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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and biological evaluation of novel laropiprant derivatives as potential anti-allergic agents

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Abstract DP antagonists are claimed to be useful in the treatment of allergic disorders. Laropiprant is a potent and selective DP antagonist to reduce the allergic disorders, especially niacin-induced flushing. In our study, a series of novel laropiprant derivatives **(I-1–I-18)** were synthesized and characterized by IR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectrum. The potency of these compounds was evaluated in a murine model of niacin-induced flushing. The results indicated that most compounds exhibited faster-acting effect of suppressing vasodilation than laropiprant. Among them, **I-1**, **I-2**, **I-3**, **I-9**, **I-13**, **I-15** and **I-16** exhibited substantial flushing inhibitory effect. Especially, **I-1** and **I-2** showed higher potency than laropiprant and would be valuable for further investigation.

Keywords Anti-allergic agents · Laropiprant derivatives · Synthesis · Flushing · Biological evaluation

Introduction

Prostaglandin (PG) D_2 is the major cyclooxygenase metabolite of arachidonic acid produced by mast cells in response to allergen in diseases, such as asthma, atopic dermatitis, allergic rhinitis and allergic conjunctivitis (Kabashima and Narumiya, 2003; Matsuoka *et al.*, 2000; Maicas *et al.*, 2012; Van Hecken *et al.*, 2007). Recent studies have shown PGD_2 binds to two types of specific receptor. One is DP (the PGD receptor) and the other is CRTH2 (chemoattractant receptor-homologous molecule expressed on Th2) (Pettipher *et al.*, 2007). The DP receptor has already been cloned (Boie *et al.*, 1995; Hirata *et al.*, 1994; Wright *et al.*, 1999). Since then, its ligand-binding property has been well characterized, and novel specific antagonists have been or are being developed. Laropiprant, discovered by Merck & Co., is a potent and selective DP antagonist to treat allergic disorders (Fig. 1) (Ballantyne *et al.*, 2012; Maccubbin *et al.*, 2012; McKenney *et al.*, 2010; Sturino *et al.*, 2007). It was formerly used in combination with niacin to treat dyslipidemia. Niacin induces flushing through dermal Langerhans cells where the activation of G protein-coupled receptor 109A (GPR109A) increases arachidonic acid and PGD_2. PGD_2 acts as a vasodilator via DP receptor, increasing blood flow and thus leading to flushes (Cheng *et al.*, 2006; Maciejewski-Lenoir *et al.*, 2006). Laropiprant acts as a DP antagonist, reducing the vasodilation. In order to find new active DP antagonists, several compounds (**I-1–I-18**) were synthesized and the bioactivity was evaluated in a murine model of niacin-induced flushing (Perry, 2009; Sanyal *et al.*, 2010).

Results and discussion

Chemistry

We selected laropiprant as the leading compound and replaced the acetate acid moiety with an aromatic acid group. Besides, several substituents were introduced on the benzyl group. In order to improve the solubility, title compounds (**I-1–I-18**) were converted into a form of sodium

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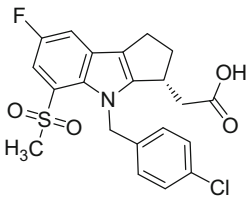
Fig. 1 The structure of laropiprant



salts (Fig. 2). The structures of title compounds are outlined in Table 1. All the synthesized compounds are racemic mixtures; the resolution process and further biological evaluation are being studied and will be reported in future.

The synthesis route for the title compounds (**I-1**–**I-18**) is outlined in Scheme 1 (the structures of the intermediates are outlined in Table 2). Firstly, the ketone **3** was synthesized by performing a Fischer indole reaction with 2-bromo-4-fluoroaniline **(1)** and 2-oxocyclopentane-1-carbaldehyde **(2)**. Secondly, **3** was treated with sodium hydroxide (NaOH) followed by corresponding substituted benzyl chloride to cleanly generate **4A**–**4I**. And then **4A**–**4I** were reduced by sodium borohydride ($NaBH_4$) to afford **5A**–**5I** (**4A**–**4I** and **5A**–**5I** were used without further purification). Secondly, **5A**–**5I** were treated with methyl 4-hydroxybenzoate at 0 °C by Mitsunobu reaction to give **6A**–**6I** (methyl 2-(4-hydroxyphenyl) acetate was also used to afford corresponding **6J**–**6R**). And **6A**–**6R** were further treated with methanesulfinic acid sodium salt (CH_3SO_2Na) and copper (I) iodide (CuI) to afford **7A**–**7R**. Finally, **7A**–**7R** were directly hydrolyzed to sodium salts as title compounds **I-1**–**I-18**.

Pharmacology

The potency of the title compounds was evaluated by suppression of niacin-induced vasodilation assay. A murine model was used, and blood flow velocity in the mouse ear (a measure of vasodilation, a prominent component of

Fig. 2 Design of title compounds (**I-1**–**I-18**)

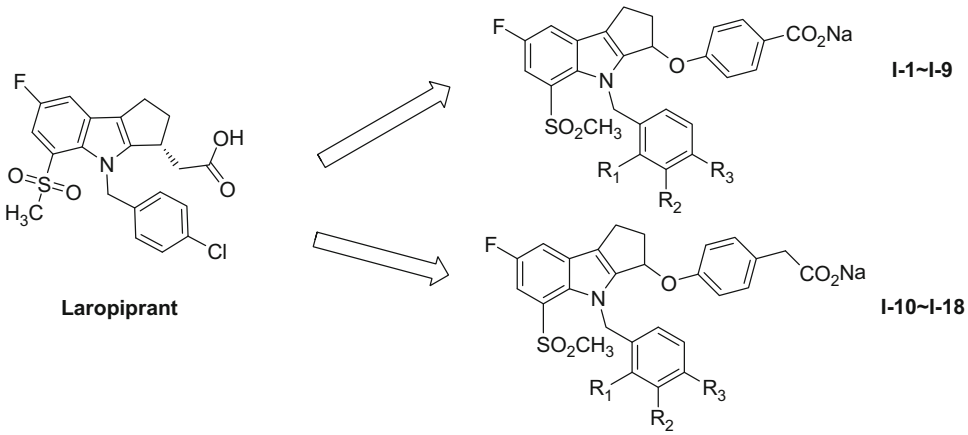
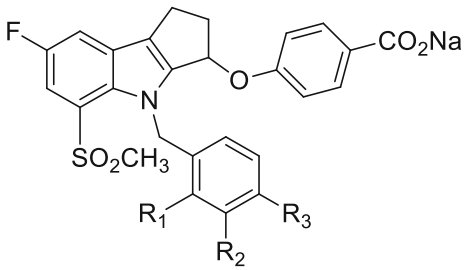
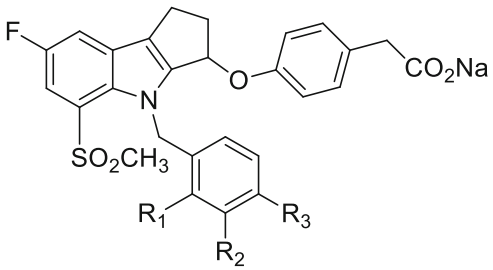
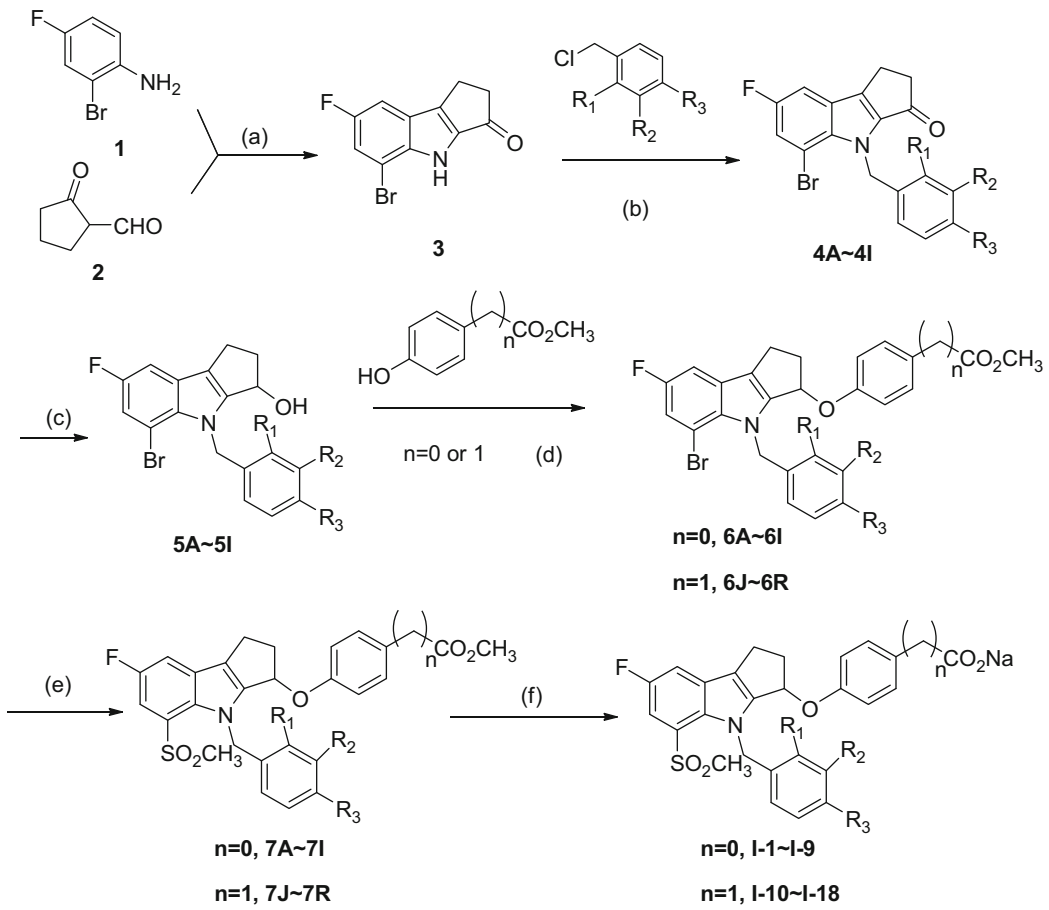


Table 1 The structure of title compounds (**I-1**–**I-18**)





Compound	I-1, I-10	I-2, I-11	I-3, I-12	I-4, I-13	I-5, I-14	I-6, I-15	I-7, I-16	I-8, I-17	I-9, I-18
R_1	H	H	Cl	H	H	F	H	H	Cl
R_2	H	H	H	Cl	H	H	F	H	H
R_3	Cl	H	H	H	F	H	H	OCH_3	Cl



Scheme 1 The synthesis route of title compound **I-1–I-18.** (*a*) (i) Sodium nitrite, hydrochloric acid, 0 °C; (ii) sodium acetate, MeOH, 0 °C; (iii) 3M sulfuric acid, acetonitrile, reflux; (*b*) NaOH, tetrabutylammonium bromide, THF, H_2O, reflux; (*c*) $NaBH_4$, CH_2Cl_2, MeOH, r.t.; (*d*) diethyl diazodicarboxylate, tributylphosphane, THF, 0 °C; (*e*) CH_3SO_2Na, CuI, NMP, 130 °C; (*f*) NaOH, THF, MeOH, H_2O, r.t.

