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Halogenation of 4-hydroxy/amino-3-methoxyphenyl acetamide TRPV1 agonists showed enhanced antagonism to capsaicin

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ABSTRACT

As an extension of our analysis of the effect of halogenation on thiourea TRPV1 agonists, we have now modified selected 4-hydroxy(or 4-amino)-3-methoxyphenyl acetamide TRPV1 agonists by 5- or 6-halogenation on the aromatic A-region and evaluated them for potency for TRPV1 binding and regulation and for their pattern of agonism/antagonism (efficacy). Halogenation shifted the functional activity at TRPV1 toward antagonism with a greater extent of antagonism as the size of the halogen increased (I > Br > Cl), as previously observed for the thiourea series. The extent of antagonism was greater for halogenation at the 5-position than at the 6-position, in contrast to SAR for the thiourea series. In this series, compounds **55** and **75** showed the most potent antagonism, with K_i (ant) = 2.77 and 2.19 nM, respectively, on rTRPV1 expressed in Chinese hamster ovary cells. The compounds were thus ca. 40–60-fold more potent than 6′-iodononivamide.

1. Introduction

The transient receptor potential cation channel, subfamily V, member 1 (TRPV1) is a molecular integrator of nociceptive stimuli expressed predominantly on unmyelinated pain-sensing nerve fibers (C-fibers) and small A δ fibers in the dorsal root, trigeminal, and nodose ganglia.[1–3] TRPV1 is structurally a homotetramer and functions as a non-selective cation channel with high Ca^{2+} permeability. The receptor is activated not only by protons,[4] heat,[5] and endogenous substances such as anandamide[6] and lipoxygenase products[7] but also by natural vanilloids such as capsaicin (CAP)[8] and resiniferatoxin (RTX)[9] or indirectly by bradykinin.[10] Its activation by these agents leads to an increase in intracellular Ca^{2+} resulting in excitation of the primary sensory neurons. The functional blockade of this receptor, by antagonism or by desensitization subsequent to stimulation by agonists, promises considerable therapeutic utility targeting inflammatory and neuropathic pain, cystitis, and bladder hyperreflexia.[11–15]

It was previously reported that the halogenation of the aromatic A-ring[16] of agonists shifted the agonism of the ligands toward antagonism. Two leading examples are 5-iodoresiniferatoxin (**1**)[17] and 6-iodononivamide (**2**),[18] iodinated products of the agonists RTX and nonivamide (Fig. 1), which showed potent antagonism. These findings prompted us to investigate how halogenation on the aromatic A-region of our potent *N*-(4-hydroxy-3-methoxybenzyl)thiourea agonists (**3**, **4**)[19–21] (Fig. 2) would modulate their functional activity. For this series, we found that halogenation shifted the activity of the ligands from agonism toward antagonism and that the extent depended on both the size of the halogen and the position halogenated. Iodination conferred the most enhancement of antagonism, with lesser effects from bromination and chlorination in that order.[22] The extent of antagonism upon 6-halogenation was higher than that of the corresponding 5-halogenation. The pattern of SAR resembled that of the capsaicinoids rather than that of resiniferatoxin, although the lead structure was derived from a pharmacophore model of resiniferatoxin.

As a continuing part of our SAR analysis of the effect of halogenation, we have investigated the effect of halogenation on potent acetamide TRPV1 agonists. Here, we describe the structure–activity relationships of 5- and 6-halogenated analogues of our lead agonists (**5** and **6**)[23] (Fig.2) for TRPV1 binding and regulation and for their pattern of agonism/antagonism (efficacy).

2. Result and discussion

2.1. Chemistry

The target halogenated acetamide compounds (**41–81**) were synthesized in general by the coupling of the carboxylic acids of

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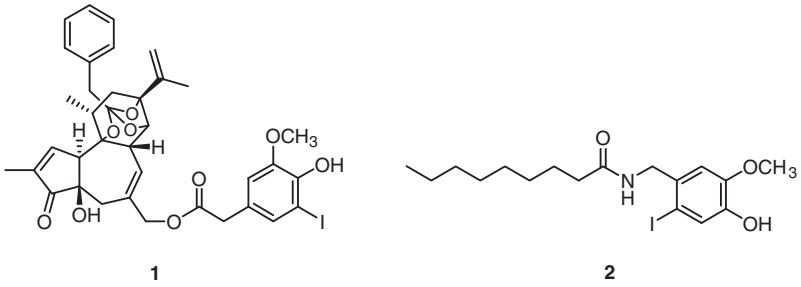


Figure 1.

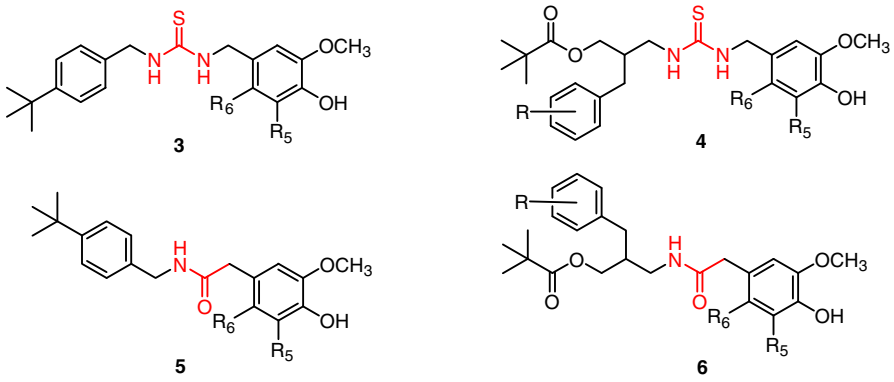
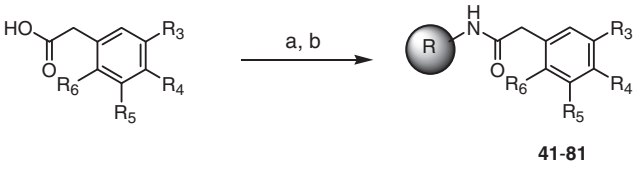


Figure 2.



Scheme 1. Reagents and conditions: (a) R-NH_2, EDC, HOBT, triethylamine, 1,4-dioxane or CH_2Cl_2, 50–98%; (b) CF_3CO_2H, CH_2Cl_2 (1:2) for R_4 = OMOM, 60–96%; pyrrolidine, CH_2Cl_2, for R_4 = OAc, 60–95%.

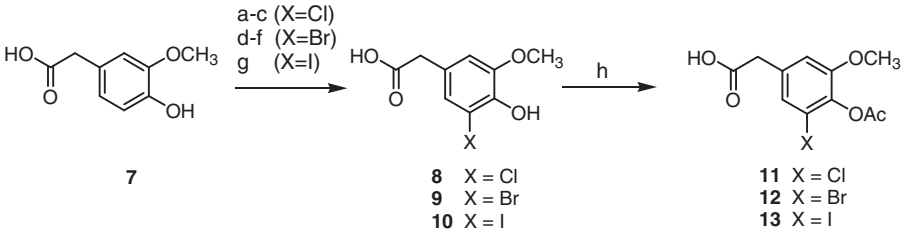
halogenated A-region moieties with the corresponding C-region amines, followed by appropriate O-deprotection if needed as represented in Scheme 1.

The syntheses of 5-halogenated 3-methoxy-4-hydroxy (or 4-acetoxy) and 6-halogenated 3-methoxy-4-hydroxy (or 4-acetoxy) A-regions were shown in Schemes 2 and 3, respectively, and the regioselectivity of halogenation was controlled by 4-hydroxy or 4-O-protected groups. The syntheses of 3-halo(or 3,5-dihalo)-4-hydroxy and 3-halo(or 3,5-dihalo)-4-amino A-regions were shown in Schemes 4 and 5 and selectivity was obtained by controlling the amount of halogenating reagent. 3-Methoxy-4-amino and 5-halo-3-methoxy-4-amino A-regions were synthesized by nitration of (3-hydroxyphenyl)acetic acid and halogenation of the 4-aminophenyl as represented in Scheme 6. 3-Methoxy-4-methylsulfonylamino and 6-bromo-3-methoxy-4-methylsulfonylamino A-regions were synthesized starting from the 3-methoxy-4-amino intermediate **31** as depicted in Scheme 7. Finally, the 3,5-dibromophenyl A-region was synthesized from 1,3-dibromo-5-fluorobenzene by nucleophilic substitution of ethyl cyanoacetate followed by decarboxylation as represented in Scheme 8.

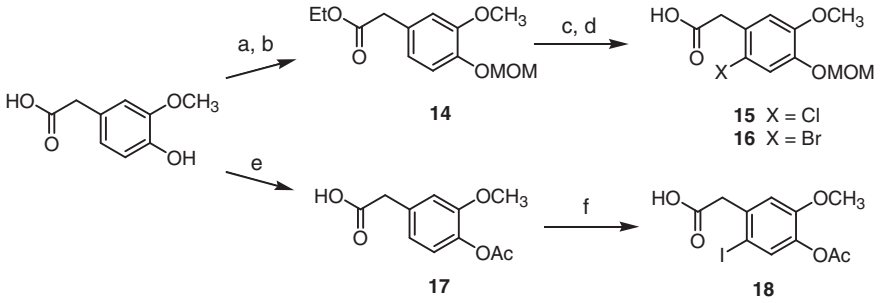
2.2. Biological activity

The binding affinities and agonistic/antagonistic functional activities of the synthesized TRPV1 ligands were assessed in vitro by a binding competition assay with [^{3}H]RTX and a functional $^{45}Ca^{2+}$ uptake assay using rat TRPV1 heterologously expressed in Chinese hamster ovary (CHO) cells, as previously described.[24] The results are summarized in Tables 1–3, together with the potencies of the parent agonists **5** and **6**. In particularly, compound **6**, *N*-[3-pivaloyloxy-2-(4-*t*-butylbenzyl)propyl]-2-(4-hydroxy-3-methoxyphenyl)acetamide, was previously reported as a simplified RTX analogue and was a potent high affinity TRPV1 agonist with K_i (binding) = 13.1 nM and EC_{50} (agonism) = 4.08 nM. 6′-Iodononivamide (**2**),[18] previously reported as the most potent antagonist in a series of nonivamides, was also evaluated as a reference and displayed full antagonism with K_i (binding) = 1320 nM and K_i (antagonism) = 127 nM, respectively.

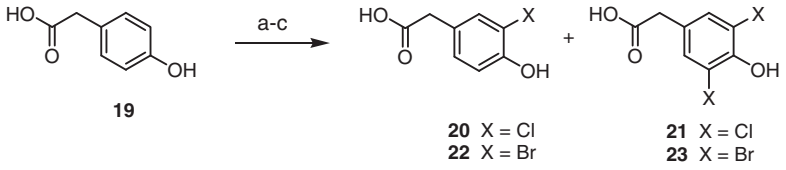
The structure–activity relationship analysis for A-region halogenation of (4-hydroxy-3-methoxyphenyl)acetamide agonists used a simple 4-*t*-butylbenzyl C-region as an initial choice. The TRPV1 binding and functional activity of halogenated analogues of *N*-(4-*t*-butylbenzyl)-2-(4-hydroxy-3-methoxyphenyl)acetamide (**5**) are outlined in Table 1. Starting with agonist **5**, 5-halogenation on the A-region progressively shifted the agonism toward antagonism as the size of halogen increased. For example, whereas 5-chlorination produced a partial antagonist **41** with 66% antagonism, 5-bromination gave an almost full antagonist **42** with only residual agonism, and 5-iodination afforded a full antagonist **43** with K_i (ant) = 17.2 nM. The 5-halogenated analogues (**41–43**) bound with higher affinity than did 6′-iodononivamide (**2**) and the parent compound (**5**), but showed little difference as the size of the halogen increased. In contrast, although 6-halogenation also shifted the agonism of **5** toward antagonism, the extent of the antagonism



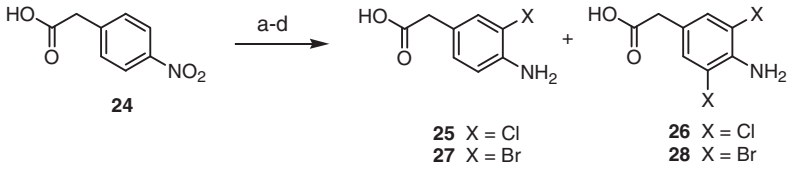
Scheme 2. Reagents and conditions: (a) MOMCl, NEt_3, CH_2Cl_2, 66%; (b) NCS, NaH, THF, 90%; (c) NaOH, THF–H_2O, 100%; (d) cat H_2SO_4, EtOH, 99%; (e) oxone, NaBr, acetone–H_2O, 56%; (f) NaOH, THF–H_2O, 100%; (g) KI, I_2, NH_4OH, 7%; (h) Ac_2O, cat H_2SO_4, CH_2Cl_2, 71% for Cl, 95% for Br, 100% for I.



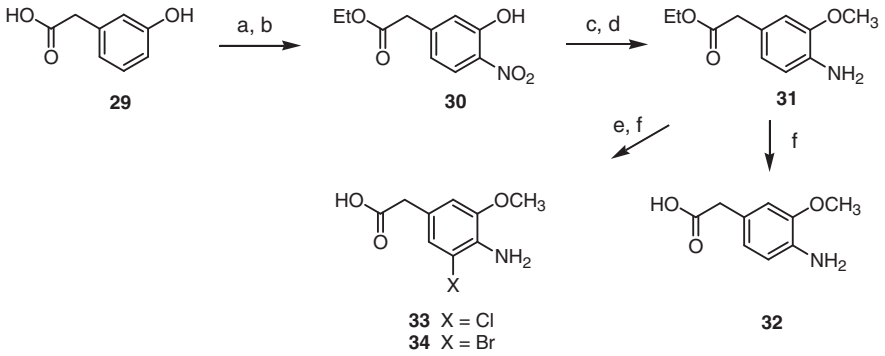
Scheme 3. Reagents and conditions: (a) cat H_2SO_4, EtOH, 99%; (b) MOMCl, DBU, DMF, 87%; (c) oxone, NaCl, acetone-H_2O, 79% for X = Cl; oxone, NaBr, acetone–H_2O, 91% for X = Br; (d) NaOH, THF–H_2O, 94–98%; (e) Ac_2O, cat H_2SO_4, CH_2Cl_2, 75%; (f) CF_3COOAg, I_2, CH_2Cl_2, 96%.



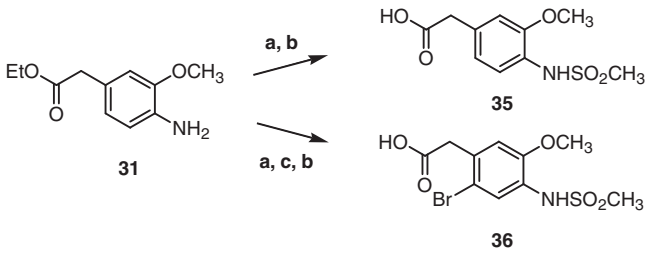
Scheme 4. Reagents and conditions: for X = Cl: (a) cat H_2SO_4, MeOH, 98%; (b) NCS, pyridine, toluene, 19%; (c) NaOH, THF–H_2O, 97%. for X = Br: (a) cat H_2SO_4, EtOH, 98%; (b) oxone, NaBr, acetone–H_2O; (c) NaOH, THF–H_2O, 100%.



