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Antiplatelet Activity of Benzylisoquinoline Derivatives Oxidized by Cerium(IV) Ammonium Nitrate

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Abstract—Oxidation of 1-benzyl-3,4-dihydroisoquinolines with cerium(IV) ammonium nitrate (CAN) under mild condition yielded the mixture of corresponding 1-benzylisoquinolines (b-type) and 1-benzoylisoquinolines (a- or c-type) in an equal yields. The selective oxidation products (c-type) can be prepared by using MeCN instead of MeOH. In the antiplatelet assays, four inducers were employed, including AA, Col, PAF, and Thr. In the PAF or Col induced platelet aggregation, compounds belonging to a- and b-type showed stronger inhibitory effects than aspirin.

Benzylisoquinolines showed variable biological activities, such as smooth muscle relaxant,[1] adreno-receptor antagonist,[2] antiplatelet[3] and vasorelaxing actions.[3] In our previous investigation of the antiplatelet agents, pyrrolo-benzylisoquinolines were synthesized and some of them exhibited selective antiplatelet activity.[4] Now we report, herein, the oxidation of 1-benzyl-3,4-dihydroisoquinolines (**1**–**9**) to the corresponding 1-benzoylisoquinolines (**1a**–**9a**), 1-benzylisoquinolines (**1b**–**9b**), and 1-benzoy-3,4-dihydrolisoquinolines (**1c**–**9c**) by cerium(IV) ammonium nitrate (CAN) (Scheme 1). The reaction mechanism, antiplatelet activity, and the structure–activity relationship of them are also revealed.

Chemistry

In previous reports, mostly Pd/C was used for the preparation of 1-benzyl-3,4-dihydroisoquinoline to 1-benzylisoquinoline[5] and chromium reagents or DDQ were used for the oxidation of 1-benzyl-3,4-dihydroisoquinoline to 1-benzoylisoquinolines.[6] However, in recent decades, CAN has received considerable attention as an catalyst for selective organic reactions,[7,8] especially for the regioselective oxidations to give the methoxylated products of methoxy-isochromans, methoxy-isochromanones and δ-oxoerythrinan derivatives at the benzylic position,[7] and the deprotection of dihydropyrans, cyclic ketals or acetals.[8] Thus, we start to study the oxidation of 1-benzyl-3,4-dihydroisoquinolines using CAN in mild conditions.

In a prototype experiment,[9] a methanolic solution of **1** was treated with CAN (4 equiv) for 12 h to afford **1a**, **1b**, and **1c** in almost equal yield. When other substituted 1-benzyl-3,4-dihydroisoquinolines (**2**–**9**) were treated with same condition, the same three types (a–c) of products were also obtained in the ca. equal yield. In entry 9, an α-hydroxylbenzylisoquinoline **9d** (13%) (Fig. 1) was isolated, while this type of oxidative products was not found in other entries.

Interestingly, the solvent contributes a strong effect on the ratio of three different types of products. In the prototype experiments (Table 1, entries 1–9), MeOH was used as solvent and three types of products were obtained at almost equal amounts. However, when MeCN replaced MeOH as the solvent (Table 1, entries 10–18), the composition of the oxidative products dramatically changed. 3,4-Dihydro-1-benzoylisoquinolines (**1c**–**9c**) were derived as major products, and 1-benzylisoquinolines (**1b**–**9b**) were totally absent in these entries. Therefore, solvent selection plays an important role in the yields of these derivatives. Interestingly, selective oxidation was also reported in a similar reaction with Pd/C.[5]