Table 2 The substituents of the intermediates

Intermediate								
4A	**4B**	**4C**	**4D**	**4E**	**4F**	**4G**	**4H**	**4I**
5A	**5B**	**5C**	**5D**	**5E**	**5F**	**5G**	**5H**	**5I**
6A	**6B**	**6C**	**6D**	**6E**	**6F**	**6G**	**6H**	**6I**
6J	**6K**	**6L**	**6M**	**6N**	**6O**	**6P**	**6Q**	**6R**
7A	**7B**	**7C**	**7D**	**7E**	**7F**	**7G**	**7H**	**7I**
7J	**7K**	**7L**	**7M**	**7N**	**7O**	**7P**	**7Q**	**7R**
R_1								
H	H	Cl	H	H	F	H	H	Cl
R_2								
H	H	H	Cl	H	H	F	H	H
R_3								
Cl	H	H	H	F	H	H	OCH_3	Cl

flushing) was measured after administration of niacin to mice that had been pretreated with vehicle (as a control), laropiprant or the test compounds **I-1–I-18**.

As was shown in Tables 3 and 4, most of the test compounds were found to exhibit good inhibitive activity against niacin-induced vasodilation (the percentage of

Table 3 Suppression of niacin-induced vasodilation assay of the compounds (effect on blood flow velocity in the mouse ear)[a]

Group	Initial velocity (μm/s)	Velocity after administration of niacin[b] (μm/s)				
		2 min	4 min	6 min	8 min	10 min
Control[c]	684 ± 34	867 ± 190	943 ± 177	1071 ± 195	1149 ± 205	1172 ± 230
Positive[d]	589 ± 88	724 ± 112	744 ± 134	715 ± 130	688 ± 147	672 ± 122
I-1	709 ± 92	795 ± 55	859 ± 45	902 ± 70	855 ± 85	811 ± 77
I-2	677 ± 77	746 ± 64	788 ± 68	839 ± 46	834 ± 71	765 ± 46
I-3	699 ± 53	749 ± 39	836 ± 37	866 ± 68	849 ± 55	803 ± 46
I-4	691 ± 53	782 ± 46	853 ± 25	930 ± 23	883 ± 34	840 ± 52
I-5	614 ± 41	673 ± 76	715 ± 68	753 ± 72	753 ± 47	741 ± 74
I-6	635 ± 56	729 ± 55	803 ± 52	847 ± 46	813 ± 45	769 ± 34
I-7	667 ± 35	770 ± 50	837 ± 40	920 ± 66	954 ± 84	915 ± 641
I-8	649 ± 38	749 ± 34	847 ± 28	935 ± 53	897 ± 60	823 ± 32
I-9	685 ± 53	765 ± 65	830 ± 33	906 ± 44	880 ± 22	823 ± 46
I-10	633 ± 63	776 ± 26	829 ± 22	898 ± 20	896 ± 58	835 ± 342
I-11	606 ± 47	734 ± 39	786 ± 30	857 ± 40	906 ± 54	934 ± 52
I-12	689 ± 61	803 ± 22	916 ± 27	1000 ± 42	939 ± 25	908 ± 23
I-13	612 ± 59	663 ± 60	685 ± 66	707 ± 61	711 ± 50	689 ± 49
I-14	691 ± 48	769 ± 17	841 ± 22	926 ± 24	905 ± 36	845 ± 14
I-15	629 ± 33	736 ± 45	773 ± 76	779 ± 94	749 ± 72	726 ± 72
I-16	733 ± 70	847 ± 52	895 ± 81	950 ± 65	956 ± 50	880 ± 66
I-17	703 ± 24	812 ± 49	895 ± 54	1031 ± 92	1186 ± 83	1053 ± 518
I-18	683 ± 20	655 ± 15	800 ± 43	844 ± 41	889 ± 23	829 ± 23

[a] Number of animals in each group $n = 6$; laropiprant and test compounds were injected at the dose of 10 mg/kg; niacin was injected at the dose of 100 mg/kg

[b] The blood flow velocity was measured every 2 min, and the results were expressed as mean ± SEM

[c] Mice in control group were pretreated with vehicle before administration of niacin

[d] Mice in positive/control group were pretreated with laropiprant before administration of niacin

inhibition of 12 compounds >30 % at 10 min). Among them, compounds **I-1**, **I-2**, **I-3**, **I-9**, **I-13**, **I-15** and **I-16** exhibited substantial effect against vasodilation. Especially, **I-1** and **I-2** showed higher potency than laropiprant (the inhibition (%) of **I-1** and **I-2** totally exceeded the positive from 2 to 10 min) and would be valuable for further investigation. The biological studies also revealed that compounds with benzoic acid group (**I-1**–**I-9**) mostly exhibited better inhibitive effect than compounds with phenyl acetic acid group (**I-10**–**I-18**). We found that **I-1**–**I-9** had better solubility than **I-10**–**I-18** and attributed it to the stronger acidity of the benzoic acid group. Besides, it was observed that the inhibition (%) of all the test compounds exceeded laropiprant at 2 min (most of the compounds exceeded laropiprant at 4 min). It indicated that the test compounds showed faster-acting inhibitory effect against niacin-induced flushing than laropiprant. To illustrate this, the pharmacokinetic profiles of the test compounds (especially **I-1** and **I-2**) have been studied and the results will be reported in due course.

Experimental section

Chemistry

General information

Melting points (uncorrected) were determined on an XT-5 microscopic melting point spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on an ACF* 300Q or ACF* 500Q Bruker spectrometer in $CDCl_3$, DMSO-d_6 or CD_3OD, with Me_4Si as the internal reference. The IR spectra were recorded in film or in potassium bromide disks on a Perkin-Elmer 398 spectrometer. High-resolution mass spectra (HRMS) were recorded in electron impact mode. The procedure for synthesis of **I-1** was described as an example as follows (**I-2**–**I-18** were prepared similarly):

5-Bromo-7-fluoro-1, 2-dihydrocyclopenta[b]indol-3(4H)-one (3) Firstly, a diazonium salt of 2-bromo-4-fluoroaniline was prepared as follows: To a mixture of **1**

Table 4 Percentage of inhibition of niacin-induced vasodilation

Group	Inhibition (%)				
	2 min	4 min	6 min	8 min	10 min
Control	–	–	–	–	–
Laropiprant	3.15	8.63	22.78	31.36	34.10
I-1	13.71	15.69	23.99	36.12	36.40
I-2	15.52	19.31	25.61	34.04	36.58
I-3	14.38	13.40	23.23	33.08	33.57
I-4	13.31	14.42	19.99	32.40	32.50
I-5	13.87	16.24	22.49	27.38	30.38
I-6	12.12	12.48	20.71	32.35	32.76
I-7	11.73	13.32	18.34	24.71	24.19
I-8	11.76	9.80	14.68	27.06	29.69
I-9	14.47	16.13	21.46	32.07	33.18
I-10	5.55	8.87	15.39	25.18	26.66
I-11	4.04	6.16	10.21	11.36	10.72
I-12	10.61	7.55	13.47	27.72	26.60
I-13	14.63	19.46	26.74	30.99	34.72
I-14	14.79	15.74	20.38	30.89	32.16
I-15	7.72	11.70	21.75	29.60	33.35
I-16	11.22	14.80	22.47	30.95	33.15
I-17	11.81	12.25	13.25	11.18	17.23
I-18	15.84	19.10	26.80	31.46	32.83

(6.00 g, 0.032 mol) in 4N hydrochloric acid (30 mL), a solution of sodium nitrite (2.42 g, 0.035 mol) in water (10 mL) was added dropwise at 0 °C and was aged for another hour. Secondly, a mixture of 2-oxocyclopentane-1-carbaldehyde (**2**) (3.58 g, 0.032 mol) and sodium acetate (5.25 g, 0.064 mol) in methanol (30 mL) was added slowly at 0 °C. Upon complete addition, the mixture was aged for 2 h. The resulting precipitate was filtered and dissolved in acetonitrile (50 mL). After addition of 3 M sulfuric acid (35 mL), the mixture was refluxed for 6 h under N_2 atmosphere. Acetonitrile was removed by concentration, and the resulting precipitate was filtered and dried to give 5.60 g of **3** as a brown solid. Yield: 65.3 %. mp 202–204 °C; 1H NMR (DMSO-d6, 300 MHz,): $\delta = 7.58$–7.64 (2H, m, H-6, H-8), 3.00–3.02 (2H, m, CH_2), 2.91–2.93 (2H, m, CH_2); 13C NMR (CDCl3, 300 MHz,): $\delta = 194.0$ (C=O), 158.4 (C-7), 155.2 (C-4a), 146.2 (C-3a), 140.0 (C-8a), 138.5 (C-8b), 118.2 (C-8), 117.8 (C-6), 105.2 (C-5), 40.4 (C-2), 19.6 (C-1); EIMS *m/z* 290.0, 292.0 $[M + Na]^+$.

*General procedure for the synthesis of intermediates **6A**–**6R** (**6A** as an example)*

Firstly, to a solution of NaOH (1.30 g, 0.033 mol) in water (15 mL) and THF (30 mL) were added **3** (1.88 g, 0.007 mol), 4-chlorobenzyl chloride (1.13 g, 0.007 mol) and tetrabutylammonium bromide (0.05 g), and the mixture was stirred and refluxed for 6 h. After concentration, the residual precipitate was filtered and dried to give **4A** as a brown solid. Secondly, **5A** was prepared by reduction of **4A** using sodium borohydride (0.53 g, 0.014 mol) in methanol (15 mL) cleanly. Thirdly, **6A** was prepared from **5A** by Mitsunobu reaction. **5A** (crude but dried) and methyl 4-hydroxybenzoate (1.06 g, 0.007 mol), anhydrous THF (20 mL) and tributylphosphane (3.5 mL, 0.014 mol) were added to a 50-mL three-necked flask subsequently. A solution of diethyl diazodicarboxylate (2.2 mL, 0.014 mol) in THF (10 mL) was added dropwise at 0 °C to the mixture that was predegassed by N_2 gas. It was stirred at 0 °C for 3 h, concentrated and purified by flash chromatography to give 2.65 g of **6A** as a white solid. Yield in 3 steps: 71.7 %.

