, H-3'), 7.09 (1H, dd, *J* = 8.8, 2.0 Hz, H-5), 4.33 (2H, t, *J* = 6.4 Hz, OCH₂CH₂CH₂CH₃), 1.75 (2H, m, OCH₂CH₂CH₂CH₃), 1.47 (2H, m, OCH₂CH₂CH₂CH₃), 0.97 (3H, t, *J* = 7.2 Hz, OCH₂CH₂CH₂CH₃); ¹³C NMR (CDCl₃) δ 167.27 (s, COOR), 162.37 (s, CONH, *J*_{C-F} = 2.3 Hz), 160.17 (s, C-2'), *J*_{C-F} = 249.3 Hz), 141.96 (s, C-2), 140.56 (s, C-4), 133.72 (d, C-4', *J*_{C-F} = 9.1 Hz), 131.84 (d, C-6), 131.66 (d, C-6', *J*_{C-F} = 1.9 Hz), 124.71 (d, C-5', *J*_{C-F} = 3.5 Hz), 123.12 (d, C-5), 122.22 (s, C-1'), *J*_{C-F} = 12.2 Hz), 121.09 (d, C-3), 116.43 (d, C-3', *J*_{C-F} = 23.5 Hz), 114.37 (s, C-1), 65.46 (t, OCH₂CH₂CH₂CH₃), 30.46 (t, OCH₂CH₂CH₂CH₃), 19.16 (t, OCH₂CH₂CH₂CH₃), 13.65 (q, OCH₂CH₂CH₂CH₃); HRESI-MS *m/z* 372.0777 [M+Na]⁺ (calcd for C₁₈H₁₇ClFNO₃Na 372.0779).

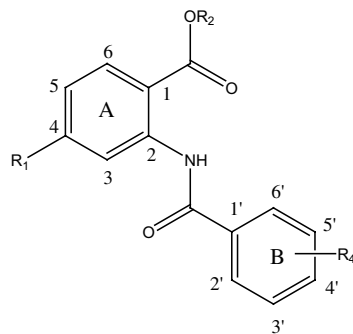
4.5. Butyl 4-chloro-2-(2-chlorobenzamido)benzoate (23)

Yield (52%) from **3** and 2-chlorobenzoyl chloride; EI-MS (*m/z*, %): 365(4) [M]⁺, 351(7), 348(11), 266(11), 264(14), 141(54), 139(100); ¹H NMR (CDCl₃) δ 11.63 (1H, br, NH), 8.99 (1H, d, *J* = 2.0 Hz, H-3), 7.98 (1H, d, *J* = 8.8 Hz, H-6), 7.63 (1H, dd, *J* = 7.6, 2.0 Hz, H-

6'), 7.44 (1H, dd, *J* = 8.0, 1.6 Hz, H-3'), 7.39 (2H, m, H-4' 5'), 7.09 (1H, dd, *J* = 8.8, 2.0 Hz, H-5), 4.27 (2H, t, *J* = 6.8 Hz, OCH₂CH₂CH₂CH₃), 1.71 (2H, m, OCH₂CH₂CH₂CH₃), 1.42 (2H, m, OCH₂CH₂CH₂CH₃), 0.94 (3H, t, *J* = 7.6 Hz, OCH₂CH₂CH₂CH₃); ¹³C NMR (CDCl₃) δ 167.43 (s, COOR), 165.35 (s, CONH), 141.87 (s, C-2), 140.75 (s, C-4), 135.61 (s, C-1'), 131.81 (d, C-6), 131.51 (d, C-4'), 131.17 (s, C-2'), 130.54 (d, C-3'), 129.08 (d, C-6'), 127.05 (d, C-5'), 123.14 (d, C-5), 120.29 (d, C-3), 113.79 (s, C-1), 65.47 (t, OCH₂CH₂CH₂CH₃), 30.34 (t, OCH₂CH₂CH₂CH₃), 19.07 (t, OCH₂CH₂CH₂CH₃), 13.57 (q, OCH₂CH₂CH₂CH₃); HRESI-MS *m/z* 388.0485 [M+Na]⁺ (calcd for C₁₈H₁₇Cl₂NO₃Na 388.0483).

4.6. Butyl 4-chloro-2-(2-bromobenzamido)benzoate (24)

Yield (44%) from **3** and 2-bromobenzoyl chloride; EI-MS (*m/z*, %): 411 [M]⁺(11), 230(38), 185(100), 184(35), 183(46); ¹H NMR (CDCl₃) δ 11.56 (1H, s, NH), 8.98 (1H, d, *J* = 2.4 Hz, H-3), 7.97 (1H, d, *J* = 8.8 Hz, H-6), 7.62 (1H, dd, *J* = 8.0, 1.2 Hz, H-3'), 7.57 (1H, dd, *J* = 8.0, 1.6 Hz, H-6'), 7.39 (1H, td, *J* = 8.0, 1.2 Hz, H-5'), 7.30 (1H, td, *J* = 8.0, 1.6 Hz, H-4'), 7.08 (1H, dd, *J* = 8.8, 2.4 Hz, H-5), 4.26 (2H, t, *J* = 6.8 Hz, OCH₂CH₂CH₂CH₃), 1.70 (2H, m, OCH₂CH₂CH₂CH₃), 1.42 (2H, m, OCH₂CH₂CH₂CH₃), 0.93 (3H, t, *J* = 7.6 Hz, OCH₂CH₂CH₂CH₃); ¹³C NMR (CDCl₃) δ 167.41(s, COOR), 166.15 (s, CONH), 141.83 (s, C-2), 140.74 (s, C-4), 137.75 (s, C-1'), 133.70 (d, C-3'), 131.80 (d, C-6), 131.53 (d, C-4'), 128.74 (d, C-6'), 127.57 (d, C-5'), 123.15 (d, C-5), 120.22 (d, C-3), 119.58 (s, C-2'), 113.74 (s, C-1), 65.46 (t, OCH₂CH₂CH₂CH₃).

Table 3. Replacement of the 4-substitution in 2-benzoylamino-4-chlorobenzoate analogs and their anti-platelet aggregation effects

Compound	Substituents			Anti-platelet aggregation, IC ₅₀ ^{a,b} (μM)		
	R ₁	R ₂	R ₄	AA (150 μM)	Thr (0.1 U/ml)	Col (10 μg/ml)
Aspirin ^c				149.8 ± 0.7 ^{a,b}	>100	153.2 ± 12.0 ^{a,b}
Indomethacin ^c				0.12 ± 0.0	>100	0.4 ± 0.0
27	F	Propyl	2'-F	1.6 ± 0.5	>100	14.5 ± 2.3
28	F	Propyl	2'-Cl	1.6 ± 0.6	>100	9.3 ± 2.2
29	F	Propyl	2'-Br	3.3 ± 0.1	>100	16.7 ± 2.9
30	F	Propyl	2'-CH ₃	2.0 ± 0.5	>100	25.1 ± 4.1
31	F	Propyl	2'-OCH ₃	31.5 ± 5.3	>100	33.2 ± 3.9
32	F	Ethyl	2'-Cl	4.1 ± 1.4	87.8 ± 3.5	11.0 ± 2.7
33	F	Ethyl	2'-CH ₃	21.1 ± 5.3	77.0 ± 1.0	36.1 ± 8.8
34	CH ₃	Propyl	2'-F	0.9 ± 0.2	>100	11.3 ± 3.0
35	CH ₃	Propyl	2'-Cl	1.6 ± 0.4	>100	7.8 ± 0.4
36	CH ₃	Propyl	2'-Br	3.1 ± 0.2	>100	27.3 ± 1.7
37	CH ₃	Propyl	2'-CH ₃	5.8 ± 1.3	>100	20.1 ± 4.1
38	CH ₃	Propyl	2'-OCH ₃	10.4 ± 2.6	>100	62.5 ± 15.1
39	NO ₂	Propyl	2'-F	4.7 ± 1.1	>100	3.5 ± 0.5
40	NO ₂	Propyl	2'-Cl	2.0 ± 0.5	>100	2.9 ± 0.6
41	NO ₂	Propyl	2'-Br	2.5 ± 0.7	>100	4.9 ± 1.3
42	NO ₂	Propyl	2'-CH ₃	4.7 ± 1.0	>100	8.0 ± 2.2
43	NO ₂	Propyl	2'-OCH ₃	>100	>100	>100

^a Platelets were pre-incubated with DMSO (0.5%, control) or test compounds at 37 °C for 3 min before addition of the inducers.

^b The IC₅₀ values are presented as means ± SEM (*n* = 3).

^c Aspirin and indomethacin, two cyclooxygenase inhibitors, were used as positive controls in platelet aggregation assay.

Table 4. Effects of Compounds **18**, **44**, and **46** on the TxB₂ formations in washed human platelets caused by arachidonic acid

Treatment	TxB ₂ (ng/3 × 10 ⁸ platelets) AA (150 μM)
Resting	0.09 ± 0.01
DMSO (control)	58.68 ± 1.39
Aspirin 200 μM	26.68 ± 1.56***
Indomethacin 0.5 μM	3.09 ± 0.90***
18 1 μM	32.52 ± 2.09***
18 0.5 μM	62.56 ± 1.05**
44 1 μM	29.48 ± 4.46***
44 0.5 μM	61.18 ± 3.76
46 1 μM	7.74 ± 1.97***
46 0.5 μM	45.47 ± 16.21

Washed human platelets were pre-incubated with DMSO or test compounds at 37 °C for 3 min and then arachidonic acid (200 μM) was added. The reactions were terminated by EDTA (2 mM) and indomethacin (50 μM) 5 min after the addition of AA. The platelet suspensions were centrifuged for 3 min at 13,000 rpm, the thromboxane B₂ in the supernatants was assayed using enzyme immunoassay kits. Values are presented as means ± SEM (*n* = 3). ***P* < 0.01, ****P* < 0.001 as compared with the respective controls.

CH₂CH₃), 30.31 (t, OCH₂CH₂CH₂CH₃), 19.05 (t, OCH₂CH₂CH₂CH₃), 13.56 (q, OCH₂CH₂CH₂CH₃);

HRESI-MS *m/z* 431.9976 [M+Na]⁺ (calcd for C₁₈H₁₇BrClNO₃Na 431.9978).

