(Aryloxyacetylamino)benzoic Acid Analogues: A New Class of Hypoxia-Inducible Factor-1 Inhibitors

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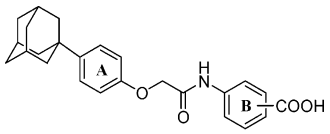
Structural modification of a compound discovered during screening using an HRE-dependent reporter assay has revealed a novel class of HIF-1 inhibitors, which potently inhibit the HIF-1α protein accumulation and its target gene expression under hypoxic conditions in human hepatocellular carcinoma Hep3B cells.

Development of intratumoral hypoxia is a hallmark of rapidly growing solid tumors and of their metastases. Hypoxic tumor cells are resistant to conventional chemotherapy and radiotherapy[1−3] and consequently the presence of hypoxia in tumors plays a negative role in patient prognosis. A key modulator expressed in many cancer cells in response to hypoxic stress is hypoxia-inducible factor-1 (HIF-1), a heterodimeric transcription factor that consists of an HIF-1α subunit and a HIF-1β subunit, both of which are members of the basic helix-loop-helix PER/Arnt/Sim (bHLH-PAS) transcription family. HIF-1β is also known as the aryl hydrocarbon nuclear translocator (ARNT). HIF-1 activity is dependent on the availability of the HIF-1α subunit, which is regulated by cellular oxygen levels. At normal oxygen levels, HIF-1α is degraded via the pVHL-mediated ubiquitin-proteosomal pathway. Under hypoxic conditions, however, HIF-1α rapidly accumulates in the cell and dimerizes with HIF-1β, which is constitutively expressed.[4] Binding of HIF-1 with co-activators to a specific DNA sequence within the target gene promoter, called the hypoxia-responsive elements (HRE), leads to transcriptional activation of a variety of genes involved in angiogenesis, glycolysis, growth factor signaling, tumor invasion, and metastasis.[5] In many cancers, the HIF-1 pathway is not only activated by low oxygen tension but is also induced or amplified by a wide range of growth-promoting stimuli and oncogenic signals. Clinically, HIF-1α overexpression has been shown to be a marker of highly aggressive cancers,[6] and inhibition of HIF-1 production and function significantly reduces tumor growth in animal models.[7] Accordingly, HIF-1 represents an attractive molecular target for the development of novel anticancer agents.[8]

In recent years, a number of anticancer agents have been identified as inhibitors of HIF-1 activity.[9] All of these inhibitors share in common an ability to decrease HIF-1α protein levels, inhibit the expression of HIF-1 target genes, such as *VEGF* and *EPO*, and impair tumor growth in animal models. In addition, a number of inhibitors targeting the HIF regulation pathways[10−13] as well as signal-transduction pathways[8,14−15] have also been reported.

As part of our ongoing efforts to identify small-molecule HIF-1 inhibitors, we have carried out a high-throughput cell-based reporter assay for our chemical library in human hepatocellular carcinoma Hep3B cells. The activity of HIF-1 was monitored using a luciferase reporter gene under the control of HRE from the VEGF gene.[16] This resulted in the identification of several hits. Among these, compound **1** (Figure 1) with an IC_{50} value of 5.0 μM in Hep3B cells was chosen as a starting point for the generation of a new class of HIF-1 inhibitors, because of its unique structure and its synthetic accessibility. Herein, we report the discovery of novel class of HIF-1 inhibitors identified by structural modification of **1**.



m-isomer(**1**) : IC_{50} 5.0 μM
o-isomer (**2**) : IC_{50}10.5 μM
p-isomer (**3**) : IC_{50} >30 μM

Figure 1. Compound **1** and its isomers.

The synthesis of compound **1** and its analogues **8**−**10** was accomplished as outlined in Scheme 1. Reaction of appropriate phenols **4** with ethyl chloroacetate followed by saponification yielded the required intermediates **5**. Compounds **9b**,**c** were commercially available and synthesis of compounds **9d**−**i** has been reported elsewhere.[17] Coupling of **6** with the appropriate aryloxyacetic acids **5a**,**d**−**i**, furnished the corresponding esters **8a**,**d-i**, which upon subsequent alkaline hydrolysis provided the corresponding acids **1**, **9d**−**i**. A similar sequence of reactions was followed to obtain ortho and para derivatives of **1** (**2** and **3** respectively, Figure 1). Compound **1** was further coupled with appropriate amines to obtain the respective amide derivatives **11**−**14**. A single-step coupling of **7** with the appropriate aryloxyacetic acids **5a**−**d**,**j** produced the corresponding amides **10a**−**d**,**j**, respectively. The Suzuki cross-coupling[18] of methyl 3-(2-(4-bromophenoxy)acetamido)benzoate **8h** with the appropriate aryl boronic acids followed by subsequent alkaline hydrolysis afforded cross-coupled products **15**−**18**.

