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Synthesis and anti-platelet evaluation of 2-benzoylaminobenzoate analogs

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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 B_2 formation at 1.0 μM. These 2-benzoylaminobenzoate analogs were therefore proposed as cyclooxygenase inhibitors.

1. Introduction

Arterial thromboembotic 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-benzoylamino-4-chlorobenzoic 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 ring[4] 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) B_2 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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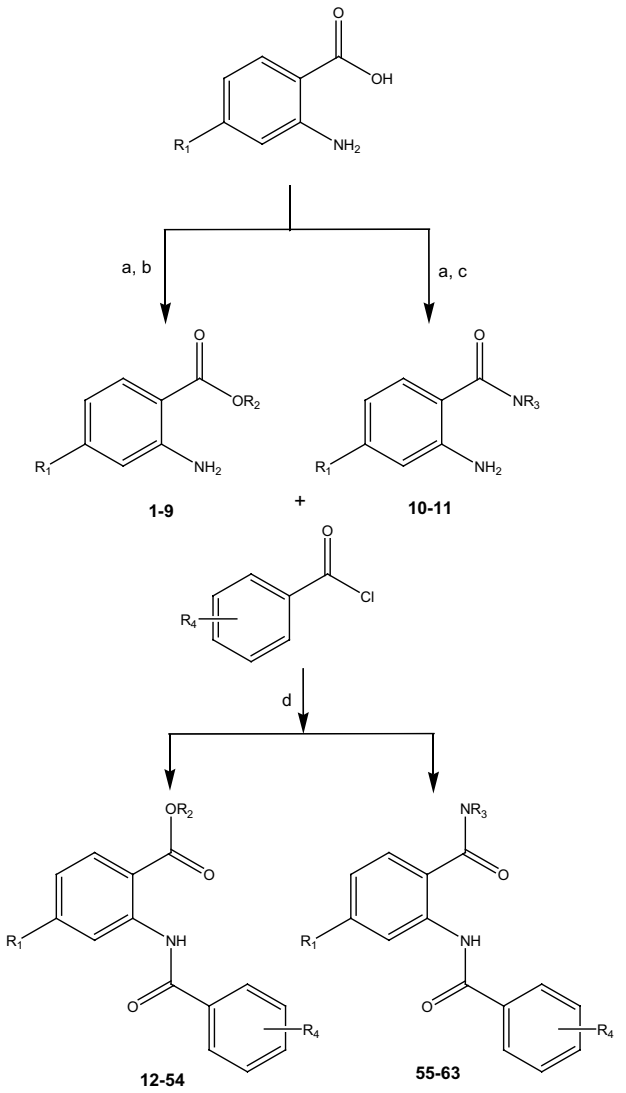


Scheme 1. The straightforward synthesis of 52 new 2-benzoylaminobenzoate analogs (**12**–**63**). Reagents: (a) SO_2Cl, DCM; (b) R_2OH; (c) R_3NH_2; (d) DCM.

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 effects 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.

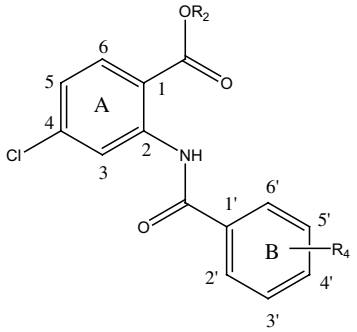
Anti-platelet aggregation assay data and SAR analysis confirmed that activity depended on the substituents on 2′- or 2′,6′-disubstitution in the B ring, the length of carbon chain of ester/amide at C-1, as well as the straight-chain and branched-chain of the ester/amide at C-1. Conversely, in our previous 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 isosteres[4] (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	*iso*-Propyl	2′-F	>100	>100	36.7 ± 0.6	>100
53	*iso*-Propyl	2′-Cl	82.2 ± 8.9	>100	8.51 ± 0.5	>100
54	*iso*-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 IC_{50} 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 C_5D_5N and $CDCl_3$ 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 $CDCl_3$ (^1H, δ 7.26; ^{13}C: 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.

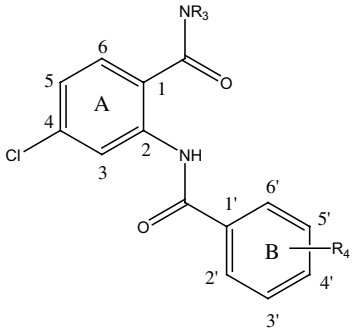
4.2. General procedure for the synthesis of compounds 1–11

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 $CHCl_3$/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 IC_{50} 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); ^{1}H NMR ($CDCl_3$) 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, $OCH_2CH_2CH_2CH_3$), 1.75 (2H, m, $OCH_2CH_2CH_2CH_3$), 1.47 (2H, m, $OCH_2CH_2CH_2CH_3$), 0.97 (3H, t, $J = 7.2$ Hz, $OCH_2CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 167.27 (s, *C*OOR), 162.37 (s, *C*ONH, $J_{C-F} = 2.3$ 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, $OCH_2CH_2CH_2CH_3$), 30.46 (t, $OCH_2CH_2CH_2CH_3$), 19.16 (t, $OCH_2CH_2CH_2CH_3$), 13.65 (q, $OCH_2CH_2CH_2CH_3$); HRESI-MS *m/z* 372.0777 $[M+Na]^+$ (calcd for $C_{18}H_{17}ClFNO_3Na$ 372.0779).