4.7. Butyl 4-chloro-2-(2-methylbenzamido)benzoate (**25**)

Yield (67%) from **3** and 2-methylbenzoyl chloride; EI-MS (*m/z*, %): 345 [M]⁺ (7), 228(11), 118(100), 119(96); ¹H NMR (CDCl₃) δ 11.61 (1H, br, NH), 9.03 (1H, d, *J* = 2.0 Hz, H-3), 7.97 (1H, d, *J* = 8.4 Hz, H-6), 7.61 (1H, dd, *J* = 0.8, 7.6 Hz, H-6'), 7.36 (1H, td, *J* = 0.8, 7.2 Hz, H-4'), 7.27 (2H, m, H-5' 3'), 7.06 (1H, dd, *J* = 8.4, 2.0 Hz, H-5), 4.28 (2H, t, *J* = 6.8 Hz, OCH₂CH₂CH₂CH₃), 2.56 (3H, s, CH₃), 1.72 (2H, m, OCH₂CH₂CH₂CH₃), 1.44 (2H, m, OCH₂CH₂CH₂CH₃), 0.96 (3H, t, *J* = 7.6 Hz, OCH₂CH₂CH₂CH₃); ¹³C NMR (CDCl₃) δ 168.11 (s, COOR), 167.50 (s, CONH), 142.43 (s, C-2), 140.66 (s, C-4), 137.13 (s, C-2'), 135.61 (s, C-1'), 131.74 (d, C-6), 131.42 (d, C-4'), 130.49 (d, C-3'), 126.85 (d, C-6'), 125.95 (d, C-5'), 122.63 (d, C-5), 119.92 (d, C-3), 113.45 (s, C-1), 65.34 (t, OCH₂CH₂CH₂CH₃), 30.32 (t, OCH₂CH₂CH₂CH₃), 20.16 (q, CH₃), 19.05 (t, OCH₂CH₂CH₂CH₃), 13.54 (q, OCH₂CH₂CH₂CH₃); HRESI-MS *m/z* 368.1031 [M+Na]⁺ (calcd for C₁₉H₂₀ClNO₃Na 368.1029).

4.8. Butyl 4-chloro-2-(2-methoxybenzamido)benzoate (26)

Yield (54%) from **3** and 2-methoxybenzoyl chloride; EI-MS (*m/z*, %): 347 [M]⁺ (6), 229(21), 227(62), 137(54), 135(100); ¹H NMR (CDCl₃) δ 12.31 (1H, br, NH), 9.09 (1H, d, *J* = 2.0 Hz, H-3), 8.17 (1H, dd, *J* = 7.6, 1.6 Hz, H-6'), 7.92 (1H, d, *J* = 8.4 Hz, H-6), 7.44 (1H, m, H-4'), 7.03 (2H, m, H-5, 5'), 6.97 (1H, d, *J* = 8.0 Hz, H-3'), 4.29 (2H, t, *J* = 6.8 Hz, OCH₂CH₂CH₂CH₃), 4.02 (3H, s, OCH₃), 1.73 (2H, m, OCH₂CH₂CH₂CH₃), 1.46 (2H, m, OCH₂CH₂CH₂CH₃), 0.97 (3H, t, *J* = 7.2 Hz, OCH₂CH₂CH₂CH₃); ¹³C NMR (CDCl₃) δ 166.48 (s, COOR), 164.45 (s, CONH), 157.43 (s, C-2'), 142.14 (s, C-2), 139.89 (s, C-4), 133.26 (d, C-6', *J*_{C-F} = 9.1 Hz), 132.20 (d, C-4'), 131.58 (d, C-6), 122.37 (d, C-5), 121.98 (s, C-1'), 121.44 (d, C-3), 120.71 (d, C-5'), 114.92 (s, C-1), 111.14 (d, C-3'), 64.84 (t, OCH₂CH₂CH₂CH₃), 55.27 (q, OCH₃), 30.47 (t, OCH₂CH₂CH₂CH₃), 19.11 (t, OCH₂CH₂CH₂CH₃), 13.59 (q, OCH₂CH₂CH₂CH₃); HRESI-MS *m/z* 384.0979 [M +Na]⁺ (calcd for C₁₉H₂₀ClNO₄Na 384.0978).

4.9. Propyl 4-fluoro-2-(2-fluorobenzamido)benzoate (27)

Yield (69%) from **4** and 2-fluorobenzoyl chloride; EI-MS (*m/z*, %): 320(19), 319 [M]⁺ (61), 233(23), 232(82), 125(30), 123(100); ¹H NMR (CDCl₃) δ 12.06 (1H, br, NH), 8.74 (1H, dd, *J* = 12.0, 2.4 Hz, H-3), 8.09 (1H, dd, *J* = 8.8, 6.4 Hz, H-6), 8.04 (1H, td, *J* = 7.6, 1.6 Hz, H-6'), 7.51 (1H, m, H-4'), 7.28 (1H, t, *J* = 8.0 Hz, H-5'), 7.19 (1H, dd, *J* = 11.2, 8.4 Hz, H-3'), 6.82 (1H, m, H-5), 4.29 (2H, t, *J* = 6.8 Hz, OCH₂CH₂CH₃), 1.79 (2H, m, OCH₂CH₂CH₃), 1.02 (3H, t, *J* = 7.2 Hz, OCH₂CH₂CH₃); ¹³C NMR (CDCl₃) δ 167.22 (s, COOR), 166.01 (s, C-4, *J*_{C-F} = 250.9 Hz), 162.54 (s, CONH), 160.17 (s, C-2', *J*_{C-F} = 249.4 Hz), 143.26 (s, C-2, *J*_{C-F} = 12.9 Hz), 133.70 (d, C-4', *J*_{C-F} = 9.1 Hz), 132.54 (d, C-6, *J*_{C-F} = 10.6 Hz), 131.64 (d, C-6', *J*_{C-F} = 3.2 Hz), 124.69 (d, C-5', *J*_{C-F} = 3.8 Hz), 122.29 (s, C-1', *J*_{C-F} = 12.1 Hz), 116.43 (d, C-3', *J*_{C-F} = 23.5 Hz), 112.35 (s, C-1), 110.14 (d, C-5, *J*_{C-F} = 22.0 Hz), 108.36 (d, C-3, *J*_{C-F} = 28.1 Hz), 66.99 (t, OCH₂CH₂CH₃), 21.87 (t, OCH₂CH₂CH₃), 10.37 (q, OCH₂CH₂CH₃); HRESI-MS *m/z* 320.1097 [M +H]⁺ (calcd for C₁₇H₁₆F₂NO₃ 320.1098).

4.10. Propyl 4-fluoro-2-(2-chlorobenzamido)benzoate (28)

Yield (40%) from **4** and 2-chlorobenzoyl chloride; EI-MS (*m/z*, %): 337(22), 335 [M]⁺ (61), 248(45), 214(29), 140(100); ¹H NMR (CDCl₃) δ 11.73 (1H, br, NH), 8.73 (1H, dd, *J* = 2.4, 11.6 Hz, H-3), 8.11 (1H, dd, *J* = 6.4, 8.8 Hz, H-6), 7.65 (1H, dd, *J* = 7.2, 2.0 Hz, H-3'), 7.47 (1H, dd, *J* = 8.0, 1.6 Hz, H-6'), 7.40 (2H, m, H-5' 4'), 6.84 (1H, m, H-5), 4.25 (2H, t, *J* = 6.8 Hz, OCH₂CH₂CH₃), 1.78 (2H, m, OCH₂CH₂CH₃), 1.01 (3H, t, *J* = 7.2 Hz, OCH₂CH₂CH₃); ¹³C NMR (CDCl₃) δ 167.49 (s, COOR), 166.60 (s, CONH), 165.19 (s, C-4, *J*_{C-F} = 252.4 Hz), 143.25 (s, C-2, *J*_{C-F} = 12.9 Hz), 135.78 (s, C-1'), 131.09 (d, C-6, *J*_{C-F} = 11.4 Hz), 131.56 (d, C-4'), 131.24 (s, C-2'), 130.62 (d, C-3'), 129.19 (d, C-6'), 127.11 (d, C-5'), 111.85 (s, C-1, *J*_{C-F} = 3.0 Hz), 110.27 (d, C-5, *J*_{C-F} = 22.0 Hz), 107.80 (d, C-3, *J*_{C-F} = 28.0 Hz), 67.06 (t, OCH₂CH₂CH₃),

21.84 (t, OCH₂CH₂CH₃), 10.36 (q, OCH₂CH₂CH₃); HRESI-MS *m/z* 336.0800 [M +H]⁺ (calcd for C₁₇H₁₆ClFNO₃ 336.0803).

4.11. Propyl 4-fluoro-2-(2-bromobenzamido)benzoate (29)

Yield (32%) from **4** and 2-bromobenzoyl chloride; EI-MS (*m/z*, %): 380(8), 379 [M]⁺ (8), 216(17), 214(54), 185(100), 184(51), 183(38); ¹H NMR (CDCl₃) δ 11.67 (1H, br, NH), 8.72 (1H, dd, *J* = 2.4, 11.6 Hz, H-3), 8.10 (1H, dd, *J* = 6.4, 8.8 Hz, H-6), 7.65 (1H, dd, *J* = 7.6, 0.8 Hz, H-3'), 7.59 (1H, dd, *J* = 7.6, 1.6 Hz, H-6'), 7.41 (1H, td, *J* = 7.6, 0.8 Hz, H-5'), 7.32 (1H, td, *J* = 7.6, 1.6 Hz, H-4'), 6.84 (1H, m, H-5), 4.24 (2H, t, *J* = 6.4 Hz, OCH₂CH₂CH₃), 1.77 (2H, m, OCH₂CH₂CH₃), 1.00 (3H, t, *J* = 7.2 Hz, OCH₂CH₂CH₃); ¹³C NMR (CDCl₃) δ 167.49 (s, COOR), 166.42 (s, CONH), 166.17 (s, C-4, *J*_{C-F} = 252.4 Hz), 143.21 (s, C-2, *J*_{C-F} = 13.0 Hz), 137.93 (s, C-1'), 133.80 (d, C-3'), 131.11 (d, C-6, *J*_{C-F} = 10.6 Hz), 131.60 (d, C-4'), 128.86 (d, C-6'), 127.64 (d, C-5'), 119.65 (s, C-2'), 111.81 (s, C-1), 110.30 (d, C-5, *J*_{C-F} = 22.0 Hz), 107.73 (d, C-3, *J*_{C-F} = 28.0 Hz), 67.08 (t, OCH₂CH₂CH₃), 21.83 (t, OCH₂CH₂CH₃), 10.36 (q, OCH₂CH₂CH₃); HRESI-MS *m/z* 380.0297 [M +H]⁺ (calcd for C₁₇H₁₆BrFNO₃ 380.0298).