*Methyl 4-((5-bromo-4-(4-chlorobenzyl)-7-fluoro-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) benzoate (**6A**)* White solid. mp 116–118 °C; 1H NMR (CDCl3, 300 MHz,): $\delta = 7.94$–7.98 (2H, m, H-6; H-8), 7.16–7.21 (4H, m, H-3″, benzyl; H-5″; H-2″; H-6″), 6.83–6.87 (2H, m, H-2′, methyl benzoate; H-6′), 6.77–6.79 (2H, m, H-3′; H-5′), 5.88 (1H, d, $J = 17.0$ Hz, Ar$\underline{CH_2}$), 5.65 (1H, m, O$\underline{CH}$), 5.53 (1H, d, $J = 17.0$ Hz, Ar$\underline{CH_2}$), 3.89 (3H, s, $CO_2\underline{CH_3}$), 3.02–3.09 (2H, m, CH_2), 2.84–2.89 (1H, m, $\underline{CH_2}$), 2.53–2.56 (1H, m, $\underline{CH_2}$); 13C NMR (CDCl3, 300 MHz,): $\delta = 160.6$ (C=O, CO_2CH_3), 159.6 (C-7), 144.8 (C-1′, methyl benzoate), 138.2 (C-4a), 137.5 (C-3a), 137.0 (C-1″, benzyl), 133.8 (C-8a), 132.5 (C-4″), 131.4 (C-2″), 128.2 (C-6″), 126.9 (C-3″), 126.8 (C-5″), 122.5 (C-3′), 121.1 (C-5′), 115.9 (C-4′), 115.5 (C-2′), 115.2 (C-6′), 114.7 (C-6), 114.4 (C-8), 104.2 (C-8b), 103.9 (C-5), 103.6 (C-3), 54.4 (CH_3, CO_2CH_3), 51.5 (CH_2, benzyl), 35.7 (C-2), 22.2 (C-1); EIMS *m/z* 552.1 $[M + Na]^+$.

*Methyl 4-((4-benzyl-5-bromo-7-fluoro-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) benzoate (**6B**)* White solid. mp 160–164 °C; 1H NMR (CDCl3, 300 MHz,): $\delta = 7.95$ (2H, m, H-6; H-8), 7.22–7.25 (4H, m, H-3″, benzyl; H-5″; H-2″; H-6″), 6.65–7.01 (5H, m, H-4″; H-2′, methyl benzoate; H-6′; H-3′; H-5′), 6.01 (1H, d, $J = 16.7$ Hz, Ar$\underline{CH_2}$), 5.63 (1H, s, OCH), 5.50 (1H, d, $J = 16.4$ Hz, Ar$\underline{CH_2}$), 3.89 (3H, s, CO_2CH_3), 3.02 (2H, m, CH_2), 2.85–2.88 (1H, m, CH_2), 2.17 (1H, m, CH_2).

*Methyl 4-((5-bromo-4-(2-chlorobenzyl)-7-fluoro-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) benzoate (**6C**)* White solid. mp 161–163 °C; 1H NMR (CDCl3, 300 MHz,): $\delta = 7.92$–7.95 (2H, m, H-6; H-8), 7.31–7.39 (2H, m, H-3″, benzyl; H-5″), 7.06–7.21 (3H, m, H-4″; H-2′, methyl benzoate; H-6′), 6.66–6.72 (2H, m, H-3′, H-5′), 6.41 (1H, d, $J = 7.6$ Hz, H-6″), 5.71–5.76 (2H, m, $ArCH_2$), 5.69 (1H, s, OCH), 3.88 (3H, s, CO_2CH_3),

3.02–3.12 (2H, m, CH_2), 2.87–2.92 (1H, m, CH_2), 2.55–2.59 (1H, m, CH_2).

*Methyl 4-((5-bromo-4-(3-chlorobenzyl)-7-fluoro-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) benzoate (**6D**)* White solid. mp 162–166 °C; 1H NMR (CDCl3, 300 MHz,): δ = 7.94–7.98 (2H, m, H-6; H-8), 7.12–7.25 (3H, m, H-2″, benzyl; H-4″; H-6″), 6.85–6.95 (1H, m, H-5″), 6.72–6.79 (3H, m, H-2′, methyl benzoate; H-6′; H-3′), 6.58–6.62 (1H, m, H-5′), 5.88 (1H, dd, J = 9.8 and 17.1 Hz, Ar$\underline{CH_2}$), 5.68 (1H, d, J = 2.7 Hz, OCH), 5.55 (1H, d, J = 17.1 Hz, Ar$\underline{CH_2}$), 3.88 (3H, s, CO_2CH_3), 3.03–3.10 (2H, m, CH_2), 2.81–2.87 (1H, m, CH_2), 2.50–2.59 (1H, m, CH_2).

*Methyl 4-((5-bromo-7-fluoro-4-(4-fluorobenzyl)-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) benzoate (**6E**)* White solid. mp 124–126 °C; 1H NMR (CDCl3, 300 MHz,): δ = 7.94–7.98 (2H, m, H-6; H-8), 7.17 (2H, d, J = 8.6 Hz, H-2″, benzyl; H-6″), 6.85–6.90 (4H, m, H-3″; H-5″; H-2′, methyl benzoate; H-6′), 6.78 (2H, d, J = 8.9 Hz, H-3′; H-5′), 5.91 (1H, d, J = 16.7 Hz, Ar$\underline{CH_2}$), 5.64 (1H, d, J = 6.5 Hz, OCH), 5.51 (1H, d, J = 16.7 Hz, Ar$\underline{CH_2}$), 3.89 (3H, s, CO_2CH_3), 2.99–3.09 (2H, m, CH_2), 2.83–2.88 (1H, m, CH_2), 2.50–2.57 (1H, m, CH_2).

*Methyl 4-((5-bromo-7-fluoro-4-(2-fluorobenzyl)-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) benzoate (**6F**)* White solid. mp 154–156 °C; 1H NMR (CDCl3, 300 MHz,): δ = 7.95 (2H, d, J = 9.0 Hz, H-6; H-8), 7.34–7.37 (1H, m, H-3″, benzyl), 7.16–7.23 (3H, m, H-4″; H-5″; H-6″), 7.09–7.14 (1H, m, H-2′, methyl benzoate), 6.73 (2H, d, J = 9.0 Hz, H-3′; H-5′), 6.41–6.44 (1H, m, H-6′), 5.78 (2H, d, J = 1.8 Hz, $ArCH_2$), 5.71–5.73 (1H, m, OCH), 3.90 (3H, s, CO_2CH_3), 3.07–3.14 (2H, m, CH_2), 2.87–2.94 (1H, m, CH_2), 2.54–2.64 (1H, m, CH_2).

*Methyl 4-((5-bromo-7-fluoro-4-(3-fluorobenzyl)-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) benzoate (**6G**)* White solid. mp 158–160 °C; 1H NMR (CDCl3, 300 MHz,): δ = 7.96 (2H, d, J = 8.8 Hz, H-6; H-8), 7.16–7.20 (3H, m, H-2″, benzyl; H-4″; H-5″), 6.88–6.93 (1H, m, H-6″), 6.78 (1H, d, J = 8.8 Hz, H-2′, methyl benzoate), 6.70 (1H, d, J = 7.5 Hz, H-6′), 6.60 (2H, d, J = 9.6 Hz, H-3′; H-5′), 5.90 (1H, d, J = 17.1 Hz, Ar$\underline{CH_2}$), 5.67 (1H, d, J = 4.7 Hz, OCH), 5.56 (1H, d, J = 17.1 Hz, Ar$\underline{CH_2}$), 3.88 (3H, s, CO_2CH_3), 2.99–3.06 (2H, m, CH_2), 2.81–2.89 (1H, m, CH_2), 2.50–2.57 (1H, m, CH_2).

*Methyl 4-((5-bromo-7-fluoro-4-(4-methoxybenzyl)-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) benzoate (**6H**)* White solid. mp 168–172 °C; 1H NMR (CDCl3, 300 MHz,): δ = 7.96–8.02 (2H, m, H-6; H-8), 7.14–7.20 (2H, m, H-2″, benzyl; H-6″), 6.80–6.91 (4H, m, H-3″; H-5″; H-2′, methyl benzoate; H-6′), 6.75 (2H, d, J = 8.7 Hz, H-3′; H-5′), 5.99 (1H, d, J = 16.5 Hz, Ar$\underline{CH_2}$), 5.61 (1H, d, J = 6.5 Hz, OCH), 5.40 (1H, d, J = 16.5 Hz, Ar$\underline{CH_2}$), 3.89 (3H, s, OCH_3), 3.75 (3H, s, CO_2CH_3), 2.95–3.08 (2H, m, CH_2), 2.80–2.87 (1H, m, CH_2), 2.48–2.56 (1H, m, CH_2).

*Methyl 4-((5-bromo-4-(2,4-dichlorobenzyl)-7-fluoro-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) benzoate (**6I**)* White solid. mp 180–182 °C; 1H NMR (CDCl3, 300 MHz,): δ = 7.93–7.98 (2H, m, H-6; H-8), 7.35 (1H, d, J = 1.8 Hz, H-3″, benzyl), 7.17–7.21 (2H, m, H-5″; H-6″), 7.13 (1H, d, J = 9.8 Hz, H-2′, methyl benzoate), 6.72 (2H, d, J = 8.8 Hz, H-3′; H-5′), 6.35 (1H, d, J = 8.4 Hz, H-6′), 5.70–5.79 (3H, m, $ArCH_2$, OCH), 3.88 (3H, s, CO_2CH_3), 3.01–3.11 (2H, m, CH_2), 2.86–2.92 (1H, m, CH_2), 2.52–2.59 (1H, m, CH_2).

*Methyl 2-(4-((5-bromo-4-(4-chlorobenzyl)-7-fluoro-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) phenyl) acetate (**6J**)* White solid. mp 136–138 °C; 1H NMR (CDCl3, 300 MHz,): δ = 7.12–7.20 (6H, m, H-6; H-8; H-3″, benzyl; H-5″; H-2″; H-6″), 6.85 (2H, d, J = 8.4 Hz, H-2′, methyl phenyl acetate; H-6′), 6.73 (2H, d, J = 8.6 Hz, H-3′; H-5′), 5.88 (1H, d, J = 17.0 Hz, Ar$\underline{CH_2}$), 5.58–5.60 (1H, m, OCH), 5.51 (1H, d, J = 17.0 Hz, Ar$\underline{CH_2}$), 3.69 (3H, s, $CH_2CO_2\underline{CH_3}$), 3.57 (2H, s, $\underline{CH_2}CO_2CH_3$), 2.94–3.08 (2H, m, CH_2), 2.79–2.87 (1H, m, CH_2), 2.52–2.60 (1H, m, CH_2).