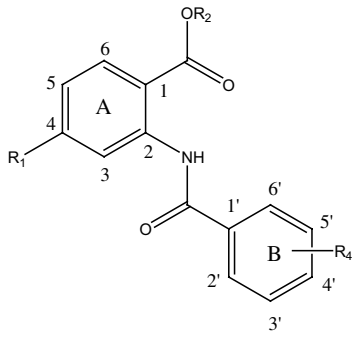
4.5. Butyl 4-chloro-2-(2-chlorobenzamido)benzoate (23)

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); ^{1}H NMR ($CDCl_3$) 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, $OCH_2CH_2CH_2CH_3$), 1.71 (2H, m, $OCH_2CH_2CH_2CH_3$), 1.42 (2H, m, $OCH_2CH_2CH_2CH_3$), 0.94 (3H, t, $J = 7.6$ Hz, $OCH_2CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 167.43 (s, *C*OOR), 165.35 (s, *C*ONH), 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, $OCH_2CH_2CH_2CH_3$), 30.34 (t, $OCH_2CH_2CH_2CH_3$), 19.07 (t, $OCH_2CH_2CH_2CH_3$), 13.57 (q, $OCH_2CH_2CH_2CH_3$); HRESI-MS *m/z* 388.0485 $[M+Na]^+$ (calcd for $C_{18}H_{17}Cl_2NO_3Na$ 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); ^{1}H NMR ($CDCl_3$) 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, $OCH_2CH_2CH_2CH_3$), 1.70 (2H, m, $OCH_2CH_2CH_2CH_3$), 1.42 (2H, m, $OCH_2CH_2CH_2CH_3$), 0.93 (3H, t, $J = 7.6$ Hz, $OCH_2CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 167.41(s, *C*OOR), 166.15 (s, *C*ONH), 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, OCH_2CH_2

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 IC_{50} 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 TxB_2 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 B_2 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.

CH_2CH_3), 30.31 (t, $OCH_2CH_2CH_2CH_3$), 19.05 (t, $OCH_2CH_2CH_2CH_3$), 13.56 (q, $OCH_2CH_2CH_2CH_3$); HRESI-MS *m/z* 431.9976 $[M+Na]^+$ (calcd for $C_{18}H_{17}BrClNO_3Na$ 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 ($CDCl_3$) 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, $OCH_2CH_2CH_2CH_3$), 2.56 (3H, s, CH_3), 1.72 (2H, m, $OCH_2CH_2CH_2CH_3$), 1.44 (2H, m, $OCH_2CH_2CH_2CH_3$), 0.96 (3H, t, $J = 7.6$ Hz, $OCH_2CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 168.11 (s, *C*OOR), 167.50 (s, *C*ONH), 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, $OCH_2CH_2CH_2CH_3$), 30.32 (t, $OCH_2CH_2CH_2CH_3$), 20.16 (q, CH_3), 19.05 (t, $OCH_2CH_2CH_2CH_3$), 13.54 (q, $OCH_2CH_2CH_2CH_3$); HRESI-MS *m/z* 368.1031 $[M+Na]^+$ (calcd for $C_{19}H_{20}ClNO_3Na$ 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); ^{1}H NMR ($CDCl_3$) 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, OCH_2CH$_2$ CH$_2$CH$_3$), 4.02 (3H, s, OCH_3), 1.73 (2H, m, OCH$_2$CH_2CH$_2$CH$_3$), 1.46 (2H, m, OCH$_2$CH$_2$CH_2CH$_3$), 0.97 (3H, t, J = 7.2 Hz, OCH$_2$CH$_2$CH$_2$CH_3); ^{13}C NMR ($CDCl_3$) δ 166.48 (s, *C*OOR), 164.45 (s, *C*ONH), 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, O*C*H$_2$CH$_2$CH$_2$CH$_3$), 55.27 (q, O*C*H$_3$), 30.47 (t, OCH$_2$*C*H$_2$CH$_2$CH$_3$), 19.11 (t, OCH$_2$CH$_2$*C*H$_2$CH$_3$), 13.59 (q, OCH$_2$CH$_2$CH$_2$*C*H$_3$); HRESI-MS *m*/*z* 384.0979 $[M+Na]^+$ (calcd for $C_{19}H_{20}ClNO_4Na$ 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); ^{1}H NMR ($CDCl_3$) 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, OCH_2CH$_2$CH$_3$), 1.79 (2H, m, OCH$_2$CH_2 CH$_3$), 1.02 (3H, t, J = 7.2 Hz, OCH$_2$CH$_2$CH_3); ^{13}C NMR ($CDCl_3$) δ 167.22 (s, *C*OOR), 166.01 (s, C-4, J_{C-F} = 250.9 Hz), 162.54 (s, *C*ONH), 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, O*C*H$_2$CH$_2$CH$_3$), 21.87 (t, OCH$_2$*C*H$_2$CH$_3$), 10.37 (q, OCH$_2$CH$_2$*C*H$_3$); HRESI-MS *m*/*z* 320.1097 $[M+H]^+$ (calcd for $C_{17}H_{16}F_2NO_3$ 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); ^{1}H NMR ($CDCl_3$) 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, OCH_2 CH$_2$CH$_3$), 1.78 (2H, m, OCH$_2$ CH_2CH$_3$), 1.01 (3H, t, J = 7.2 Hz, OCH$_2$ CH$_2$CH_3); ^{13}C NMR ($CDCl_3$) δ167.49 (s, *C*OOR), 166.60 (s, *C*ONH), 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, O*C*H$_2$CH$_2$CH$_3$), 21.84 (t, OCH$_2$*C*H$_2$CH$_3$), 10.36 (q, OCH$_2$CH$_2$*C*H$_3$); HRESI-MS *m*/*z* 336.0800 $[M+H]^+$ (calcd for $C_{17}H_{16}ClFNO_3$ 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); ^{1}H NMR ($CDCl_3$) 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, OCH_2CH$_2$CH$_3$), 1.77 (2H, m, OCH$_2$CH_2CH$_3$), 1.00 (3H, t, J = 7.2 Hz, OCH$_2$CH$_2$CH_3); ^{13}C NMR ($CDCl_3$) δ 167.49 (s, *C*OOR), 166.42 (s, *C*ONH), 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, O*C*H$_2$CH$_2$CH$_3$), 21.83 (t, OCH$_2$*C*H$_2$CH$_3$), 10.36 (q, OCH$_2$CH$_2$*C*H$_3$); HRESI-MS *m*/*z* 380.0297 $[M+H]^+$ (calcd for $C_{17}H_{16}BrFNO_3$ 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); ^{1}H NMR ($CDCl_3$) 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 (1 H, 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, OCH_2CH$_2$CH$_3$), 2.56 (3H, s, CH_3), 1.78 (2H, m, OCH$_2$CH_2CH$_3$), 1.02 (3H, t, J = 7.2 Hz, OCH$_2$CH$_2$CH_3); ^{13}C NMR ($CDCl_3$) δ 168.50 (s, *C*OOR), 167.65 (s, *C*ONH), 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, O*C*H$_2$CH$_2$CH$_3$), 21.89 (t, OCH$_2$*C*H$_2$ CH$_3$), 20.24 (q, *C*H$_3$), 10.42 (q, OCH$_2$CH$_2$*C*H$_3$); HRES-I-MS *m*/*z* 338.1168 $[M+Na]^+$ (calcd for $C_{18}H_{18}FNO_3Na$ 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); ^{1}H NMR ($CDCl_3$) 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, OCH_2CH$_2$CH$_3$), 4.06 (3H, s, OCH_3), 1.80 (2H, m, OCH$_2$CH_2CH$_3$), 1.04 (3H, t, J = 7.6 Hz, OCH$_2$CH$_2$CH_3); ^{13}C NMR ($CDCl_3$) δ 166.70 (s, *C*OOR), 165.89 (s, C-4, J_{C-F} = 250.1 Hz),