4.12. Propyl 4-fluoro-2-(2-methylbenzamido)benzoate (30)

Yield (46%) from **4** and 2-methylbenzoyl chloride; EI-MS (*m/z*, %): 315 [M]⁺ (7), 119(100), 118(84), 91(40); ¹H NMR (CDCl₃) δ 11.68 (1H, br, NH), 8.75 (1H, dd, *J* = 12.0, 2.0 Hz, H-3), 8.10 (1H, dd, *J* = 6.4, 8.8 Hz, H-6), 7.60 (1H, dd, *J* = 1.2, 7.6 Hz, H-6'), 7.38 (1H, td, *J* = 1.2, 7.2 Hz, H-4'), 7.29 (2H, m, H-5' 3'), 6.82 (1H, m, H-5), 4.25 (2H, t, *J* = 6.8 Hz, OCH₂CH₂CH₃), 2.56 (3H, s, CH₃), 1.78 (2H, m, OCH₂CH₂CH₃), 1.02 (3H, t, *J* = 7.2 Hz, OCH₂CH₂CH₃); ¹³C NMR (CDCl₃) δ 168.50 (s, COOR), 167.65 (s, CONH), 166.25 (s, C-4, *J*_{C-F} = 251.5 Hz), 143.86 (s, C-2, *J*_{C-F} = 13.6 Hz), 137.18 (s, C-2'), 135.89 (s, C-1'), 131.11 (d, C-6, *J*_{C-F} = 10.6 Hz), 131.53 (d, C-4'), 130.61 (d, C-3'), 127.00 (d, C-6'), 126.10 (d, C-5'), 111.59 (s, C-1, *J*_{C-F} = 3.0 Hz), 109.89 (d, C-5, *J*_{C-F} = 22.0 Hz), 107.44 (d, C-3, *J*_{C-F} = 28.0 Hz), 67.02 (t, OCH₂CH₂CH₃), 21.89 (t, OCH₂CH₂CH₃), 20.24 (q, CH₃), 10.42 (q, OCH₂CH₂CH₃); HRESI-MS *m/z* 338.1168 [M +Na]⁺ (calcd for C₁₈H₁₈FNO₃Na 338.1168).

4.13. Propyl 4-fluoro-2-(2-methoxybenzamido)benzoate (31)

Yield (43%) from **4** and 2-methoxybenzoyl chloride; EI-MS (*m/z*, %): 331 [M]⁺ (5), 198(13), 197(86), 137(44), 135(100); ¹H NMR (CDCl₃) δ 12.40 (1H, br, NH), 8.83 (1H, dd, *J* = 12.8, 2.8 Hz, H-3), 8.17 (1H, dd, *J* = 7.6, 1.6 Hz, H-6'), 8.07 (1H, dd, *J* = 8.8, 6.8 Hz, H-6), 7.49 (1H, m, H-4'), 7.08 (1H, td, *J* = 7.6, 0.8 Hz, H-3'), 7.02 (1H, d, *J* = 8.4 Hz, H-5'), 6.79 (1H, m, H-5), 4.28 (2H, t, *J* = 6.4 Hz, OCH₂CH₂CH₃), 4.06 (3H, s, OCH₃), 1.80 (2H, m, OCH₂CH₂CH₃), 1.04 (3H, t, *J* = 7.6 Hz, OCH₂CH₂CH₃); ¹³C NMR (CDCl₃) δ 166.70 (s, COOR), 165.89 (s, C-4, *J*_{C-F} = 250.1 Hz),

164.78 (s, CONH), 157.54 (s, C-2'), 143.56 (s, C-2, $J_{\text{C-F}} = 13.0$ Hz), 133.34 (d, C-4'), 132.83 (d, C-6, $J_{\text{C-F}} = 10.6$ Hz), 132.35 (d, C-6'), 122.32 (s, C-1'), 120.92 (d, C-5'), 112.92 (s, C-1, $J_{\text{C-F}} = 3.1$ Hz), 111.29 (d, C-3'), 109.60 (d, C-5, $J_{\text{C-F}} = 21.9$ Hz), 108.82 (d, C-3, $J_{\text{C-F}} = 28.0$ Hz), 66.57 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 55.43 (q, OCH_3), 21.98 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 10.53 (q, $\text{OCH}_2\text{CH}_2\text{CH}_3$); HRESI-MS m/z 354.1120 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{18}\text{H}_{18}\text{FNO}_4\text{Na}$ 354.1118).

4.14. Ethyl 4-fluoro-2-(2-chlorobenzamido)benzoate (32)

Yield (41%) from **5** and 2-chlorobenzoyl chloride; EI-MS (m/z , %): 321 $[\text{M}]^+$ (6), 141(37), 139(100), 111(54); ^1H NMR (CDCl_3) δ 11.73 (1H, br, NH), 8.72 (1H, dd, $J = 2.4, 12.0$ Hz, H-3), 8.10 (1H, dd, $J = 6.4, 8.8$ Hz, H-6), 7.64 (1H, dd, $J = 7.2, 1.6$ Hz, H-3'), 7.46 (1H, dd, $J = 7.6, 1.2$ Hz, H-6'), 7.39 (2H, m, H-5' 4'), 6.83 (1H, m, H-5), 4.34 (2H, q, $J = 6.8$ Hz, OCH_2CH_3), 1.37 (3H, t, $J = 6.8$ Hz, OCH_2CH_3); ^{13}C NMR (CDCl_3) δ 167.73 (s, COOR), 165.89 (s, CONH), 166.46 (s, C-4, $J_{\text{C-F}} = 251.9$ Hz), 143.52 (s, C-2, $J_{\text{C-F}} = 12.9$ Hz), 136.04 (s, C-1'), 133.47 (d, C-6, $J_{\text{C-F}} = 10.0$ Hz), 131.88 (d, C-4'), 131.53 (s, C-2'), 130.92 (d, C-3'), 129.48 (d, C-6'), 127.42 (d, C-5'), 112.10 (s, C-1, $J_{\text{C-F}} = 2.6$ Hz), 110.55 (d, C-5, $J_{\text{C-F}} = 22.0$ Hz), 108.02 (d, C-3, $J_{\text{C-F}} = 28.4$ Hz), 61.86 (t, OCH_2CH_3), 14.38 (q, OCH_2CH_3); HRESI-MS m/z 344.0464 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{16}\text{H}_{13}\text{ClFNO}_3\text{Na}$ 344.0466).

4.15. Ethyl 4-fluoro-2-(2-methylbenzamido)benzoate (33)

Yield (44%) from **5** and 2-methylbenzoyl chloride; EI-MS (m/z , %): 301 $[\text{M}]^+$ (10), 119(100), 118(23), 91(61); ^1H NMR (CDCl_3) δ 11.67 (1H, br, NH), 8.75 (1H, dd, $J = 12.0, 2.8$ Hz, H-3), 8.11 (1H, dd, $J = 9.2, 6.4$ Hz, H-6), 7.61 (1H, dd, $J = 1.2, 7.6$ Hz, H-6'), 7.38 (1H, td, $J = 1.2, 7.2$ Hz, H-4'), 7.30 (2H, m, H-5' 3'), 6.82 (1H, m, H-5), 4.35 (2H, q, $J = 7.2$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 2.56 (3H, s, CH_3), 1.39 (3H, t, $J = 7.2$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) δ 168.54 (s, COOR), 167.62 (s, CONH), 166.27 (s, C-4, $J_{\text{C-F}} = 251.6$ Hz), 143.87 (s, C-2, $J_{\text{C-F}} = 12.9$ Hz), 137.18 (s, C-2'), 135.92 (s, C-1'), 133.19 (d, C-6, $J_{\text{C-F}} = 10.6$ Hz), 131.55 (d, C-4'), 130.63 (d, C-3'), 127.02 (d, C-6'), 126.11 (d, C-5'), 111.59 (s, C-1, $J_{\text{C-F}} = 3.0$ Hz), 109.91 (d, C-5, $J_{\text{C-F}} = 22.0$ Hz), 107.47 (d, C-3, $J_{\text{C-F}} = 28.0$ Hz), 61.51 (t, OCH_2CH_3), 20.26 (q, CH_3), 14.15 (q, OCH_2CH_3); HRESI-MS m/z 324.1009 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{17}\text{H}_{16}\text{FNO}_3\text{Na}$ 324.1012).

4.16. Propyl 2-(2-fluorobenzamido)-4-methylbenzoate (34)

Yield (46%) from **6** and 2-fluorobenzoyl chloride; EI-MS (m/z , %): 315 $[\text{M}]^+$ (33), 229(19), 228(92), 124(62), 123(100); ^1H NMR (CDCl_3) δ 11.90 (1H, br, NH), 8.75 (1H, d, $J = 1.2$ Hz, H-3), 8.05 (1H, td, $J = 8.0, 1.2$ Hz, H-6'), 7.97 (1H, d, $J = 8.0$ Hz, H-6), 7.50 (1H, m, H-4'), 7.28 (1H, td, $J = 8.0, 1.2$ Hz, H-5'), 7.19 (1H, ddd, $J = 11.6, 8.4, 1.2$ Hz, H-3'), 6.95 (1H, dd, $J = 8.0, 1.2$ Hz, H-5), 4.28 (2H, t, $J = 6.4$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 2.43 (3H, s, CH_3), 1.79 (2H, m,

$\text{OCH}_2\text{CH}_2\text{CH}_3$), 1.02 (3H, t, $J = 7.2$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) δ 167.96 (s, COOR), 162.37 (s, CONH, $J_{\text{C-F}} = 2.2$ Hz), 160.25 (s, C-2', $J_{\text{C-F}} = 249.3$ Hz), 145.46 (s, C-4), 141.01 (s, C-2), 133.36 (d, C-4', $J_{\text{C-F}} = 9.1$ Hz), 131.51 (d, C-6', $J_{\text{C-F}} = 2.3$ Hz), 130.76 (d, C-6), 124.62 (d, C-5', $J_{\text{C-F}} = 3.8$ Hz), 123.94 (d, C-5), 122.83 (s, C-1', $J_{\text{C-F}} = 12.2$ Hz), 121.57 (d, C-3), 116.42 (d, C-3', $J_{\text{C-F}} = 23.5$ Hz), 113.65 (s, C-1), 66.70 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 22.08 (q, CH_3), 21.91 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 10.44 (q, $\text{OCH}_2\text{CH}_2\text{CH}_3$); HRESI-MS m/z 338.1169 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{18}\text{H}_{18}\text{FNO}_3\text{Na}$ 338.1168).