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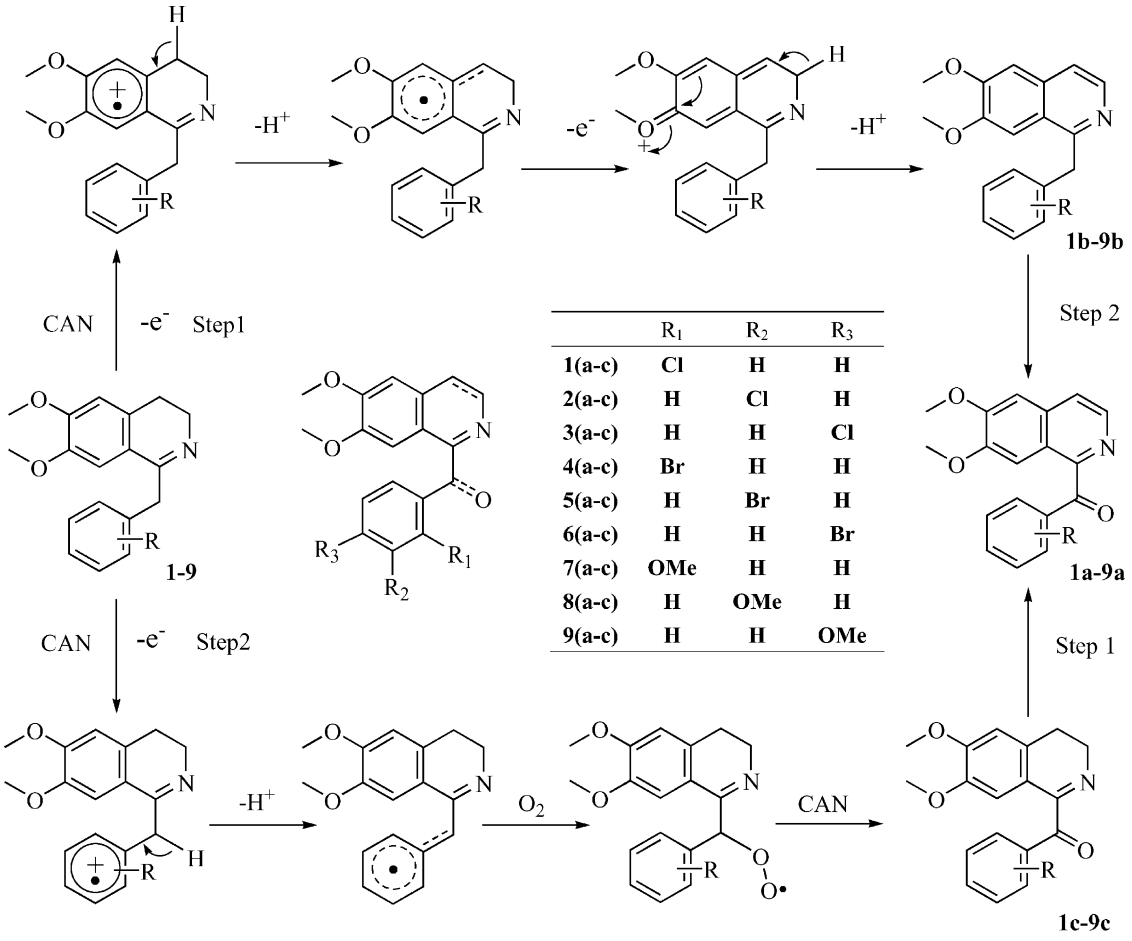

	R_1	R_2	R_3
1(a-c)	Cl	H	H
2(a-c)	H	Cl	H
3(a-c)	H	H	Cl
4(a-c)	Br	H	H
5(a-c)	H	Br	H
6(a-c)	H	H	Br
7(a-c)	OMe	H	H
8(a-c)	H	OMe	H
9(a-c)	H	H	OMe

Scheme 1. Hypothetic mechanism of cerium(IV) ammonium nitrate catalyzed oxidation of 1-benzyl-3,4-dihydroisoquinolines.

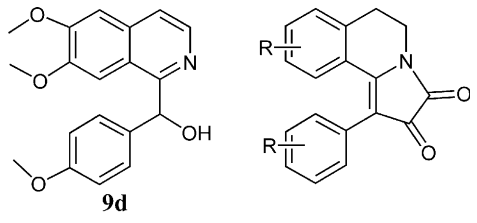

Figure 1. Structures of **9d** and pyrrolobenzylisoquinoline.

Although the mechanistic details of the reaction are not clear,[7] we have proposed a tentative mechanism to explain the product formation (Scheme 1). The main advantages of this methodology using CAN, a cheap, stable and easily available chemical, in MeCN for selective oxidizing on 3,4-dihydrobenzylisoquinolines are quite economical and tolerance to a wide range of functional groups. All the products were fully characterized by the spectral data (^{1}H NMR, UV, IR, and MS).[9]

Pharmacological Evaluation and Discussion

Our previous studies indicated that benzylisoquinoline possessed significant antiplatelet activity than cytotoxicity or adrenoceptor affinities.[4] Therefore, we focused on the antiplatelet aggregation activity of compounds **1a–9a**, **1b–9b**, **1c–9c** and **9d**. In the platelet aggregation assays, four inducers were employed, including AA (arachidonic acid), Col (collagen), PAF (platelet activating factor), and Thr (thrombin), and aspirin was screened as positive control. The results of the antiplatelet aggregatory