164.78 (s, *C*ONH), 157.54 (s, C-2′), 143.56 (s, C-2, J_{C-F} = 13.0 Hz), 133.34 (d, C-4′), 132.83 (d, C-6, J_{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_{C-F} = 3.1 Hz), 111.29 (d, C-3′), 109.60 (d, C-5, J_{C-F} = 21.9 Hz), 108.82 (d, C-3, J_{C-F} = 28.0 Hz), 66.57 (t, O*C*H$_2$CH$_2$CH$_3$), 55.43 (q, O*C*H$_3$), 21.98 (t, OCH$_2$*C*H$_2$CH$_3$), 10.53 (q, OCH$_2$CH$_2$ *C*H$_3$); HRESI-MS *m*/*z* 354.1120 [M+Na]$^+$ (calcd for $C_{18}H_{18}FNO_4Na$ 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 [M]$^+$ (6), 141(37), 139(100), 111(54); ^{1}H 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, OC*H*$_2$CH$_3$), 1.37 (3H, t, *J* = 6.8 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 167.73 (s, *C*OOR), 165.89 (s, *C*ONH), 166.46 (s, C-4, J_{C-F} = 251.9 Hz), 143.52 (s, C-2, J_{C-F} = 12.9 Hz), 136.04 (s, C-1′), 133.47 (d, C-6, J_{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_{C-F} = 2.6 Hz), 110.55 (d, C-5, J_{C-F} = 22.0 Hz), 108.02 (d, C-3, J_{C-F} = 28.4 Hz), 61.86 (t, O*C*H$_2$CH$_3$), 14.38 (q, OCH$_2$*C*H$_3$); HRESI-MS *m*/*z* 344.0464 [M+Na]$^+$ (calcd for $C_{16}H_{13}ClFNO_3Na$ 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 [M]$^+$ (10), 119(100), 118(23), 91(61); ^{1}H 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, OC*H*$_2$CH$_2$CH$_3$), 2.56 (3H, s, C*H*$_3$), 1.39 (3H, t, *J* = 7.2 Hz, OCH$_2$CH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 168.54 (s, *C*OOR), 167.62 (s, *C*ONH), 166.27 (s, C-4, J_{C-F} = 251.6 Hz), 143.87 (s, C-2,J_{C-F} = 12.9 Hz), 137.18 (s, C-2′), 135.92 (s, C-1′), 133.19 (d, C-6, J_{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_{C-F} = 3.0 Hz), 109.91 (d, C-5, J_{C-F} = 22.0 Hz), 107.47 (d, C-3, J_{C-F} = 28.0 Hz), 61.51 (t, O*C*H$_2$CH$_3$), 20.26 (q, *C*H$_3$), 14.15 (q, OCH$_2$*C*H$_3$); HRESI-MS *m*/*z* 324.1009 [M+Na]$^+$ (calcd for $C_{17}H_{16}FNO_3Na$ 324.1012).