4.17. Propyl 2-(2-chlorobenzamido)-4-methylbenzoate (35)

Yield (43%) from **6** and 2-chlorobenzoyl chloride; EI-MS (m/z , %): 333(15), 331(45) $[\text{M}]^+$, 244(24), 141(74), 139(100), 111(41); ^1H NMR (CDCl_3) δ 11.57 (1H, br, NH), 8.75 (1H, s, H-3), 7.97 (1H, d, $J = 8.0$ Hz, H-6), 7.64 (1H, dd, $J = 7.2, 2.0$ Hz, H-6'), 7.47 (1H, dd, $J = 7.6, 1.6$ Hz, H-3'), 7.38 (2H, m, H-4' 5'), 6.96 (1H, d, $J = 8.0$ Hz, H-5), 4.23 (2H, t, $J = 6.4$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 2.45 (3H, s, CH_3), 1.77 (2H, m, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 1.01 (3H, t, $J = 7.6$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) δ 168.26 (s, COOR), 166.52 (s, CONH), 145.89 (s, C-4), 141.11 (s, C-2), 136.29 (s, C-1'), 131.31 (d, C-6, s, C-2'), 130.79 (d, C-4'), 130.59 (d, C-3'), 129.08 (d, C-6'), 127.09 (d, C-5'), 124.02 (d, C-5), 120.88 (d, C-3), 113.09 (s, C-1), 66.79 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 22.14 (q, CH_3), 21.91 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 10.45 (q, $\text{OCH}_2\text{CH}_2\text{CH}_3$); HRESI-MS m/z 354.0871 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{18}\text{H}_{18}\text{ClNO}_3\text{Na}$ 354.0873).

4.18. Propyl 2-(2-bromobenzamido)-4-methylbenzoate (36)

Yield (33%) from **6** and 2-bromobenzoyl chloride; EI-MS (m/z , %): 377(11), 375(11) $[\text{M}]^+$, 185(64), 183(64), 157(16), 155(16); ^1H NMR (CDCl_3) δ 11.50 (1H, br, NH), 8.75 (1H, s, H-3), 7.97 (1H, d, $J = 8.0$ Hz, H-6), 7.65 (1H, dd, $J = 8.0, 1.2$ Hz, H-3'), 7.59 (1H, dd, $J = 8.0, 1.6$ Hz, H-6'), 7.41 (1H, td, $J = 8.0, 1.2$ Hz, H-5'), 7.32 (1H, td, $J = 8.0, 1.6$ Hz, H-4'), 7.11 (1H, dd, $J = 8.0, 1.2$ Hz, H-5), 4.23 (2H, t, $J = 6.8$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 2.45 (3H, s, CH_3), 1.77 (2H, m, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 1.01 (3H, t, $J = 7.2$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) δ 168.27 (s, COOR), 166.35 (s, CONH), 145.91 (s, C-4), 141.11 (s, C-2), 138.49 (s, C-1'), 133.77 (d, C-3'), 131.37 (d, C-6), 130.80 (d, C-4'), 128.83 (d, C-6'), 127.64 (d, C-5'), 124.05 (d, C-5), 120.87 (d, C-3), 119.78 (s, C-2'), 113.11 (s, C-1), 66.81 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 21.12 (q, CH_3), 21.91 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 10.44 (q, $\text{OCH}_2\text{CH}_2\text{CH}_3$); HRESI-MS m/z 398.0370 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{18}\text{H}_{18}\text{BrNO}_3\text{Na}$ 398.0368).

4.19. Propyl 2-(2-methylbenzamido)-4-methylbenzoate (37)

Yield (40%) from **6** and 2-methylbenzoyl chloride; EI-MS (m/z , %): 311 $[\text{M}]^+$ (9), 119(100), 118(46), 91(74); ^1H NMR (CDCl_3) δ 11.52 (1H, br, NH), 8.76 (1H, s, H-3), 7.97 (1H, d, $J = 8.0$ Hz, H-6), 7.61 (1H, dd, $J = 0.8, 7.6$ Hz, H-6'),

7.37 (1H, td, $J = 0.8, 7.6$ Hz, H-4'), 7.28 (2H, m, H-5' 3'), 6.94 (1H, dd, $J = 8.0, 0.8$ Hz, H-5), 4.23 (2H, t, $J = 6.8$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 2.56 (3H, s, CH_3), 2.45 (3H, s, CH_3), 1.78 (2H, m, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 1.01 (3H, t, $J = 7.6$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) δ 168.46 (s, COOR), 168.33 (s, CONH), 145.79 (s, C-4), 141.67 (s, C-2), 136.96 (s, C-2'), 136.48 (s, C-1'), 131.41 (d, C-6), 130.79 (d, C-4'), 130.30 (d, C-3'), 127.02 (d, C-6'), 126.04 (d, C-5'), 123.63 (d, C-5), 120.61 (d, C-3), 112.90 (s, C-1), 66.71 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 22.13 (q, CH_3), 21.92 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 20.22 (q, CH_3), 10.45 (q, $\text{OCH}_2\text{CH}_2\text{CH}_3$); HRESI-MS m/z 334.1419 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_3\text{Na}$ 334.1419).

4.20. Propyl 2-(2-methoxybenzamido)-4-methyl-benzoate (38)

Yield (38%) from **6** and 2-methoxybenzoyl chloride; EI-MS (m/z , %): 327 $[\text{M}]^+$ (7), 193(10), 135(100), 92(33); ^1H NMR (CDCl_3) δ 12.20 (1H, br, NH), 8.80 (1H, d, $J = 0.8$ Hz, H-3), 8.17 (1H, dd, $J = 8.0, 1.2$ Hz, H-6'), 7.94 (1H, d, $J = 8.0$ Hz, H-6), 7.48 (1H, m, H-4'), 7.08 (2H, td, $J = 8.0, 1.2$ Hz, H-5'), 7.02 (2H, d, $J = 8.0$ Hz, H-5), 6.92 (1H, dd, $J = 1.2, 8.4$ Hz, H-3'), 4.26 (2H, t, $J = 6.8$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 4.06 (3H, s, OCH_3), 2.43 (3H, s, CH_3), 1.79 (2H, m, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 1.04 (3H, t, $J = 7.2$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) δ 167.46 (s, COOR), 164.59 (s, CONH), 157.52 (s, C-2'), 144.96 (s, C-4), 141.18 (s, C-2), 133.00 (d, C-6), 132.19 (d, C-4'), 130.61 (d, C-6'), 123.48 (d, C-5), 122.93 (s, C-1'), 122.21 (d, C-3), 120.89 (d, C-5'), 114.37 (s, C-1), 111.31 (d, C-3'), 66.32 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 55.49 (q, OCH_3), 22.11 (q, CH_3), 22.03 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 10.56 (q, $\text{OCH}_2\text{CH}_2\text{CH}_3$); HRESI-MS m/z 350.1369 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_4\text{Na}$ 350.1368).

4.21. Propyl 2-(2-fluorobenzamido)-4-nitrolbenzoate (39)

Yield (42%) from **7** and 2-fluorobenzoyl chloride; EI-MS (m/z , %): 346(12) $[\text{M}]^+$, 259 (8), 135(16), 123(100), 95(68); ^1H NMR (CDCl_3) δ 11.99 (1H, br, NH), 9.80 (1H, d, $J = 2.4$ Hz, H-3), 8.24 (1H, d, $J = 8.8$ Hz, H-6), 8.10 (1H, td, $J = 8.0, 1.6$ Hz, H-6'), 7.92 (1H, dd, $J = 8.8, 2.4$ Hz, H-5), 7.55 (1H, m, H-4'), 7.31 (1H, td, $J = 8.0, 0.8$ Hz, H-5'), 7.20 (1H, dd, $J = 10.8, 8.0$ Hz, H-3'), 4.36 (2H, t, $J = 6.4$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 1.84 (2H, m, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 1.04 (3H, t, $J = 7.2$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) δ 166.43 (s, COOR), 162.48 (s, CONH, $J_{\text{C-F}} = 2.3$ Hz), 160.28 (s, C-2'), $J_{\text{C-F}} = 248.6$ Hz), 150.95 (s, C-4), 141.96 (s, C-2), 134.20 (d, C-4'), $J_{\text{C-F}} = 9.1$ Hz), 131.94 (d, C-6', $J_{\text{C-F}} = 2.3$ Hz), 131.90 (d, C-6), 124.90 (d, C-5', $J_{\text{C-F}} = 3.8$ Hz), 121.55 (s, C-1', $J_{\text{C-F}} = 11.4$ Hz), 120.66 (s, C-1), 116.99 (d, C-5), 116.47 (d, C-3', $J_{\text{C-F}} = 23.5$ Hz), 116.24 (d, C-3), 67.89 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 21.81 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 10.38 (q, $\text{OCH}_2\text{CH}_2\text{CH}_3$); HRESI-MS m/z 369.0861 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{17}\text{H}_{15}\text{FN}_2\text{O}_5\text{Na}$ 369.0863).

4.22. Propyl 2-(2-chlorobenzamido)-4-nitrolbenzoate (40)

Yield (86%) from **7** and 2-chlorobenzoyl chloride; EI-MS (m/z , %): 362(1) $[\text{M}]^+$, 275(14), 141(35), 139(100); ^1H NMR (CDCl_3) δ 11.65 (1H, br, NH), 9.78 (1H, d,

$J = 2.4$ Hz, H-3), 8.25 (1H, d, $J = 8.8$ Hz, H-6), 7.94 (1H, dd, $J = 8.8, 2.4$ Hz, H-6'), 7.68 (1H, dd, $J = 7.2, 1.6$ Hz, H-3'), 7.48 (1H, td, $J = 8.0, 1.6$ Hz, H-5'), 7.42 (2H, m, H-4' 5), 4.32 (2H, t, $J = 6.4$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 1.82 (2H, m, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 1.03 (3H, t, $J = 7.6$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) δ 166.74 (s, COOR), 165.59 (s, CONH), 151.17 (s, C-4), 141.98 (s, C-2), 135.23 (s, C-1'), 131.98 (d, C-3'), 131.94 (d, C-4'), 131.23 (s, C-2'), 130.73 (d, C-6), 129.46 (d, C-6'), 127.25 (d, C-5'), 120.06 (s, C-1), 117.09 (d, C-5), 115.55 (d, C-3), 67.99 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 21.80 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 10.38 (q, $\text{OCH}_2\text{CH}_2\text{CH}_3$); HRESI-MS m/z 363.0746 $[\text{M}+\text{H}]^+$ (calcd for $\text{C}_{17}\text{H}_{16}\text{ClN}_2\text{O}_5$ 363.0748).