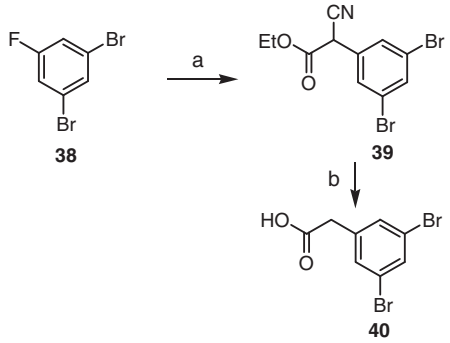
Scheme 5. Reagents and conditions: (a) cat H_2SO_4, EtOH, 95%, for **25** and **26**; cat H_2SO_4, MeOH, 98%, for **27** and **28**; (b) 10% Pd/C, H_2, THF–MeOH, 60–99%; (c) NCS (1.2 equiv), pyridine, toluene, 58% for mono-chloro compound; NCS (2.5 equiv), pyridine, toluene, 46% for dichloro compound; oxone, NaBr, acetone–H_2O, 36% for monobromo, 26% for dibromo; (d) NaOH or LiOH, THF–H_2O, 60–98%.



Scheme 6. Reagents and conditions: (a) cat H_2SO_4, EtOH, 97%; (b) HNO_3, AcOH, 30–58%; (c) K_2CO_3, CH_3I, acetone, 71%; (d) 10% Pd/C, H_2, THF–EtOH, 97%; (e) oxone, NaCl or NaBr, acetone–H_2O, 30%; (f) LiOH, THF–H_2O, 70–98%.



Scheme 7. Reagents and conditions: (a) methanesulfonyl chloride, pyridine, 99%; (b) LiOH, THF–H_2O, 30–56%; (c) oxone, NaBr, acetone–H_2O, 29%.



Scheme 8. Reagents and conditions: (a) ethyl cyanoacetate, NaH, DMF, 25%; (b) NaOH, H_2O 100%.

was less compared to 5-halogenation, full antagonism was not achieved even with the 6-iodo derivative (**46**), and the binding affinities of the 6-halogenated analogues (**44–46**) were weaker than those of the corresponding 5-halogenated analogues. A similar SAR pattern was observed with the 4-O-acetylated analogues (**47–52**) of 5- and 6-halogenated parent compounds.

The corresponding SAR of halogenated analogues possessing an *N*-(3-pivaloyloxy-2-benzylpropyl) C-region are described in Table 2. Similar to the SAR of the derivatives with an *N*-(4-*t*-butylbenzyl) C-region shown in Table 1, the halogenation of parent compound **6** converted the agonists to partial or full antagonists, and the extent of antagonism reflected the order of I > Br > Cl and 5-halogenation > 6-halogenation. Consequently, the 5- and 6-iodo analogues (**55** and **58**) were potent, full antagonists with K_i (ant) = 2.8 and 13.5 nM, respectively. Also, the 5-bromo compound (**54**) showed high affinity with a K_i = 9.4 nM and potent antagonism with a K_i (ant) = 8.77 nM.

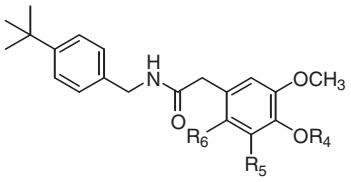
A similar SAR pattern was again observed for the 4-O-acetylated analogues (**59–64**) of the halogenated parent compounds. Their extents of functional antagonism were similar to those of the corresponding 4-hydroxy compounds, and the binding affinities were comparable or weaker.

The SAR of halogenated analogues possessing an *N*-3-pivaloyloxy-2-(3,4-dimethylbenzyl)propyl C-region was similar to that of the 4-*t*-butylbenzyl series, although they variably showed weaker binding or less antagonism, emphasizing the contribution of the C-region to the pattern of functional response (Table 2).

Since compound **54** was found to be a potent high affinity TRPV1 antagonist, further optimization was conducted with its derivatives and the results are shown in Table 3. Removal of the 3-methoxy group in **54** led to partial agonist **69** with lower binding affinity. Incorporation of an additional halogen, providing 3,5-dichloro and -dibromo analogues, gave potent antagonists **70** and **71** with K_i (ant) = 4.26 and 10.7 nM, respectively. Deletion of the 4-hydroxyl group in **71** led to the reduction in both binding affinity and antagonist potency as expected, although complete antagonism was still retained.

Next, the halogenated 4-amino-3-methoxy analogues as biosteres of the corresponding 4-hydroxy-3-methoxy agonists were explored as shown in Table 3. The 4-amino surrogate (**73**) of lead agonist **6** was also a full agonist with K_i = 108 nM and EC_{50} = 22.9 nM. However its binding affinity and potency as an agonist were 8-fold and 5.6-fold higher than for **6**. The 5-halogenation

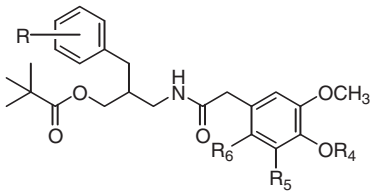
Table 1
rRPV1 activities of 4-*tert*-butylbenzyl C-region compounds



	R_4	R_5	R_6	K_i (nM) binding affinity	EC_{50} (nM) agonism[a]	K_i (nM) antagonism[b]
2				1320 ± 120	NE	127 ± 29
5	H	H	H	667 ± 86	82 ± 34	NE
41	H	Cl	H	164 ± 26	(25%)	(66%)
42	H	Br	H	91 ± 30	(11%)	168 ± 89
43	H	I	H	89 ± 9.2	NE	17.2 ± 2.4
44	H	H	Cl	486 ± 13	135 ± 18	NE
45	H	H	Br	364 ± 43	(37%)	(42%)
46	H	H	I	850 ± 200	(17%)	(55%)
47	Ac	Cl	H	205 ± 55	(22%)	570 ± 212
48	Ac	Br	H	166 ± 25	(9%)	(89%)
49	Ac	I	H	94 ± 14	NE	47.9 ± 5.6
50	Ac	H	Cl	388 ± 62	(83%)	(62%)
51	Ac	H	Br	393 ± 39	(60%)	(59%)
52	Ac	H	I	378 ± 63	(8%)	(85%)

NE, no effect.
Values represent mean ± SEM from three or more experiments.
[a] The values in parentheses indicates the% of maximal calcium uptake compared with that induced by 300 nM capsaicin.
[b] The values in parenthesis indicate the extent of partial antagonism.

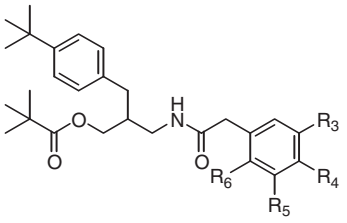
Table 2
rTRPV1 activities of 3-pivaloyloxy-2-benzylpropyl C-region compounds



	R	R_4	R_5	R_6	K_i (nM) binding affinity	EC_{50} (nM) agonism[a]	K_i (nM) antagonism[b]
6	4-*t*-Bu	H	H	H	13.1	4.08	NE
53	4-*t*-Bu	H	Cl	H	31 ± 13	(25%)	(76%)
54	4-*t*-Bu	H	Br	H	9.4 ± 1.4	NE	8.77 ± 0.48
55	4-*t*-Bu	H	I	H	22 ± 8.0	NE	2.8 ± 1.7
56	4-*t*-Bu	H	H	Cl	37.6 ± 4.6	(61%)	(39%)
57	4-*t*-Bu	H	H	Br	25.3 ± 6.9	(21%)	(76%)
58	4-*t*-Bu	H	H	I	20.9 ± 1.9	NE	13.5 ± 2.4
59	4-*t*-Bu	Ac	Cl	H	21.0 ± 6.3	(28%)	(58%)
60	4-*t*-Bu	Ac	Br	H	13.6 ± 1.1	NE	72 ± 13
61	4-*t*-Bu	Ac	I	H	20.3 ± 0.20	NE	19.1 ± 6.3
62	4-*t*-Bu	Ac	H	Cl	25.1 ± 4.2	(53%)	(36%)
63	4-*t*-Bu	Ac	H	Br	34.9 ± 9.3	(22%)	(63%)
64	4-*t*-Bu	Ac	H	I	19.5 ± 4.3	NE	53 ± 15
65	3,4-Me_2	H	Br	H	56.4 ± 8.8	(43%)	(62%)
66	3,4-Me_2	H	I	H	1630 ± 650	(6%)	225 ± 99
67	3,4-Me_2	Ac	I	H	4530 ± 990	(12%)	(59%)
68	3,4-Me_2	H	H	I	116 ± 42	(23%)	(53%)

NE, no effect.
Values represent mean ± SEM from three or more experiments.
[a] The values in parentheses indicates the % of maximal calcium uptake compared with that induced by 300 nM capsaicin.
[b] The values in parenthesis indicate the extent of partial antagonism.

Table 3
rTRPV1 activities of 3-pivaloyloxy-2-benzylpropyl C-region compounds



	R_4	R_3	R_5	R_6	K_i (nM) binding affinity	EC_{50} (nM) agonism[a]	K_i (nM) antagonism[b]
54	OH	OCH_3	Br	H	9.36	NE	8.77
69	OH	H	Br	H	25.1 ± 1.7	(72%)	(38%)
70	OH	Cl	Cl	H	9.3 ± 1.5	NE	4.26 ± 0.92
71	OH	Br	Br	H	20.2 ± 2.3	NE	10.7 ± 2.1
72	H	Br	Br	H	210 ± 97	NE	108 ± 14
73	NH_2	OCH_3	H	H	108 ± 32	22.9 ± 6.0	NE
74	NH_2	OCH_3	Cl	H	33.5 ± 2.0	NE	4.09 ± 0.47
75	NH_2	OCH_3	Br	H	79.1 ± 35	NE	3.4 ± 1.3
76	NH_2	Cl	H	H	790 ± 250	(85%)	(24%)
77	NH_2	Br	H	H	57 ± 16	(59%)	(27%)
78	NH_2	Cl	Cl	H	9.43 ± 0.52	NE	3.96 ± 0.68
79	NH_2	Br	Br	H	11.3 ± 2.2	NE	4.3 ± 1.7
80	$NHSO_2CH_3$	OCH_3	H	H	84.5 ± 0.34	(72%)	(15%)
81	$NHSO_2CH_3$	OCH_3	H	Br	42.9 ± 6.9	(14%)	(64%)

NE, no effect.
Values represent mean ± SEM from three or more experiments.
[a] The values in parentheses indicates the % of maximal calcium uptake compared with that induced by 300 nM capsaicin.
[b] The values in parenthesis indicate the extent of partial antagonism.

of **73**, providing **74** and **75**, shifted the agonism to full and potent antagonism for both derivatives, whereas the 5-chloro derivative (**41**) of the corresponding 4-hydroxy analogue had been only a partial antagonist. Of particular note, the 5-bromo compound **75**

displays very potent antagonism with K_i (ant) = 3.4 nM. The 5-halogenated 4-amino compounds (**76** and **77**) demonstrated mixed functional activity. However, incorporation of an additional halogen, giving 3,5-dihalo-4-amino analogues (**78** and **79**), was able to convert the partial antagonism to full antagonism.

The halogenation of the 4-methylsulfonylamino-3-methoxy analogue (**80**), another biostere of the 4-hydroxy-3-methoxy agonist, also caused a shift to more antagonism. Thus, the 6-bromo analogue (**81**) had more antagonistic activity compared to **80**.

Previously, halogenated resiniferatoxin (RTX) and capsaicinoid analogues were shown to have different structure–activity relationships for the reversal of activity from agonism to antagonism. In the RTX series, whereas 5-iodination produced full antagonism,[17] 6-iodination led to partial agonism with 50% efficacy.[25] On the other hand, in the capsaicinoid series, although both 5- and 6-iodo derivatives behaved as powerful antagonists under the same assay conditions, the 6-iodo derivatives showed a greater extent of antagonism than did the corresponding 5-iodo analogues. We describe here that halogenation at the 5-position of our TRPV1 ligands possessing an amide B-region was more effective than halogenation at the 6-position to confer antagonism. This contrasts with the SAR we have previously reported for halogenated analogues with a thiourea containing B-region.[22] We conclude that halogenated analogues with an amide containing B-region behave more like RTX-related ligands, whereas those with a thiourea containing B-region behave more like capsaicinoid-type ligands.

3. Conclusion

We have systematically modified the aromatic A-region of potent acetamide agonists by 5- and 6-halogenation in order to explore the role of halogens in the reversal of activity from agonism to antagonism and we have analyzed their structure–activity relationships. In general, the halogenation of 4-hydroxy, 4-acetoxy, 4-amino and 4-methylsulfonylamino parent compounds shifted the activity of the ligands from agonism to antagonism and the extent of the shift depended on both the size of the halogen, the halogenated position, and number of halogens added. As was the case with the thiourea B-region analogues previously reported,[22] the amide B-region analogues showed more antagonism as the size of the halogen increased, I > Br > Cl. However, in contrast to the results with the thiourea B-region analogues, the amide B-region analogues showed more antagonism upon 5-halogenation than upon 6-halogenation. Among the halogenated ligands synthesized, compounds **55** and **75** were found to be very potent full antagonists with K_i (antagonism) = 2.8 and 3.4 nM, being 45-fold and 37-fold more potent than 6′-iodononivamide, respectively. Our analysis indicated that the SAR of acetamide B-region agonists upon halogenation is similar to that of resiniferatoxin.

4. Experimental

4.1. General

All chemical reagents were commercially available. ROPA was purchased from LC Laboratories, Woburn, MA. Melting points were determined on a Büchi Melting Point B-540 apparatus and are uncorrected. Silica gel column chromatography was performed on Silica Gel 60, 230–400 mesh, Merck. Proton NMR spectra were recorded on a JEOL JNM-LA 300 at 300 MHz. Chemical shifts are reported in ppm units with Me_4Si as a reference standard. Infrared spectra were recorded on a Perkin-Elmer 1710 Series FTIR. Mass spectra were recorded on a VG Trio-2 GC–MS. Elemental analyses were performed with an EA 1110 Automatic Elemental Analyzer, CE Instruments.

4.2. (3-Chloro-4-hydroxy-5-methoxyphenyl)acetic acid (8)

A cooled solution of homovanillic acid (0.62 g, 3.4 mmol) in dichloromethane (10 mL) was treated with triethylamine (0.73 g, 7.2 mmol) and chloromethylmethyl ether (0.27 g, 3.4 mmol) at 0 °C. The reaction mixture was stirred for 1 h at room temperature and then dichloromethane was removed under low pressure. The residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (2:1) as eluant to give (4-hydroxy-3-methoxyphenyl)acetic acid methoxymethyl ester as a colorless oil (0.51 g, 66%): ^{1}H NMR ($CDCl_3$) δ 6.88–6.77 (m, 3H, Ar), 5.57 (s, 1H, OH), 5.24 (s, 2H, OCH_2O), 3.89 (s, 3H, OCH_3), 3.59 (s, 2H, CH_2CO), 3.41 (s, 3H, CH_2OCH_3); IR (neat) 3437, 2943, 1739, 1517, 1274, 1133, 1090 cm^{-1}.