Table 1. The yields and material recovered percentage of entries 1–18[9]

Entry	Subtrate	Solvent	RP[a] (%)	Yield (%)[b]		
				a	b	c
1	**1**	MeOH	26	30	29	35
2	**2**	MeOH	21	30	32	36
3	**3**	MeOH	22	25	28	33
4	**4**	MeOH	25	22	24	30
5	**5**	MeOH	24	24	22	36
6	**6**	MeOH	23	25	24	30
7	**7**	MeOH	25	23	20	29
8	**8**	MeOH	23	28	21	35
9	**9**	MeOH	25	25	23	33
10	**1**	MeCN	3	12	<3	75
11	**2**	MeCN	11	10	<3	70
12	**3**	MeCN	10	12	<3	67
13	**4**	MeCN	5	10	<3	71
14	**5**	MeCN	4	8	<3	67
15	**6**	MeCN	15	15	<3	75
16	**7**	MeCN	20	10	<3	69
17	**8**	MeCN	25	12	<3	70
18	**9**	MeCN	18	13	<3	70

[a]RP: Recovery percentage of starting material.
[b]Yields were calculated base on the reacted material.

screening were presented in Table 2. While most compounds inhibited Col-induced platelet aggregation, all compounds were inactive toward Thr-induced aggregation. In comparison with the reference drug, aspirin and these tested compounds, compound **8a** showed an almost equal activity to the aggregation induced by AA and compounds **3b**, **8a** and **9b** demonstrated almost equal potency to the aggregation induced by Col. Compounds **1a**, **3a**, **5a**, **5c**, **8a** and **9a** showed stronger inhibition than aspirin toward the aggregation induced by PAF. In our knowledge, aspirin inhibits the activity of cycloxygenase and selectively blocks the AA- and Col-induced aggregation. Based on our results mentioned above, these benzylisoquinoline derivatives have a different inhibition pattern and mechanism of action from the aspirin in the antiplatelet aggregation.

Several structure–activity relationships were summarized from these results:

1. C-type derivatives obviously showed less activity than other two types of compounds in the AA induced aggregation, which suggested that the presence of double bond at C_3–C_4 position in the molecular is required for their activity.
2. Except for **5c**, all derivatives that inhibited PAF-induced aggregation were a-type. The specific relationship further indicates the importance of the benzylic ketone. In comparing with our published study,[4] the previously evaluated pyrrolo-benzylisoquinolines (Fig. 1) were more potent than the current compounds toward platelet aggregation induced by AA and Col. However, the new a-type compounds showed an additional inhibition to PAF-induced aggregation. Therefore, incorporation of the pyrrolo moiety increases the potency toward AA- and Col-induced aggregation but reduces the PAF-induced one. Such a structure relationship has not been studied before.
3. From the results mentioned above, substitutions on the benzyl ring with different groups did not improve their antiaggregatory effects. The type and oxidation states of these benzylisoquinolines contribute more than their substitution to the antiplatelet aggregatory activity.

Table 2. Antiplatelet aggregation activity of compounds **1a**–**9a**, **1b**–**9b**, and **1c**–**9c**[10]