Scheme 2 describes the synthesis of the hydroxylated analogues **23**−**30**. Compound **19** underwent benzylation, followed by hydrolysis to produce **20**, which upon subsequent protection with trimethylsilyl ethanol and hydrogenolysis furnished **22**. Coupling of adamantyl phenoxyacetic acid **5a** with amine intermediates **21** or **22** gave the corresponding esters **23** and **24**, respectively. The benzoic acid **25** was readily obtained from the trimethylsilylethyl (TME) ester **24** in higher yields than from the corresponding methyl ester **23** (79% vs 5.5%). Reaction of ester **23** with the appropriate amines in the presence of trimethylaluminum afforded the corresponding amide derivatives **26**−**28**. Compounds **29** and **30** were prepared under usual coupling conditions from the acid **25**.

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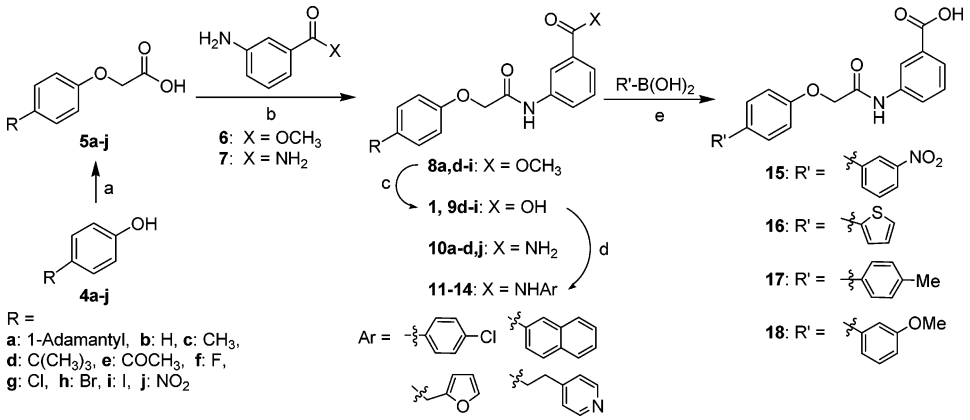
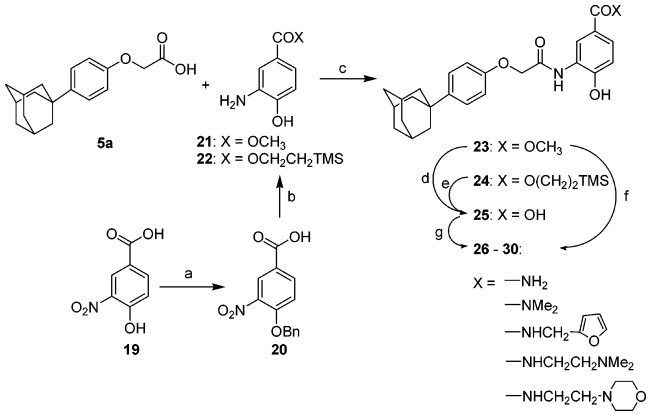
Scheme 1[a]



[a] Reaction conditions: (a) (i) Ethyl chloroacetate, K_2CO_3, DMF; (ii) LiOH·H_2O, dioxane, H_2O; (b) EDCI, HOBT, DIPEA, DMF; (c) LiOH·H_2O, dioxane, H_2O; (d) **1**, $ArNH_2$, EDCI, HOBT, DIPEA, DMF; (e) (i) **8h**, R = Br, X = OCH_3, $(PPh_3)_4Pd$, $NaHCO_3$, H_2O/DME, or [bmim][BF_4]; (ii) LiOH·H_2O, dioxane, H_2O.