4.23. Propyl 2-(2-bromobenzamido)-4-nitrolbenzoate (41)

Yield (45%) from **7** and 2-bromobenzoyl chloride; EI-MS (m/z , %): 408(7), 406 $[\text{M}]^+$ (7), 321(15), 319(15), 185(100), 184(92); ^1H NMR (CDCl_3) δ 11.56 (1H, br, NH), 9.78 (1H, d, $J = 2.4$ Hz, H-3), 8.25 (1H, d, $J = 8.8$ Hz, H-6), 7.95 (1H, dd, $J = 8.8, 2.4$ Hz, H-5), 7.68 (1H, dd, $J = 7.6, 1.2$ Hz, H-3'), 7.62 (1H, dd, $J = 7.6, 2.0$ Hz, H-6'), 7.44 (1H, td, $J = 7.6, 1.2$ Hz, H-5'), 7.36 (1H, td, $J = 7.6, 2.0$ Hz, H-4'), 4.32 (2H, t, $J = 6.8$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 1.82 (2H, m, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 1.03 (3H, t, $J = 7.6$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) δ 166.77 (s, COOR), 166.45 (s, CONH), 151.25 (s, C-4), 142.00 (s, C-2), 137.53 (s, C-1'), 133.95 (d, C-3'), 131.99 (d, C-4'), 131.95 (d, C-6), 129.11 (d, C-6'), 127.78 (d, C-5'), 120.06 (s, C-1), 119.65 (s, C-2'), 117.13 (d, C-5), 115.55 (d, C-3), 68.02 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 21.81 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 10.39 (q, $\text{OCH}_2\text{CH}_2\text{CH}_3$); HRESI-MS m/z 407.0244 $[\text{M}+\text{H}]^+$ (calcd for $\text{C}_{17}\text{H}_{16}\text{BrN}_2\text{O}_5$ 407.0243).

4.24. Propyl 2-(2-methylbenzamido)-4-nitrolbenzoate (42)

Yield (74%) from **7** and 2-methylbenzoyl chloride; EI-MS (m/z , %): 342 $[\text{M}]^+$ (5), 119(100), 118(88), 92(65); ^1H NMR (CDCl_3) δ 11.59 (1H, br, NH), 9.80 (1H, d, $J = 2.4$ Hz, H-3), 8.25 (1H, dd, $J = 0.4, 8.8$ Hz, H-6), 7.91 (1H, dd, $J = 8.8, 2.4$ Hz, H-5), 7.63 (1H, dd, $J = 1.2, 8.8$ Hz, H-6'), 7.41 (1H, td, $J = 1.2, 7.2$ Hz, H-4'), 7.31 (2H, m, H-5' 3'), 4.32 (2H, t, $J = 6.8$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 2.57 (3H, s, CH_3), 1.82 (2H, m, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 1.04 (3H, t, $J = 7.2$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) δ 168.34 (s, COOR), 166.91 (s, CONH), 151.20 (s, C-4), 142.61 (s, C-2), 137.56 (s, C-2'), 135.26 (s, C-1'), 131.94 (d, C-4'), 131.70 (d, C-6), 130.94 (d, C-3'), 127.00 (d, C-6'), 126.16 (d, C-5'), 119.73 (s, C-1), 116.59 (d, C-5), 115.24 (d, C-3), 67.91 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 21.80 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 20.32 (q, CH_3), 10.38 (q, $\text{OCH}_2\text{CH}_2\text{CH}_3$); HRESI-MS m/z 365.1111 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_5\text{Na}$ 365.1113).

4.25. Propyl 2-(2-methoxybenzamido)-4-nitrolbenzoate (43)

Yield (38%) from **7** and 2-methoxybenzoyl chloride; EI-MS (m/z , %): 358 $[\text{M}]^+$ (2), 224(72), 136(11), 135(100), 92(6); ^1H NMR (CDCl_3) δ 12.39 (1H, br, NH), 9.87 (1H, d, $J = 2.4$ Hz, H-3), 8.23 (1H, dd, $J = 2.0, 8.0$ Hz, H-6'), 8.17 (1H, d, $J = 8.8$ Hz, H-6), 7.86 (1H, dd,

$J = 2.4, 8.8$ Hz, H-5), 7.51 (1H, m, H-4'), 7.05 (1H, td, $J = 0.8, 8.0$ Hz, H-5'), 7.03 (1H, d, $J = 8.4$ Hz, H-3'), 4.34 (2H, t, $J = 6.4$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 4.09 (3H, s, OCH_3), 1.84 (2H, m, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 1.06 (3H, t, $J = 7.2$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) δ 165.95 (s, COOR), 164.72 (s, CONH), 157.65 (s, C-2'), 50.81 (s, C-4), 142.21 (s, C-2), 133.79 (d, C-4'), 132.64 (d, C-6), 131.61 (d, C-6'), 121.56 (s, C-1), 121.40 (s, C-1'), 121.10 (d, C-5'), 116.88 (d, C-5), 116.42 (d, C-3), 111.33 (d, C-3'), 67.42 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 55.50 (q, OCH_3), 21.91 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 10.50 (q, $\text{OCH}_2\text{CH}_2\text{CH}_3$); HRESI-MS m/z 381.1061 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_6\text{Na}$ 381.1062).

4.26. Methyl 4-chloro-2-(2,6-difluorobenzamido)benzoate (44)

Yield (38%) from **8** and 2,6-difluorobenzoyl chloride; EI-MS (m/z , %): 327(10), 325 $[\text{M}]^+$ (30), 266(18), 141(100), 113(52); ^1H NMR (CDCl_3) δ 11.66 (1H, br, NH), 9.01 (1H, d, $J = 2.0$ Hz, H-3), 8.01 (1H, d, $J = 8.4$ Hz, H-6), 7.43 (1H, m, H-4'), 7.14 (1H, dd, $J = 8.4, 2.0$ Hz, H-5), 7.02 (2H, m, H-5' 3'), 6.43 (1H, br, NHC_3H_8), 3.91 (3H, s, OCH_3); ^{13}C NMR (CDCl_3) δ 168.01 (s, COOR), 160.03 (s, C-2', $J_{\text{C-F}} = 251.6$ Hz), 159.96 (s, C-6', $J_{\text{C-F}} = 252.3$ Hz), 159.04 (s, CONH), 141.74 (s, C-2), 141.18 (s, C-4), 132.30 (d, C-4', $J_{\text{C-F}} = 10.3$ Hz), 131.95 (d, C-6), 123.57 (d, C-5), 120.64 (d, C-3), 113.53 (s, C-1), 112.30 (d, C-5', $J_{\text{C-F}} = 20.4$ Hz), 112.25 (d, C-3', $J_{\text{C-F}} = 20.4$ Hz), 112.15 (s, C-1'), 52.62 (q, OCH_3); HRESI-MS m/z 348.0217 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{15}\text{H}_{10}\text{ClF}_2\text{NO}_3\text{Na}$ 348.0215).

4.27. Ethyl 4-chloro-2-(2,6-difluorobenzamido)benzoate (45)

Yield (46%) from **1** and 2,6-difluorobenzoyl chloride; EI-MS (m/z , %): 339 $[\text{M}]^+$ (12), 266(33), 141(100), 114(24); ^1H NMR (CDCl_3) δ 11.71 (1H, br, NH), 9.00 (1H, d, $J = 2.4$ Hz, H-3), 8.01 (1H, d, $J = 8.4$ Hz, H-6), 7.43 (1H, m, H-4'), 7.13 (1H, dd, $J = 8.4, 2.4$ Hz, H-5), 7.01 (2H, m, H-5' 3'), 4.36 (2H, q, $J = 7.2$ Hz, OCH_2CH_3), 1.39 (3H, t, $J = 7.2$ Hz, OCH_2CH_3); ^{13}C NMR (CDCl_3) δ 167.52 (s, COOR), 159.98 (s, C-2', $J_{\text{C-F}} = 251.6$ Hz), 159.92 (s, C-6', $J_{\text{C-F}} = 251.6$ Hz), 159.01 (s, CONH), 141.70 (s, C-2), 140.96 (s, C-4), 132.24 (d, C-4', $J_{\text{C-F}} = 10.2$ Hz), 131.92 (d, C-6), 123.47 (d, C-5), 120.56 (d, C-3), 113.82 (s, C-1), 112.26 (d, C-5', $J_{\text{C-F}} = 20.4$ Hz), 112.21 (d, C-3', $J_{\text{C-F}} = 19.7$ Hz), 112.11 (s, C-1'), 61.76 (t, OCH_2CH_3), 14.08 (q, OCH_2CH_3); HRESI-MS m/z 340.0554 $[\text{M}+\text{H}]^+$ (calcd for $\text{C}_{16}\text{H}_{13}\text{ClF}_2\text{NO}_3$ 340.0552).

4.28. Propyl 4-chloro-2-(2,6-difluorobenzamido)benzoate (46)

Yield (58%) from **2** and 2,6-difluorobenzoyl chloride; EI-MS (m/z , %): 355(9), 353 $[\text{M}]^+$ (22), 268(24), 266(54), 142(100), 141(90); ^1H NMR (CDCl_3) δ 11.71(1H, br, NH), 9.00 (1H, d, $J = 2.0$ Hz, H-3), 8.01 (1H, d, $J = 8.8$ Hz, H-6), 7.42 (1H, m, H-4'), 7.13 (1H, dd, $J = 8.8, 2.0$ Hz, H-5), 7.02 (2H, m, H-5' 3'), 4.26 (2H, t, $J = 6.4$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 1.78 (2H, m,

$\text{OCH}_2\text{CH}_2\text{CH}_3$), 1.01 (3H, t, $J = 7.6$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) δ 167.58 (s, COOR), 159.98 (s, C-2', $J_{\text{C-F}} = 251.6$ Hz), 159.92 (s, C-6', $J_{\text{C-F}} = 251.6$ Hz), 159.01 (s, CONH), 141.71 (s, C-2), 140.96 (s, C-4), 132.25 (d, C-4', $J_{\text{C-F}} = 10.3$ Hz), 131.86 (d, C-6), 123.49 (d, C-5), 120.57 (d, C-3), 113.84 (s, C-1), 112.26 (d, C-5', $J_{\text{C-F}} = 20.5$ Hz), 112.21 (d, C-3', $J_{\text{C-F}} = 19.7$ Hz), 112.11 (s, C-1'), 67.27 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 21.83 (t, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 10.40 (q, $\text{OCH}_2\text{CH}_2\text{CH}_3$); HRESI-MS m/z 354.0709 $[\text{M}+\text{H}]^+$ (calcd for $\text{C}_{17}\text{H}_{15}\text{ClF}_2\text{NO}_3$ 354.0708).

4.29. Butyl 4-chloro-2-(2,6-difluorobenzamido)benzoate (47)

Yield (43%) from **3** and 2,6-difluorobenzoyl chloride; EI-MS (m/z , %): 369(10), 367 $[\text{M}]^+$ (29), 266(24), 141(100), 113(31); ^1H NMR (CDCl_3) δ 11.71 (1H, br, NH), 9.01 (1H, d, $J = 2.4$ Hz, H-3), 8.00 (1H, d, $J = 8.8$ Hz, H-6), 7.43 (1H, m, H-4'), 7.13 (1H, dd, $J = 8.8, 2.4$ Hz, H-5), 7.01 (2H, m, H-5' 3'), 4.30 (2H, t, $J = 6.8$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.74 (2H, m, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.45 (2H, m, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.97 (3H, t, $J = 7.6$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) δ 167.59 (s, COOR), 160.00 (s, C-2', $J_{\text{C-F}} = 251.6$ Hz), 159.93 (s, C-6', $J_{\text{C-F}} = 251.6$ Hz), 159.03 (s, CONH), 141.72 (s, C-2), 140.97 (s, C-4), 132.25 (d, C-4', $J_{\text{C-F}} = 10.3$ Hz), 131.88 (d, C-6), 123.51 (d, C-5), 120.60 (d, C-3), 113.85 (s, C-1), 112.27 (d, C-5', $J_{\text{C-F}} = 19.7$ Hz), 112.22 (d, C-3', $J_{\text{C-F}} = 20.5$ Hz), 112.12 (s, C-1'), 65.61 (t, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 30.45 (t, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 19.17 (t, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 13.67 (q, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$); HRESI-MS m/z 368.0866 $[\text{M}+\text{H}]^+$ (calcd for $\text{C}_{18}\text{H}_{17}\text{ClF}_2\text{NO}_3$ 368.0865).