*Methyl 2-(4-((4-benzyl-5-bromo-7-fluoro-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) phenyl) acetate (**6K**)* White solid. mp 136–138 °C; 1H NMR (CDCl3, 300 MHz,): δ = 7.15–7.18 (2H, m, H-6; H-8), 7.12–7.14 (4H, m, H-3″, benzyl; H-5″; H-2″; H-6″), 6.90–6.92 (3H, m, H-4″; H-2′, methyl phenyl acetate; H-6′), 6.74 (2H, d, J = 8.5 Hz, H-3′; H-5′), 6.01 (1H, d, J = 17.0 Hz, Ar$\underline{CH_2}$), 5.58 (1H, m, OCH), 5.49 (1H, d, J = 17.0 Hz, Ar$\underline{CH_2}$), 3.69 (3H, s, $CH_2CO_2\underline{CH_3}$), 3.56 (2H, s, $\underline{CH_2}$-CO_2CH_3), 2.92–3.04 (2H, m, CH_2), 2.80–2.83 (1H, m, CH_2), 2.53–2.57 (1H, m, CH_2).

*Methyl 2-(4-((5-bromo-4-(2-chlorobenzyl)-7-fluoro-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) phenyl) acetate (**6L**)* White solid. mp 144–146 °C; 1H NMR (CDCl3, 300 MHz,): δ = 7.32–7.36 (1H, m, H-6), 7.09–7.19 (5H, m, H-8; H-3″, benzyl; H-4″; H-5″; H-6″), 7.05–7.07 (1H, m, H-2′, methyl phenyl acetate), 6.65–6.70 (2H, m, H-3′; H-5′), 6.37 (1H, d, J = 7.6 Hz, H-6′), 5.75 (2H, d, J = 11.1 Hz, $ArCH_2$), 5.62–5.67 (1H, m, OCH), 3.68 (3H, s, $CH_2CO_2\underline{CH_3}$), 3.55 (2H, s, $\underline{CH_2}CO_2CH_3$), 2.96–3.10 (2H, m, CH_2), 2.84–2.90 (1H, m, CH_2), 2.56–2.62 (1H, m, CH_2).

*Methyl 2-(4-((5-bromo-4-(3-chlorobenzyl)-7-fluoro-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) phenyl) acetate (**6M**)* White solid. mp 130–132 °C; 1H NMR (CDCl3, 300 MHz,): $\delta = 7.14$–7.24 (5H, m, H-6; H-8; H-2″, benzyl; H-4″; H-6″), 6.95 (1H, s, H-5″), 6.75–6.80 (3H, m, H-2′, methyl phenyl acetate; H-3′; H-5′), 6.66–6.73 (1H, m, H-6′), 5.85–5.94 (1H, m, Ar$\underline{CH_2}$), 5.56–5.61 (1H, m, Ar$\underline{CH_2}$), 5.50 (1H, s, OCH), 3.69 (3H, s, $CH_2CO_2\underline{CH_3}$), 3.56 (2H, s, $\underline{CH_2}CO_2CH_3$), 2.96–3.08 (2H, m, CH_2), 2.82–2.87 (1H, m, CH_2), 2.54–2.59 (1H, m, CH_2).

*Methyl 2-(4-((5-bromo-7-fluoro-4-(4-fluorobenzyl)-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) phenyl) acetate (**6N**)* White solid. mp 114–116 °C; 1H NMR (CDCl3, 300 MHz,): $\delta = 7.14$–7.19 (4H, m, H-6; H-8; H-2″, benzyl; H-6″), 6.86–6.95 (4H, m, H-3″; H-5″; H-2′, methyl phenyl acetate; H-6′), 6.74 (2H, d, $J = 8.6$ Hz, H-3′; H-5′), 5.90 (1H, d, $J = 16.7$ Hz, Ar$\underline{CH_2}$), 5.58–5.60 (1H, m, OCH), 5.51 (1H, d, $J = 16.7$ Hz, Ar$\underline{CH_2}$), 3.69 (3H, s, $CH_2CO_2\underline{CH_3}$), 3.57 (2H, s, $\underline{CH_2}CO_2CH_3$), 2.93—3.08 (2H, m, CH_2), 2.79–2.86 (1H, m, CH_2), 2.51–2.60 (1H, m, CH_2).

*Methyl 2-(4-((5-bromo-7-fluoro-4-(2-fluorobenzyl)-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) phenyl) acetate (**6O**)* White solid. mp 132–134 °C; 1H NMR (CDCl3, 300 MHz,): $\delta = 7.33$—7.35 (2H, m, H-6; H-8), 7.07–7.16 (5H, m, H-3″, benzyl; H-4″; H-5″; H-6″; H-2′, methyl phenyl acetate), 6.67–6.70 (2H, m, H-3′; H-5′), 6.35—6.38 (1H, m, H-6′), 5.73–5.83 (2H, m, $ArCH_2$), 5.64 (1H, m, OCH), 3.68 (3H, s, $CH_2CO_2\underline{CH_3}$), 3.55 (2H, s, $\underline{CH_2}CO_2CH_3$), 3.04 (2H, m, CH_2), 2.86–2.90 (1H, m, CH_2), 2.58 (1H, s, CH_2).

*Methyl 2-(4-((5-bromo-7-fluoro-4-(3-fluorobenzyl)-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) phenyl) acetate (**6P**)* White solid. mp 116–118 °C; 1H NMR (CDCl3, 300 MHz,): $\delta = 7.20$–7.24 (2H, m, H-6; H-8), 7.15–7.18 (2H, m, H-2″, benzyl; H-4″), 6.91–6.96 (1H, m, H-5″), 6.79–6.83 (2H, m, H-6″; H-2′, methyl phenyl acetate), 6.69–6.78 (2H, m, H-3′; H-5′), 6.61–6.65 (1H, m, H-6′), 3.72 (3H, s, $CH_2CO_2\underline{CH_3}$), 3.59 (2H, s, $\underline{CH_2}CO_2CH_3$), 2.90–3.09 (2H, m, CH_2), 2.82–2.87 (1H, m, CH_2), 2.56–2.63 (1H, m, CH_2).

*Methyl 2-(4-((5-bromo-7-fluoro-4-(4-methoxybenzyl)-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) phenyl) acetate (**6Q**)* White solid. mp 123–125 °C; 1H NMR (CDCl3, 300 MHz,): $\delta = 7.12$–7.19 (4H, m, H-6; H-8; H-2″, benzyl; H-6″), 6.85–6.90 (2H, m, H-3″, H-5″), 6.74–6.81 (4H, m, H-2′, methyl phenyl acetate; H-6′; H-3′; H-5′), 5.98 (1H, d, $J = 16.6$ Hz, Ar$\underline{CH_2}$), 5.57 (1H, d, $J = 4.8$ Hz, OCH), 5.40 (1H, d, $J = 16.6$ Hz, Ar$\underline{CH_2}$), 3.80 (3H, s, OCH_3), 3.75 (3H, s, $CH_2CO_2\underline{CH_3}$), 3.57 (2H, s, $\underline{CH_2}CO_2CH_3$), 2.90–3.06 (2H, m, CH_2), 2.77–2.85 (1H, m, CH_2), 2.50–2.56 (1H, m, CH_2).

*Methyl 2-(4-((5-bromo-4-(2,4-dichlorobenzyl)-7-fluoro-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) phenyl) acetate (**6R**)* White solid. mp 134–136 °C; 1H NMR (CDCl3, 300 MHz,): $\delta = 7.36$ (1H, m, H-6), 7.18–7.21 (1H, m, H-8), 7.14–7.17 (2H, m, H-3″, benzyl; H-6″), 7.11–7.13 (1H, m, H-5″), 7.04–7.08 (1H, m, H-2′, methyl phenyl acetate), 6.73 (2H, d, $J = 21.2$ Hz, H-3′; H-5′), 6.32 (1H, d, $J = 8.4$ Hz, H-6′), 5.62–5.71 (3H, m, $ArCH_2$, OCH), 3.69 (3H, s, $CH_2CO_2\underline{CH_3}$), 3.57 (2H, s, $\underline{CH_2}CO_2CH_3$), 2.99–3.07 (2H, m, CH_2), 2.84–2.89 (1H, m, CH_2), 2.57–2.58 (1H, m, CH_2).

*General procedure for the synthesis of compound **I-1**–**I-16** (**I-1** as an example)*

The sulfonylation was accomplished by **6** (0.60 g, 1.1 mmol) and thus formed with methanesulfinic acid sodium salt (0.34 g, 3.3 mmol) and copper(I) iodide (1.05 g, 5.5 mmol) in *N*-methylpyrrolidinone (10 mL). The resulting suspension was degassed under N_2, heated to 130 °C, stirred for 3 h and then cooled to r.t. The reaction was quenched by the addition of ethyl acetate (EtOAc) (20 mL) and hexane (20 mL), filtered through a pad of silica gel, eluting with EtOAc, concentrated and further purified by flash chromatography to give **7** as a white solid. **I-1** was prepared by the treatment of the ester **7** in methanol (10 mL) with 1 N NaOH (0.48 g, 1.2 mmol) and purified by recrystallization in isopropyl alcohol (IPA). Yield in 2 steps: 55.3 %.

*Sodium 4-((4-(4-chlorobenzyl)-7-fluoro-5-(methylsulfonyl)-1, 2, 3, 4-tetrahydrocyclopenta[b] indol-3-yl) oxy) benzoate (**I-1**)* White solid (IPA), mp: 250–252 °C; IR (KBr) νmax 3430, 1594, 1547, 1492, 1409, 1310, 1235, 1146, 1123, 1014, 963, 791, 540 cm^{-1}; 1H NMR (DMSO-d6 and D2O, 500 MHz,): $\delta = 7.72$–7.74 (3H, m, H-6; H-3′, sodium benzoate; H-5′), 7.60 (1H, m, H-8), 7.19 (2H, m, H-2′; H-6′), 6.75 (2H, m, H-2″, benzyl; H-6″), 6.61 (2H, m, H-3″; H-5″), 5.84 (1H, d, $J = 17.5$ Hz, Ar$\underline{CH_2}$), 5.68 (1H, d, $J = 17.3$ Hz, Ar$\underline{CH_2}$), 5.55 (1H, m, OCH), 2.93–2.99 (2H, m, CH_2), 2.79–2.82 (1H, m, $\underline{CH_2}$), 2.52 (3H, s, $SO_2\underline{CH_3}$), 2.30–2.31 (1H, m, $\underline{CH_2}$); 13C NMR (DMSO-d6 and D2O, 500 MHz,): $\delta = 178.0$ (CO_2Na, sodium benzoate), 171.8 (C-7), 159.1 (C-1′, sodium benzoate), 156.7 (C-3a), 154.8 (C-4a), 148.6 (C-1″, benzyl), 138.3 (C-3′), 133.5 (C-5′), 132.7 (C-4″), 132.4 (C-8a, C-4′), 131.7 (C-2″), 129.2 (C-6″), 128.6 (C-3″), 126.9 (C-5″), 124.9 (C-5), 114.7 (C-2′), 113.5 (C-6′), 113.3 (C-8), 112.7 (C-8b), 112.5 (C-6), 75.9 (C-3), 50.1 (CH_2, benzyl), 44.8 (CH_3, SO_2CH_3), 36.7 (C-2), 23.0 (C-1). HRESIMS *m*/*z* (pos): 536.0692 $C_{26}H_{20}ClFNNaO_5S$ (calcd. 536.0632).