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

Yield (46%) from **6** and 2-fluorobenzoyl chloride; EI-MS (*m*/*z*, %): 315 [M]$^+$ (33), 229(19), 228(92), 124(62), 123(100); ^{1}H 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, OC*H*$_2$CH$_2$CH$_3$), 2.43 (3H, s, C*H*$_3$), 1.79 (2H, m, OCH$_2$C*H*$_2$CH$_3$), 1.02 (3H, t, *J* = 7.2 Hz, OCH$_2$CH$_2$ C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 167.96 (s, *C*OOR), 162.37 (s, *C*ONH, J_{C-F} = 2.2 Hz), 160.25 (s, C-2′, J_{C-F} = 249.3 Hz), 145.46 (s, C-4), 141.01 (s, C-2), 133.36 (d, C-4′, J_{C-F} = 9.1 Hz), 131.51 (d, C-6′, J_{C-F} = 2.3 Hz), 130.76 (d, C-6), 124.62 (d, C-5′, J_{C-F} = 3.8 Hz), 123.94 (d, C-5), 122.83 (s, C-1′, J_{C-F} = 12.2 Hz), 121.57 (d, C-3), 116.42 (d, C-3′, J_{C-F} = 23.5 Hz), 113.65 (s, C-1), 66.70 (t, O*C*H$_2$CH$_2$CH$_3$), 22.08 (q, *C*H$_3$), 21.91 (t, OCH$_2$*C*H$_2$CH$_3$), 10.44 (q, OCH$_2$CH$_2$*C*H$_3$); HRESI-MS *m*/*z* 338.1169 [M+Na]$^+$ (calcd for $C_{18}H_{18}FNO_3Na$ 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) [M]$^+$, 244(24), 141(74), 139(100), 111(41); ^{1}H 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, OC*H*$_2$ CH$_2$CH$_3$), 2.45 (3H, s, C*H*$_3$), 1.77 (2H, m, OCH$_2$C*H*$_2$ CH$_3$), 1.01 (3H, t, *J* = 7.6 Hz, OCH$_2$CH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 168.26 (s, *C*OOR), 166.52 (s, *C*ONH), 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, O*C*H$_2$CH$_2$CH$_3$), 22.14 (q, *C*H$_3$), 21.91 (t, OCH$_2$*C*H$_2$CH$_3$), 10.45 (q, OCH$_2$ CH$_2$*C*H$_3$); HRESI-MS *m*/*z* 354.0871 [M+Na]$^+$ (calcd for $C_{18}H_{18}ClNO_3Na$ 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) [M]$^+$, 185(64), 183(64), 157(16), 155(16); ^{1}H 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, OC*H*$_2$CH$_2$CH$_3$), 2.45 (3H, s, C*H*$_3$), 1.77 (2H, m, OCH$_2$C*H*$_2$CH$_3$), 1.01 (3H, t, *J* = 7.2 Hz, OCH$_2$CH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 168.27 (s, *C*OOR), 166.35 (s, *C*ONH), 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, O*C*H$_2$CH$_2$CH$_3$), 21.12 (q, *C*H$_3$), 21.91 (t, OCH$_2$*C*H$_2$CH$_3$), 10.44 (q, OCH$_2$CH$_2$ *C*H$_3$); HRESI-MS *m*/*z* 398.0370 [M+Na]$^+$ (calcd for $C_{18}H_{18}BrNO_3Na$ 398.0368).