Scheme 2[a]



[a] Reaction conditions: (a) (i) BnBr, K_2CO_3, acetone; (ii) NaOH, MeOH; (b) (i) 2-(trimethylsilyl)ethanol, HBTU, DIPEA, DMF; (ii) Pd/C, H_2, MeOH; (c) **5a**, oxalyl chloride, THF, DMF, and then **21** in pyridine for **23**; **22**, HBTU, DIPEA, DMF, 50 °C for **24**; (d) LiOH·H_2O, dioxane, H_2O; (e) TBAF, DMF; (f) amine, trimethylaluminum, toluene, 80 °C for **26**−**28**; (g) EDCI, HOBT, DIPEA, DMF for **29**; HATU, DIPEA, DMF for **30**.

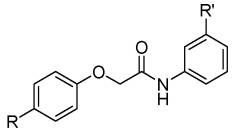
The newly synthesized compounds were evaluated for their potential to inhibit HIF-1 activation induced by hypoxia (1% O_2, 94% N_2, and 5% CO_2) using a HIF-1-mediated cell-based reporter assay in human hepatocellular carcinoma Hep3B and human gastric adenocarcinoma AGS cell lines (Table 1 and 2). All the assays were performed under standard assay conditions by employing hypoxic condition and following the previously described assay protocol.[19] Cell viability, as measured by the MTT assay, showed that most of the compounds had no significant cytotoxicity at their effective concentrations for the inhibition of HIF-1 activation (data not shown). YC-1,[9b] a known small-molecule HIF-1 inhibitor, was used as a reference compound for a comparison, which showed IC_{50} 13.8 and 2.0 μM in Hep3B and AGS cells, respectively.

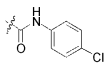
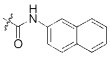
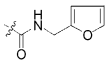
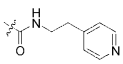
In order to define the key structural requirements for HIF-1 inhibition of aryloxyacetylaminobenzoic acid derivatives of **1**, our optimization strategy centered on two discrete areas: (1) the aminophenyl ring B, which could be derivatized and (2) the adamantyl phenyl ring A which could be replaced by a phenyl ring containing various ring activating groups. In view of the weak inhibitory activity of the ester **8a**, we first examined the significance of the carboxyl group on the *N*-phenyl ring B. We synthesized the corresponding ortho and para isomers **2** and **3** (Figure 1), which were found to be less potent than the meta isomer **1**, suggesting that the compound with the carboxylic acid moiety at the meta position is the best isomer for inhibitory activity. Subsequently, we investigated the effects of different aromatic substituents on the adamantyl phenyl ring A, retaining the carboxyl group at the meta position of ring B. Almost all derivatives **9b**−**i**, **15**−**18**, with various functionalities, displayed poor inhibitory activity in both the cell lines, with the exception of compounds **9h** and **9i**, which demonstrated considerable inhibitory potency in the AGS cell line. These results strongly suggested that the replacement of adamantyl group with a substituted phenyl ring caused a significant loss of activity and that the presence of the adamantyl substituent, or an equivalent, on ring A is essential for effective inhibition of HIF-1 activation in hypoxia.

The *m*-aminobenzamide derivative **10a**, which was moderately active in Hep3B cell line, demonstrated appreciably more inhibitory potency relative to **1** in AGS cell line. On the basis of increased inhibitory potency of **10a**, we substituted adamantyl group with a proton or with different functional groups (**10b-d**, **j**) while retaining the acylamino moiety meta to the carboxyl group in ring B, but this modification resulted in significantly diminished inhibitory activity. We then explored the effects of altering the amide group by preparing the amide derivatives **11**−**14**, in which *p*-chlorobenzene, 2-naphthyl, furfuryl, or ethyl pyridine rings attached *via* an amide bond. Compounds **13** and **14**, linked through one carbon and two carbon chain respectively, demonstrated considerable potency in AGS cells, while **11** and **12** exhibited poor inhibition ability in both the cell lines. The impact of modification to the B-ring carboxylic acid moiety is of particular interest in the light of preliminary SAR results, which suggests that a free acid or amide group at this position is optimal for HIF-1 inhibition and that further derivatization results in the significant loss of activity, except in the case of analogues **9h**,**i**, **13**, and **14** which were as active as **1** in AGS cells. Having established the primary structure−activity relationship of rings A and B, we then introduced hydroxyl group para to the amide in ring B, while retaining the adamantyl group on ring A. This modification provided compounds **23** and **25**, which showed significantly enhanced inhibition of HIF-1 activity in both the cell lines. On the other hand, although **26** and **29** were active in AGS cells, compounds **27**, **28**, and **30** showed a marked decrease in inhibitory activity.