*Sodium 4-((4-benzyl-7-fluoro-5-(methylsulfonyl)-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) benzoate (**I-2**)* White solid (IPA), mp: 234–236 °C; IR (KBr) νmax

3406, 2925, 1603, 1549, 1493, 1453, 1397, 1301, 1236, 1196, 1143, 1121, 1036, 958, 860, 788, 756, 701, 619, 539 cm^{-1}; 1H NMR (MeOD, 300 MHz,): $\delta = 7.87$ (2H, d, $J = 8.7$ Hz, H-6; H-8), 7.71 (1H, m, H-3′, sodium benzoate), 7.65 (1H, m, H-5′), 7.21–7.23 (3H, m, H-2″, benzyl; H-6″; H-4″), 6.81–6.83 (2H, m, H-2′; H-6′), 6.72 (2H, d, $J = 9.0$ Hz, H-3″; H-5″), 6.15 (1H, d, $J = 17.1$ Hz, Ar$\underline{CH_2}$), 5.80 (1H, d, $J = 17.4$ Hz, Ar$\underline{CH_2}$), 5.61–5.65 (1H, m, O$\underline{CH}$), 3.05–3.13 (2H, m, CH_2), 2.90–2.95 (1H, m, $\underline{CH_2}$), 2.72 (3H, s, $SO_2\underline{CH_3}$), 2.46–2.55 (1H, m, $\underline{CH_2}$); 13C NMR (MeOD, 300 MHz,): $\delta = 173.3$ (CO_2Na, sodium benzoate), 158.7 (C-7), 156.6 (C-1′, sodium benzoate), 153.5 (C-3a), 147.6 (C-4a), 138.4 (C-1″, benzyl), 132.7 (C-3′), 130.2 (C-5′), 130.1 (C-4′), 127.9 (C-8a), 127.8 (C-4″), 127.5 (C-2″), 126.5 (C-6″), 125.2 (C-3″), 122.9 (C-5″), 122.8 (C-5), 113.4 (C-2′), 112.8 (C-6′), 112.4 (C-8), 110.7 (C-8b), 110.4 (C-6), 74.9 (C-3), 49.9 (CH_2, benzyl), 42.9 (CH_3, SO_2CH_3), 35.4 (C-2), 21.4 (C-1); HRESIMS *m/z* (pos): 501.9683 $C_{26}H_{21}FNNaO_5S$ (calcd. 502.1022).

*Sodium 4-((4-(2-chlorobenzyl)-7-fluoro-5-(methylsulfonyl)-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) benzoate (**I-3**)* White solid (IPA), mp: 242–246 °C; IR (KBr) νmax 3386, 1601, 1549, 1446, 1393, 1307, 1234, 1171, 1121, 1039, 957, 861, 788, 755, 617, 567, 540, 467 cm^{-1}; 1H NMR (MeOD, 300 MHz,): $\delta = 7.84$ (2H, d, $J = 8.7$ Hz, H-6; H-8), 7.67–7.74 (2H, m, H-3′, sodium benzoate; H-5′), 7.38 (1H, m, H-2′), 7.21–7.26 (1H, m, H-6′), 7.08–7.13 (1H, m, H-3″, benzyl), 6.62 (2H, d, $J = 8.7$ Hz, H-4″; H-6″), 6.47 (1H, d, $J = 7.8$ Hz, H-5″), 6.17 (1H, d, $J = 18.3$ Hz, Ar$\underline{CH_2}$), 5.97 (1H, d, $J = 18.3$ Hz, Ar$\underline{CH_2}$), 5.72 (1H, m, O$\underline{CH}$), 3.08–3.18 (2H, m, CH_2), 2.90–2.98 (1H, m, $\underline{CH_2}$), 2.75 (3H, s, $SO_2\underline{CH_3}$), 2.48–2.56 (1H, m, $\underline{CH_2}$); 13C NMR (MeOD, 300 MHz,): $\delta = 173.3$ (CO_2Na, sodium benzoate), 158.7 (C-7), 156.8 (C-1′, sodium benzoate), 155.3 (C-3a), 153.7 (C-4a), 147.4 (C-1″, benzyl), 136.0 (C-3′), 130.9 (C-5′), 130.2 (C-4′), 130.1 (C-8a), 128.6 (C-2″), 128.0 (C-6″), 127.9 (C-3″), 126.3 (C-5″), 126.0 (C-4″), 123.2 (C-5), 113.3 (C-2′), 112.9 (C-6′), 112.5 (C-8), 110.9 (C-8b), 110.6 (C-6), 74.9 (C-3), 49.9 (CH_3, SO_2CH_3; CH_2, benzyl), 35.6 (C-2), 21.5 (C-1); HRESIMS *m/z* (pos): 536.0713 $C_{26}H_{20}ClFNNaO_5S$ (calcd. 536.0632).

*Sodium 4-((4-(3-chlorobenzyl)-7-fluoro-5-(methylsulfonyl)-1, 2, 3, 4-tetrahydrocyclopenta[b] indol-3-yl) oxy) benzoate (**I-4**)* White solid (IPA), mp: 208–210 °C; IR (KBr) νmax 3404, 1601, 1553, 1489, 1412, 1302, 1237, 1145, 1120, 1036, 957, 861, 787, 567, 539, 466 cm^{-1}; 1H NMR (MeOD, 300 MHz,): $\delta = 7.88$ (2H, d, $J = 9.0$ Hz, H-6; H-8), 7.72 (1H, m, H-3′, sodium benzoate), 7.65 (1H, m, H-5′), 7.19–7.27 (1H, m, H-2″, benzyl), 6.91–6.97 (1H, m, H-4″), 6.71 (2H, d, $J = 8.7$ Hz, H-2′; H-6′), 6.66 (1H, d, $J = 8.1$ Hz, H-5″), 6.54 (1H, d, $J = 9.9$ Hz, H-6″), 6.07 (1H, d, $J = 17.4$ Hz, Ar$\underline{CH_2}$), 5.86 (1H, d, $J = 17.7$ Hz, Ar$\underline{CH_2}$), 5.67 (1H, m, O$\underline{CH}$), 3.06–3.12 (2H, m, CH_2), 2.93–2.96 (1H, m, $\underline{CH_2}$), 2.89 (3H, s, $SO_2\underline{CH_3}$), 2.46–2.54 (1H, m, $\underline{CH_2}$); 13C NMR (MeOD, 300 MHz,): $\delta = 173.3$ (CO_2Na, sodium benzoate), 164.2 (C-7), 161.0 (C-1′, sodium benzoate), 158.7 (C-3a), 153.6 (C-4a), 147.4 (C-1″, benzyl), 141.4 (C-3′), 141.3 (C-5′), 132.7 (C-4′), 130.3 (C-8a), 130.1 (C-3″), 129.6 (C-6″), 129.5 (C-2″), 128.0 (C-4″), 123.2 (C-5″,C-5), 121.1 (C-2′), 113.3 (C-6′), 112.3 (C-8), 110.8 (C-8b), 110.5 (C-6), 74.8 (C-3), 49.6 (CH_2, benzyl), 43.0 (CH_3, SO_2CH_3), 35.5 (C-2), 21.4 (C-1); HRESIMS *m/z* (pos): 536.0730 $C_{26}H_{20}ClFNNaO_5S$ (calcd. 536.0632).

*Sodium 4-((7-fluoro-4-(4-fluorobenzyl)-5-(methylsulfonyl)-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) benzoate (**I-5**)* White solid (IPA), mp:238–240 °C; IR (KBr) νmax 3433, 1639, 1559, 1510, 1412, 1302, 1235, 1145, 1121, 791, 647, 539 cm^{-1}; 1H NMR (MeOD, 300 MHz,): $\delta = 7.89$ (2H, d, $J = 9.0$ Hz, H-6; H-8), 7.72 (1H, m, H-3′, sodium benzoate), 7.63–7.67 (1H, m, H-5′), 6.92–6.98 (2H, m, H-2′; H-6′), 6.83–6.88 (2H, m, H-2″, benzyl; H-6″), 6.73–6.75 (2H, m, H-3″; H-5″), 6.10(1H, d, $J = 17.1$ Hz, Ar$\underline{CH_2}$), 5.78 (1H, d, $J = 16.8$ Hz, Ar$\underline{CH_2}$), 5.60–5.64 (1H, m, O$\underline{CH}$), 3.03–3.13 (2H, m, CH_2), 2.91–2.96 (1H, m, $\underline{CH_2}$), 2.92(3H, s, $SO_2\underline{CH_3}$), 2.46–2.55 (1H, m, $\underline{CH_2}$); 13C NMR (MeOD, 300 MHz,): $\delta = 178.5$ (CO_2Na, sodium benzoate), 173.3 (C-7), 163.2 (C-4″, benzyl), 159.9 (C-1′, sodium benzoate), 158.7 (C-3a), 147.4 (C-4a), 134.3 (C-1″), 134.2 (C-4′), 132.7 (C-3′), 130.3 (C-5′), 130.1 (C-8a), 127.3 (C-2″), 127.2 (C-6″), 123.2 (C-3″), 114.6 (C-5″), 114.3 (C-5), 113.4 (C-2′), 112.8 (C-6′), 112.4 (C-8), 110.7 (C-8b), 110.4 (C-6), 74.9 (C-3), 43.0 (CH_2, benzyl), 35.5 (CH_3, SO_2CH_3), 22.3 (C-2), 21.4 (C-1); HRESIMS *m/z* (pos): 520.1017 $C_{26}H_{20}F_2NNaO_5S$ (calcd. 520.0928).