A solution of (4-hydroxy-3-methoxyphenyl)acetic acid methoxymethyl ester (0.21 g, 0.93 mmol) in THF (3 mL) was cooled to 0 °C and then sodium hydride (0.076 g, 1.9 mmol) and *N*-chlorosuccinimide (0.13 g, 0.97 mmol) were added. The reaction mixture was stirred for 16 h at ambient temperature. Water (10 mL) was added and the mixture was then acidified with 1 N aqueous HCl solution to pH 3–4 and extracted with EtOAc several times. The combined organic layers were dried over magnesium sulfate, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (2:1) as eluant to give (3-chloro-4-hydroxy-3-methoxyphenyl)acetic acid methoxymethyl ester as a colorless oil (0.22 g, 90%): ^{1}H NMR ($CDCl_3$) δ 6.89 (d, 1H, J = 2.0 Hz, Ar), 6.74 (d, 1H, J = 1.8 Hz, Ar), 5.81 (s, 1H, OH), 5.25 (s, 2H, OCH_2O), 3.91 (s, 3H, OCH_3), 3.57 (s, 2H, CH_2CO), 3.43 (s, 3H, CH_2OCH_3); IR (neat) 3431, 2945, 1739, 1506, 1285, 1140, 1090, 1053, 930 cm^{-1}.

A solution of 2-[3-chloro-5-methoxy-4-(methoxymethoxy) phenyl]acetic acid (0.15 g, 0.58 mmol) in dichloromethane (2 mL) was treated with trifluoroacetic acid (1 mL) at 0 °C. The reaction mixture was stirred for 40 min at the same temperature and then quenched with sodium bicarbonate. Water was added and the mixture was extracted with dichloromethane several times. The combined organic layers were dried over magnesium sulfate, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using CH_2Cl_2/MeOH (2:1–1:1) as eluant to give 2-(3-chloro-4-hydroxy-5-methoxyphenyl)acetic acid as a white solid (0.11 g, 90%): ^{1}H NMR (CD_3OD) δ 7.12 (d, 1H, J = 2.0 Hz, Ar), 6.85 (d, 1H, J = 2.0 Hz, Ar), 3.88 (s, 3H, OCH_3), 3.60 (s, 2H, CH_2CO).

4.3. (3-Bromo-4-hydroxy-5-methoxyphenyl)acetic acid (9)

A mixture of homovanillic acid (**7**) (1.60 g, 8.8 mmol) and sulfuric acid (0.1 mL) in ethanol was refluxed for 2 h and cooled to room temperature. Water was added and the mixture was extracted with EtOAc several times. The combined organic layers were dried over magnesium sulfate, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (2:1) as eluant to give (4-hydroxy-3-methoxyphenyl)acetic acid ethyl ester as a white solid (1.83 g, 99%). The solution of (4-hydroxy-3-methoxyphenyl)acetic acid ethyl ester (2.21 g, 10.5 mmol) in acetone (30 mL) and water (30 mL) was treated with oxone (6.48 g, 21 mmol) and sodium bromide (4.38 g, 43 mmol). The reaction mixture was stirred 3 min at room temperature, diluted with EtOAc, quenched with 5% aqueous sodium thiosulfate (150 mL), and extracted with EtOAc. The organic layers were dried over magnesium sulfate, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (2:1) as eluant to give (3-bromo-4-hydroxy-5-methoxyphenyl)acetic acid ethyl ester as a yellow oil (1.71 g, 56%): ^{1}H NMR ($CDCl_3$) δ 7.02 (d, 1H, J = 1.7 Hz, Ar), 6.77 (d, 1H, J = 1.7 Hz, Ar), 5.87 (s, 1H,

OH), 4.16 (q, 2H, J = 7.1 Hz, CH_2CH_3), 3.90 (s, 3H, OCH_3), 3.50 (s, 2H, CH_2CO), 1.26 (t, 3H, J = 7.1 Hz, CH_2CH_3).

To a solution of (3-bromo-4-hydroxy-5-methoxyphenyl)acetic acid ethyl ester (1.68 g, 5.8 mmol) in THF (20 mL) and water (20 mL) was added sodium hydroxide (0.47 g, 11.8 mmol). The reaction mixture was stirred for 14 h at room temperature and then acidified with acetic acid to pH 3–4. The mixture was diluted with water (20 mL) and extracted with dichloromethane several times. The combined organic layers were dried over magnesium sulfate, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using CH_2Cl_2/MeOH (15:1) as eluant to give **9** as a white solid (1.51 g, 100%): ^{1}H NMR (CD_3OD) δ 7.10 (d, 1H, J = 2.0 Hz, Ar), 6.83 (d, 1H, J = 2.0 Hz, Ar), 3.85 (s, 3H, OCH_3), 3.57 (s, 2H, CH_2CO).

4.4. (4-Hydroxy-3-iodo-5-methoxyphenyl)acetic acid (10)

A solution of homovanillic acid (0.54 g, 3.0 mmol) in ammonium hydroxide (10 mL) was stirred for 20 min at room temperature. A suspension of potassium iodide (2.46 g, 14.8 mmol) and iodine (0.76 g, 3.0 mmol) in water (20 mL) was added to the reaction mixture and stirred for 20 min. The mixture was acidified with 2 N aqueous HCl solution to pH 3–4 and extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using CH_2Cl_2/MeOH (15:1) as eluant to give titled compound **10** (0.06 g, 7%): mp 177–179 °C; ^{1}H NMR (CD_3OD) δ 7.17 (d, 1H, J = 1.8 Hz, Ar), 6.85 (d, 1H, J = 1.8 Hz, Ar), 3.84 (s, 3H, OCH_3), 3.47 (s, 2H, CH_2CO).

4.5. General procedure for acetylation of phenols (11–13)

A solution of phenols (**8–10**, 1 mmol) in dichloromethane (5 mL) was treated with acetic anhydride (2 mmol) and sulfuric acid (0.05 mL) at room temperature. The reaction mixture was stirred for 1 h, water (10 mL) was added, and the mixture was extracted with dichloromethane several times. The combined organic layers were dried over magnesium sulfate, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using CH_2Cl_2/MeOH (15:1) as eluant to give acetylated compounds **11–13**.

4.5.1. (4-Acetoxy-3-chloro-5-methoxyphenyl)acetic acid (11)

A white solid (71%): mp 125–128 °C; ^{1}H NMR ($CDCl_3$) δ 6.97 (d, 1H, J = 1.7 Hz, Ar), 6.81 (d, 1H, J = 1.7 Hz, Ar), 3.83 (s, 3H, OCH_3), 3.60 (s, 2H, CH_2CO), 2.36 (s, 3H, OAc); IR (neat) 2943, 1767, 1713, 1420, 1283, 1190, 1052 cm^{-1}.

4.5.2. (4-Acetoxy-3-bromo-5-methoxyphenyl)acetic acid (12)

A yellow solid (95%): mp 110–112 °C; ^{1}H NMR ($CDCl_3$) δ 7.13 (d, 1H, J = 1.8 Hz, Ar), 6.85 (d, 1H, J = 1.8 Hz, Ar), 3.83 (s, 3H, OCH_3), 3.61 (s, 2H, CH_2CO), 2.36 (s, 3H, OAc); IR (neat) 2943, 1766, 1713, 1417, 1281, 1189, 1144, 1045 cm^{-1}.

4.5.3. (4-Acetoxy-3-iodo-5-methoxyphenyl)acetic acid (13)

A dark red solid (100%): mp 97–99 °C; ^{1}H NMR ($CDCl_3$) δ 7.32 (d, 1H, J = 1.7 Hz, Ar), 7.01 (d, 1H, J = 1.7 Hz, Ar), 3.80 (s, 3H, OCH_3), 3.58 (s, 2H, CH_2CO), 2.29 (s, 3H, OAc).

4.6. (3-Methoxy-4-methoxymethoxyphenyl)acetic acid ethyl ester (14)

(4-Hydroxy-3-methoxyphenyl)acetic acid ethyl ester was obtained by following the general esterification procedure described for compound **9** to afford a white solid (99%). A cooled solution of (4-hydroxy-3-methoxyphenyl)acetic acid ethyl ester (1.81 g, 8.6 mmol) in DMF (10 mL) was treated with DBU (1.95 g, 12.8 mmol) and chloromethylmethyl ether (1.05 g, 13.0 mmol) at 0 °C. The reaction mixture was stirred for 16 h at ambient temperature, water (50 mL) was added, and the mixture was extracted with EtOAc. The combined organic layers were dried over magnesium sulfate, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (4:1) as eluant to give titled compound **14** as a colorless oil (1.90 g, 87%): ^{1}H NMR ($CDCl_3$) δ 7.09 (d, 1H, J = 8.3 Hz, Ar), 6.87–6.75 (m, 2H, Ar), 5.21 (s, 2H, OCH_2O), 4.15 (q, 2H, J = 7.1 Hz, CH_2CH_3), 3.88 (s, 3H, OCH_3), 3.55 (s, 2H, CH_2CO), 3.51 (s, 3H, CH_2OCH_3), 1.26 (t, 3H, J = 7.1 Hz, CH_2CH_3); IR (neat) 2940, 1734, 1514, 1267, 1155, 1078, 1033, 998 cm^{-1}.

4.7. (2-Chloro-5-methoxy-4-methoxymethoxyphenyl)acetic acid (15)

To the solution of compound **14** (1.0 g, 3.93 mmol) in acetone (5 mL) and water (5 mL) was slowly added oxone (2.42 g, 7.87 mmol) and sodium chloride (1.60 g, 27.4 mmol). The reaction mixture was stirred for only 5 min at room temperature and then diluted with EtOAc (50 mL). The mixture was washed with 5% aqueous sodium sulfate. The organic layers were dried over magnesium sulfate, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (4:1) as eluant to give (2-chloro-5-methoxy-4-methoxymethoxyphenyl)acetic acid ethyl ester as a brown solid (0.90 g, 79%): mp 49–51 °C; ^{1}H NMR ($CDCl_3$) δ 7.20 (s, 1H, Ar), 6.81 (s, 1H, Ar), 5.21 (s, 2H, OCH_2O), 4.19 (q, 2H, J = 7.1 Hz, CH_2CH_3), 3.87 (s, 3H, OCH_3), 3.70 (s, 2H, CH_2CO), 3.51 (s, 3H, CH_2OCH_3), 1.28 (t, 3H, J = 7.0 Hz, CH_2CH_3); IR (neat) 2938, 1737, 1507, 1262, 1158, 1084, 996 cm^{-1}.

Hydrolysis of (2-chloro-5-methoxy-4-methoxymethoxyphenyl)acetic acid ethyl ester was performed following the procedure as described for compound **9** to obtain titled compound **15** as a white solid (98%): mp 101–103 °C; ^{1}H NMR (CD_3OD) δ 7.12 (s, 1H, Ar), 6.97 (s, 1H, Ar), 5.14 (s, 2H, OCH_2O), 3.82 (s, 3H, OCH_3), 3.69 (s, 2H, CH_2CO), 3.46 (s, 3H, CH_2OCH_3); IR (neat) 2945, 1708, 1510, 1266, 1172, 1085, 999 cm^{-1}.

4.8. (2-Bromo-5-methoxy-4-methoxymethoxyphenyl)acetic acid (16)

The titled compound **16** was obtained by following the procedure as described for compound **15** using sodium bromide instead of sodium chloride to afford a white solid: mp 117–119 °C; ^{1}H NMR (CD_3OD) δ 7.27 (s, 1H, Ar), 6.99 (s, 1H, Ar), 5.14 (s, 2H, OCH_2O), 3.82 (s, 3H, OCH_3), 3.71 (s, 2H, CH_2CO), 3.47 (s, 3H, CH_2OCH_3).

4.9. (4-Acetoxy-3-methoxyphenyl)acetic acid (17)

This compound **17** was obtained from homovanillic acid by following the general procedure for acetylation of phenols to afford a white solid: mp 131–133 °C; ^{1}H NMR (DMSO-d_6) δ 12.35 (s, 1H, COOH), 7.02 (d, 1H, J = 1.4 Hz, Ar), 7.00 (d, 1H, J = 7.9 Hz, Ar), 6.83 (dd, 1H, J = 7.9, 1.3 Hz, Ar), 3.75 (s, 3H, OCH_3), 3.57 (s, 2H, CH_2CO), 2.24 (s, 3H, OAc); IR (neat) 3442, 2940, 1751, 1705, 1228, 1157, 1029 cm^{-1}.

4.10. (4-Acetoxy-2-iodo-5-methoxyphenyl)acetic acid (18)

A mixture of compound **17** (0.20 g, 0.89 mmol), silver trifluoroacetate (0.22 g, 1.0 mmol), and iodine (0.24 g, 0.94 mmol) in dichloromethane (20 mL) was stirred for 2 h at room temperature. The solid in the reaction mixture was removed by filtration and washed with dichloromethane. The filtrate was washed with brine.

The organic layer was dried over magnesium sulfate, filtered, and the filtrate was concentrated in vacuo to afford titled compound **18** as a white solid (0.30 g, 96%): mp 156–158 °C; ^{1}H NMR (CD_3OD) δ 7.46 (s, 1H, Ar), 7.11 (s, 1H, Ar), 3.80 (s, 3H, OCH_3), 3.79 (s, 2H, CH_2CO), 2.24 (s, 3H, OAc); IR (neat) 3480, 2940, 1761, 1496, 1377, 1267, 1206, 1157 cm^{-1}.

4.11. (3,5-Dichloro-4-hydroxyphenyl)acetic acid (21)

A solution of (4-hydroxyphenyl)acetic acid methyl ester (**19**) (0.40 g, 2.41 mmol) in toluene (20 mL) was treated with *N*-chlorosuccinimide (0.81 g, 6.02 mmol) and pyridine (0.57 g, 7.20 mmol). The reaction mixture was refluxed for 1 day and then cooled to room temperature. Pyridine and toluene were removed under low pressure, water was added, and the mixture was extracted with EtOAc several times. The combined organic layers were dried over magnesium sulfate, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (6:1) as eluant to afford (3,5-dichloro-4-hydroxyphenyl)acetic acid methyl ester as a white solid (0.11 g, 19%): ^{1}H NMR ($CDCl_3$) δ 7.19 (s, 2H, Ar), 5.80 (s, 1H, OH), 3.71 (s, 3H, OCH_3), 3.51 (s, 2H, CH_2CO); IR (neat) 3427, 1732, 1491, 1418, 1283, 1239, 1165 cm^{-1}; The titled compound **21** was obtained from (3,5-dichloro-4-hydroxyphenyl)acetic acid methyl ester by following the general hydrolysis procedure for compound **9** to afford a white solid (97%): ^{1}H NMR (300 MHz, CD_3OD) δ 7.19 (s, 2H, Ar), 3.50 (s, 2H, CH_2CO); IR (neat) 3333, 2477, 1666, 1488, 1367, 1304, 1240, 1153 cm^{-1}.