To confirm their inhibition of HIF-1 activation, compounds **1**, **10a**, **23**, and **25**, which showed good inhibitory activity in both cell lines, were evaluated by Western blot analysis for their

Table 1. In Vitro Inhibition of HIF-1 Transcriptional Activity in Cell-Based HRE Reporter Assay[a]

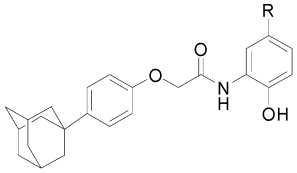


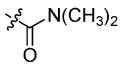
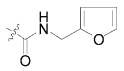
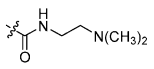
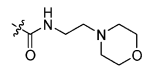
compd	R	R'	Hep3B IC_{50} (μM)	AGS IC_{50} (μM)
8a		$COOCH_3$	9.9	7.4
1		COOH	5.0	2.5
9b	H	COOH	>30	>30
9c	CH_3	COOH	>30	>30
9d	$C(CH_3)_3$	COOH	29	9.5
9e	$COCH_3$	COOH	>30	>30
9f	F	COOH	>30	>30
9g	Cl	COOH	>30	10
9h	Br	COOH	>30	1.6
9i	I	COOH	7.2	3.5
10a		$CONH_2$	4.3	1.0
10b	H	$CONH_2$	>30	>30
10c	CH_3	$CONH_2$	>30	>30
10d	$C(CH_3)_3$	$CONH_2$	>30	>30
10j	NO_2	$CONH_2$	>30	>30
11			>30	9.5
12			>30	>30
13			14.08	2.1
14			8.2	3.1
15		COOH	>30	>30
16		COOH	>30	>30
17		COOH	23.2	>30
18		COOH	>30	35
YC-1			13.8	2.0

[a] Values were obtained as described in the Supporting Information.

effect on hypoxia-induced HIF-1α accumulation. As shown in Figure 2, all four of these inhibitors blocked HIF-1α accumulation in a dose-dependent manner without affecting the expression level of HIF-1β protein. Of the four compounds, **23** was the most potent inhibitor of HIF-1α accumulation. Accordingly,

Table 2. Structure−Activity Relationships of Hydroxybenzoic Acid Derivatives Based in Cell-Based HRE Reporter Assay[a]



compd	R	Hep3B IC_{50} (μM)	AGS IC_{50} (μM)
23	$COOCH_3$	2.6	0.7
25	COOH	0.4	0.35
26	$CONH_2$	>30	1.5
27		>30	>30
28		12.6	5.9
29		>30	3
30		>30	>30

[a] Values were obtained as described in the Supporting Information.

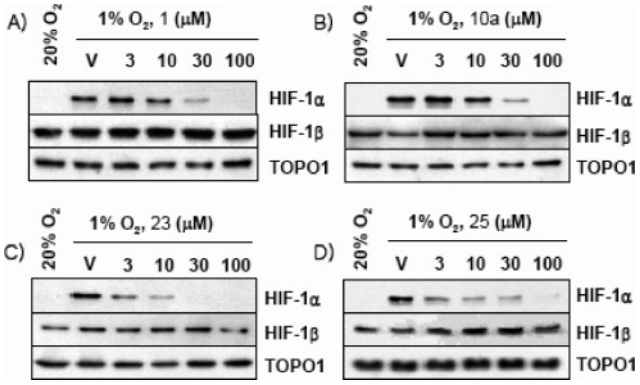


Figure 2. Western Blot analysis for the effect of compounds **1** (A), **10a** (B), **23** (C) and **25** (D) on the accumulation of HIF-1α and HIF-1β proteins in Hep3B cells under hypoxic condition. TOPO1 was used as load control and V is DMSO as a control.

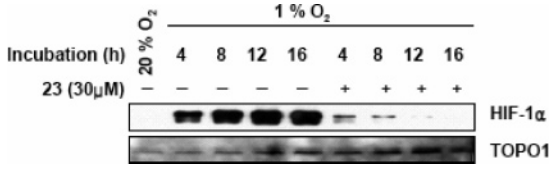


Figure 3. Time course effect of compound **23** on the accumulation of HIF-1α in Hep3B cells under hypoxic condition.

time course data for the HIF-1α accumulation was determined in the presence or absence of 30 μM of **23** under hypoxic condition (Figure 3). The HIF-1α accumulation increased in a time-dependent manner and reached its highest level at about 12 h incubation in the Hep3B cells. Conversely, HIF-1α accumulation was inhibited by addition of **23** in a time-dependent manner; however, TOPO1 expression was not significantly inhibited by 16 h incubation, indicating that **23** is not toxic at the concentration of 30 μM.