*Sodium 4-((7-fluoro-4-(2-fluorobenzyl)-5-(methylsulfonyl)-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) benzoate (**I-6**)* White solid (IPA), mp:230–232 °C; IR (KBr) νmax 3385, 1601, 1552, 1491, 1396, 1303, 1235, 1198, 1121, 1039, 958, 860, 788, 755, 617, 539, 468 cm^{-1}; 1H NMR (MeOD, 300 MHz,): $\delta = 7.84$ (2H, d, $J = 8.7$ Hz, H-6; H-8), 7.67–7.74 (2H, m, H-3′, sodium benzoate; H-5′), 7.37 (1H, m, H-3″, benzyl), 7.20–7.26 (1H, m, H-4″), 7.07–7.13 (1H, m, H-5″), 6.60–6.63 (2H, m, H-2′; H-6′), 6.16–6.19 (1H, m, H-6″), 6.07 (1H, d, $J = 18.0$ Hz, Ar$\underline{CH_2}$), 5.96 (1H, d, $J = 18.3$ Hz, Ar$\underline{CH_2}$), 5.69–5.73 (1H, m, O$\underline{CH}$), 3.07–3.16 (2H, m, CH_2), 2.92–2.99 (1H, m, $\underline{CH_2}$), 2.87 (3H, s, $SO_2\underline{CH_3}$), 2.47–2.56 (1H, m, $\underline{CH_2}$); 13C NMR (MeOD, 300 MHz,): $\delta = 173.3$ (CO_2Na, sodium benzoate), 158.7 (C-7), 156.8 (C-2″, benzyl), 153.7 (C-1′, sodium benzoate), 147.4 (C-3a), 136.0 (C-4a), 130.9 (C-1″), 130.2 (C-3′), 130.1 (C-5′), 128.6 (C-4′), 128.0 (C-8a), 127.9 (C-3″), 126.3 (C-4″), 126.0 (C-6″), 123.3 (C-5″), 123.2 (C-5), 113.3 (C-2′), 112.9 (C-6′), 112.5 (C-8), 110.9

(C-8b), 110.6 (C-6), 74.9 (C-3), 48.4 (CH_2, benzyl; CH_3, SO_2CH_3), 35.6 (C-2), 21.5 (C-1); HRESIMS *m/z* (neg): 496.1050 $C_{26}H_{20}F_2NNaO_5S$ (calcd. 496.1036).

*Sodium 4-((7-fluoro-4-(3-fluorobenzyl)-5-(methylsulfonyl)-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) benzoate (**I-7**)* White solid (IPA), mp: 220–224 °C; IR (KBr) νmax 3411, 2926, 1601, 1553, 1489, 1403, 1302, 1268, 1197, 1147, 1120, 1037, 958, 860, 787, 567, 540, 467 cm^{-1}; 1H NMR (MeOD, 300 MHz,): $\delta = 7.86–7.92$ (2H, m, H-6; H-8), 7.73 (1H, m, H-3′, sodium benzoate), 7.66 (1H, m, H-5′), 7.17–7.27 (2H, m, H-4″, benzyl; H-5″), 6.86–6.98 (2H, m, H-2′; H-6′), 6.72 (1H, m, H-6″), 6.52–6.70 (1H, m, H-2″), 6.02–6.12 (1H, m, Ar$\underline{CH_2}$), 5.86 (1H, d, $J = 14.5$ Hz, Ar$\underline{CH_2}$), 5.66–5.68 (1H, m, O$\underline{CH}$), 3.05–3.14 (2H, m, CH_2), 2.89–2.98 (1H, m, $\underline{CH_2}$), 2.94 (3H, s, $SO_2\underline{CH_3}$), 2.47–2.55 (1H, m, $\underline{CH_2}$); 13C NMR (MeOD, 300 MHz,): $\delta = 173.3$ (CO_2Na, sodium benzoate), 158.7 (C-7), 158.6 (C-3″, benzyl), 147.4 (C-1′, sodium benzoate), 147.3 (C-3a), 140.8 (C-4a), 133.8 (C-1″), 130.3 (C-3′), 129.5 (C-5′), 129.3 (C-4′), 126.6 (C-8a), 125.5 (C-2″), 123.8 (C-4″), 121.1 (C-5″), 113.3 (C-6″), 113.0 (C-5), 112.0 (C-2′, C-6), 110.8 (C-6′, C-8), 110.5 (C-8b), 74.8 (C-3), 49.6 (CH_2, benzyl; CH_3, SO_2CH_3), 35.4 (C-2), 21.4 (C-1); HRESIMS *m/z* (pos): 520.1024 $C_{26}H_{20}F_2NNaO_5S$ (calcd. 520.0928).

*Sodium 4-((7-fluoro-4-(4-methoxybenzyl)-5-(methylsulfonyl)-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) benzoate (**I-8**)* White solid (IPA), mp: 220–224 °C; IR (KBr) νmax 3423, 1594, 1510, 1414, 1385, 1299, 1231, 1178, 1143, 1122, 1036, 960, 818, 757, 541 cm^{-1}; 1H NMR (MeOD, 300 MHz,): $\delta = 7.89–7.92$ (2H, m, H-6; H-8), 7.71–7.76 (1H, m, H-3′, sodium benzoate), 7.63–7.68 (1H, m, H-5′), 6.76–6.81 (4H, m, H-2′; H-6′; H-3″, benzyl; H-5″), 6.70–6.73 (2H, m, H-2″; H-6″), 6.10–6.16 (1H, m, Ar$\underline{CH_2}$), 5.66–5.73 (1H, m, Ar$\underline{CH_2}$), 5.60–5.62 (1H, m, O$\underline{CH}$), 3.73 (3H, s, OCH_3), 3.05–3.13 (2H, m, CH_2), 2.97 (3H, s, $SO_2\underline{CH_3}$), 2.87–2.95 (1H, m, $\underline{CH_2}$), 2.47–2.55 (1H, m, $\underline{CH_2}$); 13C NMR (MeOD, 300 MHz,): $\delta = 178.7$ (CO_2Na, sodium benzoate), 158.6 (C-7), 155.3 (C-4″, benzyl), 148.0 (C-1′, sodium benzoate), 130.4 (C-3a), 130.2 (C-4a), 128.2 (C-8a, C-2″), 129.3 (C-6″), 126.5 (C-3″), 126.3 (C-5″), 114.4 (C-1″, C-4′), 113.2 (C-8), 112.6 (C-5), 112.2 (C-3′), 110.6 (C-5′), 110.3 (C-2′), 109.8 (C-6′), 108.4 (C-6), 107.6 (C-8b), 75.0 (C-3), 53.8 (OCH_3), 49.3 (CH_2, benzyl), 43.6 (CH_3, SO_2CH_3), 35.5 (C-2), 21.3 (C-1);HRESIMS *m/z* (pos): 532.1241 $C_{27}H_{23}FNNaO_6S$ (calcd. 532.1128).

*Sodium 4-((4-(2, 4-dichlorobenzyl)-7-fluoro-5-(methylsulfonyl)-1, 2, 3, 4-tetrahydro cyclopenta[b]indol-3-yl) oxy) benzoate (**I-9**)* White solid (IPA), mp: 248–250 °C; IR (KBr) νmax 3406, 1600, 1552, 1451, 1389, 1352, 1315, 1234, 1171, 1146, 1122, 1307, 959, 863, 834, 788, 539 cm^{-1}; 1H NMR (MeOD, 300 MHz,): $\delta = 7.86$ (2H, d, $J = 9.0$ Hz, H-6; H-8), 7.67–7.74 (2H, m, H-3′, sodium benzoate; H-5′), 7.42 (1H, d, $J = 2.1$ Hz, H-3″, benzyl), 7.15 (1H, m, H-5″), 6.61–6.66 (2H, m, H-2′; H-6′), 6.20 (1H, d, $J = 8.4$ Hz, H-6″), 6.04 (1H, d, $J = 18.3$ Hz, Ar$\underline{CH_2}$), 5.89 (1H, d, $J = 18.0$ Hz, Ar$\underline{CH_2}$), 5.75 (1H, m, O$\underline{CH}$), 3.08–3.17 (2H, m, CH_2), 2.90–2.99 (1H, m, $\underline{CH_2}$), 2.87 (3H, s, $SO_2\underline{CH_3}$), 2.48–2.55 (1H, m, $\underline{CH_2}$); 13C NMR (MeOD, 300 MHz,): $\delta = 173.3$ (CO_2Na, sodium benzoate), 158.6 (C-1′, sodium benzoate), 156.9 (C-7), 153.7 (C-1″, benzyl), 147.3 (C-2″), 135.0 (C-4″), 132.7 (C-3a), 132.6 (C-4a), 131.6 (C-6″), 130.2 (C-5″), 128.1 (C-3″), 127.4 (C-3′), 126.5 (C-5′), 126.0 (C-8a), 123.5 (C-4′), 123.4 (C-5), 113.2 (C-8), 112.7 (C-2′), 112.3 (C-6′), 110.9 (C-6), 110.6 (C-8b), 74.7 (C-3), 49.8 (CH_2, benzyl; CH_3, SO_2CH_3), 35.6 (C-2), 21.5 (C-1); HRMS (ESI) calcd. HRESIMS *m/z* (pos): 570.0343 $C_{26}H_{19}Cl_2FNNaO_5S$ (calcd. 570.0243).

*Sodium 2-(4-((4-(4-chlorobenzyl)-7-fluoro-5-(methylsulfonyl)-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) phenyl) acetate (**I-10**)* White solid (IPA), mp: 242–246 °C; IR (KBr) νmax 3426, 1570, 1509, 1404, 1312, 1233, 1145, 1123, 1039, 1014, 959, 810, 757, 568, 540, 468 cm^{-1}; 1H NMR (MeOD, 300 MHz,): $\delta = 7.83$ (1H, m, H-6), 7.64 (1H, m, H-8), 7.30 (2H, d, $J = 8.5$ Hz, H-3′, sodium phenyl acetate; H-5′), 7.10 (2H, d, $J = 8.5$ Hz, H-3″, benzyl; H-5″), 6.79 (2H, d, $J = 8.5$ Hz, H-2′; H-6′), 6.61 (2H, d, $J = 8.5$ Hz, H-2″; H-6″), 6.00 (1H, d, $J = 17.5$ Hz, Ar$\underline{CH_2}$), 5.71 (1H, d, $J = 17.5$ Hz, Ar$\underline{CH_2}$), 5.54 (1H, m, O$\underline{CH}$), 3.14 (2H, s, $\underline{CH_2}CO_2Na$), 3.12 (3H, s, $SO_2\underline{CH_3}$), 2.98–3.02 (2H, m, CH_2), 2.81–2.86 (1H, m, $\underline{CH_2}$), 2.35–2.38 (1H, m, $\underline{CH_2}$); 13C NMR (MeOD, 300 MHz,): $\delta = 174.8$ (C=O, CH_2CO_2Na), 155.7 (C-7), 154.7 (C-1′, sodium phenyl acetate), 153.9 (C-1″, benzyl), 148.0 (C-3a), 137.7 (C-4a), 132.7 (C-4″), 132.5 (C-3′), 131.5 (C-5′), 130.1 (C-8a), 128.4 (C-2″), 127.7 (C-6″), 127.5 (C-3″), 126.6 (C-5″), 123.4 (C-4′), 114.4 (C-5), 112.5 (C-8), 111.5 (C-8b, C-2′), 111.3 (C-6; C-6′), 74.9 (C-3), 49.9 (CH_2, benzyl), 45.1 (CH_3, SO_2CH_3), 40.0 (CH_2, CH_2CO_2Na), 35.3 (C-2), 22.2 (C-1); HRESIMS *m/z* (pos): 550.0858 $C_{27}H_{22}ClFNNaO_5S$ (calcd. 550.0789).