4.12. (3-Bromo-4-hydroxyphenyl)acetic acid (22) and (3,5-dibr omo-4-hydroxyphenyl)acetic acid (23)

(4-Hydroxyphenyl)acetic acid ethyl ester was obtained by following the general esterification procedure described for compound **9** to afford a yellow oil (98%): ^{1}H NMR ($CDCl_3$) δ 7.12 (d, 2H, J = 8.6 Hz, Ar), 6.75 (d, 2H, J = 8.6 Hz, Ar), 5.51 (br s, 1H, OH), 4.15 (q, 2H, J = 7.1 Hz, CH_2CH_3), 3.54 (s, 2H, CH_2CO), 1.26 (t, 3H, J = 7.1 Hz, CH_2CH_3); IR (neat) 3396, 2923, 1708, 1515, 1223, 1027 cm^{-1}.

These titled compounds **22** and **23** were obtained from (4-hydroxyphenyl)acetic acid ethyl ester by following the previous procedure described for compound **9** to afford the mono-brominated compound (**22**) as a white solid (50%, two steps overall) and the di-brominated compound (**23**) as a white solid (37%, two steps overall). Compound **22**: mp 100–102 °C; ^{1}H NMR (CD_3OD) δ 7.35 (d, 1H, J = 2.0 Hz, Ar), 7.04 (dd, 1H, J = 8.0, 2.0 Hz, Ar), 6.67 (d, 1H, J = 8.0 Hz), 3.56 (s, 2H, CH_2CO); IR (neat) 3366, 2919, 1700, 1497, 1410, 1250, 1196, 904 cm^{-1}. Compound **23**: ^{1}H NMR (CD_3OD) δ 7.40 (s, 2H, Ar), 3.50 (s, 2H, CH_2CO); IR (neat) 3417, 2363, 1712, 1669, 1480, 1295, 1236, 1143 cm^{-1}.

4.13. (4-Amino-3-chlorophenyl)acetic acid (25)

(4-Nitrophenyl)acetic acid ethyl ester was obtained from **24** by following the general esterification procedure described for compound **9** to afford a white solid (95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, 2H, J = 9.0 Hz, Ar), 7.45 (d, 2H, J = 9.0 Hz, Ar), 4.18 (q, 2H, CH_2CH_3), 3.72 (s, 2H, CH_2CO), 1.26 (t, 3H, CH_2CH_3); IR (neat) 2984, 1732, 1604, 1513, 1345, 1223, 1179, 1110 cm^{-1}. The (4-nitrophenyl)acetic acid ethyl ester (6.22 g, 29.7 mmol) was dissolved in THF (60 mL) and ethanol (60 mL) and 10% Pd/C (0.62 g) was slowly added at room temperature. The reaction mixture was stirred for 20 h under a hydrogen atmosphere. The palladium carbon was removed by filtration and washed with EtOAc. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (2:1) as eluant to afford (4-aminophenyl)acetic acid ethyl ester as a yellow oil (3.20 g, 60%): ^{1}H NMR ($CDCl_3$) δ 7.06 (d, 2H, J = 9.0 Hz, Ar), 6.64 (d, 2H, J = 9.0 Hz, Ar), 4.13 (q, 2H, CH_2CH_3), 3.61 (br s, 2H, NH_2), 3.49 (s, 2H, CH_2CO), 1.26 (t, 3H, CH_2CH_3); IR (neat) 3369, 2982, 1728, 1627, 1517, 1368, 1260, 1152 cm^{-1}.

The (4-amino-3-chlorophenyl)acetic acid ethyl ester was obtained by following the chlorination procedure with *N*-chlorosuccinimide (1.2 equiv) as described for compound **21** to afford a pale brown oil (58%): ^{1}H NMR ($CDCl_3$) δ 7.18 (d, 1H, J = 2.0 Hz, Ar), 6.98 (dd, 1H, J = 8.3, 2.0 Hz, Ar), 6.72 (d, 1H, J = 8.0 Hz, Ar), 4.14 (q, 2H, J = 7.1 Hz, CH_2CH_3), 4.00 (br s, NH_2), 3.47 (s, 2H, CH_2CO), 1.25 (t, 3H, J = 7.1 Hz, CH_2CH_3); IR (neat) 3373, 2983, 1731, 1628, 1509, 1155, 1032 cm^{-1}.

The titled compound **25** was obtained from (4-amino-3-chlorophenyl)acetic acid ethyl ester by following the general hydrolysis procedure as described for compound **9** to afford a yellow solid (86%): ^{1}H NMR (CD_3OD) δ 7.19 (d, 1H, J = 2.0 Hz, Ar), 6.99 (dd, 1H, J = 8.3, 2.0 Hz, Ar), 6.75 (d, 1H, J = 8.0 Hz, Ar), 3.85 (br s, NH_2), 3.48 (s, 2H, $COCH_2$); IR (neat) 3437, 2922, 1697, 1626, 1511, 1413, 1370 cm^{-1}.

4.14. (4-Amino-3,5-dichlorophenyl)acetic acid (26)

(4-Amino-3,5-dichlorophenyl)acetic acid ethyl ester was obtained from (4-aminophenyl)acetic acid ethyl ester (**24**) by following the chlorination procedure with *N*-chlorosuccinimide (2.5 equiv) as described for compound **21** to afford a yellow solid (46%): ^{1}H NMR ($CDCl_3$) δ 7.12 (s, 2H, Ar), 4.40 (br s, NH_2), 4.14 (q, 2H, CH_2CH_3), 3.44 (s, 2H, CH_2CO), 1.25 (t, 3H, CH_2CH_3); IR (neat) 3381, 2983, 1732, 1621, 1417, 1225, 1160, 1031 cm^{-1}.

The titled compound **26** was obtained from (4-amino-3,5-dichlorophenyl)acetic acid ethyl ester by following the general hydrolysis procedure as described for compound **25** to afford a yellow solid (98%): ^{1}H NMR ($CDCl_3$) δ 7.11 (s, 2H, Ar), 3.45 (s, 2H, $COCH_2$); IR (neat) 2917, 1695, 1499, 1353, 1302, 1071 cm^{-1}.

4.15. (4-Amino-3-bromophenyl)acetic acid (27) and (4-amino-3,5-dibromophenyl)acetic acid (28)

(4-Nitrophenyl)acetic acid was followed by the general esterification procedure to afford (4-nitrophenyl)acetic acid methyl ester as a white solid (98%): ^{1}H NMR (300 MHz, $CDCl_3$) 8.20 (d, 2H, J = 8.6 Hz, Ar), 7.47 (d, 2H, J = 8.4 Hz, Ar), 3.75 (s, 2H, CH_2CO), 3.73 (s, 3H, OCH_3). The (4-nitrophenyl)acetic acid methyl ester (3.24 g, 16.6 mmol) was dissolved in THF (30 mL) and methanol (30 mL) and 10% Pd/C (0.28 g) was slowly added at room temperature. The reaction mixture was stirred for 20 h under a hydrogen atmosphere. The palladium carbon was removed by filtration and washed with EtOAc. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (2:1) as eluant to afford (4-aminophenyl)acetic acid methyl ester as a pale yellow oil (2.72 g, 99%): ^{1}H NMR ($CDCl_3$) δ 7.06 (d, 2H, J = 8.3 Hz, Ar), 6.65 (d, 2H, J = 8.4 Hz, Ar), 3.67 (s, 3H, OCH_3), 3.63 (br s, 2H, NH_2), 3.51 (s, 2H, CH_2CO); IR (neat) 3369, 2952, 1731, 1627, 1518, 1268, 1158 cm^{-1}.

The titled compounds **27** and **28** were obtained from (4-aminophenyl)acetic acid methyl ester by following the previous procedure as described for compound **9** to afford mono-brominated compound (**27**) as a pale pink solid (36%) and di-brominated compound (**28**) as a white solid (26%). Compound **27**: ^{1}H NMR (CD_3OD) δ 7.32 (d, 1H, J = 2.0 Hz, Ar), 7.00 (dd, 1H, J = 8.2, 2.0 Hz, Ar), 6.64 (d, 1H, J = 8.2 Hz), 3.52 (s, 2H, CH_2CO). Compound **28**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.30 (s, 2H, Ar), 4.40 (br s, 2H, NH_2), 3.50 (s, 2H, CH_2CO).

4.16. (3-Hydroxy-4-nitrophenyl)acetic acid ethyl ester (30)

(3-Hydroxyphenyl)acetic acid ethyl ester was obtained from **29** by following the general esterification procedure as described for

compound **9** to afford a yellow oil (97%): ^{1}H NMR ($CDCl_3$) δ 7.18 (dd, 1H, J = 7.9, 7.9 Hz, Ar), 6.85–6.72 (m, 3H, Ar), 5.28 (br s, 1H, OH), 4.16 (q, 2H, J = 7.1 Hz, CH_2CH_3), 3.56 (s, 2H, CH_2CO), 1.26 (t, 3H, J = 7.1 Hz, CH_2CH_3); IR (neat) 3398, 2984, 1711, 1595, 1458, 1280, 1155, 1029 cm^{-1}.

(3-Hydroxyphenyl)acetic acid ethyl ester was followed by the general nitration procedure using nitric acid and acetic acid to afford (3-hydroxy-4-nitrophenyl)acetic acid ethyl ester **30** as a yellow solid (30%): ^{1}H NMR ($CDCl_3$) δ 10.6 (s, 1H, OH), 8.07 (d, 1H, J = 8.8 Hz, Ar), 7.09 (d, 1H, J = 1.8 Hz, Ar), 6.92 (dd, 1H, J = 8.6, 1.8 Hz, Ar), 4.18 (q, 2H, J = 7.1 Hz, CH_2CH_3), 3.65 (s, 2H, CH_2CO), 1.27 (t, 3H, J = 7.1 Hz, CH_2CH_3); IR (neat) 3274, 2982, 1724, 1586, 1476, 1328, 1266, 1198 cm^{-1}.

4.17. (4-Amino-3-methoxyphenyl)acetic acid ethyl ester (31)

The mixture of **30** (0.25 g, 1.09 mmol), potassium carbonate (0.17 g, 1.25 mmol), and iodomethane (0.19 g, 1.32 mmol) in acetone (8 mL) was refluxed for 20 h and then cooled to room temperature. Water (30 mL) was added to the reaction mixture and the mixture was extracted with EtOAc several times. The combined organic layers were dried over magnesium sulfate, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (4:1) as eluant to afford (3-methoxy-4-nitrophenyl)acetic acid ethyl ester as a pale yellow oil (0.18 g, 71%): ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, J = 8.2 Hz, Ar), 7.04 (s, 1H, Ar), 6.95 (d, 1H, J = 8.2, 1.8 Hz, Ar), 4.18 (q, 2H, J = 7.1 Hz, CH_2CH_3), 3.97 (s, 3H, OCH_3), 3.67 (s, 2H, CH_2CO), 1.27 (t, 3H, J = 7.1 Hz, CH_2CH_3); IR (neat) 2981, 1734, 1608, 1520, 1349, 1275, 1169, 1027 cm^{-1}. (3-Methoxy-4-nitrophenyl)acetic acid ethyl ester was hydrogenated with 10% Pd/C by following the general procedure as described for compound **25** to afford **31** as a pale yellow oil (97%): ^{1}H NMR ($CDCl_3$) δ 6.74–6.64 (m, 3H, Ar), 4.13 (q, 2H, J = 7.1 Hz, CH_2CH_3), 3.85 (s, 3H, OCH_3), 3.75 (br s, 2H, NH_2), 3.51 (s, 2H, CH_2CO), 1.25 (t, 3H, J = 7.1 Hz, CH_2CH_3); IR (neat) 3369, 2932, 1728, 1518, 1246, 1151, 1033 cm^{-1}.

4.18. (4-Amino-3-methoxyphenyl)acetic acid (32)

The titled compound **32** was obtained from (4-amino-3-methoxyphenyl)acetic acid ethyl ester **31** by following the general hydrolysis procedure as described for compound **9**, but lithium hydroxide monohydrate was used instead of sodium hydroxide to afford a white solid (70%): ^{1}H NMR (CD_3OD) δ 6.70–6.60 (m, 3H, Ar), 3.85 (s, 3H, OCH_3), 3.49 (s, 2H, CH_2CO).

4.19. (4-Amino-3-chloro-5-methoxyphenyl)acetic acid (33)

(4-Amino-3-chloro-5-methoxyphenyl)acetic acid ethyl ester was obtained from **31** by following the previous procedure as described for compound **9** to afford a pale brown oil (58%): ^{1}H NMR ($CDCl_3$) δ 7.18 (d, 1H, J = 2.0 Hz, Ar), 6.98 (dd, 1H, J = 8.3, 2.0 Hz, Ar), 6.72 (d, 1H, J = 2.0 Hz, Ar), 4.14 (q, 2H, J = 7.1 Hz, CH_2CH_3), 4.00 (br s, NH_2), 3.47 (s, 2H, CH_2CO), 1.25 (t, 3H, J = 7.1 Hz, CH_2CH_3); IR (neat) 3373, 2983, 1731, 1628, 1509, 1155, 1032 cm^{-1}.

The titled compound **33** was obtained from the above ethyl ester by following the general hydrolysis procedure as described for compound **9** to afford a yellow solid (86%): ^{1}H NMR (CD_3OD) δ 7.19 (d, 1H, J = 2.0 Hz, Ar), 6.99 (dd, 1H, J = 8.3, 2.0 Hz, Ar), 6.75 (d, 1H, J = 2.0 Hz, Ar), 3.85 (br s, NH_2), 3.48 (s, 2H, CH_2CO); IR (neat) 3437, 2922, 1697, 1626, 1511, 1413, 1270, 903 cm^{-1}.

4.20. (4-Amino-3-bromo-5-methoxyphenyl)acetic acid (34)

(4-Amino-3-bromo-5-methoxyphenyl)acetic acid ethyl ester was obtained from **31** by following the previous procedure as described for compound **9** to afford a pale brown oil (30%): ^{1}H NMR ($CDCl_3$) δ 6.97 (d, 1H, J = 1.3 Hz, Ar), 6.67 (d, 1H, J = 1.4 Hz, Ar), 4.18–4.09 (m, 4H, CH_2CH_3 and NH_2), 3.85 (s, 3H, OCH_3), 3.47 (s, 2H, CH_2CO), 1.26 (t, 3H, J = 7.1 Hz, CH_2CH_3); IR (neat) 3375, 2979, 1732, 1577, 1501, 1288, 1254, 1158, 1045 cm^{-1}.

The titled compound **34** was obtained from the above ethyl ester by following the general hydrolysis procedure as described for compound **9** to afford a brown solid (98%): ^{1}H NMR ($CDCl_3$) δ 6.93 (d, 1H, J = 1.7 Hz, Ar), 6.75 (d, 1H, J = 1.7 Hz), 3.85 (s, 3H, OCH_3), 3.46 (s, 2H, CH_2CO); IR (neat) 3329, 2917, 1704, 1574, 1500, 1415, 1284 cm^{-1}.