	IC_{50} (μM)[a,b]			
	AA (100 μM)	Col (10 μg/mL)	Thr (0.1 U)	PAF (2 ng/mL)
Aspirin	**34.6±1.0**	**34.9±0.1**	>100 (81)[c]	>100 (2)
1a	77.1±8.6	52.1±2.9	>100 (30)	**82.0±1.9**
1b	>100 (34)	72.3±3.1	>100 (8)	>100 (13)
1c	>100 (27)	88.1±1.4	>100 (9)	>100 (20)
2a	>100 (35)	72.6±5.1	>100 (4)	>100 (47)
2b	90.2±2.1	73.6±3.8	>100 (18)	>100 (11)
2c	>100 (25)	>100 (35)	>100 (3)	>100 (32)
3a	>100 (11)	89.2±10.3	>100 (9)	**78.4±1.5**
3b	51.3±5.3	**32.7±0.3**	>100 (28)	>100 (26)
3c	>100 (48)	66.1±2.3	>100 (18)	>100 (22)
4a	>100 (49)	77.3±8.9	>100 (6)	>100 (25)
4b	>100 (46)	99.2±5.7	>100 (7)	>100 (8)
5a	>100 (35)	69.0±0.7	>100 (5)	**85.0±1.6**
5b	68.8±2.7	48.9±10.0	>100 (8)	>100 (23)
5c	>100 (23)	74.5±4.4	>100 (4)	**75.8±2.7**
6a	>100 (22)	>100 (36)	>100 (5)	>100 (44)
6b	94.0±3.2	55.6±7.5	>100 (11)	>100 (8)
6c	>100 (6)	>100 (20)	>100 (4)	>100 (10)
7a	>100 (50)	>100 (39)	>100 (1)	>100 (35)
7b	66.2±7.2	51.2±7.6	>100 (8)	>100 (20)
7c	>100 (21)	>100 (18)	>100 (8)	>100 (26)
8a	**37.7±1.5**	**39.1±3.1**	>100 (46)	**73.0±3.7**
8b	>100 (39)	>100 (46)	>100 (5)	>100 (12)
8c	>100 (48)	>100 (31)	>100 (14)	>100 (15)
9a	>100 (20)	97.0±20.7	>100 (4)	**64.7±2.9**
9b	59.2±5.0	**36.7±3.9**	>100 (26)	>100 (52)
9c	>100 (19)	87.0±15.0	>100 (10)	>100 (41)
9d	>100 (44)	58.9±2.4	>100 (9)	>100 (18)

[a]Platelet were preincubated with DMSO (0.5%, control), aspirin or tested compounds at 37 °C for 3 min, then four inducers was add.
[b]The IC_{50} values were presented as means±SE ($n=3$).
[c]Inhibition percentage was showed for compounds with IC_{50} higher than 100 μM.

In conclusion, a mild, efficient, and convenient methodology for the preparation of benzylisoquinoline derivatives with CAN was developed. By changing the solvent from MeOH to MeCN, 1-benzoyl-3,4-dihydroisoquinolines (**1c**–**9c**) were obtained predominantly over 1-benzoyl- (**1a**–**9a**) and 1-benzyl- (**1b**–**9b**) isoquinolines. In the further pharmacological studies, these compounds showed wide range of inhibitory effects on platelet aggregation induced by AA, Col, and PAF. Some of them showed equal or even better potency than the reference drug, aspirin. The mechanistic study of their pharmacological effect is an ongoing work, and these compounds merit further investigating as the drug leads in continuing studies.