4.30. Methyl 4-chloro-2-(2,6-dichlorobenzamido)benzoate (48)

Yield (29%) from **8** and 2,6-dichlorobenzoyl chloride; EI-MS (m/z , %): 359(12), 357 $[\text{M}]^+$ (12), 175(94), 173(100), 147(19), 145(28); ^1H NMR (CDCl_3) δ 11.41 (1H, br, NH), 9.00 (1H, d, $J = 2.0$ Hz, H-3), 8.01 (1H, d, $J = 8.8$ Hz, H-6), 7.34 (3H, m, H-3' 4' 5'), 7.16 (1H, dd, $J = 8.8, 2.0$ Hz, H-5), 3.90 (3H, s, OCH_3); ^{13}C NMR (CDCl_3) δ 168.01 (s, COOR), 163.11 (s, CONH), 141.63 (s, C-2), 140.26 (s, C-4), 135.92 (s, C-1'), 132.17 (s, C-2', d, C-6'), 131.97 (d, C-4'), 131.04 (d, C-6), 128.28 (d, C-3', d, C-5'), 123.72 (d, C-5), 120.75 (d, C-3), 113.62 (s, C-1), 52.61 (q, OCH_3); HRESI-MS m/z 357.9807 $[\text{M}+\text{H}]^+$ (calcd for $\text{C}_{15}\text{H}_{11}\text{Cl}_3\text{NO}_3$ 357.9805).

4.31. Ethyl 4-chloro-2-(2,6-dichlorobenzamido)benzoate (49)

Yield (32%) from **1** and 2,6-dichlorobenzoyl chloride; EI-MS (m/z , %): 373(15), 371 $[\text{M}]^+$ (15), 175(93), 173(100), 147(18), 145(26); ^1H NMR (CDCl_3) δ 11.46 (1H, br, NH), 8.99 (1H, d, $J = 2.0$ Hz, H-3), 8.02 (1H, d, $J = 8.8$ Hz, H-6), 7.32 (3H, m, H-3' 4' 5'), 7.14 (1H, dd, $J = 8.4, 2.0$ Hz, H-5), 4.33 (2H, q, $J = 7.0$ Hz, OCH_2CH_3), 1.37 (3H, t, $J = 7.2$ Hz, OCH_2CH_3); ^{13}C NMR (CDCl_3) δ 167.50 (s, COOR), 163.06 (s, CONH), 141.56 (s, C-2), 141.00 (s, C-4), 135.89 (s, C-1'), 132.11

(s, C-2', d, C-6'), 131.95 (d, C-4'), 131.01 (d, C-6), 128.24 (d, C-3', d, C-5'), 123.63 (d, C-5), 120.66 (d, C-3), 113.90 (s, C-1), 61.78 (t, OCH₂CH₃), 14.04 (q, OCH₂CH₃); HRESI-MS *m/z* 371.9962 [M+H]⁺ (calcd for C₁₆H₁₃Cl₃NO₃ 371.9961).

4.32. Propyl 4-chloro-2-(2,6-dichlorobenzamido)benzoate (50)

Yield (32%) from **2** and 2,6-dichlorobenzoyl chloride; EI-MS (*m/z*, %): 387(10), 385 [M]⁺ (10), 175(78), 173(100), 147(11), 145(15); ¹H NMR (CDCl₃) δ 11.46 (1H, br, NH), 9.00 (1H, d, *J* = 2.0 Hz, H-3), 8.02 (1H, d, *J* = 8.8 Hz, H-6), 7.33 (3H, m, H-3' 4' 5'), 7.15 (1H, dd, *J* = 8.8, 2.0 Hz, H-5), 4.24 (2H, t, *J* = 6.8 Hz, OCH₂CH₂CH₃), 1.77 (2H, m, OCH₂CH₂CH₃), 1.00 (3H, t, *J* = 7.6 Hz, OCH₂CH₂CH₃); ¹³C NMR (CDCl₃) δ 167.57 (s, COOR), 163.10 (s, CONH), 141.58 (s, C-2), 141.05 (s, C-4), 135.91 (s, C-1'), 132.15 (s, C-2', d, C-6'), 131.90 (d, C-4'), 131.00 (d, C-6), 128.25 (d, C-3', d, C-5'), 123.67 (d, C-5), 120.72 (d, C-3), 113.96 (s, C-1), 67.29 (t, OCH₂CH₂CH₃), 21.82 (t, OCH₂CH₂CH₃), 10.40 (q, OCH₂CH₂CH₃); HRESI-MS *m/z* 386.0119 [M+H]⁺ (calcd for C₁₇H₁₅Cl₃NO₃ 386.0117).

4.33. Butyl 4-chloro-2-(2,6-dichlorobenzamido)benzoate (51)

Yield (26%) from **3** and 2,6-dichlorobenzoyl chloride; EI-MS (*m/z*, %): 401(16), 399 [M]⁺ (16), 175(37), 173(100), 147(12), 145(17); ¹H NMR (CDCl₃) δ 11.45 (1H, br, NH), 9.00 (1H, d, *J* = 2.0 Hz, H-3), 8.01 (1H, d, *J* = 8.8 Hz, H-6), 7.33 (3H, m, H-3' 4' 5'), 7.15 (1H, dd, *J* = 8.8, 2.0 Hz, H-5), 4.28 (2H, t, *J* = 6.4 Hz, OCH₂CH₂CH₂CH₃), 1.73 (2H, m, OCH₂CH₂CH₂CH₃), 1.44 (2H, m, OCH₂CH₂CH₂CH₃), 0.96 (3H, t, *J* = 7.2 Hz, OCH₂CH₂CH₂CH₃); ¹³C NMR (CDCl₃) δ 167.55 (s, COOR), 163.07 (s, CONH), 141.58 (s, C-2), 141.04 (s, C-4), 135.92 (s, C-1'), 132.15 (s, C-2', d, C-6'), 131.92 (d, C-4'), 131.00 (d, C-6), 128.28 (d, C-3', d, C-5'), 123.66 (d, C-5), 120.71 (d, C-3), 113.97 (s, C-1), 65.62 (t, OCH₂CH₂CH₂CH₃), 30.43 (t, OCH₂CH₂CH₂CH₃), 19.16 (t, OCH₂CH₂CH₂CH₃), 13.66 (q, OCH₂CH₂CH₂CH₃); HRESI-MS *m/z* 400.0276 [M+H]⁺ (calcd for C₁₈H₁₇Cl₃NO₃ 400.0274).

4.34. Isopropyl 4-chloro-2-(2-fluorobenzamido)benzoate (52)

Yield (40%) from **9** and 2-fluorobenzoyl chloride; EI-MS (*m/z*, %): 335(26) [M]⁺, 250(16), 249(46), 124(49), 123(100); ¹H NMR (CDCl₃) δ 11.99 (1H, br, NH), 9.02 (1H, d, *J* = 2.0 Hz, H-3), 8.05 (1H, td, *J* = 7.6, 1.6 Hz, H-6'), 8.00 (1H, d, *J* = 8.4 Hz, H-6), 7.52 (1H, m, H-4'), 7.30 (1H, td, *J* = 7.6, 0.8 Hz, H-5'), 7.21 (1H, ddd, *J* = 10.4, 8.4, 0.8 Hz, H-3'), 7.11 (1H, dd, *J* = 8.4, 2.0 Hz, H-5), 5.29 (1H, m, OCH(CH₃)₂), 1.38 (6H, d, *J* = 6.0 Hz, OCH(CH₃)₂); ¹³C NMR (CDCl₃) δ 166.80 (s, COOR), 162.48 (s, CONH, *J*_{C-F} = 2.7 Hz), 160.21 (s, C-2', *J*_{C-F} = 249.3 Hz), 141.97 (s, C-2), 140.48 (s, C-4), 133.73 (d, C-4', *J*_{C-F} = 9.1 Hz), 131.93 (d, C-6), 131.69 (d, C-6', *J*_{C-F} = 1.9 Hz), 124.76 (d, C-5', *J*_{C-F} = 3.8 Hz), 123.13 (d, C-5), 122.38 (s, C-1', *J*_{C-F} = 12.1 Hz), 121.13

(d, C-3), 116.49 (d, C-3', *J*_{C-F} = 23.1 Hz), 114.87 (s, C-1), 69.34 (d, OCH(CH₃)₂), 21.83 (q, OCH(CH₃)₂); HRESI-MS *m/z* 358.0623 [M+Na]⁺ (calcd for C₁₇H₁₅ClFNO₃Na 358.0622).

4.35. Isopropyl 4-chloro-2-(2-chlorobenzamido)benzoate (53)

Yield (36%) from **9** and 2-chlorobenzoyl chloride; EI-MS (*m/z*, %): 353(11), 351(17) [M]⁺, 266(15), 264(21), 141(38), 139(100); ¹H NMR (CDCl₃) δ 11.66 (1H, br, NH), 9.00 (1H, d, *J* = 2.0 Hz, H-3), 8.00 (1H, d, *J* = 8.8 Hz, H-6), 7.64 (1H, dd, *J* = 7.2, 2.0 Hz, H-6'), 7.42 (3H, m, H-3' 4' 5'), 7.11 (1H, dd, *J* = 8.8, 2.0 Hz, H-5), 5.21 (1H, m, OCH(CH₃)₂), 1.35 (6H, d, *J* = 6.0 Hz, OCH(CH₃)₂); ¹³C NMR (CDCl₃) δ 167.01 (s, COOR), 165.50 (s, CONH), 141.95 (s, C-2), 140.77 (s, C-4), 135.81 (s, C-1'), 131.93 (d, C-4'), 131.56 (d, C-6), 131.27 (s, C-2'), 130.64 (d, C-3'), 129.19 (d, C-6'), 127.14 (d, C-5'), 123.19 (d, C-5), 120.43 (d, C-3), 114.28 (s, C-1), 69.51 (d, OCH(CH₃)₂), 21.75 (q, OCH(CH₃)₂); HRESI-MS *m/z* 374.0329 [M+Na]⁺ (calcd for C₁₇H₁₅Cl₂NO₃Na 374.0326).