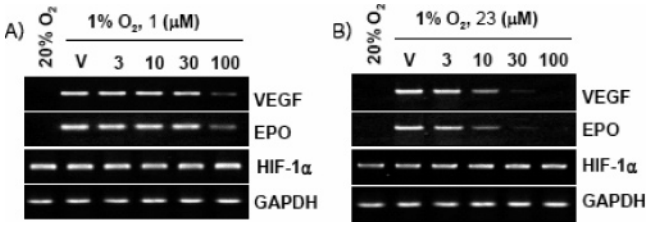


Figure 4. RT PCR analysis for the effect of compounds **1** (A) and **23** (B) on the hypoxia-induced mRNA expression of *VEGF* and *EPO* in Hep3B cells. *GAPDH* was used as load control and V is DMSO as control.

To confirm that inhibition of HIF-1α results in decreased expression of its target genes, compounds **1** and **23** were analyzed by RT-PCR analysis for their effect on the mRNA expression of two well-known HIF-1 target genes *VEGF* and *EPO*, both of which are associated with the aggressive tumor phenotype.[20] The hypoxia-induced mRNA expression of *VEGF* and *EPO* was suppressed dose-dependently by **1** or **23** without any affect on the mRNA expression level of *HIF-1*α and *GAPDH* (Figure 3) in Hep3B cells. Of particular interest, compound **23** significantly suppressed the hypoxia-induced mRNA expression of *VEGF* and *EPO* at a concentration of 10μM.

On the basis of this preliminary SAR, involving structural modification, we have defined the structural requirements for the HIF-1 inhibition of aryloxyacetylaminobenzoic acid analogues and identified several highly potent HIF-1 inhibitors. Some of these inhibitors, including compound **23**, were further evaluated for their inhibitory effect on the HIF-1α protein accumulation and mRNA expression of the target genes under hypoxic conditions. HIF-1 is known to play an important role in solid tumors, and although the detailed mechanism of its inhibition is still unclear, the compounds described in this study could serve as valuable leads for chemotherapeutic intervention in HIF-1-mediated tumor progression and angiogenesis.

Experimental Section

General. All of the commercial chemicals and solvents are of reagent grade and were used without further purification. 3-(2-Phenoxyacetamido)benzoic acid (**9b**), 3-(2-(*p*-tolyloxy)acetamido)-benzoic acid (**9c**), 3-aminobenzoic acid methyl ester (**6**), 3-aminobenzamide (**7**), 4-hydroxy-3-nitrobenzoic acid (**19**), 3-amino-4-hydroxy-benzoic acid methyl ester (**21**), tetrakis(triphenylphosphine)-palladium [$Pd(PPh_3)_4$], *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU), diisopropylethylamine (DIPEA), *O*-(benzotriazol-1-yl)- *N*,*N*,*N*′,N′-tetramethyluronium hexafluorophosphate (HBTU), 1-hydroxybenzotriazole (HOBT), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), and 1-n-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) were purchased from commercial sources. All reactions were carried out under an atmosphere of dried argon in flame-dried glassware. Melting points were determined in open capillary tubes on an Electrothermal apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were determined on a Varian (300 MHz) spectrometer. Chemical shifts are provided in parts per million (ppm) downfield from tetramethylsilane (internal standard) with coupling constants in hertz (Hz). Multiplicity is indicated by the following abbreviations: singlet (s), doublet (d), doublet of doublet (dd), triplet (t), pseudo triplet (ps-t), quartet (q), multiplet (m), broad (br). Mass spectra were recorded on a Finnigan ESI mass spectrometer, and HRMS (ESI-MS) was obtained on a Mariner instrument (Perseptive Biosystem). Products from all reactions were purified to a minimum purity of 96% as determined by HPLC, either by flash column chromatography using silica gel 60 (230−400 mesh Kieselgel 60) or by preparative thin layer chromatography using glass-backed silica gel plates (1 mm thickness) unless otherwise indicated. Additionally, thin-layer chromatography on 0.25 mm silica plates (E. Merck, silica gel 60 F254) was used to monitor reactions. The chromatograms were visualized using ultraviolet illumination, exposure to iodine vapors, dipping in PMA, or Hanessian's solution. The purity of the products was checked by reversed phase high-pressure liquid chromatography (RP-HPLC), which was performed either on Dionex Corp. HPLC system or on Waters Corp. HPLC system equipped with a UV detector set at 254 nm. The mobile phases used were A: H_2O containing 0.05% TFA, and B: CH_3CN. The HPLC employed an YMC Hydrosphere C18 (HS-302) column (5μ particle size, 12 nM pore size), 4.6 mm diameter × 150 mm with a flow rate of 1.0 mL/min. The purity of compounds was assessed using the following methods: Method A: gradient 20% B to 100% B in 30 min; Method B: gradient 20% B to 100% B in 20 min; Method C: gradient 40% B to 100% B in 30 min; Method D: gradient 50% B to 100% B in 20 min; Method E: gradient 60% B to 100% B in 20 min. A table listing HPLC retention times and purities in two different systems for **1**, **8a**, **9d**−**i**, **10a**−**j**, **11**−**18**, **23**, and **25**−**30** are shown in Supporting Information.