4.21. (4-Methanesulfonylamino-3-methoxyphenyl)acetic acid (35)

A solution of **31** (0.71 g, 3.49 mmol) in pyridine (3 mL) was treated with methanesulfonyl chloride (0.59 g, 5.16 mmol) in an ice-water bath. The reaction mixture was stirred for 30 min at 0 °C and kept stirring for 14 h at room temperature. The reaction was quenched with 1 N aqueous HCl (30 mL) and extracted with EtOAc. The combined organic layers were dried over magnesium sulfate, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (1:1) as eluant to give (4-methanesulfonylamino-3-methoxyphenyl)acetic acid ethyl ester as a yellow oil (0.97 g, 99%): ^{1}H NMR ($CDCl_3$) δ 7.47 (d, 1H, J = 8.6 Hz, Ar), 6.88 (m, 2H, Ar), 6.74 (br s, 1H, NH), 4.16 (q, 2H, J = 7.1 Hz, CH_2CH_3), 3.89 (s, 3H, OCH_3), 3.59 (s, 2H, CH_2CO), 2.95 (s, 3H, SO_2CH_3), 1.27 (t, 3H, J = 7.1 Hz, CH_2CH_3); IR (neat) 3268, 2980, 1732, 1513, 1336, 1271, 1157, 1033 cm^{-1}.

The titled compound **35** was obtained from (4-methanesulfonylamino-3-methoxyphenyl)acetic acid ethyl ester by following the general hydrolysis procedure as described for compound **9**, but lithium hydroxide monohydrate was used instead of sodium hydroxide to afford a white solid (56%): mp 143–145 °C; ^{1}H NMR (CD_3OD) δ 7.32 (d, 1H, J = 8.0 Hz, Ar), 6.99 (d, 1H, J = 1.8 Hz, Ar), 6.85 (dd, 1H, J = 8.3, 2.0 Hz, Ar), 3.89 (s, 3H, OCH_3), 3.60 (s, 2H, CH_2CO), 2.89 (s, 3H, SO_2CH_3).

4.22. (2-Bromo-4-methanesulfonylamino-5-methoxyphenyl) acetic acid (36)

(2-Bromo-4-methanesulfonylamino-5-methoxyphenyl)acetic acid ethyl ester was obtained from (4-methanesulfonylamino-3-methoxyphenyl)acetic acid ethyl ester by following the bromination procedure described as described for compound **9** to afford a yellow oil (29%): ^{1}H NMR ($CDCl_3$) δ 7.73 (s, 1H, Ar), 6.86 (s, 1H, Ar), 6.79 (br, NH), 4.20 (q, 2H, J = 7.1 Hz, CH_2CH_3), 3.88 (s, 3H, OCH_3), 3.74 (s, 2H, CH_2CO), 3.00 (s, 3H, SO_2CH_3), 1.29 (t, 3H, J = 7.0 Hz, CH_2CH_3); IR (neat) 3266, 2980, 1732, 1502, 1332, 1151, 1034, 972 cm^{-1}.

The titled compound **36** was obtained from the above ethyl ester by following the general hydrolysis procedure as described for compound **9** to afford a yellow solid (30%): ^{1}H NMR (CD_3OD) δ 7.59 (s, 1H, Ar), 7.07 (s, 1H, Ar), 3.89 (s, 3H, OCH_3), 3.77 (s, 2H, CH_2CO), 2.92 (s, 3H, SO_2CH_3).

4.23. Cyano-(3,5-dibromophenyl)acetic acid ethyl ester (39)

A mixture of sodium hydride (0.5 2 g, 13.0 mmol), ethyl cyanoacetate (1.49 g, 13.2 mmol), and 1,3-dibromo-5-fluorobenzene (1.11 g, 4.37 mmol) in DMF (3 mL) was stirred at 110 °C for 36 h in a sealed tube and then cooled to room temperature. Water was added to the reaction mixture and the mixture extracted with ethyl ether several times. The combined organic layers were dried over magnesium sulfate, filtered, and the filtrate was concentrated in

vacuo. The residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (10:1) as eluant to afford titled compound **39** as a white solid (0.39 g, 25%): ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 1H, J = 1.7 Hz, Ar), 7.57 (d, 2H, J = 1.7 Hz, Ar), 4.65 (s, 1H, CHCN), 4.29 (q, 2H, J = 7.1 Hz, CH_2CH_3), 1.32 (t, 3H, J = 7.1 Hz, CH_2CH_3); IR (neat) 2920, 1748, 1585, 1561, 1427, 1260, 1026, 859 cm^{-1}.

4.24. (3,5-Dibromophenyl)acetic acid (40)

A mixture of **39** (0.37 g, 1.08 mmol) and sodium hydroxide (0.29 g, 7.23 mmol) in water (5 mL) was refluxed for 18 h and then cooled to room temperature. The reaction mixture was acidified with 1 N aqueous HCl solution to pH 2–4 and extracted with EtOAc several times. The combined organic layers were dried over magnesium sulfate, filtered, and the filtrate was concentrated in vacuo to give titled compound **40** as a pale yellow solid (0.32 g, 100%): mp 133–135 °C; ^{1}H NMR (CD_3OD) δ 7.70 (d, 1H, J = 1.7 Hz, Ar), 7.52 (d, 2H, J = 1.7 Hz, Ar), 3.60 (s, 2H, CH_2CO).

4.25. General procedure for amide coupling

A mixture of derivative phenyl acetic acid (1.0 mmol), alkyl amine (1.0 mmol), EDC (1.5 mmol), HOBT (1.5 mmol), and triethylamine (2.5 mmol) in 1,4-dioxane or dichloromethane was stirred for 12–24 h at room temperature. Water was added to the mixture and the mixture was extracted with EtOAc several times. The combined organic layers were dried over magnesium sulfate, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (4:1–1:1) as eluant to give the titled compound.

4.26. General procedure for acetylation

A solution of derivative 4-hydroxyphenyl acetamide (1.0 mmol) in dichloromethane (20 mL) was treated with acetic anhydride (1.2 mmol) and DBU (1.2 mmol) at room temperature. The reaction mixture was stirred for 2–8 h at the same temperature, water was added, and the mixture was then extracted with dichloromethane several times. The combined organic layers were dried over magnesium sulfate, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (2:1–1:1) as eluant to give the titled compound.

4.27. General procedure for deacetylation

A cooled solution of derivative 4-acetoxyphenyl acetamide (1.0 mmol) in dichloromethane (20 mL) was treated with pyrrolidine (20 mmol) at 0 °C. The reaction mixture was stirred for 1 h at the same temperature, water was added, and the mixture was extracted with dichloromethane several times. The combined organic layers were dried over magnesium sulfate, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (2:1–1:1) as eluant to give the titled compound.

4.28. General procedure for demethoxymethylation

A solution of derivative 4-methoxymethoxyphenyl acetamide (1.0 mmol) in dichloromethane (3 mL) was treated with trifluoroacetic acid (1.5 mL) at 0 °C. The reaction mixture was stirred for 40 min at the same temperature and then quenched with sodium bicarbonate. Water was added to the mixture, and the mixture was extracted with dichloromethane several times. The combined organic layers were dried over magnesium sulfate, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (2:1–1:1) as eluant to give the titled compound.

4.29. *N*-(4-*tert*-Butyl-benzyl)-2-(3-chloro-4-hydroxy-5-methoxy phenyl)acetamide (41)

A white solid (81%); mp 142–144 °C; ^{1}H NMR ($CDCl_3$) δ 7.54 (d, 2H, Ar), 7.15 (d, 2H, J = 8.0 Hz, Ar), 6.84 (s, 1H, Ar), 6.70 (s, 1H, Ar), 5.85 (s, 1H, OH), 5.72 (br s, 1H, NH), 4.39 (d, 2H, CH_2NH), 3.88 (s, 3H, OCH_3), 3.50 (s, 2H, CH_2CO), 1.30 (s, 9H, $C(CH_3)_3$); IR (neat) 3299, 2961, 1646, 1506, 1287, 1053 cm^{-1}; LRMS (FAB) m/z 362, 364 $[M+1]^+$. Anal. Calcd for $C_{20}H_{24}ClNO_3$: C, 66.38; H, 6.69; N, 3.87. Found: C, 66.64; H, 6.72; N, 3.84.

4.30. *N*-(4-*tert*-Butyl-benzyl)-2-(3-bromo-4-hydroxy-5-methoxy phenyl)acetamide (42)

A white solid (88%); mp 149–150 °C; ^{1}H NMR ($CDCl_3$) δ 7.34 (d, 2H, J = 8.3 Hz, Ar), 7.15 (d, 2H, J = 8.2 Hz, Ar), 6.98 (d, 1H, J = 1.6 Hz, Ar), 6.74 (d, 1H, J = 1.8 Hz, Ar), 5.98 (s, 1H, OH), 5.78 (br s, 1H, NH), 4.39 (d, 2H, J = 5.7 Hz, CH_2NH), 3.86 (s, 3H, OCH_3), 3.49 (s, 2H, CH_2CO), 1.30 (s, 9H, $C(CH_3)_3$); IR (neat) 3291, 2961, 1644, 1501, 1423, 1282, 1047 cm^{-1}; LRMS (FAB) m/z 406, 408 $[M+1]^+$. Anal. Calcd for $C_{20}H_{24}BrNO_3$: C, 59.12; H, 5.95; N, 3.45. Found: C, 59.41; H, 5.98; N, 3.43.

4.31. *N*-(4-*tert*-Butyl-benzyl)-2-(3-iodo-4-hydroxy-5-methoxy phenyl)acetamide (43)

A pale yellow solid (94%); mp 158–160 °C; ^{1}H NMR ($CDCl_3$) δ 7.34 (d, 2H, J = 8.3 Hz, Ar), 7.16 (m, 3H, Ar), 6.76 (s, 1H, Ar), 6.10 (s, 1H, OH), 5.73 (br s, 1H, NH), 4.39 (d, 2H, J = 5.7 Hz, CH_2NH), 3.86 (s, 3H, OCH_3), 3.49 (s, 2H, CH_2CO), 1.30 (s, 9H, $C(CH_3)_3$); IR (neat) 3257, 2960, 1627, 1494, 1420, 1279 cm^{-1}; LRMS (FAB) m/z 454 $[M+1]^+$, 476 $[M+Na]^+$. Anal. Calcd for $C_{20}H_{24}INO_3$: C, 52.99; H, 5.34; N, 3.09. Found: C, 53.26; H, 5.37; N, 3.07.

4.32. *N*-(4-*tert*-Butyl-benzyl)-2-(2-chloro-4-hydroxy-5-methoxy phenyl)acetamide (44)

A white solid (85%); mp 147–149 °C; ^{1}H NMR ($CDCl_3$) δ 7.34 (d, 2H, J = 8.3 Hz, Ar), 7.16 (d, 2H, J = 8.0 Hz, Ar), 6.96 (s, 1H, Ar), 6.82 (s, 1H, Ar), 5.78 (br s, 2H, OH and NH), 4.41 (d, 2H, J = 5.9 Hz, CH_2NH), 3.87 (s, 3H, OCH_3), 3.65 (s, 2H, CH_2CO), 1.30 (s, 9H, $C(CH_3)_3$); IR (neat) 3357, 2957, 1632, 1513, 1424, 1215, 1167 cm^{-1}; LRMS (FAB) m/z 362 $[M+1]^+$. Anal. Calcd for $C_{20}H_{24}ClNO_3$: C, 66.38; H, 6.69; N, 3.87. Found: C, 66.61; H, 6.73; N, 3.85.

4.33. *N*-(4-*tert*-Butyl-benzyl)-2-(2-bromo-4-hydroxy-5-methoxy phenyl)acetamide (45)

A white solid (80%); mp 168–170 °C; ^{1}H NMR ($CDCl_3$) δ 7.34 (d, 2H, J = 8.4 Hz, Ar), 7.17 (d, 2H, J = 8.3 Hz, Ar), 7.13 (s, 1H, Ar), 6.84 (s, 1H, Ar), 5.78 (br s, 1H, NH), 5.69 (s, 1H, OH), 4.41 (d, 2H, J = 5.7 Hz, CH_2NH), 3.87 (s, 3H, OCH_3), 3.67 (s, 2H, CH_2CO), 1.30 (s, 9H, $C(CH_3)_3$); IR (neat) 3357, 2958, 1631, 1511, 1424, 1214 cm^{-1}; LRMS (FAB) m/z 406 $[M+1]^+$. Anal. Calcd for $C_{20}H_{24}BrNO_3$: C, 59.12; H, 5.95; N, 3.45. Found: C, 59.42; H, 5.98; N, 3.42.

4.34. *N*-(4-*tert*-Butyl-benzyl)-2-(4-hydroxy-2-iodo-5-methoxyphenyl)acetamide (46)

A white solid; mp 90–92 °C; ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 2H, Ar), 7.11 (d, 2H, J = 8.43 Hz, Ar), 6.79 (s, 1H, Ar), 5.66 (br s, 1H, NH), 4.34 (d, 2H, J = 5.67 Hz, CH_2NH), 3.79 (s, 3H, OCH_3), 3.62 (s, 2H, CH_2CO), 1.20 (s, 9H, $C(CH_3)_3$); IR (neat) 3321, 2987, 1649, 1510,

1492, 1240, 1150, 1062, 987 cm^{-1}; LRMS (FAB) *m/z* 454 $[M+1]^+$. Anal. Calcd for $C_{20}H_{24}INO_3$: C, 52.99; H, 5.34; N, 3.09. Found: C, 53.30; H, 5.37; N, 3.06.

4.35. *N*-(4-*tert*-Butyl-benzyl)-2-(4-acetoxy-3-chloro-5-methoxy phenyl)acetamide (47)

A white solid (67%); mp 66–68 °C; ^1H NMR ($CDCl_3$) δ 7.35 (d, 2H, *J* = 8.3 Hz, Ar), 7.17 (d, 2H, *J* = 8.0 Hz, Ar), 6.92 (d, 1H, *J* = 1.8 Hz, Ar), 6.80 (d, 1H, *J* = 1.7 Hz, Ar), 5.81 (br t, 1H, NH), 4.40 (d, 2H, *J* = 5.7 Hz, CH_2NH), 3.80 (s, 3H, OCH_3), 3.53 (s, 2H, CH_2CO), 2.36 (s, 3H, OAc), 1.30 (s, 9H, $C(CH_3)_3$); IR (neat) 3290, 2961, 1769, 1648, 1544, 1191, 1052 cm^{-1}; LRMS (FAB) *m/z* 404 $[M+1]^+$. Anal. Calcd for $C_{22}H_{28}ClNO_4$: C, 65.42; H, 6.49; N, 3.47. Found: C, 65.69; H, 6.53; N, 3.44.