4.36. Isopropyl 4-chloro-2-(2,6-difluorobenzamido)benzoate (54)

Yield (33%) from **9** and 2,6-difluorobenzoyl chloride; EI-MS (*m/z*, %): 355 (9), 353 [M]⁺ (27), 268 (14), 266 (37), 153 (22), 143 (52), 141 (100); ¹H NMR (CDCl₃) δ 11.74 (1H, br, NH), 9.00 (1H, d, *J* = 2.0 Hz, H-3), 8.00 (1H, d, *J* = 8.8 Hz, H-6), 7.43 (1H, m, H-4'), 7.13 (1H, dd, *J* = 8.8, 2.0 Hz, H-5), 7.02 (2H, m, H-5' 3'), 5.22 (1H, m, OCH(CH₃)₂), 1.36 (6H, d, *J* = 6.0 Hz, OCH(CH₃)₂); ¹³C NMR (CDCl₃) δ 167.05 (s, COOR), 160.02 (s, C-2', *J*_{C-F} = 251.5 Hz), 159.96 (s, C-6', *J*_{C-F} = 252.4 Hz), 159.03 (s, CONH), 141.71 (s, C-2), 140.84 (s, C-4), 132.21 (d, C-4', *J*_{C-F} = 10.2 Hz), 131.93 (d, C-6), 123.45 (d, C-5), 120.59 (d, C-3), 114.27 (s, C-1'), 112.38 (s, C-1), 112.23 (d, C-5', *J*_{C-F} = 23.5 Hz), 112.28 (d, C-3', *J*_{C-F} = 19.8 Hz), 69.60 (d, OCH(CH₃)₂), 21.78 (q, OCH(CH₃)₂); HRESI-MS *m/z* 376.0531 [M+Na]⁺ (calcd for C₁₇H₁₄ClF₂NO₃Na 376.0528).

4.37. 4-Chloro-2-(2-fluorobenzamido)-*N*-propylbenzamide (55)

Yield (37%) from **10** and 2-fluorobenzoyl chloride; EI-MS (*m/z*, %): 334 [M]⁺ (3), 276(16), 248(6), 123(100), 95(47); ¹H NMR (CDCl₃) δ 11.77 (1H, br, NH), 8.78 (1H, d, *J* = 2.4 Hz, H-3), 8.01 (1H, td, *J* = 7.6, 2.0 Hz, H-6'), 7.51 (1H, m, H-4'), 7.38 (1H, d, *J* = 8.4 Hz, H-6), 7.28 (1H, td, *J* = 7.6, 1.2 Hz, H-5'), 7.19 (1H, ddd, *J* = 10.4, 8.4, 1.2 Hz, H-3'), 7.01 (1H, dd, *J* = 8.4, 2.4 Hz, H-5), 6.48 (1H, br, NHC₃H₈), 3.40 (2H, q, *J* = 6.8 Hz, NHCH₂CH₂CH₃), 1.65 (2H, m, NHCH₂CH₂CH₃), 0.99 (3H, t, *J* = 7.2 Hz, NHCH₂CH₂CH₃); ¹³C NMR (CDCl₃) δ 167.98 (s, CONHC₃H₈), 162.43 (s, CONH, *J*_{C-F} = 2.5 Hz), 160.25 (s, C-2', *J*_{C-F} = 250.0 Hz), 139.77 (s, C-2), 138.11 (s, C-4), 133.67 (d, C-4', *J*_{C-F} = 8.4 Hz), 131.42 (d, C-6', *J*_{C-F} = 2.3 Hz), 127.61 (d, C-6), 124.68 (d, C-5', *J*_{C-F} = 3.8 Hz), 123.25 (d, C-5), 122.29 (s, C-1'), 122.13 (d, C-3), 120.31 (s, C-1), 116.57 (d, C-3',

$J_{\text{C-F}} = 23.5$ Hz), 41.79 (t, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 22.65 (t, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 11.39 (q, $\text{NHCH}_2\text{CH}_2\text{CH}_3$); HRESI-MS m/z 357.0781 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{17}\text{H}_{16}\text{ClF}_2\text{N}_2\text{O}_2$ Na 357.0782).

4.38. 4-Chloro-2-(2-chlorobenzamido)-*N*-propylbenzamide (56)

Yield (58%) from **10** and 2-chlorobenzoyl chloride; EI-MS (m/z , %): 350 $[\text{M}]^+$ (10), 294 (18), 292 (23), 141 (33), 139 (100); ^1H NMR (CDCl_3) δ 11.65 (1H, br, NH), 8.85 (1H, d, $J = 2.0$ Hz, H-3), 7.62 (1H, dd, $J = 7.2$, 2.4 Hz, H-6), 7.46 (1H, dd, $J = 8.0$, 1.6 Hz, H-6'), 7.38 (3H, m, H-3' 4' 5'), 7.12 (1H, dd, $J = 8.0$, 2.0 Hz, H-5), 6.37 (1H, br, NHC_3H_8), 3.36 (2H, q, $J = 6.4$ Hz, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 1.63 (2H, m, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 0.97 (3H, t, $J = 7.6$ Hz, $\text{NHCH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) δ 168.07 (s, CONHC_3H_8), 165.49 (s, CONH), 140.17 (s, C-2), 138.61 (s, C-4), 135.67 (s, C-1'), 131.54 (d, C-4'), 131.36 (s, C-2'), 130.67 (d, C-6), 129.22 (d, C-3'), 127.47 (d, C-6'), 127.17 (d, C-5'), 123.32 (d, C-5), 121.57 (d, C-3), 119.15 (s, C-1), 41.78 (t, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 22.63 (t, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 11.38 (q, $\text{NHCH}_2\text{CH}_2\text{CH}_3$); HRESI-MS m/z 373.0487 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{17}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_2$ Na 373.0486).

4.39. 4-Chloro-2-(2-bromobenzamido)-*N*-propylbenzamide (57)

Yield (33%) from **10** and 2-bromobenzoyl chloride; EI-MS (m/z , %): 396 (14), 394 $[\text{M}]^+$ (11), 338 (25), 336 (20), 185 (96), 183 (100), 155 (24); ^1H NMR (CDCl_3) δ 11.64 (1H, s, NH), 8.79 (1H, d, $J = 2.0$ Hz, H-3), 7.63 (1H, dd, $J = 7.6$, 1.2 Hz, H-3'), 7.55 (1H, dd, $J = 7.6$, 1.6 Hz, H-6'), 7.40 (2H, m, H-6 5'), 7.31 (1H, td, $J = 7.6$, 1.6 Hz, H-4'), 7.01 (1H, dd, $J = 8.4$, 2.0 Hz, H-5), 6.67 (1H, br, NHC_3H_8), 3.33 (2H, q, $J = 6.4$ Hz, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 1.61 (2H, m, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 0.95 (3H, t, $J = 7.2$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) δ 168.05 (s, CONHC_3H_8), 166.36 (s, CONH), 140.02 (s, C-2), 138.40 (s, C-4), 137.75 (s, C-1'), 133.82 (d, C-3'), 131.60 (d, C-4'), 128.84 (d, C-6), 127.70 (d, C-6'), 127.69 (d, C-5'), 123.31 (d, C-5), 121.34 (d, C-3), 119.73 (s, C-2'), 119.09 (s, C-1), 41.76 (t, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 22.56 (t, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 11.38 (q, $\text{NHCH}_2\text{CH}_2\text{CH}_3$); HRESI-MS m/z 416.9979 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{17}\text{H}_{16}\text{BrClN}_2\text{O}_2\text{Na}$ 416.9981).

4.40. 4-Chloro-2-(2-methylbenzamido)-*N*-propylbenzamide (58)

Yield (40%) from **10** and 2-methylbenzoyl chloride; EI-MS (m/z , %): 330 $[\text{M}]^+$ (6), 271 (10), 119 (100), 91 (100); ^1H NMR (CDCl_3) δ 11.59 (1H, br, NH), 8.81 (1H, d, $J = 2.0$ Hz, H-3), 7.57 (1H, dd, $J = 1.2$, 7.6 Hz, H-6'), 7.38 (1H, d, $J = 8.4$ Hz, H-6), 7.36 (1H, td, $J = 1.2$, 7.6 Hz, H-4'), 7.27 (2H, m, H-5' 3'), 6.96 (1H, dd, $J = 8.4$, 2.0 Hz, H-5), 6.66 (1H, br, NHC_3H_8), 3.34 (2H, q, $J = 6.8$ Hz, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 2.54 (3H, s, CH_3), 1.69 (2H, m, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 0.96 (3H, t, $J = 7.6$ Hz, $\text{NHCH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) δ 168.43 (s, CONHC_3H_8), 168.19 (s, CONH), 140.49 (s, C-2), 138.32 (s, C-4), 137.00 (s, C-2'), 135.73 (s, C-1'),

131.50 (d, C-4'), 130.57 (d, C-6), 127.68 (d, C-3'), 127.09 (d, C-6'), 126.15 (d, C-5'), 122.85 (d, C-5), 121.13 (d, C-3), 118.99 (s, C-1), 41.74 (t, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 22.59 (t, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 20.25 (q, CH_3), 11.38 (q, $\text{NHCH}_2\text{CH}_2\text{CH}_3$); HRESI-MS m/z 353.1032 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{18}\text{H}_{19}\text{ClN}_2\text{O}_2\text{Na}$ 353.1033).

4.41. 4-Chloro-2-(2-methoxybenzamido)-*N*-propylbenzamide (59)

Yield (57%) from **10** and 2-methoxybenzoyl chloride; EI-MS (m/z , %): 346 $[\text{M}]^+$ (2), 288(2), 135(100), 92(22); ^1H NMR (CDCl_3) δ 11.69 (1H, br, NH), 8.72 (1H, d, $J = 1.6$ Hz, H-3), 8.18 (1H, dd, $J = 7.6$, 1.6 Hz, H-6), 7.50 (1H, td, $J = 8.8$, 2.0 Hz, H-6'), 7.24 (1H, d, $J = 8.4$ Hz, H-4')M, 7.09 (1H, t, $J = 7.2$ Hz, H-3'), 7.02 (1H, d, $J = 8.8$ Hz, H-5), 6.82 (1H, dd, $J = 8.8$, 1.2 Hz, H-5'), 6.64 (1H, br, NHC_3H_8), 4.09 (3H, s, OCH_3), 3.42 (2H, q, $J = 6.4$ Hz, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 1.69 (2H, m, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 1.02 (3H, t, $J = 7.6$ Hz, $\text{NHCH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) δ 168.02 (s, CONHC_3H_8), 164.46 (s, CONH), 157.73 (s, C-2'), 139.04 (s, C-2), 137.11 (s, C-4), 133.46 (d, C-4'), 132.23 (d, C-6), 132.27 (d, C-6'), 127.86 (d, C-5), 121.46 (d, C-3), 121.74 (s, C-1'), 120.88 (d, C-5'), 111.34 (s, C-1, d, C-3'), 55.66 (q, OCH_3), 41.67 (t, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 22.78 (t, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 11.51 (q, $\text{NHCH}_2\text{CH}_2\text{CH}_3$); HRESI-MS m/z 369.0982 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{18}\text{H}_{19}\text{ClN}_2\text{O}_3\text{Na}$ 369.0982).