(4-Adamantan-1-yl-phenoxy)acetic Acid (5a). A suspension of 4-(1-adamantyl)phenol **4a** (2.0 g, 8.76 mmol), anhydrous potassium carbonate (3.63 g, 26.29 mmol), and ethyl chloroacetate (1.289 g, 10.51 mmol) in DMF (10 mL) was stirred overnight at room temperature. Reaction mixture was diluted with EtOAc and sequentially washed with aqueous sodium bicarbonate, brine, and water and dried over anhydrous $MgSO_4$. The solvent was filtered and evaporated under reduced pressure to afford a crude solid, which was purified by column chromatography on silica gel (EtOAc:n-hexane = 1:9 to 1:3) to afford (4-adamantan-1-yl-phenoxy)acetic acid ethyl ester as a colorless solid (2.62 g, 94.6% yield). R_f = 0.29 (EtOAc:n-hexane = 1:9); mp 86.6−88.6 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (2H, m, aromatic-H), 6.86 (2H, m, aromatic-H), 4.60 (2H, s, OCH_2CO), 4.27 (2H, q, J = 7.2 Hz, OCH_2CH_3), 2.08 (3H, brs, adamantyl-H), 1.88 (6H, d, J = 3.0 Hz, adamantyl-H), 1.76 (6H, m, adamantyl-H), 1.30 (3H, t, J = 6.9 Hz, OCH_2CH_3); MS (ESI) m/z 337 $(M + Na)^+$. To a mixture of (4-adamantan-1-yl-phenoxy)-acetic acid ethyl ester (1.1 g, 3.50 mmol) in THF/H_2O (1:1, 20 mL) was added lithium hydroxide monohydrate (0.29 g, 7.00 mmol) and stirred overnight at room temperature. Reaction mixture was neutralized with 10% HCl, diluted with EtOAc, sequentially washed with aqueous sodium bicarbonate, brine, and water, and dried over anhydrous $MgSO_4$. The solvent was filtered and evaporated under reduced pressure to afford a crude solid, which was purified by column chromatography on silica gel column chromatography (CH_2Cl_2:MeOH = 30:1) to give (4-adamantan-1-yl-phenoxy)acetic acid as a white solid (0.61 g, 61.3% yield). R_f = 0.16 (CH_2Cl_2:MeOH = 15:1); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.26 (2H, m, aromatic-H), 6.85 (2H, m, aromatic-H), 4.59 (2H, s, OCH_2-CO), 2.05 (3H, m, adamantyl-H), 1.89 (6H, m, adamantyl-H), 1.75−1.84 (6H, m, adamantyl-H).