4.36. *N*-(4-*tert*-Butyl-benzyl)-2-(4-acetoxy-3-bromo-5-methoxy phenyl)acetamide (48)

A white solid (72%); mp 61–63 °C; ^1H NMR ($CDCl_3$) δ 7.34 (d, 2H, *J* = 8.4 Hz, Ar), 7.16 (d, 2H, *J* = 8.4 Hz, Ar), 7.06 (d, 1H, *J* = 1.8 Hz, Ar), 6.83 (d, 1H, *J* = 1.8 Hz, Ar), 5.99 (br s, 1H, NH), 4.38 (d, 2H, *J* = 5.7 Hz, CH_2NH), 3.78 (s, 3H, OCH_3), 3.49 (s, 2H, CH_2CO), 2.34 (s, 3H, OAc), 1.30 (s, 9H, $C(CH_3)_3$); IR (neat) 3290, 2961, 1769, 1647, 1189, 1046 cm^{-1}; LRMS (FAB) *m/z* 450 $[M+1]^+$. Anal. Calcd for $C_{22}H_{28}BrNO_4$: C, 58.94; H, 5.85; N, 3.12. Found: C, 59.25; H, 5.88; N, 3.09.

4.37. *N*-(4-*tert*-Butyl-benzyl)-2-(4-acetoxy-3-iodo-5-methoxy phenyl)acetamide (49)

A pale yellow solid (58%); mp 118–120 °C; ^1H NMR ($CDCl_3$) δ 7.35 (d, 2H, *J* = 8.3 Hz, Ar), 7.27 (d, 1H, Ar), 7.17 (d, 2H, *J* = 8.4 Hz, Ar), 6.87 (d, 1H, *J* = 1.7 Hz, Ar), 5.78 (br t, 1H, NH), 4.40 (d, 2H, *J* = 5.7 Hz, CH_2NH), 3.78 (s, 3H, OCH_3), 3.52 (s, 2H, CH_2CO), 2.36 (s, 3H, OAc), 1.30 (s, 9H, $C(CH_3)_3$); IR (neat) 3291, 2961, 1767, 1646, 1543, 1465, 1187 cm^{-1}; LRMS (FAB) *m/z* 496 $[M+1]^+$. Anal. Calcd for $C_{22}H_{28}INO_4$: C, 53.34; H, 5.29; N, 2.83. Found: C, 53.58; H, 5.32; N, 2.81.

4.38. *N*-(4-*tert*-Butyl-benzyl)-2-(4-acetoxy-2-chloro-5-methoxy phenyl)acetamide (50)

A white solid (62%); mp 53–55 °C; ^1H NMR ($CDCl_3$) δ 7.34 (d, 2H, *J* = 8.4 Hz, Ar), 7.18 (d, 2H, *J* = 8.4 Hz, Ar), 7.10 (s, 1H, Ar), 6.97 (s, 1H, Ar), 5.83 (br s, 1H, NH), 4.42 (d, 2H, *J* = 5.5 Hz, CH_2NH), 3.81 (s, 3H, OCH_3), 3.69 (s, 2H, CH_2CO), 2.31 (s, 3H, OAc), 1.30 (s, 9H, $C(CH_3)_3$); IR (neat) 3298, 2961, 1769, 1650, 1504, 1205, 1164 cm^{-1}; LRMS (FAB) *m/z* 404 $[M+1]^+$. Anal. Calcd for $C_{22}H_{28}ClNO_4$: C, 65.42; H, 6.49; N, 3.47. Found: C, 65.70; H, 6.53; N, 3.48.

4.39. *N*-(4-*tert*-Butyl-benzyl)-2-(4-acetoxy-2-bromo-5-methoxy phenyl)acetamide (51)

A white solid (51%); mp 67–69 °C; ^1H NMR ($CDCl_3$) δ 7.34 (d, 2H, *J* = 8.4 Hz, Ar), 7.26 (s, 1H, Ar), 7.18 (d, 2H, *J* = 8.4 Hz, Ar), 6.99 (s, 1H, Ar), 5.88 (br s, 1H, NH), 4.41 (d, 2H, CH_2NH), 3.80 (s, 3H, OCH_3), 3.71 (s, 2H, CH_2CO), 2.30 (s, 3H, OAc), 1.30 (s, 9H, $C(CH_3)_3$); IR (neat) 3296, 2961, 1767, 1652, 1499, 1206, 1161 cm^{-1}; LRMS (FAB) *m/z* 448, 450 $[M+1]^+$. Anal. Calcd for $C_{22}H_{28}BrNO_4$: C, 58.94; H, 5.85; N, 3.12. Found: C, 59.12; H, 5.88; N, 3.10.

4.40. *N*-(4-*tert*-Butyl-benzyl)-2-(4-acetoxy-2-iodo-5-methoxyphenyl)acetamide (52)

A white solid (74%); mp 124–126 °C; ^1H NMR ($CDCl_3$) δ 7.47 (s, 1H, Ar), 7.34 (d, 2H, *J* = 8.4 Hz, Ar), 7.20 (d, 2H, *J* = 8.3 Hz, Ar), 7.00 (s, 1H, Ar), 5.83 (br t, 1H, NH), 4.42 (d, 2H, *J* = 5.7 Hz, CH_2NH), 3.80 (s, 3H, OCH_3), 3.72 (s, 2H, CH_2CO), 2.30 (s, 3H, OAc), 1.30 (s, 9H, $C(CH_3)_3$); IR (neat) 3295, 2961, 1766, 1650, 1495, 1266, 1206, 1157 cm^{-1}; LRMS (FAB) *m/z* 496 $[M+1]^+$. Anal. Calcd for $C_{22}H_{28}INO_4$: C, 53.34; H, 5.29; N, 2.83. Found: C, 53.60; H, 5.32; N, 2.80.

4.41. 2-(4-*tert*-Butylbenzyl)-3-[2-(3-chloro-4-hydroxy-5-meth oxyphenyl)acetamido]propyl pivalate (53)

A white solid (90%); mp 109–111 °C; ^1H NMR ($CDCl_3$) δ 7.30 (m, 2H, Ar), 7.06 (m, 2H, Ar), 6.83 (d, 1H, *J* = 1.8 Hz, Ar), 6.72 (d, 1H, *J* = 1.8 Hz, Ar), 5.90 (s, 1H, OH), 5.85 (br s, 1H, NH), 4.05 (m, 1H, OCH_2), 3.90 (s, 3H, OCH_3), 3.83 (m, 1H, OCH_2), 3.41 (s, 2H, CH_2CO), 3.31 (m, 1H, $NHCH_2$), 3.06 (m, 1H, $NHCH_2$), 2.55 (d, 2H, *J* = 7.6 Hz, $ArCH_2$), 2.12 (m, 1H, CH), 1.30 (s, 9H, $C(CH_3)_3$), 1.21 (s, 9H, $C(CH_3)_3$); IR (neat) 3304, 2962, 1725, 1645, 1507, 1286, 1160 cm^{-1}; LRMS (FAB) *m/z* 505 $[M+1]^+$. Anal. Calcd for $C_{28}H_{38}ClNO_5$: C, 66.72; H, 7.60; N, 2.78. Found: C, 66.99; H, 7.64; N, 2.76.

4.42. 2-(4-*tert*-Butylbenzyl)-3-[2-(3-bromo-4-hydroxy-5-meth oxyphenyl)acetamido]propyl pivalate (54)

A white solid (85%); mp 63–65 °C; ^1H NMR ($CDCl_3$) δ 7.30 (d, 2H, *J* = 8.2 Hz, Ar), 7.05 (d, 2H, *J* = 8.3 Hz, Ar), 6.97 (d, 1H, *J* = 1.7 Hz, Ar), 6.76 (d, 1H, *J* = 1.7 Hz, Ar), 5.89 (s, 1H, OH), 5.83 (br s, 1H, NH), 4.05 (m, 1H, OCH_2), 3.90 (s, 3H, OCH_3), 3.83 (m, 1H, OCH_2), 3.41 (s, 2H, CH_2CO), 3.35 (m, 1H, $NHCH_2$), 3.05 (m, 1H, $NHCH_2$), 2.55 (d, 2H, *J* = 7.3 Hz, $ArCH_2$), 2.12 (m, 1H, CH), 1.30 (s, 9H, $C(CH_3)_3$), 1.21 (s, 9H, $C(CH_3)_3$); IR (neat) 3301, 2962, 1723, 1645, 1501, 1283, 1160, 1047 cm^{-1}; LRMS (EI) *m/z* 548 $[M]^+$, 570 $[M+Na]^+$. Anal. Calcd for $C_{28}H_{38}BrNO_5$: C, 61.31; H, 6.98; N, 2.55. Found: C, 61.58; H, 7.01; N, 2.52.

4.43. 2-(4-*tert*-Butylbenzyl)-3-[2-(4-hydroxy-3-iodo-5-meth oxyphenyl)acetamido]propyl pivalate (55)

A white solid (60%); mp 55–57 °C; ^1H NMR ($CDCl_3$) δ 7.30 (d, 2H, *J* = 8.4 Hz, Ar), 7.16 (d, 1H, *J* = 1.8 Hz, Ar), 7.05 (d, 2H, *J* = 8.4 Hz, Ar), 6.78 (d, 1H, *J* = 1.8 Hz, Ar), 6.11 (br s, 1H, OH), 5.83 (br s, 1H, NH), 4.04 (m, 1H, OCH_2), 3.88 (s, 3H, OCH_3), 3.83 (m, 1H, OCH_2), 3.39 (s, 2H, CH_2CO), 3.35 (m, 1H, $NHCH_2$), 3.05 (m, 1H, $NHCH_2$), 2.55 (d, 2H, *J* = 7.3 Hz, $ArCH_2$), 2.14 (m, 1H, CH), 1.30 (s, 9H, $C(CH_3)_3$), 1.21 (s, 9H, $C(CH_3)_3$); IR (neat) 3302, 2962, 1723, 1648, 1493, 1281, 1160, 1043 cm^{-1}; LRMS (FAB) *m/z* 596 $[M+1]^+$. Anal. Calcd for $C_{28}H_{38}INO_5$: C, 56.47; H, 6.43; N, 2.35. Found: C, 56.71; H, 6.48; N, 2.33.

4.44. 2-(4-*tert*-Butylbenzyl)-3-[2-(2-chloro-4-hydroxy-5-meth oxyphenyl)acetamido]propyl pivalate (56)

A white solid (98%); mp 92–94 °C; ^1H NMR ($CDCl_3$) δ 7.29 (d, 2H, *J* = 8.2 Hz, Ar), 7.04 (d, 2H, *J* = 8.3 Hz, Ar), 6.97 (s, 1H, Ar), 6.82 (s, 1H, Ar), 5.87 (br t, 1H, NH), 5.74 (s, 1H, OH), 4.03 (m, 1H, OCH_2), 3.89 (s, 3H, OCH_3), 3.83 (m, 1H, OCH_2), 3.58 (s, 2H, CH_2CO), 3.33 (m, 1H, $NHCH_2$), 3.11 (m, 1H, $NHCH_2$), 2.57 (m, 2H, $ArCH_2$), 2.13 (m, 1H, CH), 1.29 (s, 9H, $C(CH_3)_3$), 1.20 (s, 9H, $C(CH_3)_3$); IR (neat) 3365, 2962, 1723, 1649, 1512, 1281, 1161 cm^{-1}; LRMS (FAB) *m/z* 504 $[M+1]^+$. Anal. Calcd for $C_{28}H_{38}ClNO_5$: C, 66.72; H, 7.60; N, 2.78. Found: C, 67.00; H, 7.64; N, 2.75.

4.45. 2-(4-*tert*-Butylbenzyl)-3-[2-(2-bromo-4-hydroxy-5-metho xyphenyl)acetamido]propyl pivalate (57)

A white solid (95%); mp 101–103 °C; ^1H NMR ($CDCl_3$) δ 7.28 (d, 2H, *J* = 8.0 Hz, Ar), 7.13 (s, 1H, Ar), 7.04 (d, 2H, *J* = 8.0 Hz, Ar), 6.84

(s, 1H, Ar), 5.92 (s, 1H, OH), 5.89 (br t, 1H, NH), 4.03 (m, 1H, OCH_2), 3.88 (s, 3H, OCH_3), 3.84 (m, 1H, OCH_2), 3.61 (s, 2H, CH_2CO), 3.32 (m, 1H, $NHCH_2$), 3.11 (m, 1H, $NHCH_2$), 2.56 (m, 2H, $ArCH_2$), 2.13 (m, 1H, CH), 1.29 (s, 9H, $C(CH_3)_3$), 1.20 (s, 9H, $C(CH_3)_3$); IR (neat) 3303, 2962, 1724, 1648, 1509, 1279, 1210, 1161 cm^{-1}; LRMS (FAB) *m*/*z* 548 $[M+1]^+$. Anal. Calcd for $C_{28}H_{38}BrNO_5$: C, 61.31; H, 6.98; N, 2.55. Found: C, 61.50; H, 7.01; N, 2.52.

4.46. 2-(4-*tert*-Butylbenzyl)-3-[2-(4-hydroxy-2-iodo-5-methoxyphenyl)acetamido]propyl pivalate (58)

A white solid (86%); mp 145–147 °C; ^1H NMR ($CDCl_3$) δ 7.38 (s, 1H, Ar), 7.28 (d, 2H, *J* = 8.4 Hz, Ar), 7.04 (d, 2H, *J* = 8.3 Hz, Ar), 6.86 (s, 1H, Ar), 5.80 (br t, 1H, NH), 5.61 (s, 1H, OH), 4.04 (m, 1H, OCH_2), 3.88 (s, 3H, OCH_3), 3.85 (m, 1H, OCH_2), 3.63 (s, 2H, CH_2CO), 3.34 (m, 1H, $NHCH_2$), 3.12 (m, 1H, $NHCH_2$), 2.58 (m, 2H, $ArCH_2$), 2.14 (m, 1H, CH), 1.29 (s, 9H, $C(CH_3)_3$), 1.20 (s, 9H, $C(CH_3)_3$); IR (neat) 3360, 2962, 1721, 1649, 1508, 1277, 1161 cm^{-1}; LRMS (EI) *m*/*z* 596 $[M+1]^+$, 618 $[M+Na]^+$. Anal. Calcd for $C_{28}H_{38}INO_5$: C, 56.47; H, 6.43; N, 2.35. Found: C, 56.72; H, 6.45; N, 2.32.

4.47. 2-(4-*tert*-Butylbenzyl)-3-[2-(4-acetoxy-3-chloro-5-methoxyphenyl)acetamido]propyl pivalate (59)

A white solid (56%); mp 63–65 °C; ^1H NMR ($CDCl_3$) δ 7.30 (m, 2H, Ar), 7.06 (m, 2H, Ar), 6.91 (d, 1H, Ar), 6.82 (d, 1H, Ar), 4.06 (m, 1H, OCH_2), 3.83 (s, 3H, OCH_3), 3.44 (s, 2H, CH_2CO), 3.39 (m, 1H, $NHCH_2$), 3.07 (m, 1H, $NHCH_2$), 2.57 (d, 2H, *J* = 7.5 Hz, $ArCH_2$), 2.35 (s, 3H, OAc), 2.15 (m, 1H, CH), 1.30 (s, 9H, $C(CH_3)_3$), 1.22 (s, 9H, $C(CH_3)_3$); LRMS (FAB) *m*/*z* 546 $[M+1]^+$. Anal. Calcd for $C_{30}H_{40}ClNO_6$: C, 65.98; H, 7.38; N, 2.56. Found: C, 66.27; H, 7.41; N, 2.53.