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

Yield (40%) from **6** and 2-methylbenzoyl chloride; EI-MS (*m*/*z*, %): 311 [M]$^+$ (9), 119(100), 118(46), 91(74); ^{1}H 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, $OCH_2CH_2CH_3$), 2.56 (3H, s, CH_3), 2.45 (3H, s, CH_3), 1.78 (2H, m, $OCH_2CH_2CH_3$), 1.01 (3H, t, J = 7.6 Hz, $OCH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 168.46 (s, *C*OOR), 168.33 (s, *C*ONH), 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, $OCH_2CH_2CH_3$), 22.13 (q, CH_3), 21.92 (t, $OCH_2CH_2CH_3$), 20.22 (q, CH_3), 10.45 (q, $OCH_2CH_2CH_3$); HRESI-MS m/z 334.1419 $[M+Na]^+$ (calcd for $C_{19}H_{21}NO_3Na$ 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 $[M]^+$ (7), 193(10), 135(100), 92(33); ^{1}H 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, $OCH_2CH_2CH_3$), 4.06 (3H, s, OCH_3), 2.43 (3H, s, CH_3), 1.79 (2H, m, $OCH_2CH_2CH_3$), 1.04 (3H, t, J = 7.2 Hz, $OCH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 167.46 (s, *C*OOR), 164.59 (s, *C*ONH), 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, $OCH_2CH_2CH_3$), 55.49 (q, OCH_3), 22.11 (q, CH_3), 22.03 (t, $OCH_2CH_2CH_3$), 10.56 (q, $OCH_2CH_2CH_3$); HRESI-MS m/z 350.1369 $[M+Na]^+$ (calcd for $C_{19}H_{21}NO_4Na$ 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) $[M]^+$, 259 (8), 135(16), 123(100), 95(68); ^{1}H 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, $OCH_2CH_2CH_3$), 1.84 (2H, m, $OCH_2CH_2CH_3$), 1.04 (3H, t, J = 7.2 Hz, $OCH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 166.43 (s, *C*OOR), 162.48 (s, *C*ONH, J_{C-F} = 2.3 Hz), 160.28 (s, C-2′, J_{C-F} = 248.6 Hz), 150.95 (s, C-4), 141.96 (s, C-2), 134.20 (d, C-4′, J_{C-F} = 9.1 Hz), 131.94 (d, C-6′, J_{C-F} = 2.3 Hz), 131.90 (d, C-6), 124.90 (d, C-5′, J_{C-F} = 3.8 Hz), 121.55 (s, C-1′, J_{C-F} = 11.4 Hz), 120.66 (s, C-1), 116.99 (d, C-5), 116.47 (d, C-3′, J_{C-F} = 23.5 Hz), 116.24 (d, C-3), 67.89 (t, $OCH_2CH_2CH_3$), 21.81 (t, $OCH_2CH_2CH_3$), 10.38 (q, $OCH_2CH_2CH_3$); HRESI-MS m/z 369.0861 $[M+Na]^+$ (calcd for $C_{17}H_{15}FN_2O_5Na$ 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) $[M]^+$, 275(14), 141(35), 139(100); ^{1}H 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, $OCH_2CH_2CH_3$), 1.82 (2H, m, $OCH_2CH_2CH_3$), 1.03 (3H, t, J = 7.6 Hz, $OCH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 166.74 (s, *C*OOR), 165.59 (s, *C*ONH), 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, $OCH_2CH_2CH_3$), 21.80 (t, $OCH_2CH_2CH_3$), 10.38 (q, $OCH_2CH_2CH_3$); HRESI-MS m/z 363.0746 $[M+H]^+$ (calcd for $C_{17}H_{16}ClN_2O_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 $[M]^+$ (7), 321(15), 319(15), 185(100), 184(92); ^{1}H 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, $OCH_2CH_2CH_3$), 1.82 (2H, m, $OCH_2CH_2CH_3$), 1.03 (3H, t, J = 7.6 Hz, $OCH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 166.77 (s, *C*OOR), 166.45 (s, *C*ONH), 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, $OCH_2CH_2CH_3$), 21.81 (t, $OCH_2CH_2CH_3$), 10.39 (q, $OCH_2CH_2CH_3$); HRESI-MS m/z 407.0244 $[M+H]^+$ (calcd for $C_{17}H_{16}BrN_2O_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 $[M]^+$ (5), 119(100), 118(88), 92(65); ^{1}H 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, $OCH_2CH_2CH_3$), 2.57 (3H, s, CH_3), 1.82 (2H, m, $OCH_2CH_2CH_3$), 1.04 (3H, t, J = 7.2 Hz, $OCH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 168.34(s, *C*OOR), 166.91 (s, *C*ONH), 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, $OCH_2CH_2CH_3$), 21.80 (t, $OCH_2CH_2CH_3$), 20.32 (q, CH_3), 10.38 (q, $OCH_2CH_2CH_3$); HRESI-MS m/z 365.1111 $[M+Na]^+$ (calcd for $C_{18}H_{18}N_2O_5Na$ 365.1113).