4.42. 4-Chloro-2-(2,6-difluorobenzamido)-*N*-propylbenzamide (60)

Yield (21%) from **10** and 2,6-difluorobenzoyl chloride; EI-MS (m/z , %): 352 $[\text{M}]^+$ (19), 294(60), 180(93), 142(52), 141(100); ^1H NMR (CDCl_3) δ 11.75 (1H, br, NH), 8.83 (1H, d, $J = 2.0$ Hz, H-3), 7.40 (2H, m, H-4' 6), 7.08 (1H, dd, $J = 8.4$, 2.0 Hz, H-5), 6.99 (2H, m, H-5' 3'), 6.43 (1H, br, NHC_3H_8), 3.36 (2H, q, $J = 6.8$ Hz, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 1.63 (2H, m, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 0.97 (3H, t, $J = 7.2$ Hz, $\text{NHCH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) δ 168.02 (s, CONHC_3H_8), 160.01 (s, C-2', $J_{\text{C-F}} = 251.6$ Hz), 159.94 (s, C-6', $J_{\text{C-F}} = 251.6$ Hz), 159.04 (s, CONH), 139.90 (s, C-2), 138.64 (s, C-4), 132.09 (d, C-4'), $J_{\text{C-F}} = 9.9$ Hz), 127.43 (d, C-6), 123.55 (d, C-5), 121.69 (d, C-3), 119.06 (s, C-1), 112.24 (d, C-5', $J_{\text{C-F}} = 23.5$ Hz), 112.20 (d, C-3', $J_{\text{C-F}} = 19.8$ Hz), 112.10 (s, C-1'), 41.81 (t, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 22.60 (t, $\text{NHCH}_2\text{CH}_2\text{CH}_3$), 11.36 (q, $\text{NHCH}_2\text{CH}_2\text{CH}_3$); HRESI-MS m/z 375.0686 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{17}\text{H}_{15}\text{ClF}_2\text{N}_2\text{O}_2\text{Na}$ 375.0688).

4.43. *N*-Butyl-4-chloro-2-(2-fluorobenzamido)benzamide (61)

Yield (35%) from **11** and 2-fluorobenzoyl chloride; EI-MS (m/z , %): 348 $[\text{M}]^+$ (12), 278 (27), 276 (80), 180 (37), 124 (100); ^1H NMR (CDCl_3) δ 11.76 (1H, br, NH), 8.75 (1H, d, $J = 2.4$ Hz, H-3), 8.00 (1H, td, $J = 7.6$, 1.6 Hz, H-6'), 7.51 (1H, m, H-4'), 7.37 (1H, d, $J = 8.4$ Hz, H-6), 7.27 (1H, td, $J = 7.6$, 1.2 Hz, H-5'), 7.18 (1H, ddd, $J = 10.2$, 8.4, 1.2 Hz, H-3'), 6.97 (1H, dd, $J = 8.4$, 2.4 Hz, H-5), 6.57 (1H, br, NHC_4H_9), 3.43 (2H, q, $J = 6.8$ Hz, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.61 (2H, m,

NHCH₂CH₂CH₂CH₃), 1.40 (2H, m, NHCH₂CH₂CH₂CH₃), 0.94 (3H, t, $J = 7.2$ Hz, NHCH₂CH₂CH₂CH₃); ¹³C NMR (CDCl₃) δ 167.96 (s, CONHC₄H₉), 162.44 (s, CONH), 160.29 (s, C-2', $J_{C-F} = 250.1$ Hz), 139.70 (s, C-2), 138.02 (s, C-4), 133.66 (d, C-4', $J_{C-F} = 9.1$ Hz), 131.37 (d, C-6', $J_{C-F} = 1.5$ Hz), 127.69 (d, C-6), 124.66 (d, C-5', $J_{C-F} = 3.1$ Hz), 123.23 (d, C-5), 122.25 (s, C-1', $J_{C-F} = 12.1$ Hz), 122.06 (d, C-3), 120.35 (s, C-1), 116.57 (d, C-3', $J_{C-F} = 22.7$ Hz), 39.87 (t, NHCH₂CH₂CH₂CH₃), 31.36 (t, NHCH₂CH₂CH₂CH₃), 20.10 (t, NHCH₂CH₂CH₂CH₃), 13.71 (q, NHCH₂CH₂CH₂CH₃); HRESI-MS m/z 371.0935[M+Na]⁺ (calcd for C₁₈H₁₈ClFN₂O₂Na 371.0938).

4.44. N-Butyl-4-chloro-2-(2-chlorobenzamido)benzamide (62)

Yield (45%) from **11** and 2-chlorobenzoyl chloride; EI-MS (m/z , %): 364 [M]⁺ (10), 292 (48), 181 (36), 154 (25), 141 (48), 139 (100); ¹H NMR (CDCl₃) δ 11.67 (1H, br, NH), 8.78 (1H, d, $J = 2.0$ Hz, H-3), 7.60 (1H, dd, $J = 7.6, 2.0$ Hz, H-6'), 7.39 (4H, m, H-3' 4' 5' 6), 7.00 (1H, dd, $J = 8.4, 2.0$ Hz, H-5), 6.65 (1H, br, NHC₄H₉), 3.37 (2H, q, $J = 6.8$ Hz, NHCH₂CH₂CH₂CH₃), 1.57 (2H, m, NHCH₂CH₂CH₂CH₃), 1.37 (2H, m, NHCH₂CH₂CH₂CH₃), 0.92 (3H, t, $J = 7.2$ Hz, NHCH₂CH₂CH₂CH₃); ¹³C NMR (CDCl₃) δ 168.01 (s, CONHC₄H₉), 165.52 (s, CONH), 139.97 (C-2), 138.35 (C-4), 135.57 (C-1'), 131.55 (C-4'), 131.31 (C-2'), 130.65 (C-6), 129.11 (C-3'), 127.49 (C-6'), 127.15 (C-5'), 123.29 (C-5), 121.38 (C-3), 119.21 (C-1), 39.85 (t, NHCH₂CH₂CH₂CH₃), 31.30 (t, NHCH₂CH₂CH₂CH₃), 20.09 (t, NHCH₂CH₂CH₂CH₃), 13.69 (q, NHCH₂CH₂CH₂CH₃); HRESI-MS m/z 387.0642 [M+Na]⁺ (calcd for C₁₈H₁₈Cl₂N₂O₂Na 387.0643).

4.45. N-Butyl-4-chloro-2-(2,6-difluorobenzamido)benzamide (63)

Yield (28%) from **11** and 2,6-difluorobenzoyl chloride; EI-MS (m/z , %): 366 [M]⁺ (12), 296(30), 294(89), 182(38), 180(77), 142 (37), 141(100); ¹H NMR (CDCl₃) δ 11.76 (1H, br, NH), 8.78 (1H, d, $J = 2.0$ Hz, H-3), 7.40 (2H, m, H-4' 6), 7.04 (1H, dd, $J = 8.4, 2.0$ Hz, H-5), 6.98 (2H, m, H-5' 3'), 6.57 (1H, br, NHC₄H₉), 3.39 (2H, q, $J = 6.8$ Hz, NHCH₂CH₂CH₂CH₃), 1.58 (2H, m, NHCH₂CH₂CH₂CH₃), 1.38 (2H, m, NHCH₂CH₂CH₂CH₃), 0.93 (3H, t, $J = 7.2$ Hz, NHCH₂CH₂CH₂CH₃); ¹³C NMR (CDCl₃) δ 167.96 (s, CONHC₄H₉), 159.94 (s, C-2', $J_{C-F} = 251.6$ Hz), 159.88 (s, C-6', $J_{C-F} = 251.6$ Hz), 159.09 (s, CONH), 139.73 (s, C-2), 138.45 (s, C-4), 132.13 (d, C-4', $J_{C-F} = 10.2$ Hz), 127.59 (d, C-6), 123.54 (d, C-5), 121.55 (d, C-3), 119.09 (s, C-1), 112.24 (d, C-5', $J_{C-F} = 20.1$ Hz), 112.18 (d, C-3', $J_{C-F} = 20.1$ Hz), 112.08 (s, C-1'), 39.88 (t, NHCH₂CH₂CH₂CH₃), 31.28 (t, NHCH₂CH₂CH₂CH₃), 20.08 (t, NHCH₂CH₂CH₂CH₃), 13.68 (q, NHCH₂CH₂CH₂CH₃); HRESI-MS m/z 389.0843 [M+Na]⁺ (calcd for C₁₈H₁₇ClF₂N₂O₂Na 389.0844).

4.46. Preparation of washed human platelets

Human blood anti-coagulated with acid citrate dextrose (ACD) was obtained from healthy human volunteers who had not taken any drugs within the last two weeks. The platelet suspension was then prepared according to the washing procedure previously described.⁷ Platelets were finally suspended in Tyrode's solution containing Ca²⁺ (2 mM), glucose (11.1 mM) and bovine serum albumin (3.5 mg/ml) at a concentration of 3×10^8 platelets/ml.

4.47. Measurement of platelet aggregation⁶

Platelet aggregation was measured turbidimetrically with a light-transmission aggregometer (Chrono-Log Co., U.S.A.). The platelet suspension was incubated with dimethyl sulfoxide (DMSO, vehicle) or test compounds at 37 °C for 3 min under a stirring condition (1200 rpm) prior to the addition of the platelet aggregation inducers. The extent of platelet aggregation was measured as the maximal increase of light transmission within 5 min after the addition of inducers.

4.48. Measurement of the formation of TxB₂^{6,7}

Because TxA₂ is very unstable and rapidly converted to more stable metabolite TxB₂, we measured the latter instead of TxA₂. After the challenge of platelets with AA for 5 min, EDTA (2 mM) and indomethacin (50 μ M) were added. The platelet suspensions were centrifuged for 3 min at 13,000 rpm, the contents of TxB₂ in the supernatants were assayed using an enzyme immunoassay kit according to the procedure described by the manufacturer.

Acknowledgment

The investigation was supported by Research Grants to P.W. Hsieh from the National Science Council of the Republic of China (NSC94-2314-B-037-105) in Taiwan.

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