4.48. 2-(4-*tert*-Butylbenzyl)-3-[2-(4-acetoxy-3-bromo-5-methoxyphenyl)acetamido]propyl pivalate (60)

A white solid (53%); mp 42–44 °C; ^1H NMR ($CDCl_3$) δ 7.31 (d, 2H, *J* = 8.2 Hz, Ar), 7.07 (m, 3H, Ar), 6.86 (d, 1H, *J* = 1.8 Hz, Ar), 4.09 (m, 1H, OCH_2), 3.84 (m, 1H, OCH_2), 3.82 (s, 3H, OCH_3), 3.44 (s, 2H, CH_2CO), 3.37 (m, 1H, $NHCH_2$), 3.06 (m, 1H, $NHCH_2$), 2.57 (d, 2H, *J* = 7.3 Hz, $ArCH_2$), 2.36 (s, 3H, OAc), 2.14 (m, 1H, CH), 1.30 (s, 9H, $C(CH_3)_3$), 1.22 (s, 9H, $C(CH_3)_3$); IR (neat) 3299, 2963, 1770, 1727, 1647, 1283, 1188, 1046 cm^{-1}; LRMS (EI) *m*/*z* 590 $[M]^+$. Anal. Calcd for $C_{30}H_{40}BrNO_6$: C, 61.01; H, 6.83; N, 2.37. Found: C, 61.30; H, 6.86; N, 2.35.

4.49. 2-(4-*tert*-Butylbenzyl)-3-[2-(4-acetoxy-3-iodo-5-methoxyphenyl)acetamido]propyl pivalate (61)

A white solid (51%); mp 91–93 °C; ^1H NMR ($CDCl_3$) δ 7.34–7.25 (m, 3H, Ar), 7.11–7.06 (m, 2H, Ar), 6.88 (d, 1H, *J* = 1.8 Hz, Ar), 5.92 (br s, 1H, NH), 4.08 (m, 1H, OCH_2), 3.87–3.81 (m, 4H, OCH_3 and OCH_2), 3.42 (s, 2H, CH_2CO), 3.35 (m, 1H, $NHCH_2$), 3.06 (m, 1H, $NHCH_2$), 2.58 (m, 2H, $ArCH_2$), 2.36 (s, 3H, OAc), 2.14 (m, 1H, CH), 1.31 and 1.30 (s, 9H, $C(CH_3)_3$), 1.22 and 1.17 (s, 9H, $C(CH_3)_3$); IR (neat) 3301, 2962, 1768, 1726, 1648, 1541, 1469, 1281, 1187 cm^{-1}; LRMS (FAB) *m*/*z* 638 $[M+1]^+$. Anal. Calcd for $C_{30}H_{40}INO_6$: C, 56.52; H, 6.32; N, 2.20. Found: C, 56.79; H, 6.35; N, 2.22.

4.50. 2-(4-*tert*-Butylbenzyl)-3-[2-(4-acetoxy-2-chloro-5-methoxyphenyl)acetamido]propyl pivalate (62)

A white solid (50%); mp 51–53 °C; ^1H NMR ($CDCl_3$) δ 7.30 (d, 2H, *J* = 8.3 Hz, Ar), 7.10 (s, 1H, Ar), 7.06 (d, 2H, *J* = 8.2 Hz, Ar), 6.97 (s, 1H, Ar), 5.94 (br t, 1H, NH), 4.07 (m, 1H, OCH_2), 3.86 (m, 1H, OCH_2), 3.83 (s, 3H, OCH_3), 3.62 (s, 2H, CH_2CO), 3.35 (m, 1H, $NHCH_2$), 3.11 (m, 1H, $NHCH_2$), 2.56 (m, 2H, $ArCH_2$), 2.31 (s, 3H, OAc), 2.15 (m, 1H, CH), 1.30 (s, 9H, $C(CH_3)_3$), 1.21 (s, 9H, $C(CH_3)_3$); IR (neat) 3301, 2963, 1770, 1727, 1651, 1504, 1203, 1162 cm^{-1}; LRMS (FAB) *m*/*z* 546 $[M]^+$, 568 $[M+Na]^+$. Anal. Calcd for $C_{30}H_{40}ClNO_6$: C, 65.98; H, 7.38; N, 2.56. Found: C, 65.70; H, 7.36; N, 2.58.

4.51. 2-(4-*tert*-Butylbenzyl)-3-[2-(4-acetoxy-2-bromo-5-methoxyphenyl)acetamido]propyl pivalate (63)

A white solid (57%); mp 63–65 °C; ^1H NMR ($CDCl_3$) δ 7.29 (d, 2H, *J* = 8.4 Hz, Ar), 7.26 (s, 1H, Ar), 7.06 (d, 2H, *J* = 8.3 Hz, Ar), 6.99 (s, 1H, Ar), 5.94 (br t, 1H, NH), 4.06 (m, 1H, OCH_2), 3.85 (m, 1H, OCH_2), 3.83 (s, 3H, OCH_3), 3.64 (s, 2H, CH_2CO), 3.35 (m, 1H, $NHCH_2$), 3.12 (m, 1H, $NHCH_2$), 2.56 (m, 2H, $ArCH_2$), 2.30 (s, 3H, OAc), 2.15 (m, 1H, CH), 1.30 (s, 9H, $C(CH_3)_3$), 1.21 (s, 9H, $C(CH_3)_3$); IR (neat) 3300, 1263, 1769, 1726, 1651, 1502, 1204, 1160 cm^{-1}; LRMS (FAB) *m*/*z* 590, 592 $[M]^+$. Anal. Calcd for $C_{30}H_{40}BrNO_6$: C, 61.01; H, 6.83; N, 2.37. Found: C, 61.32; H, 6.85; N, 2.34.

4.52. 2-(4-*tert*-Butylbenzyl)-3-[2-(4-acetoxy-2-iodo-5-methoxyphenyl)acetamido]propyl pivalate (64)

A white solid (50%); mp 58–60 °C; ^1H NMR ($CDCl_3$) δ 7.48 (s, 1H, Ar), 7.29 (d, 2H, *J* = 8.3 Hz, Ar), 7.06 (d, 2H, *J* = 8.3 Hz, Ar), 7.00 (s, 1H, Ar), 5.86 (br t, 1H, NH), 4.08 (m, 1H, OCH_2), 3.90 (m, 1H, OCH_2), 3.83 (s, 3H, OCH_3), 3.66 (s, 2H, CH_2CO), 3.35 (m, 1H, $NHCH_2$), 3.13 (m, 1H, $NHCH_2$), 2.61 (m, 2H, $ArCH_2$), 2.30 (s, 3H, OAc), 2.16 (m, 1H, CH), 1.30 (s, 9H, $C(CH_3)_3$), 1.21 (s, 9H, $C(CH_3)_3$); IR (neat) 3302, 2963, 1767, 1725, 1652, 1495, 1205, 1159 cm^{-1}; LRMS (EI) *m*/*z* 638 $[M+1]^+$, 660 $[M+Na]^+$. Anal. Calcd for $C_{30}H_{40}INO_6$: C, 56.52; H, 6.32; N, 2.20. Found: C, 56.79; H, 6.35; N, 2.16.

4.53. 3-[2-(3-Bromo-4-hydroxy-5-methoxyphenyl)acetamido]-2-(3,4-dimethylbenzyl)propyl pivalate (65)

A pale brown solid (60%); mp 63–65 °C; ^1H NMR ($CDCl_3$) δ 7.05–6.74 (m, 5H, Ar), 5.81 (br t, 1H, NH), 4.05 (m, 1H, OCH_2), 3.90 (s, 3H, OCH_3), 3.84 (m, 1H, OCH_2), 3.41 (s, 2H, CH_2CO), 3.31 (m, 1H, $NHCH_2$), 3.09 (m, 1H, $NHCH_2$), 2.51 (d, 2H, *J* = 7.5 Hz, $ArCH_2$), 2.26–2.05 (m, 7H, 2 × CH_3 and CH), 1.22 and 1.21 (s, 9H, $C(CH_3)_3$); IR (neat) 3302, 2969, 1722, 1650, 1501, 1283, 1162, 1047 cm^{-1}; LRMS (FAB) *m*/*z* 520, 522 $[M]^+$. Anal. Calcd for $C_{28}H_{34}BrNO_5$: C, 60.00; H, 6.58; N, 2.69. Found: C, 60.19; H, 6.56; N, 2.67.

4.54. 3-[2-(4-Hydroxy-3-iodo-5-methoxyphenyl)acetamido]-2-(3,4-dimethylbenzyl)propyl pivalate (66)

A white solid (80%); mp 64–66 °C; ^1H NMR ($CDCl_3$) δ 7.25 (m, 1H, Ar), 7.03 (m, 1H, Ar), 6.88–6.81 (m, 3H, Ar), 6.07 (s, 1H, OH), 5.87 (br t, 1H, NH), 4.17 (m, 1H, OCH_2), 3.91 (m, 1H, OCH_2), 3.89 (s, 3H, OCH_3), 3.55 (d, 2H, *J* = 2.6 Hz, CH_2CO), 3.30–3.08 (m, 2H, $NHCH_2$), 2.51 (d, 2H, *J* = 8.2 Hz, $ArCH_2$), 2.26–2.16 (m, 7H, 2 × CH_3 and CH), 1.12 (s, 9H, $C(CH_3)_3$); IR (neat) 3360, 2961, 1729, 1646, 1532, 1278 cm^{-1}; LRMS (FAB) *m*/*z* 568 $[M+1]^+$, 590 $[M+Na]^+$. Anal. Calcd for $C_{28}H_{34}INO_5$: C, 55.03; H, 6.04; N, 2.47. Found: C, 55.31; H, 6.06; N, 2.45.

4.55. 3-[2-(4-Acetoxy-3-iodo-5-methoxyphenyl)acetamido]-2-(3,4-dimethylbenzyl)propyl pivalate (67)

A white solid (55%); mp 60–62 °C; ^1H NMR ($CDCl_3$) δ 7.34 (d, 1H, *J* = 1.8 Hz, Ar), 7.03 (m, 1H, Ar), 6.90–6.85 (m, 3H, Ar), 5.87 (br t, 1H,

NH), 4.17 (m, 1H, OCH_2), 3.91 (m, 1H, OCH_2), 3.82 (s, 3H, OCH_3), 3.60 (s, 2H, CH_2CO), 3.27–3.11 (m, 2H, $NHCH_2$), 2.52 (d, 2H, J = 7.3 Hz, $ArCH_2$), 2.36 (s, 3H, OAc), 2.26–2.16 (m, 7H, 2 × CH_3 and CH), 1.12 (s, 9H, $C(CH_3)_3$); IR (neat) 3430, 2925, 1767, 1734, 1648, 1530, 1463, 1278, 1188 cm^{-1}; LRMS (FAB) m/z 610 $[M+1]^+$, 632 $[M+Na]^+$. Anal. Calcd for $C_{28}H_{36}INO_6$: C, 55.18; H, 5.95; N, 2.30. Found: C, 5543; H, 5.98; N, 2.29.

4.56. 2-(3,4-Dimethylbenzyl)-3-[2-(4-hydroxy-2-iodo-5-methoxyphenyl)acetamido]propyl pivalate (68)

A white solid (52%); mp 64–66 °C; ^1H NMR ($CDCl_3$) δ 7.37 (d, 1H, J = 2.73 Hz, Ar), 7.00 (t, 1H, J = 7.5 Hz, Ar), 6.85 (m, 3H, Ar), 5.76 (br s, 1H, NH), 5.60 (s, 1H, OH), 4.02 (m, 1H, CH), 3.88 (s, 3H, OCH_3), 3.85 (m, 2H, OCH_2), 3.65 (s, 2H, $COCH_2$), 3.32 (m, 2H, $NHCH_2$), 2.55 (m, 2H, $ArCH_2$), 2.21 (s, 6H, $Ar(CH_3)_2$), 1.20 (s, 9H, $C(CH_3)_3$); IR (neat) 3304, 2977, 1726, 1650, 1533, 1467, 1254, 1067 cm^{-1}; LRMS (FAB) m/z 568 $[M+1]^+$. Anal. Calcd for $C_{26}H_{34}INO_5$: C, 55.03; H, 6.04; N, 2.47. Found: C, 54.78; H, 6.01; N, 2.49.

4.57. 3-[2-(3-Bromo-4-hydroxyphenyl)acetamido]-2-(4-tert-butylbenzyl)propyl pivalate (69)

A white solid (50%); mp 55–57 °C; ^1H NMR ($CDCl_3$) δ 7.37–7.29 (m, 3H, Ar), 7.12–6.94 (m, 4H, Ar), 5.94 (s, 1H, OH), 5.84 (br t, 1H, NH), 4.06 (m, 1H, OCH_2), 3.83 (m, 1H, OCH_2), 3.45–3.32 (m, 3H, CH_2CO and $NHCH_2$), 3.07 (m, 1H, $NHCH_2$), 2.55 (m, 2H, $ArCH_2$), 2.13 (m, 1H, CH), 1.30 (s, 9H, $C(CH_3)_3$), 1.21 (s, 9H, $C(CH_3)_3$); IR (neat) 3299, 2963, 1724, 1648, 1540, 1287, 1161 cm^{-1}; LRMS (FAB) m/z 518, 520 $[M+1]^+$. Anal. Calcd for $C_{27}H_{36}BrNO_4$: C, 62.55; H, 7.00; N, 2.70. Found: C, 62.52; H, 7.04; N, 2.67.

4.58. 2-(4-*tert*-Butylbenzyl)-3-[2-(3,5-dichloro-4-hydroxyphenyl)acetamido]propyl pivalate (70)

A white solid (50%); mp 59–61 °C; ^1H NMR ($CDCl_3$) δ 7.31 (d, 2H, J = 8.4 Hz, Ar), 7.18 (s, 2H, Ar), 7.08 (d, 2H, J = 8.2 Hz, Ar), 5.92 (br t, NH), 4.11 (m, 1H, OCH_2), 3.85 (m, 1H, OCH_2), 3.38 (m, 1H, $NHCH_2$), 3.36 (s, 2H, $COCH_2$), 3.04 (m, 1H, $NHCH_2$), 2.57 (d, 2H, J = 7.5 Hz, $ArCH_2$), 2.15 (m, 1H, CH), 1.30 (s, 9H, $C(CH_3)_3$), 1.22 (s, 9H, $C(CH_3)_3$); IR (neat) 3303, 2964, 1723, 1650, 1558, 1488, 1285, 1162 cm^{-1}; LRMS (FAB) m/z 508 & 510 $[M+H]^+$. Anal. Calcd for $C_{27}H_{35}Cl_2NO_4$: C, 63.78; H, 6.94; N, 2.75. Found: C, 63.99; H, 6.89; N, 2.72.