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

Yield (38%) from **7** and 2-methoxybenzoyl chloride; EI-MS (m/z, %): 358 $[M]^+$ (2), 224(72), 136(11), 135(100), 92(6); ^{1}H 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, $OCH_2CH_2CH_3$), 4.09 (3H, s, OCH_3), 1.84 (2H, m, $OCH_2CH_2CH_3$), 1.06 (3H, t, J = 7.2 Hz, $OCH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 165.95 (s, *C*OOR), 164.72 (s, *C*ONH), 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, $OCH_2CH_2CH_3$), 55.50 (q, OCH_3), 21.91 (t, $OCH_2CH_2CH_3$), 10.50 (q, $OCH_2CH_2CH_3$); HRESI-MS *m*/*z* 381.1061 $[M+Na]^+$ (calcd for $C_{18}H_{18}N_2O_6Na$ 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 $[M]^+$ (30), 266(18), 141(100), 113(52); ^{1}H 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, *C*OOR), 160.03 (s, C-2′, J_{C-F} = 251.6 Hz), 159.96 (s, C-6′, J_{C-F} = 252.3 Hz), 159.04 (s, *C*ONH), 141.74 (s, C-2), 141.18 (s, C-4), 132.30 (d, C-4′, J_{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_{C-F} = 20.4 Hz), 112.25 (d, C-3′, J_{C-F} = 20.4 Hz), 112.15 (s, C-1′), 52.62 (q, OCH_3); HRESI-MS *m*/*z* 348.0217 $[M+Na]^+$ (calcd for $C_{15}H_{10}ClF_2NO_3Na$ 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 $[M]^+$ (12), 266(33), 141(100), 114(24); ^{1}H 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, *C*OOR), 159.98 (s, C-2′, J_{C-F} = 251.6 Hz), 159.92 (s, C-6′, J_{C-F} = 251.6 Hz), 159.01 (s, *C*ONH), 141.70 (s, C-2), 140.96 (s, C-4), 132.24 (d, C-4′, J_{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_{C-F} = 20.4 Hz), 112.21 (d, C-3′, J_{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 $[M+H]^+$ (calcd for $C_{16}H_{13}ClF_2NO_3$ 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 $[M]^+$ (22), 268(24), 266(54), 142(100), 141(90); ^{1}H 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, $OCH_2CH_2CH_3$), 1.78 (2H, m, $OCH_2CH_2CH_3$), 1.01 (3H, t, J = 7.6 Hz, $OCH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 167.58 (s, *C*OOR), 159.98 (s, C-2′, J_{C-F} = 251.6 Hz), 159.92 (s, C-6′, J_{C-F} = 251.6 Hz), 159.01 (s, *C*ONH), 141.71 (s, C-2), 140.96 (s, C-4), 132.25 (d, C-4′, J_{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_{C-F} = 20.5 Hz), 112.21 (d, C-3′, J_{C-F} = 19.7 Hz), 112.11 (s, C-1′), 67.27 (t, $OCH_2CH_2CH_3$), 21.83 (t, $OCH_2CH_2CH_3$), 10.40 (q, $OCH_2CH_2CH_3$); HRESI-MS *m*/*z* 354.0709 $[M+H]^+$ (calcd for $C_{17}H_{15}ClF_2NO_3$ 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 $[M]^+$ (29), 266(24), 141(100), 113(31); ^{1}H 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, $OCH_2CH_2CH_2CH_3$), 1.74 (2H, m, $OCH_2CH_2CH_2CH_3$), 1.45 (2H, m, $OCH_2CH_2CH_2CH_3$), 0.97 (3H, t, J = 7.6 Hz, $OCH_2CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 167.59 (s, *C*OOR), 160.00 (s, C-2′, J_{C-F} = 251.6 Hz), 159.93 (s, C-6′, J_{C-F} = 251.6 Hz), 159.03 (s, *C*ONH), 141.72 (s, C-2), 140.97 (s, C-4), 132.25 (d, C-4′, J_{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_{C-F} = 19.7 Hz), 112.22 (d, C-3′, J_{C-F} = 20.5 Hz), 112.12 (s, C-1′), 65.61 (t, $OCH_2CH_2CH_2CH_3$), 30.45 (t, $OCH_2CH_2CH_2CH_3$), 19.17 (t, $OCH_2CH_2CH_2CH_3$), 13.67 (q, $OCH_2CH_2CH_2CH_3$); HRESI-MS *m*/*z* 368.0866 $[M+H]^+$ (calcd for $C_{18}H_{17}ClF_2NO_3$ 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 $[M]^+$ (12), 175(94), 173(100), 147(19), 145(28); ^{1}H 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, *C*OOR), 163.11 (s, *C*ONH), 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 $[M+H]^+$ (calcd for $C_{15}H_{11}Cl_3NO_3$ 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 $[M]^+$(15), 175(93), 173(100), 147(18), 145(26); ^{1}H 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, *C*OOR), 163.06 (s, *C*ONH), 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, O*C*H_2CH$_3$), 14.04 (q, OCH$_2$*C*H$_3$); HRESI-MS *m*/*z* 371.9962 $[M+H]^+$ (calcd for $C_{16}H_{13}Cl_3NO_3$ 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); ^{1}H NMR ($CDCl_3$) 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, OC*H*$_2$CH$_2$CH$_3$), 1.77 (2H, m, OCH$_2$C*H*$_2$CH$_3$), 1.00 (3H, t, *J* = 7.6 Hz, OCH$_2$CH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 167.57 (s, *C*OOR), 163.10 (s, *C*ONH), 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, O*C*H$_2$CH$_2$CH$_3$), 21.82 (t, OCH$_2$*C*H$_2$CH$_3$), 10.40 (q, OCH$_2$CH$_2$*C*H$_3$); HRESI-MS *m*/*z* 386.0119 $[M+H]^+$ (calcd for $C_{17}H_{15}Cl_3NO_3$ 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); ^{1}H NMR ($CDCl_3$) 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, OC*H*$_2$CH$_2$CH$_2$CH$_3$), 1.73 (2H, m, OCH$_2$C*H*$_2$CH$_2$CH$_3$), 1.44 (2H, m, OCH$_2$CH$_2$C*H*$_2$CH$_3$), 0.96 (3H, t, *J* = 7.2 Hz, OCH$_2$CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 167.55 (s, *C*OOR), 163.07 (s, *C*ONH), 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, O*C*H$_2$CH$_2$CH$_2$CH$_3$), 30.43 (t, OCH$_2$*C*H$_2$CH$_2$CH$_3$), 19.16 (t, OCH$_2$CH$_2$*C*H$_2$CH$_3$), 13.66 (q, OCH$_2$CH$_2$CH$_2$*C*H$_3$); HRESI-MS *m*/*z* 400.0276 $[M+H]^+$ (calcd for $C_{18}H_{17}Cl_3NO_3$ 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); ^{1}H NMR ($CDCl_3$) 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, OC*H*(CH$_3$)$_2$), 1.38 (6H, d, *J* = 6.0 Hz,OCH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$) δ 166.80 (s, *C*OOR), 162.48 (s, *C*ONH, 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, O*C*H(CH$_3$)$_2$), 