Acknowledgements

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9. **General experimental procedure for the synthesis of compounds 1a–9a, 1b–9b, 1c–9c, and 9d.** Starting materials **1**–**9** were synthesized according to ref 4. To a methanolic solution of **1**–**9** (0.5 mmol) was added a solution of CAN (2 mmol, 1.096 g) in methanol and the reaction mixture was stirred overnight at room temperature, respectively (see Table 1). The reaction was quenched by addition of water (40 mL) and the diluted mixture was extracted with ethyl acetate (3×40 mL). The combined organic extracts were washed with water, brine and dried over sodium sulfate. The solvent was evaporated at reduced pressure. The residue was purified by column chromatography (Si-Gel) using EtOAc/hexane (1:2–1:1) mixture to afford the oxidation products. The ^{1}H spectrum was recorded at 200 MHz using $CDCl_3$ as solvent. **1a**: ^{1}H NMR: δ 8.42 (1H, d, J = 5.4 Hz, Ar–H), 8.25 (1H, s, Ar–H), 7.66 (1H, d, J = 5.4 Hz, Ar–H), 7.60 (1H, m, Ar–H), 7.40 (3H, m, Ar–H), 7.14 (1H, s, Ar–H), 4.07 and 4.06 (each 3H, s, 2×OMe); UV: 233, 266 (sh), 346 nm; IR (KBr): 1674, 1503, 1480, 1433, 1277, 1262, 1234, 1071, 1039 cm^{-1}; EI–MS m/z: [327]$^+$ **1b**: ^{1}H NMR: δ 8.37 (1H, d, J = 5.2 Hz, Ar–H), 7.46 (1H, s, Ar–H), 7.42 (1H, d, J = 5.2 Hz, Ar–H), 7.26 (1H, s, Ar–H), 7.12 (1H, m, Ar–H), 7.06 (3H, m, Ar–H), 4.71 (2H, s, Ar–CH_2), 3.99 and 3.90 (each 3H, s, 2×OMe); UV: 238, 313, 325 nm; IR (KBr): 1509, 1477, 1431, 1421, 1271, 1234, 1159 cm^{-1}; EI–MS m/z: [313]$^+$ **1c**: ^{1}H NMR: δ 7.69 (1H, d, J = 6.0 Hz, Ar–H), 7.43 (3H, m, Ar–H), 7.25 and 6.74 (each 1H, s, Ar–H), 3.94 and 3.80 (each 3H, s, 2×OMe), 3.85 (2H, t, J = 8.0, N–CH_2), 2.74 (2H, t, J = 8.0, Ar–CH_2); UV: 213, 235 (sh), 265 (sh), 327 nm; IR (KBr): 1678, 1603, 1566, 1511, 1464, 1276, 1148 cm^{-1}; EI–MS m/z: [329]$^+$ **2a**: ^{1}H NMR: δ 8.47 (1H, d, J = 4.4 Hz, Ar–H), 7.95 (1H, s, Ar–H), 7.85 (1H, d, J = 8.0 Hz, Ar–H), 7.71 (1H, s, Ar–H), 7.68 (1H, d, J = 4.4 Hz, Ar–H), 7.57 (1H, dd, J = 2.8, 8.0 Hz, Ar–H), 7.42 (1H, t, J = 8.0 Hz, Ar–H), 7.16 (1H, s, Ar–H), 4.07 and 4.00 (each 3H, s, 2×OMe); UV: 237, 256 (sh), 334 nm; IR (KBr): 1666, 1619, 1565, 1504, 1433, 1264, 1158, 1052 cm^{-1}; EI–MS m/z: [327]$^+$ **2b**: ^{1}H NMR: δ 8.37 and 7.45 (each 1H, d, J = 6.0 Hz, Ar–H), 7.16–7.26 (5H, m, Ar–H), 7.07 (1H, s, Ar–H), 4.57 (2H, s, Ar–CH_2), 4.01 and 3.90 (each 3H, 2×OMe); UV: 239, 312, 326 nm; IR: 1567, 1508, 1477, 1431, 1419, 1272, 1233, 1159 cm^{-1}; EI–MS m/z: [313]$^+$ **2c**: ^{1}H NMR: δ 8.03 (1H, brs, Ar–H), 7.94 (1H, d, J = 7.4 Hz, Ar–H), 7.60 (1H, brd, J = 7.4 Hz, Ar–H), 7.45 (1H, t, J = 7.4 Hz, Ar–H), 6.98 and 6.77 (each 1H, s, Ar–H), 3.95 (2H, t, J = 7.7 Hz, N–CH_2), 3.95 and 3.82 (each 3H, 2×OMe), 2.83 (2H, t, J = 7.7 Hz, Ar–CH_2); UV: 213, 232 (sh), 257, 311 (sh) nm; IR: EI–MS m/z: [329]$^+$ **3a**: δ 8.45 (1H, d, J = 5.2 Hz, Ar–H), 7.92 (2H, d, J = 8.8 Hz, Ar–H), 7.69 (1H, s, Ar–H), 7.67 (1H, d, J = 5.2 Hz, Ar–H), 7.45 (2H, d, J = 8.8 Hz, Ar–H), 7.14 (1H, s, Ar–H), 4.05 and 3.98 (each 3H, 2×OMe); UV: 237, 266 (sh), 330 nm; IR (KBr): 1664, 1585, 1504, 1480, 1266, 1232, 1158 cm^{-1}; EI–MS m/z: [327]$^+$ **3b**: δ 8.36 (1H, d, J = 5.6 Hz, Ar–H), 7.44 (1H, d, J = 5.6 Hz, Ar–H), 7.22 (4H, m, Ar–H), 7.05 (1H, s, Ar–H), 4.55 (2H, s, Ar–CH_2), 4.00 and 3.89 (each 3H, s, 2×OMe); UV: 239, 313, 326 nm; IR (KBr): 1508, 1489, 1478, 1421, 1270, 1233, 1158 cm^{-1}; EI–MS m/z: [313]$^+$ **3c**: δ 7.98 (2H, d, J = 8.0 Hz, Ar–H), 7.45 (2H, d, J = 8.0 Hz, Ar–H), 6.96 and 6.75 (each 1H, s, Ar–H), 3.99 and 3.80 (each 3H, s, 2×OMe), 3.89 (2H, t, J = 7.4 Hz, N–CH_2), 2.80 (2H, t, J = 7.4 Hz, Ar–CH_2); UV: 239, 266, 325 nm; IR (KBr): 1671, 1585, 1567, 1510, 1274, 1143 cm^{-1}; EI–MS m/z: [329]$^+$ **4a**: ^{1}H NMR: δ 8.42 (1H, d, J = 5.2 Hz, Ar–H), 8.30 (1H, s, Ar–H), 7.67 (1H, d, J = 5.2 Hz, Ar–H), 7.60 (2H, m, Ar–H), 7.45 (1H, td, J = 7.2, 1.4 Hz, Ar–H), 7.36 (1H, td, J = 7.2, 2.2 Hz, Ar–H), 4.08 and 4.07 (each 3H, s, 2×OMe); UV: 232, 266 (sh), 347 nm; IR (KBr): 1674, 1503, 1481, 1433, 1276, 1633, 1159, 1065 cm^{-1}; EI–MS m/z: [372]$^+$ **4b**: ^{1}H NMR: δ 8.37 (1H, d, J = 5.8 Hz, Ar–H), 7.60 (1H, d, J = 7.4 Hz, Ar–H), 7.45 (1H, d, J = 5.8 Hz, Ar–H), 7.23 (1H, s, Ar–H), 7.06 (4H, m, Ar–H), 4.72 (2H, s, Ar–CH_2), 4.00 and 3.91 (each 3H, s, 2×OMe); UV: 239, 312, 326 nm; IR (KBr): 1567, 1508, 1476, 1420, 1272, 1233, 1159, 1025 cm^{-1}; EI–MS m/z: [358]$^+$ **4c**: δ 7.62 (2H, m, Ar–H), 7.41 (2H, m, Ar–H), 7.32 and 6.73 (each 1H, s, Ar–H), 3.94 and 3.89 (each 3H, s, 2×OMe), 3.84 (2H, t, J = 7.6 Hz, N–CH_2), 2.74 (2H, t, J = 7.6 Hz, Ar–CH_2); UV: 232, 266 (sh), 237 nm; IR (KBr): 1674, 1503, 1481, 1433, 1276, 1633, 1159, 1065 cm^{-1}; EI–MS m/z: [374]$^+$ **5a**: ^{1}H NMR: δ 8.47 (1H, d, J = 5.8 Hz, Ar–H), 8.10 (1H, t, J = 1.8 Hz, Ar–H), 7.89 (1H, brd, J = 7.6 Hz, Ar–H), 7.71 (3H, m, Ar–H), 7.36 (1H, t, J = 7.6 Hz, Ar–H), 7.15 (1H, s, Ar–H), 4.07 and 4.00 (each 3H, 2×OMe); UV: 237, 258 (sh), 331 nm; IR (KBr): 1664, 1561, 1503, 1479, 1370, 1263, 1232, 1157 cm^{-1}; EI–MS m/z: [372]$^+$ **5b**: ^{1}H NMR: δ 8.35 (1H, d, J = 5.2 Hz, Ar–H), 7.44 (2H, m, Ar–H), 7.21 (4H, m, Ar–H), 7.05 (1H, s, Ar–H), 4.57 (1H, s, Ar–CH_2), 3.99 and 3.89 (each 3H, 2×OMe); UV: 236, 314, 326 nm; IR (KBr): 1566, 1509, 1477, 1430, 1420, 1272, 1159 cm^{-1}; EI–MS m/z: [358]$^+$ **5c**: ^{1}H NMR: δ 8.17 (1H, d, J = 1.8 Hz, Ar–H), 7.96 (1H, dd, J = 7.2, 1.8 Hz, Ar–H) 7.72 (1H, dd, J = 7.2, 1.8 Hz, Ar–H), 7.36 (1H, t, J = 7.2 Hz, Ar–H), 6.96 and 6.76 (each 1H, s, Ar–H), 3.94 and 3.80 (each 3H, s, 2×OMe), 3.93 (2H, t, J = 7.8 Hz, N–CH_2), 2.82 (2H, t, J = 7.8 Hz, Ar–CH_2); UV: 216, 255 (sh), 277 (sh), 322 nm; IR (KBr): 1674, 