4-[2-(4-Adamantan-1-yl-phenoxy)-acetylamino]-benzoic Acid (1). EDCI (144.0 mg, 0.75 mmol) and HOBT (101 mg, 0.75 mmol) were added to a solution of (4-adamantan-1-yl-phenoxy)acetic acid (**5a**, 140 mg, 0.5 mmol), 3-aminobenzoic acid methyl ester (**6**, 110 mg, 0.75 mmol), and DIPEA (0.13 mL, 0.75 mmol) in DMF (5.0 mL), and the mixture was stirred overnight at room temperature. It was then partitioned between EtOAc and brine, and the organic layer was separated and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (n-hexane:EtOAc:MeOH = 15:3:1) to give 4-[2-(4-adamantan-1-yl-phenoxy)-acetylamino]benzoic acid methyl ester (**8a**) as a white solid (160 mg, 76% yield). R_f = 0.48 (n-hexane:EtOAc:MeOH = 15:3:1); mp 184.5 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.31 (1H, s, NH), 8.34 (1H, m, aromatic-H), 7.89 (1H, m, aromatic-H), 7.67 (1H, m, aromatic-H), 7.47 (1H, ps-t, J = 7.8 Hz, aromatic-H), 7.28 (2H, m, aromatic-H), 6.93 (2H, m, aromatic-H), 4.68 (2H, s, OCH_2CO), 3.85 (3H, s, OCH_3), 2.03 (3H, m, adamantyl-H), 1.81−1.82 (6H, m, adamantyl-H), 1.71 (6H, m, adamantyl-H); MS (ESI) m/z 420 $(M + H)^+$, 418 $(M - H)^-$; HRMS (ESI) m/z calcd for $C_{26}H_{33}N_2O_4$ $[(M + NH_4)^+]$ 437.2435, found: 437.2434). A

mixture of **8a** (306 mg, 0.72 mmol) and lithium hydroxide monohydrate (60 mg, 1.44 mmol) in THF/H_2O/1,4-dioxane (1:1:1, 300 mL) was stirred overnight at room temperature, acidified to pH 7 with 10% HCl, and diluted with EtOAc. The organic layer was separated and concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (n-hexane:EtOAc:MeOH = 15:3:1) to give **1**, as a white solid (152 mg, 43% yield). R_f = 0.45 (n-hexane:EtOAc:MeOH = 6:3:1); mp 223−224 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.21 (1H, s, NH), 8.21 (1H, s, aromatic-H), 7.79 (1H, d, J = 8.7 Hz, aromatic-H), 7.64 (1H, d, J = 7.2 Hz, aromatic-H), 7.30 (3H, m, aromatic-H), 6.93 (2H, m, aromatic-H), 4.67 (2H, s, OCH_2CO), 2.03 (3H, m, adamantyl-H), 1.82−1.83 (6H, m, adamantyl-H), 1.71 (6H, m, adamantyl-H); MS (ESI) m/z 428 $(M + Na)^+$, 404 $(M - H)^-$; HRMS (ESI) m/z calcd for $C_{25}H_{27}NO_4Na$ $[(M + Na)^+]$ 428.1832, found: 428.1822.