4.59. 2-(4-*tert*-Butylbenzyl)-3-[2-(3,5-dibromo-4-hydroxyphenyl)acetamido]propyl pivalate (71)

A white solid (50%); mp 59–61 °C; ^1H NMR ($CDCl_3$) δ 7.37 (s, 2H, Ar), 7.31 (d, 2H, J = 8.2 Hz, Ar), 7.08 (d, 2H, J = 8.3 Hz, Ar), 5.91 (br t, 1H, NH), 4.11 (m, 1H, OCH_2), 3.85 (m, 1H, OCH_2), 3.43–3.33 (m, 3H, CH_2CO and $NHCH_2$), 3.05 (m, 1H, $NHCH_2$), 2.57 (d, 2H, $ArCH_2$), 2.14 (m, 1H, CH), 1.30 (s, 9H, $C(CH_3)_3$), 1.22 (s, 9H, $C(CH_3)_3$); IR (neat) 3303, 2963, 1721, 1650, 1548, 1477, 1284, 1160 cm^{-1}; LRMS (FAB) m/z 598 $[M+1]^+$. Anal. Calcd for $C_{27}H_{35}Br_2NO_4$: C, 54.29; H, 5.91; N, 2.34. Found: C, 54.60; H, 5.95; N, 2.31.

4.60. 2-(4-*tert*-Butylbenzyl)-3-[2-(3,5-dibromophenyl)acetamido]propyl pivalate (72)

A white solid (67%); mp 62–64 °C; ^1H NMR ($CDCl_3$) δ 7.58 (m, 1H, Ar), 7.37 (d, 2H, Ar), 7.32 (d, 2H, J = 8.0 Hz, Ar), 7.08 (d, 2H, J = 8.3 Hz, Ar), 5.65 (br t, 1H, NH), 4.12 (m, 1H, OCH_2), 3.85 (m, 1H, OCH_2), 3.43–3.33 (m, 2H, $COCH_2$ and $NHCH_2$), 3.06 (m, 1H, $NHCH_2$), 2.57 (d, 2H, $ArCH_2$), 2.14 (m, 1H, CH), 1.30 (s, 9H, $C(CH_3)_3$), 1.23 (s, 9H, $C(CH_3)_3$); IR (neat) 3300, 2963, 1729, 1648, 1553, 1158 cm^{-1}; LRMS (FAB) m/z 582 $[M+H]^+$, 604 $[M+Na]^+$. Anal. Calcd for $C_{27}H_{35}Br_2NO_3$: C, 55.78; H, 6.07; N, 2.41. Found: C, 56.01; H, 6.10; N, 2.38.

4.61. 2-(4-*tert*-Butylbenzyl)-3-[2-(4-amino-3-methoxyphenyl)acetamido]propyl pivalate (73)

A yellow solid (67%); mp 51–53 °C; ^1H NMR ($CDCl_3$) 7.28 (d, 2H, J = 8.3 Hz, Ar), 7.02 (d, 2H, J = 8.1 Hz, Ar), 6.70–6.62 (m, 3H, Ar), 5.71 (br t, 1H, NH), 3.97 (m, 1H, OCH_2), 3.84 (s, 3H, OCH_3), 3.81 (m, 1H, OCH_2), 3.45 (s, 2H, CH_2CO), 3.30 (m, 1H, $NHCH_2$), 3.10 (m, 1H, $NHCH_2$), 2.53 (d, 2H, $ArCH_2$), 2.11 (m, 1H, CH), 1.30 (s, 9H, $C(CH_3)_3$), 1.20 (s, 9H, $C(CH_3)_3$); IR (neat) 3303, 2962, 1726, 1648, 1518, 1284, 1160 cm^{-1}; LRMS (FAB) m/z 468 $[M+1]^+$, 491 $[M+Na]^+$. Anal. Calcd for $C_{28}H_{40}N_2O_4$: C, 71.76; H, 8.60; N, 5.98. Found: C, 71.98; H, 8.63; N, 5.96.

4.62. 2-(4-*tert*-Butylbenzyl)-3-[2-(4-amino-3-chloro-5-methoxyphenyl)acetamido]propyl pivalate (74)

A yellow solid (74%); mp 48–50 °C; ^1H NMR ($CDCl_3$) δ 7.29 (d, 2H, J = 8.2 Hz, Ar), 7.03 (d, 2H, J = 8.1 Hz, Ar), 6.76 (d, 1H, J = 1.5 Hz, Ar), 6.60 (d, 1H, J = 1.5 Hz, Ar), 5.76 (br t, 1H, NH), 4.14 (s, 2H, NH_2), 4.01 (m, 1H, OCH_2), 3.85 (s, 3H, OCH_3), 3.82 (m, 1H, OCH_2), 3.39 (s, 2H, $COCH_2$), 3.30 (m, 1H, $NHCH_2$), 3.08 (m, 1H, $NHCH_2$), 2.54 (d, 2H, J = 7.3 Hz, $ArCH_2$), 2.13 (m, 1H, CH), 1.30 (s, 9H, $C(CH_3)_3$), 1.20 (s, 9H, $C(CH_3)_3$); IR (neat) 3304, 2962, 1726, 1647, 1504, 1288, 1160, 1051 cm^{-1}; LRMS (FAB) m/z 503 $[M+H]^+$. Anal. Calcd for $C_{28}H_{39}ClN_2O_4$: C, 66.85; H, 7.81; N, 5.57. Found: C, 67.19; H, 7.84; N, 5.55.

4.63. 2-(4-*tert*-Butylbenzyl)-3-[2-(4-amino-3-bromo-5-methoxyphenyl)acetamido]propyl pivalate (75)

A pale pink solid (76%); mp 62–64 °C; ^1H NMR ($CDCl_3$) δ 7.29 (d, 2H, J = 8.4 Hz, Ar), 7.03 (d, 2H, J = 8.3 Hz, Ar), 6.91 (d, 1H, J = 1.7 Hz, Ar), 6.64 (d, 1H, J = 1.6 Hz, Ar), 5.78 (br t, 1H, NH), 4.20 (br s, 2H, NH_2), 4.01 (m, 1H, OCH_2), 3.86–3.81 (m, 4H, OCH_3 and OCH_2), 3.39 (s, 2H, CH_2CO), 3.32 (m, 1H, $NHCH_2$), 3.10 (m, 1H, $NHCH_2$), 2.54 (d, 2H, $ArCH_2$), 2.12 (m, 1H, CH), 1.30 (s, 9H, $C(CH_3)_3$), 1.20 (s, 9H, $C(CH_3)_3$); IR (neat) 2924, 1648, 1540, 1460, 1159 cm^{-1}; LRMS (FAB) m/z 548 $[M+1]^+$, 571 $[M+Na]^+$. Anal. Calcd for $C_{28}H_{39}BrN_2O_4$: C, 61.42; H, 7.18; N, 5.12. Found: C, 61.68; H, 7.15; N, 5.10.

4.64. 2-(4-*tert*-Butylbenzyl)-3-[2-(4-amino-3-chlorophenyl)acetamido]propyl pivalate (76)

A white solid (50%); mp 58–60 °C; ^1H NMR ($CDCl_3$) δ 7.30 (d, 2H, J = 8.2 Hz, Ar), 7.21 (d, 1H, J = 1.8 Hz, Ar), 7.06 (d, 2H, J = 8.0 Hz, Ar), 7.00 (dd, 1H, J = 8.0, 1.8 Hz, Ar), 6.74 (d, 1H, J = 8.3 Hz, Ar), 5.90 (br t, 1H, NH), 4.18 (m, 1H, OCH_2), 4.04 (br s, 2H, NH_2), 3.90 (m, 1H, OCH_2), 3.52 (s, 2H, $COCH_2$), 3.30 (m, 1H, $NHCH_2$), 3.04 (m, 1H, $NHCH_2$), 2.54 (d, 2H, J = 7.4 Hz, $ArCH_2$), 2.15 (m, 1H, CH), 1.29 (s, 9H, $C(CH_3)_3$), 1.11 (s, 9H, $C(CH_3)_3$); IR (neat) 3349, 2962, 1729, 1643, 1512, 1270, 1155 cm^{-1}; LRMS (FAB) m/z 473 $[M+H]^+$. Anal. Calcd for $C_{27}H_{37}ClN_2O_3$: C, 68.55; H, 7.88; N, 5.92. Found: C, 68.80; H, 7.86; N, 5.90.

4.65. 2-(4-*tert*-Butylbenzyl)-3-[2-(4-amino-3-bromophenyl)acetamido]propyl pivalate (77)

A white solid (73%); mp 47–49 °C; ^1H NMR ($CDCl_3$) δ 7.30 (m, 3H, Ar), 7.00 (m, 3H, Ar), 6.73 (d, 1H, J = 8.0 Hz, Ar), 5.74 (br t, 1H, NH), 4.10 (br s, 2H, NH_2), 4.02 (m, 1H, OCH_2), 3.83 (m, 1H, OCH_2), 3.38 (s, 2H, CH_2CO), 3.31 (m, 1H, $NHCH_2$), 3.09 (m, 1H,

$NHCH_2$), 2.54 (d, 2H, J = 7.3 Hz, $ArCH_2$), 2.13 (m, 1H, CH), 1.30 (s, 9H, $C(CH_3)_3$), 1.21 (s, 9H, $C(CH_3)_3$); IR (neat) 3328, 2962, 1724, 1649, 1505, 1284, 1161 cm^{-1}; LRMS (FAB) m/z 517 $[M+1]^+$, 541 $[M+Na]^+$. Anal. Calcd for $C_{27}H_{37}BrN_2O_3$: C, 62.66; H, 7.21; N, 5.41. Found: C, 62.90; H, 7.24; N, 5.43.

4.66. 2-(4-*tert*-Butylbenzyl)-3-[2-(4-amino-3,5-dichlorophenyl) acetamido]propyl pivalate (78)

A white solid (55%); mp 53–55 °C; ^1H NMR ($CDCl_3$) δ 7.31 (d, 2H, J = 8.4 Hz, Ar), 7.09 (s, 2H, Ar), 7.06 (d, 2H, J = 8.3 Hz, Ar), 5.81 (br t, 1H, NH), 4.43 (br s, 2H, NH_2), 4.07 (m, 1H, OCH_2), 3.85 (m, 1H, OCH_2), 3.39–3.31 (m, 3H, $NHCH_2$ and $COCH_2$), 3.07 (m, 1H, $NHCH_2$), 2.56 (d, 2H, J = 7.4 Hz, $ArCH_2$), 2.13 (m, 1H, CH), 1.30 (s, 9H, $C(CH_3)_3$), 1.21 (s, 9H, $C(CH_3)_3$); IR (neat) 3304, 2963, 1726, 1648, 1553, 1488, 1286, 1161 cm^{-1}; LRMS (FAB) m/z 507 $[M+H]^+$. Anal. Calcd for $C_{27}H_{36}Cl_2N_2O_3$: C, 63.90; H, 7.15; N, 5.52. Found: C, 64.21; H, 7.18; N, 5.50.

4.67. 2-(4-*tert*-Butylbenzyl)-3-[2-(4-amino-3,5-dibromophe nyl)acetamido]propyl pivalate (79)

A white solid (86%); mp 58–60 °C; ^1H NMR ($CDCl_3$) 7.31 (d, 2H, J = 8.2 Hz, Ar), 7.29 (s, 2H, Ar), 7.07 (d, 2H, J = 8.2 Hz, Ar), 5.80 (br t, 1H, NH), 4.54 (br s, 2H, NH_2), 4.08 (m, 1H, OCH_2), 3.85 (m, 1H, OCH_2), 3.35 (m, 1H, $NHCH_2$), 3.33 (s, 2H, CH_2CO), 3.07 (m, 1H, $NHCH_2$), 2.56 (d, 2H, J = 7.5 Hz, $ArCH_2$), 2.14 (m, 1H, CH), 1.30 (s, 9H, $C(CH_3)_3$), 1.22 (s, 9H, $C(CH_3)_3$); IR (neat) 3300, 2962, 1726, 1647, 1543, 1478, 1286, 1160 cm^{-1}; LRMS (FAB) m/z 597 $[M+H]^+$. Anal. Calcd for $C_{27}H_{36}Br_2N_2O_3$: C, 54.37; H, 6.08; N, 4.70. Found: C, 54.70; H, 6.10; N, 4.72.

4.68. 2-(4-*tert*-Butylbenzyl)-3-[2-(4-methanesulfonylamino-3-ethoxyphenyl)acetamido] propyl pivalate (80)

A white solid (60%); mp 66–68 °C; ^1H NMR ($CDCl_3$) 7.48 (d, 1H, J = 7.9 Hz, Ar), 7.30 (d, 2H, J = 8.2 Hz, Ar), 7.05 (d, 2H, J = 8.3 Hz, Ar), 6.88 (d, 1H, J = 1.8 Hz, Ar), 6.83 (dd, 1H, J = 8.1, 1.9 Hz, Ar), 6.76 (br s, 1H, NH), 5.90 (br t, 1H, NH), 4.06 (m, 1H, OCH_2), 3.88 (s, 3H, OCH_3), 3.81 (m, 1H, OCH_2), 3.48 (s, 2H, CH_2CO), 3.36 (m, 1H, $NHCH_2$), 3.02 (m, 1H, $NHCH_2$), 2.93 (s, 3H, SO_2CH_3), 2.55 (m, 2H, $ArCH_2$), 2.11 (m, 1H, CH), 1.30 (s, 9H, $C(CH_3)_3$), 1.21 (s, 9H, $C(CH_3)_3$); IR (neat) 3297, 2964, 1724, 1652, 1512, 1336, 1284, 1158 cm^{-1}; LRMS (FAB) m/z 547 $[M+1]^+$. Anal. Calcd for $C_{30}H_{45}N_2O_6S$: C, 64.14; H, 8.07; N, 4.99. Found: C, 64.34; H, 8.09; N, 4.97.

4.69. 2-(4-*tert*-Butylbenzyl)-3-[2-(2-bromo-4-methanesulfo nylamino-5-methoxyphenyl) acetamido]-propyl pivalate (81)

A white solid (50%); mp 165–167 °C; ^1H NMR ($CDCl_3$) 7.74 (s, 1H, Ar), 7.31–7.26 (m, 3H, Ar), 7.06 (d, 2H, J = 8.1 Hz, Ar), 6.94 (s, 1H, Ar), 6.78 (br s, 1H, NH), 6.01 (br t, 1H, NH), 4.06 (m, 1H, OCH_2), 3.89 (s, 3H, OCH_3), 3.85 (m, 1H, OCH_2), 3.62 (s, 2H, CH_2CO), 3.37 (m, 1H, $NHCH_2$), 3.10 (m, 1H, $NHCH_2$), 2.97 (s, 3H, SO_2CH_3), 2.57 (m, 2H, $ArCH_2$), 2.13 (m, 1H, CH), 1.30 (s, 9H, $C(CH_3)_3$), 1.20 (s, 9H, $C(CH_3)_3$); IR (neat) 3301, 2962, 1724, 1654, 1504, 1336, 1283, 1156 cm^{-1}; LRMS (FAB) m/z 625 and 627 $[M+H]^+$, 647 and 649 $[M+Na]^+$. Anal. Calcd for $C_{29}H_{41}BrN_2O_6S$: C, 55.67; H, 6.61; N, 4.48. Found: C, 55.95; H, 6.63; N, 4.46.

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