1565, 1515, 1271, 1143 cm^{-1}; EI–MS m/z: [374]$^+$ **6a**: ^{1}H NMR: δ 8.45 (1H, d, J = 5.2 Hz, Ar–H), 7.84 (2H, d, J = 8.2 Hz, Ar–H), 7.70 (1H, s, Ar–H), 7.67 (1H, d, J = 5.2 Hz, Ar–H), 7.64 (2H, d, J = 8.2 Hz, Ar–H), 7.14 (1H, s, Ar–H), 4.06 and 3.39 (each 3H, s, 2×OMe); UV: 237, 267, 328 nm; IR (KBr): 1665, 1504, 1479, 1265, 1233, 1158 cm^{-1}; EI–MS m/z: [372]$^+$ **6b**: ^{1}H NMR: δ 8.36 and 7.42 (each 1H, d, J = 5.2 Hz, Ar–H), 7.37 (2H, d, J = 8.8 Hz, Ar–H), 7.22 (1H, s, Ar–H) 7.13 37 (2H, d, J = 8.8 Hz, Ar–H), 7.06(1H, s, Ar–H), 4.54 (2H, s, Ar–CH_2), 4.00 and 3.89 (each 3H, 2×OMe); UV: 239, 270, 312, 326 nm; IR (KBr): 1509, 1479, 1431, 1422, 1273, 1234, 1159 cm^{-1}; EI–MS m/z: [358]$^+$ **6c**: ^{1}H NMR: δ 7.90 and 7.62 (each 2H, d, J = 8.8 Hz, Ar–H), 6.95 and 6.75 (each 1H, s, Ar–H), 3.93 and 3.80 (each 3H, s, 2×OMe), 3.88 (2H, t, J = 7.2 Hz, N–CH_2), 2.80 (2H, t, J = 7.2 Hz, Ar–CH_2); UV: 215, 271, 328 nm; IR (KBr): 1672, 1584, 1567, 1515, 1276, 1143 cm^{-1}; EI–MS m/z: [374]$^+$ **7a**: ^{1}H NMR: δ 8.37 (1H, d, J = 5.4 Hz, Ar–H), 7.91 (1H, s, Ar–H), 7.71 (1H, dd, J = 7.4, 2.0 Hz, Ar–H), 7.60 (1H d, J = 5.4 Hz, Ar–H), 7.52 (1H, td, J = 8.0, 2.0 Hz), 7.12 (1H, s Ar–H), 7.08 (1H, t, J = 7.4 Hz, Ar–H), 6.95 (1H, d, J = 8.0 Hz, Ar–H), 4.06, 4.00 and 3.50 (each 3H, s, 3×OMe); UV: 235, 266, 327 nm; IR (KBr): 1663, 1597, 1503, 1480, 1434, 1233, 1158, 1040 cm^{-1}; EI–MS m/z: [323]$^+$ **7b**: ^{1}H NMR: δ 8.35 (1H, d, J = 5.6 Hz, Ar–H), 7.45 (1H, s, Ar–H), 7.40 (1H, d, J = 5.6 Hz, Ar–H), 7.15 (1H, t, J = 8.0 Hz, Ar–H), 7.10 (1H, t, J = 7.4 Hz, Ar–H), 7.02 (1H, d, J = 8.0 Hz, Ar–H), 6.79 (1H, td, J = 7.4, 1.2 Hz, Ar–H), 4.59 (2H, s, Ar–CH_2), 3.98, 3.92 and 3.89 (each 3H, s, 3×OMe); UV: 238, 279, 312, 325 nm; IR (KBr): 1566, 1508, 1240, 1202, 1160, 1028 cm^{-1}; EI–MS m/z: [309]$^+$ **7c**: ^{1}H NMR: δ 7.81 (1H, dd, J = 7.4, 1.6 Hz, Ar–H), 7.51 (1H, td, J = 8.0, 1.6 Hz), 7.06 (1H, t, Ar–H, J = 8.0 Hz), 7.01 (1H, s, Ar–H), 6.92 (1H, d, J = 8.0 Hz, Ar–H), 6.74 (1H, s, Ar–H), 3.93, 3.76, and 3.66 (each 3H, s, 3×OMe) 3.76 (2H, t, J = 5.6 Hz, N–CH_2)d 2.73 (2H, t, J = 5.6 Hz, Ar–CH_2); UV: 219, 259, 316 nm; IR (KBr): 1666, 1597, 1513, 1463, 1281, 1246, 1146, 1039, 1020 cm^{-1}; EI–MS m/z: [325]$^+$ **8a**: ^{1}H NMR: δ 8.47 and 7.67 (each 1H, d, J = 5.4 Hz, Ar–H), 7.61 (1H, s, Ar–H), 7.55 and 7.44 (each 1H, m, Ar–H), 7.36 (1H, t, J = 8.2 Hz, Ar–H), 7.15 (1H, m, Ar–H) 7.14 (1H, s, Ar–H), 4.06, 3.97, and 3.86 (each 3H, s, 3×OMe); UV: 235, 267, 317 nm; IR (KBr): 1661, 1501, 1479, 1431, 1263, 1232, 1148, 1039 cm^{-1}; EI–MS m/z: [323]$^+$ **8b**: ^{1}H NMR: δ 8.37 and 7.47 (each 1H, d, J = 6.0 Hz, Ar–H), 7.33 (1H, s, Ar–H), 7.22 (1H, t, J = 8.0 Hz, Ar–H), 7.07 (1H, s, Ar–H), 6.89 (1H, d, J = 7.8 Hz, Ar–H), 6.83 (1H, brs, Ar–H), 6.72 (1H, dd, J = 7.8, 1.8 Hz, Ar–H), 4.62 (2H, s, Ar–CH_2), 4.01, 3.89, and