21.83 (q, OCH(*C*H$_3$)$_2$); HRESI-MS *m*/*z* 358.0623$[M+Na]^+$ (calcd for $C_{17}H_{15}ClFNO_3Na$ 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); ^{1}H NMR ($CDCl_3$) 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, OC*H*(CH$_3$)$_2$), 1.35 (6H, d, *J* = 6.0 Hz,OCH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$) δ 167.01 (s, *C*OOR), 165.50 (s, *C*ONH), 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, O*C*H(CH$_3$)$_2$), 21.75 (q, OCH(*C*H$_3$)$_2$); HRESI-MS *m*/*z* 374.0329 $[M+Na]^+$ (calcd for $C_{17}H_{15}Cl_2NO_3Na$ 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); ^{1}H NMR ($CDCl_3$) 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, OC*H*(CH$_3$)$_2$), 1.36 (6H, d, *J* = 6.0 Hz,OCH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$) δ167.05 (s, *C*OOR), 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, *C*ONH), 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, O*C*H(CH$_3$)$_2$), 21.78 (q, OCH(*C*H$_3$)$_2$); HRESI-MS *m*/*z* 376.0531 $[M+Na]^+$ (calcd for $C_{17}H_{14}ClF_2NO_3Na$ 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); ^{1}H NMR ($CDCl_3$) 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, N*H*C$_3$H$_8$), 3.40 (2H, q, *J* = 6.8 Hz, NHC*H*$_2$CH$_2$CH$_3$), 1.65 (2H, m, NHCH$_2$C*H*$_2$CH$_3$), 0.99 (3H, t, *J* = 7.2 Hz, NHCH$_2$CH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 167.98 (s, *C*ONHC$_3$H$_8$), 162.43 (s, *C*ONH, 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_{C-F} = 23.5 Hz), 41.79 (t, NH*C*H_2CH$_2$CH$_3$), 22.65 (t, NHCH$_2$*C*H_2CH$_3$), 11.39 (q, NHCH$_2$CH$_2$*C*H$_3$); HRESI-MS *m/z* 357.0781 [M+Na]$^+$ (calcd for $C_{17}H_{16}ClFN_2O_2$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 [M]$^+$ (10), 294 (18), 292 (23), 141 (33), 139 (100); ^{1}H NMR (CDCl$_3$) δ 11.65 (1H, br, N*H*), 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, N*H*C$_3$H$_8$), 3.36 (2H, q, *J* = 6.4 Hz, NHC*H*$_2$CH$_2$CH$_3$), 1.63 (2H, m, NHCH$_2$C*H*$_2$CH$_3$), 0.97 (3H, t, *J* = 7.6 Hz, NHCH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$) δ 168.07 (s, *C*ONHC$_3$H$_8$), 165.49 (s, *C*ONH), 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, NH*C*H$_2$CH$_2$CH$_3$), 22.63 (t, NHCH$_2$*C*H$_2$CH$_3$), 11.38 (q, NHCH$_2$CH$_2$*C*H$_3$); HRESI-MS *m/z* 373.0487 [M+Na]$^+$ (calcd for $C_{17}H_{16}Cl_2N_2O_2$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 [M]$^+$ (11), 338 (25), 336 (20), 185 (96), 183 (100), 155 (24); ^{1}H 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, N*H*C$_3$H$_8$), 3.33 (2H, q, *J* = 6.4 Hz, NHC*H*$_2$CH$_2$CH$_3$), 1.61 (2H, m, NHCH$_2$C*H*$_2$CH$_3$), 0.95 (3H, t, *J* = 7.2 Hz, OCH$_2$ CH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$) δ 168.05 (s, *C*ONHC$_3$H$_8$), 166.36 (s, *C*ONH), 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, NH*C*H$_2$ CH$_2$CH$_3$), 22.56 (t, NHCH$_2$*C*H$_2$CH$_3$), 11.38 (q, NHCH$_2$CH$_2$*C*H$_3$); HRESI-MS *m/z* 416.9979 [M+Na]$^+$ (calcd for $C_{17}H_{16}BrClN_2O_2$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 [M]$^+$ (6), 271 (10), 119 (100), 91 (100); ^{1}H 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, N*H*C$_3$H$_8$), 3.34 (2H, q, *J* = 6.8 Hz, NHC*H*$_2$CH$_2$CH$_3$), 2.54 (3H, s, C*H*$_3$), 1.69 (2H, m, NHCH$_2$C*H*$_2$CH$_3$), 0.96 (3H, t, *J* = 7.6 Hz, NHCH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$) δ 168.43 (s, *C*ONHC$_3$H$_8$), 168.19 (s, *C*ONH), 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, NH*C*H$_2$CH$_2$CH$_3$), 22.59 (t, NHCH$_2$*C*H$_2$CH$_3$), 20.25 (q, *C*H$_3$), 11.38 (q, NHCH$_2$ CH$_2$*C*H$_3$); HRESI-MS *m/z* 353.1032 [M+Na]$^+$ (calcd for $C_{18}H_{19}ClN_2O_2$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 [M]$^+$ (2), 288(2), 135(100), 92(22); ^{1}H 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, N*H*C$_3$H$_8$), 4.09 (3H, s, OC*H*$_3$), 3.42 (2H, q, *J* = 6.4 Hz, NHC*H*$_2$CH$_2$CH$_3$), 1.69 (2H, m, NHCH$_2$C*H*$_2$CH$_3$), 1.02 (3H, t, *J* = 7.6 Hz, NHCH$_2$ CH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$) δ 168.02 (s, *C*ONHC$_3$H$_8$), 164.46 (s, *C*ONH), 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, O*C*H$_3$), 41.67 (t, NH*C*H$_2$CH$_2$CH$_3$), 22.78 (t, NHCH$_2$*C*H$_2$CH$_3$), 11.51 (q, NHCH$_2$CH$_2$*C*H$_3$); HRESI-MS *m/z* 369.0982[M+Na]$^+$ (calcd for $C_{18}H_{19}ClN_2O_3$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 [M]$^+$ (19), 294(60), 180(93), 142(52), 141(100); ^{1}H 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, N*H*C$_3$H$_8$), 3.36 (2H, q, *J* = 6.8 Hz, NHC*H*$_2$CH$_2$CH$_3$), 1.63 (2H, m, NHCH$_2$C*H*$_2$CH$_3$), 0.97 (3H, t, *J* = 7.2 Hz, NHCH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$) δ 168.02 (s, *C*ONHC$_3$H$_8$), 160.01 (s, C-2′, J_{C-F} = 251.6 Hz), 159.94 (s, C-6′, J_{C-F} = 251.6 Hz), 159.04 (s, *C*ONH), 139.90 (s, C-2), 138.64 (s, C-4), 132.09 (d, C-4′, J_{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_{C-F} = 23.5 Hz), 112.20 (d, C-3′, J_{C-F} = 19.8 Hz), 112.10 (s, C-1′), 41.81 (t, NH*C*H$_2$CH$_2$CH$_3$), 22.60 (t, NHCH$_2$*C*H$_2$ CH$_3$), 11.36 (q, NHCH$_2$CH$_2$*C*H$_3$); HRESI-MS *m/z* 375.0686 [M+Na]$^+$ (calcd for $C_{17}H_{15}ClF_2N_2O_2$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 [M]$^+$ (12), 278 (27), 276 (80), 180 (37), 123 (37), 124 (100); ^{1}H 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, N*H*C$_4$H$_9$), 3.43 (2H, q, *J* = 6.8 Hz, NH*C*H$_2$CH$_2$CH$_2$CH$_3$), 1.61 (2H, m,