*Sodium 2-(4-((4-benzyl-7-fluoro-5-(methylsulfonyl)-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) phenyl)acetate (**I-11**)* White solid (IPA), mp: 242–244 °C; IR (KBr) νmax 3423, 1578, 1509, 1491, 1416, 1400, 1359, 1315, 1301, 1234, 1175, 1146, 1122, 1039, 960, 769, 542 cm^{-1}; 1H NMR (MeOD, 300 MHz,): $\delta = 7.70$ (1H, m, H-6), 7.62 (1H, m, H-8), 7.20–7.24 (4H, m, H-3′, sodium phenyl acetate; H-5′; H-3″, benzyl; H-5″), 7.18 (1H, s, H-4″), 6.80–6.82 (2H, m, H-2″; H-6″), 6.67 (2H, d, $J = 6.6$ Hz,

H-2′; H-6′), 6.17 (1H, d, $J = 17.4$ Hz, Ar$\underline{CH_2}$), 5.77 (1H, d, $J = 17.4$ Hz, Ar$\underline{CH_2}$), 5.55–5.57 (1H, m, O$\underline{CH}$), 3.40 (2H, s, $\underline{CH_2}CO_2Na$), 3.18 (3H, s, $SO_2\underline{CH_3}$), 2.99–3.12 (2H, m, CH_2), 2.89–2.93 (1H, m, $\underline{CH_2}$), 2.47–2.55 (1H, m, $\underline{CH_2}$); 13C NMR (MeOD, 300 MHz,): $\delta = 178.7$ (C=O, CH_2CO_2Na), 156.6 (C-7), 155.3 (C-1′, sodium phenyl acetate), 153.5 (C-1″, benzyl), 148.0 (C-3a), 138.5 (C-4a), 132.7 (C-8a), 130.4 (C-3′), 129.3 (C-5′), 128.3 (C-3″), 127.9 (C-5″), 126.5 (C-2″), 125.2 (C-6″), 123.4 (C-4″), 122.7 (C-4′, C-5), 114.4 (C-8), 112.7 (C-2′), 112.3 (C-6′), 110.7 (C-8b), 110.4 (C-6), 75.0 (C-3), 49.8 (CH_2, benzyl), 43.6 (CH_3, SO_2CH_3; CH_2, CH_2CO_2Na), 35.5 (C-2), 21.4 (C-1); HRESIMS *m/z* (pos): 515.9829 $C_{27}H_{23}FNNaO_5S$ (calcd. 516.1179).

*Sodium 2-(4-((4-(2-chlorobenzyl)-7-fluoro-5-(methylsulfonyl)-1, 2, 3, 4-tetrahydrocyclopenta [b]indol-3-yl) oxy) phenyl) acetate (**I-12**)* White solid (IPA), mp: 200–202 °C; IR (KBr) νmax 3425, 1574, 1574, 1509, 1490, 1444, 1417, 1393, 1301, 1231, 1146, 1122, 1040, 959, 761, 540 cm^{-1};1H NMR (MeOD, 300 MHz,): $\delta = 7.71$ (1H, m, H-6), 7.65 (1H, m, H-8), 7.21 (2H, d, $J = 8.7$ Hz, H-3′, sodium phenyl acetate; H-5′), 6.94–7.00 (2H, m, H-3″, benzyl; H-6″), 6.83–6.88 (2H, m, H-2′; H-6′), 6.70 (2H, d, $J = 8.7$ Hz, H-4″; H-5″), 6.12 (1H, d, $J = 17.1$ Hz, Ar$\underline{CH_2}$), 5.75 (1H, d, $J = 17.1$ Hz, Ar$\underline{CH_2}$), 5.54–5.57 (1H, m, O$\underline{CH}$), 3.41 (2H, s, $\underline{CH_2}CO_2Na$), 3.02–3.11 (2H, m, CH_2), 2.90 (3H, s, $SO_2\underline{CH_3}$), 2.85–2.93 (1H, m, $\underline{CH_2}$), 2.46–2.52 (1H, m, $\underline{CH_2}$); 13C NMR (MeOD, 300 MHz,): $\delta = 178.7$ (C=O, CH_2CO_2Na), 163.2 (C-7), 159.9 (C-1′, sodium phenyl acetate), 156.7 (C-1″, benzyl), 155.3 (C-3a), 147.8 (C-4a), 134.3 (C-8a), 130.5 (C-3′), 129.4 (C-5′), 127.9 (C-6″), 127.3 (C-4″), 127.2 (C-3″), 123.0 (C-5″, C-4′), 122.9 (C-2″), 114.6 (C-5), 114.3 (C-8), 112.7 (C-2′), 112.3 (C-6′), 110.7 (C-8b), 110.4 (C-6), 75.0 (C-3), 49.3 (CH_2, benzyl), 43.6 (CH_3, SO_2CH_3), 43.0 (CH_2, CH_2CO_2Na), 35.5 (C-2), 21.3 (C-1); HRESIMS *m/z* (pos): 550.0893 $C_{27}H_{22}ClFNNaO_5S$ (calcd. 550.0789).

*Sodium 2-(4-((4-(3-chlorobenzyl)-7-fluoro-5-(methylsulfonyl)-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) phenyl) acetate (**I-13**)* White solid (IPA), mp: 140–142 °C; IR (KBr) νmax 3462, 1589, 1509, 1489, 1452, 1413, 1311, 1231, 1197, 1146, 1121, 958, 541 cm^{-1}; 1H NMR (MeOD, 300 MHz,): $\delta = 7.71$ (1H, m, H-6), 7.64 (1H, m, H-8), 7.18–7.22 (4H, m, H-3′, sodium phenyl acetate; H-5′; H-2″, benzyl; H-4″), 6.85–6.98 (1H, m, H-5″), 6.51–6.69 (3H, m, H-2′; H-6′; H-6″), 6.02–6.08 (1H, m, Ar$\underline{CH_2}$), 5.82 (1H, d, $J = 8.6$ Hz, Ar$\underline{CH_2}$), 5.57–5.60 (1H, m, O$\underline{CH}$), 3.41 (2H, s, $\underline{CH_2}CO_2Na$), 3.00–3.11(2H, m, CH_2), 2.96 (3H, s, $SO_2\underline{CH_3}$), 2.85–2.93(1H, m, $\underline{CH_2}$), 2.47–2.55(1H, m, $\underline{CH_2}$); 13C NMR (MeOD, 300 MHz,): $\delta = 178.7$ (C=O, CH_2CO_2Na), 156.7 (C-7), 155.1 (C-1′, sodium phenyl acetate), 153.5 (C-1″, benzyl), 147.7 (C-3a), 140.8 (C-4a), 133.7 (C-8a), 130.4 (C-3′), 129.6 (C-5′), 129.3 (C-2″), 129.2 (C-6″), 126.5 (C-4″), 125.4 (C-5″), 123.7 (C-3″), 121.0 (C-4′), 114.3 (C-5), 113.2 (C-8), 112.7 (C-2′), 112.2 (C-6′), 111.9 (C-8b), 110.7 (C-6), 74.9 (C-3), 49.5 (CH_2, benzyl), 43.5 (CH_3, SO_2CH_3; CH_2, CH_2CO_2Na), 35.4 (C-2), 21.3 (C-1); HRMS (ESI) calcd. HRESIMS *m/z* (pos): 550.0890 $C_{27}H_{22}ClFNNaO_5S$ (calcd. 550.0789).

*Sodium 2-(4-((7-fluoro-4-(4-fluorobenzyl)-5-(methylsulfonyl)-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) phenyl) acetate (**I-14**)* White solid (IPA), mp: 244–248 °C; IR (KBr) νmax 3408, 1575, 1509, 1411, 1314, 1232, 1159, 1146, 1122, 958, 821, 757, 541 cm^{-1}; 1H NMR (MeOD, 300 MHz,): $\delta = 7.71$ (1H, m, H-6), 7.65 (1H, m, H-8), 7.26–7.28 (1H, m, H-3′, sodium phenyl acetate), 7.20 (2H, d, $J = 7.3$ Hz, H-2′; H-6′), 6.92–6.97 (1H, m, H-5′), 6.64–6.70 (3H, m, H-2″, benzyl; H-6″; H-3″), 6.52–6.55 (1H, m, H-5″), 6.10 (1H, d, $J = 14.5$ Hz, Ar$\underline{CH_2}$), 5.83 (1H, d, $J = 14.8$ Hz, Ar$\underline{CH_2}$), 5.59–5.62 (1H, m, O$\underline{CH}$), 3.41 (2H, s, $\underline{CH_2}CO_2Na$), 2.99–3.13 (2H, m, CH_2), 2.94 (3H, s, $SO_2\underline{CH_3}$), 2.86–2.91 (1H, m, $\underline{CH_2}$), 2.47–2.56 (1H, m, $\underline{CH_2}$); 13C NMR (MeOD, 300 MHz,): $\delta = 178.4$ (C=O, CH_2CO_2Na), 164.2 (C-4″, benzyl), 161.0 (C-1′, sodium phenyl acetate), 156.7 (C-7), 155.2 (C-1″), 153.6 (C-3a), 147.8 (C-4a), 141.5 (C-8a), 141.4 (C-3′), 130.5 (C-5′), 129.7 (C-2″), 129.6 (C-6″), 129.4 (C-3″), 121.0 (C-5″), 114.3 (C-4′), 113.3 (C-5), 113.0 (C-8), 112.4 (C-2′), 112.2 (C-6′), 111.9 (C-8b), 110.8 (C-6), 74.9 (C-3), 49.5 (CH_2, benzyl), 43.6 (CH_3, SO_2CH_3; CH_2, CH_2CO_2Na), 35.5 (C-2), 21.4 (C-1); HRESIMS *m/z* (pos): 534.1168 $C_{27}H_{22}F_2NNaO_5S$ (calcd. 534.1084).