3,72 (each 3H, s, 3×OMe); UV: 234, 270, 313 (sh), 325 nm; IR (KBr): 1598, 1508, 1478, 1270, 1232, 1160, 1047 cm^{-1}; EI–MS *m*/*z*: $[309]^+$ **8c**: ^1H NMR: δ 7.56 (2H, m, Ar–H), 7.36 (1H, t, $J = 8.2$ Hz, Ar–H), 7.14 (1H, ddd, $J = 8.2$, 2.6, 2.0 Hz, Ar–H), 6.92 and 6.75 (each 1H, s, Ar–H), 3.93, 3.88, and 3.78 (each 3H s, 3×OMe), 3.91 (2H, t, $J = 7.4$ Hz, N–CH_2); and 2.81 (2H, t, $J = 7.4$ Hz, Ar–CH_2); UV: 221, 268, 321 nm; IR (KBr): 1672, 1602, 1514, 1463, 1320, 1277, 1137, 1040 cm^{-1}; EI–MS *m*/*z*: $[325]^+$ **9a**: ^1H NMR: δ 8.45 (1H, d, $J = 5.8$ Hz, Ar–H), 7.96 (2H, d, $J = 7.4$ Hz, Ar–H), 7.64 (1H, d, $J = 5.8$ Hz, Ar–H), 7.57 and 7.13 (each 1H, s, Ar–H), 6.96 (2H, d, $J = 7.4$ Hz, Ar–H), 4.05, 3.96, and 3.89 (each 3H, s, 3×OMe); UV: 236, 292, 329 (sh); IR: 1658, 1597, 1505, 1479, 1263, 1232, 1156 cm^{-1}; EI–MS *m*/*z*: $[323]^+$ **9b**: ^1H NMR: δ 8.36 and 7.42 (each 1H, d, $J = 5.8$ Hz, Ar–H), 7.31 and 7.04 (each 1H, s, Ar–H), 7.19 and 6.79 (each 2H, d, $J = 8.0$ Hz, Ar–H), 4.53 (2H, s, Ar–CH_2), 4.00, 3.90 and 3.74 (each 3H, s, 3×OMe); UV: 238, 278, 312, 326 nm; IR (KBr): 1509, 1478, 1269, 1237, 1159 cm^{-1}; EI–MS *m*/*z*: $[309]^+$ **9c**: ^1H NMR: δ 8.02 and 6.94 (each 2H, d, $J = 8.0$ Hz, Ar–H), 6.92 and 6.74 (each 1H, s, Ar–H), 3.92, 3.86 and 3.77 (each 3H, s, 3×OMe), 3.91 (2H, t, $J = 7.6$ Hz, N–CH_2), 2.80 (2H, t, $J = 7.6$ Hz, Ar–CH_2); UV: 209 (sh), 226, 290 nm; IR (KBr): 1661, 1598, 1571, 1511, 1463, 1142 cm^{-1}; EI–MS *m*/*z*: $[325]^+$.

10. **Antiplatelet aggregation assays**: see: Chen, K. S.; Ko, F. N.; Teng, C. M.; Wu, Y. C. *Planta Med.* **1996**, *62*, 133.