$NHCH_2CH_2CH_2CH_3$), 1.40 (2H, m, $NHCH_2CH_2CH_2CH_3$), 0.94 (3H, t, J = 7.2 Hz, $NHCH_2CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 167.96 (s, $CONHC_4H_9$), 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, $NHCH_2CH_2CH_2CH_3$), 31.36 (t, $NHCH_2CH_2CH_2CH_3$), 20.10 (t, $NHCH_2CH_2CH_2CH_3$), 13.71 (q, $NHCH_2CH_2CH_2CH_3$); HRESI-MS m/z 371.0935[M+Na]$^+$ (calcd for $C_{18}H_{18}ClFN_2O_2Na$ 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 ($CDCl_3$) 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, NHC_4H_9), 3.37 (2H, q, J = 6.8 Hz, $NHCH_2CH_2CH_2CH_3$), 1.57 (2H, m, $NHCH_2CH_2CH_2CH_3$), 1.37 (2H, m, $NHCH_2CH_2CH_2CH_3$), 0.92 (3H, t, J = 7.2 Hz, $NHCH_2CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 168.01 (s, $CONHC_4H_9$), 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, $NHCH_2CH_2CH_2CH_3$), 31.30 (t, $NHCH_2CH_2CH_2CH_3$), 20.09 (t, $NHCH_2CH_2CH_2CH_3$), 13.69 (q, $NHCH_2CH_2CH_2CH_3$); HRESI-MS m/z 387.0642 [M+Na]$^+$ (calcd for $C_{18}H_{18}Cl_2N_2O_2Na$ 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 ($CDCl_3$) 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, NHC_4H_9), 3.39 (2H, q, J = 6.8 Hz, $NHCH_2CH_2CH_2CH_3$), 1.58 (2H, m, $NHCH_2CH_2CH_2CH_3$), 1.38 (2H, m, $NHCH_2CH_2CH_2CH_3$), 0.93 (3H, t, J = 7.2 Hz, $NHCH_2CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 167.96 (s, $CONHC_4H_9$), 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, $NHCH_2CH_2CH_2CH_3$), 31.28 (t, $NHCH_2CH_2CH_2CH_3$), 20.08 (t, $NHCH_2CH_2CH_2CH_3$), 13.68 (q, $NHCH_2CH_2CH_2CH_3$); HRESI-MS m/z 389.0843 [M+Na]$^+$ (calcd for $C_{18}H_{17}ClF_2N_2O_2Na$ 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 Ca^{2+} (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 aggregation[6]

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 TxB_2[6,7]

Because TxA_2 is very unstable and rapidly converted to more stable metabolite TxB_2, we measured the latter instead of TxA_2. After the challenge of platelets with AA for 5 min, EDTA (2 mM) and indomethacin (50 μM) were added. The platelet suspensions were centrifuged for 3 min at 13,000 rpm, the contents of TxB_2 in the supernatants were assayed using an enzyme immunoassay kit according to the procedure described by the manufacturer.

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