*Sodium 2-(4-((7-fluoro-4-(2-fluorobenzyl)-5-(methylsulfonyl)-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) phenyl) acetate (**I-15**)* White solid (IPA), mp: 184–186 °C; IR (KBr) νmax 3397, 1574, 1509, 1490, 1457, 1417, 1393, 1350, 1301, 1231, 1146, 1121, 1152, 959, 762, 540, 468 cm^{-1}; 1H NMR (MeOD, 300 MHz,): $\delta = 7.64$–7.72 (2H, m, H-6; H-8), 7.38 (1H, m, H-3′, sodium phenyl acetate), 7.22–7.25 (1H, m, H-5′), 7.15–7.20 (2H, m, H-3″, benzyl; H-5″), 7.06–7.12 (1H, m, H-4″), 5.58 (2H, d, $J = 9.0$ Hz, H-2′; H-6′), 6.12–6.15 (1H, m, H-6″), 5.94–6.07 (2H, m, Ar$\underline{CH_2}$), 5.60–5.63 (1H, m, O$\underline{CH}$), 3.39 (2H, s, $\underline{CH_2}CO_2Na$), 3.01–3.13 (2H, m, CH_2), 2.90–2.95 (1H, m, $\underline{CH_2}$), 2.87 (3H, s, $SO_2\underline{CH_3}$), 2.45–2.54 (1H, m, $\underline{CH_2}$); 13C NMR (MeOD, 300 MHz,): $\delta = 178.8$ (C=O, CH_2CO_2Na), 156.8 (C-2″, benzyl), 155.2 (C-1′, sodium phenyl acetate), 153.6 (C-7), 147.7 (C-1″), 136.1 (C-3a), 132.7 (C-4a), 130.8 (C-8a), 130.4 (C-3′), 129.3 (C-5′), 128.6 (C-3″), 127.8 (C-6″), 126.4 (C-4″), 125.9 (C-5″), 123.1 (C-4′), 123.0 (C-5), 114.3 (C-8), 112.8 (C-2′), 112.4 (C-6′), 110.9 (C-8b), 110.6 (C-6), 75.0 (C-3), 43.6 (CH_3, SO_2CH_3; CH_2, benzyl), 42.8 (CH_2,

CH_2CO_2Na), 35.6 (C-2), 21.5 (C-1); HRESIMS *m/z* (neg): 510.1203 $C_{27}H_{22}F_2NNaO_5$ (calcd. 510.1192).

Sodium 2-(4-((7-fluoro-4-(3-fluorobenzyl)-5-(methylsulfonyl)-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) phenyl) acetate (***I-16***) White solid (IPA), mp: 226–228 °C; IR (KBr) νmax 3415, 1589, 1509, 1489, 1460, 1316, 1227, 1185, 1137, 1121, 1037, 955, 788, 765, 680, 539 cm^{-1}; 1H NMR (MeOD, 300 MHz,): $\delta = 7.67–7.73$ (2H, m, H-6; H-8), 7.39 (1H, d, $J = 4.1$ Hz, H-3′, sodium phenyl acetate), 7.07–7.25 (4H, m, H-5′; H-4″, benzyl; H-5″; H-6″), 6.59 (2H, d, $J = 4.2$ Hz, H-2′; H-6′), 6.13 (1H, d, $J = 3.8$ Hz, H-2″), 6.02 (2H, s, Ar$\underline{CH_2}$), 5.62 (1H, m, O$\underline{CH}$), 3.39 (2H, s, $\underline{CH_2}CO_2Na$), 3.06–3.13 (2H, m, CH_2), 2.97 (3H, s, $SO_2\underline{CH_3}$), 2.92–2.96 (1H, m, $\underline{CH_2}$), 2.47–2.55 (1H, m, $\underline{CH_2}$); 13C NMR (MeOD, 300 MHz,): $\delta = 178.7$ (C=O, CH_2CO_2Na), 155.2 (C-3″, benzyl), 147.8 (C-1′, sodium phenyl acetate; C-7), 136.1 (C-1″), 130.5 (C-3a), 129.3 (C-4a), 128.6 (C-8a), 128.1 (C-3′), 128.0 (C-5′), 127.8 (C-2″), 126.3 (C-4″), 125.9 (C-5″), 125.8 (C-6″), 123.1 (C-4′), 123.0 (C-5), 114.3 (C-8), 112.8 (C-2′), 112.4 (C-6′), 110.8 (C-8b), 110.5 (C-6), 75.0 (C-3), 43.6 (CH_2, CH_2CO_2Na; CH_3, SO_2CH_3; CH_2, benzyl), 35.6 (C-2), 21.5 (C-1); HRESIMS *m/z* (pos): 534.1164 $C_{27}H_{22}F_2NNaO_5S$ (calcd. 534.1084).

Sodium 2-(4-((7-fluoro-4-(4-methoxybenzyl)-5-(methylsulfonyl)-1, 2, 3, 4-tetrahydrocyclopenta[b]indol-3-yl) oxy) phenyl) acetate (***I-17***) White solid (IPA), mp: 238–240 °C; IR (KBr) νmax 3395, 1602, 1549, 1514, 1455, 1390, 1303, 1250, 1201, 1174, 1142, 1118, 1031, 964, 791, 538, 470 cm^{-1};1H NMR (MeOD, 300 MHz,): $\delta = 7.71$ (1H, m, H-6), 7.64 (1H, m, H-8), 7.21 (2H, d, $J = 4.4$ Hz, H-3′, sodium phenyl acetate; H-5′), 6.77–6.81 (4H, m, H-3″, benzyl; H-5″; H-2″; H-6″), 6.72 (2H, d, $J = 4.4$ Hz, H-2′; H-6′), 6.13 (1H, d, $J = 8.4$ Hz, Ar$\underline{CH_2}$), 5.66 (1H, d, $J = 8.4$ Hz, Ar$\underline{CH_2}$), 5.53–5.55 (1H, m, O$\underline{CH}$), 3.73 (3H, s, OCH_3), 3.41 (2H, s, $\underline{CH_2}CO_2Na$), 3.03–3.10 (2H, m, CH_2), 2.96 (3H, s, $SO_2\underline{CH_3}$), 2.84–2.93 (1H, m, $\underline{CH_2}$), 2.46–2.55 (1H, m, $\underline{CH_2}$); 13C NMR (MeOD, 300 MHz,): $\delta = 173.3$ (C=O, CH_2CO_2Na), 158.8 (C-1′, sodium phenyl acetate), 158.7 (C-7; C-4″, benzyl), 156.6 (C-1″), 153.5 (C-3a), 147.6 (C-4a), 132.7 (C-8a), 130.3 (C-3′), 130.1 (C-5′), 128.3 (C-2″), 126.6 (C-6″), 125.8 (C-3″), 125.7 (C-5″), 122.9 (C-4′), 113.5 (C-5), 113.2 (C-8), 112.7 (C-2′), 112.3 (C-6′), 110.7 (C-8b), 110.4 (C-6), 75.0 (C-3), 53.8 (CH_2, benzyl; CH_3, $PhOCH_3$), 49.4 (CH_3, SO_2CH_3; CH_2, CH_2CO_2Na), 35.4 (C-2), 21.3 (C-1); HRESIMS *m/z* (pos): 546.1390 $C_{28}H_{25}FNNaO_6S$ (calcd. 546.1284).

Sodium 2-(4-((4-(2,4-dichlorobenzyl)-7-fluoro-5-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)oxy) phenyl) acetate(***I-18***) White solid (IPA), mp: 216–218 °C; IR (KBr) νmax 3404, 1587, 1509, 1490, 1473, 1388, 1301, 1231, 1145, 1123, 1039, 958, 832, 540 cm^{-1}; 1H NMR (MeOD, 300 MHz,): $\delta = 7.66–7.73$ (2H, m, H-6; H-8), 7.44 (1H, d, $J = 2.1$ Hz, H-3′, sodium phenyl acetate), 7.16–7.19 (1H, m, H-5′), 7.12–7.16 (2H, m, H-5″, benzyl; H-6″), 6.57–6.61 (2H, m, H-2′; H-6′), 6.16 (1H, d, $J = 8.4$ Hz, H-3″), 6.01 (1H, d, $J = 15.3$ Hz, Ar$\underline{CH_2}$), 5.90 (1H, d, $J = 15.3$ Hz, Ar$\underline{CH_2}$), 5.64–5.66 (1H, m, OCH), 3.40 (2H, s, $\underline{CH_2}CO_2Na$), 3.05–3.13 (2H, m, CH_2), 2.98 (3H, s, $SO_2\underline{CH_3}$), 2.90–2.96 (1H, m, $\underline{CH_2}$), 2.46–2.55 (1H, m, $\underline{CH_2}$); 13C NMR (MeOD, 300 MHz,): $\delta = 178.7$ (C=O, CH_2CO_2Na), 156.9 (C-1′, sodium phenyl acetate), 155.2 (C-7), 153.7 (C-1″, benzyl), 147.6 (C-3a), 135.1 (C-4a), 132.7 (C-8a), 131.5 (C-3′), 130.5 (C-5′), 129.3 (C-2″), 128.1 (C-4″), 127.3 (C-3″), 126.5 (C-6″), 123.3 (C-5″), 123.6 (C-4′), 114.2 (C-5), 112.6 (C-8), 112.3 (C-2′; C-8b), 110.5 (C-6′; C-6), 74.9 (C-3), 61.4 (CH_2, benzyl), 43.6 (CH_3, SO_2CH_3; CH_2, CH_2CO_2Na), 35.6 (C-2), 21.4 (C-1); HRESIMS *m/z* (pos): 584.0501 $C_{27}H_{21}Cl_2FNNaO_5S$ (calcd. 584.0399).

Pharmacology

The biological activity test was based on the method of Paolini (Paolini *et al.*, 2008). Briefly, male SPF C57BL/6 mice ($\sim$ 25 g) were purchased from Shanghai SLAC Laboratory Animal Co. (Shanghai, China) and were acclimatized for 2 days. Six mice were evaluated in each test group. Nembutal (3 % w/v) was injected (40 mg/kg) intraperitoneally to anesthetize the mice, and the initial velocity of blood flow in mouse ear was monitored by ZL104 microcirculatory detector (Xuzhou Public Medical Devices Co., China). Laropiprant and the compounds were dissolved in 5 % hydroxypropyl-β-cyclodextrin at 5 mg/mL and administered intraperitoneally (10 mg/kg). After 30 minutes, niacin (dissolved in 5 % hydroxypropyl-β-cyclodextrin at 12.5 mg/mL and adjusted to pH = 7.4) was injected subcutaneously. And the velocity of blood flow in mouse ear was measured every 2 min out of 10. The percentage of inhibition compared with vehicle was calculated as follows:

$$\text{Percentage of inhibition } (\%) = (R_2 - R_1)/R_2 \times 100\ \%$$

$$\text{Increased rate of blood flow velocity } (R) = V_1/V_0$$

V_1 blood flow velocity after administration of niacin (measured in every 2 of 10 min); V_0 initial blood flow velocity; R_1 increased rate of control group; R_2 increased rate of positive group (laropiprant) or experimental group (**I-1**–**I-18**).

Conclusions

In our present work, a series of novel laropiprant derivatives (**I-1**–**I-18**) have been synthesized and evaluated. Most compounds exhibited potent and fast-acting inhibitory

effect against niacin-induced flushing. Among them, **I-1**, **I-2**, **I-3**, **I-9**, **I-13**, **I-15** and **I-16** exhibited substantial flushing inhibitory effect. Especially, compounds **I-1** and **I-2** showed higher percentage of inhibition than laropiprant and would be valuable for further investigation. The resolution work and further biological evaluation of **I-1** and **I-2** are being studied and will be reported in future.

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