2-[2-(4-Adamantan-1-yl-phenoxy)-acetylamino]-benzoic Acid (2). To a mixture of (4-adamantan-1-yl-phenoxy)acetic acid (**5a**, 85.9 mg, 0.30 mmol), 2-aminobenzoic acid methyl ester (0.07 mL, 0.54 mmol), EDCI (103.5 mg, 0.54 mmol), and HOBt (73.0 mg, 0.54 mmol) in DMF (3.6 mL) was added DIPEA (69.8 mg, 0.10 mL, 0.54 mmol), and it was stirred overnight at room temperature. The mixture was then partitioned between EtOAc and 10% HCl. The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by silica gel flash column chromatography (n-hexane:EtOAc:MeOH = 12:3:1) to give 2-[2-(4-adamantan-1-yl-phenoxy)-acetylamino]-benzoic acid methyl ester as a white solid (46.4 mg, 36.9% yield). R_f = 0.72 (n-hexane:EtOAc:MeOH = 12:3:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.1 (1H, s, NH), 8.79 (1H, d, J = 8.7 Hz, aromatic-H), 8.05 (1H, dd, J = 7.8, 1.8 Hz, aromatic-H), 7.54−7.60 (1H, m, aromatic-H), 7.31−7.35 (2H, m, aromatic-H), 7.12−7.16 (2H, m, aromatic-H), 7.03−7.07 (2H, m, aromatic-H), 4.62 (2H, s, CH_2), 3.93 (3H, s, CH_3), 2.08 (3H, m, adamantyl-H), 1.88 (6H, m, adamantyl-H), 1.70−1.80 (6H, m, adamantyl-H); MS (ESI) m/z 442 $(M + Na)^+$, 418 $(M - H)^-$; Purity >99% (as determined by RP-HPLC, method A, t_R = 23.7 min). A solution of 2-[2-(4-adamantan-1-yl-phenoxy)-acetylamino]-benzoic acid methyl ester (30.5 mg, 0.07 mmol) in 1,4-dioxane/H_2O (3:1, 3 mL) was treated with lithium hydroxide monohydrate (8.4 mg, 0.2 mmol) and stirred at room temperature until the reaction was complete as judged by TLC. The reaction mixture was then acidified with 10% HCl to pH 7 and then partitioned between EtOAc and brine. The organic layer was separated, washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuo. The residue was purified by silica gel flash column chromatography (n-hexane:EtOAc:MeOH = 6:3:1) to give 2-[2-(4-adamantan-1-yl-phenoxy)-acetylamino]-benzoic acid as a white solid (18.5 mg, 62.5% yield). R_f = 0.29 (n-hexane:EtOAc:MeOH = 6:3:1); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.57 (1H, d, J = 8.4 Hz, aromatic-H), 8.01−8.04 (1H, m, aromatic-H), 7.32−7.37 (1H, m, aromatic-H), 7.26 (2H, d, J = 8.4 Hz, aromatic-H), 7.00−7.05 (3H, m, aromatic-H), 4.58 (2H, s, CH_2), 2.03 (3H, m, adamantyl-H), 1.81 (6H, m, adamantyl-H), 1.71 (6H, m, adamantyl-H); MS (ESI) m/z 428 $(M + Na)^+$, 404 $(M - H)^-$; Purity >99% (as determined by RP-HPLC, method A, t_R = 17.0 min).

4-[2-(4-Adamantan-1-yl-phenoxy)-acetylamino]-benzoic Acid (3). Compound **3** was prepared from **5a** and 4-aminobenzoic acid methyl ester on a 0.5 mmol scale by the same procedure for compound **2**. Purification by silica gel flash column chromatography (n-hexane:EtOAc:MeOH = 6:3:1) for 4-[2-(4-adamantan-1-yl-phenoxy)-acetylamino]-benzoic acid methyl ester: a white solid (108.3 mg, 51.7% yield). R_f =0.48 (n-hexane:EtoAc:MeOH =12:3:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.46 (1H, s, NH), 8.04 (2H, d, J = 21.3 Hz, aromatic-H), 7.69 (2H, d, J = 9.3 Hz, aromatic-H), 7.34 (2H, d, J = 8.7 Hz, aromatic-H), 6.94 (2H, d, J = 8.7 Hz, aromatic-H), 4.61 (2H, s, CH_2), 3.90 (3H, s, CH_3), 1.75−2.09 (15H, m, adamantyl- H); MS (ESI) m/z 420 $(M + H)^+$, 418 $(M - H)^-$; Purity >99% (as determined by RP-HPLC, method A, t_R = 14.9 min). Purification by silica gel flash column chromatography (n-hexane:EtOAc:MeOH = 6:3:1) for 4-[2-(4-adamantan-1-yl-phenoxy)-acetylamino]-benzoic acid **3**: a white solid (40.7 mg, 53.1% yield). R_f = 0.45 (n-hexane:EtOAc:MeOH = 6:3:1); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.34 (1H, s, NH), 7.89 (2H, d, J = 8.4 Hz, aromatic-H), 7.73 (2H, d, J = 8.7 Hz, aromatic-H), 7.27−7.30 (2H, m, aromatic-H), 6.90−6.93 (2H, m, aromatic-H), 4.69 (2H, s, CH_2), 2.04 (3H, m, adamantyl-H), 1.82 (6H, m, adamantyl-H), 1.72 (6H, m, adamantyl-H); MS (ESI) m/z 428 $(M + Na)^+$, 404 $(M - H)^-$; Purity >99% (as determined by RP-HPLC, method A, t_R = 14.9 min).

General Procedure for the Preparation of 8d−i. EDCI (1.5−2.0 equiv) and HOBt (1.5−2.0 equiv) were added to a solution of appropriate phenoxyacetic acid **5d−i** (1.0 equiv), 3-aminobenzoic acid methyl ester **6** (1.5−2.0 equiv), and DIPEA (1.5−2.0 equiv) in DMF, and the reaction mixture was stirred at room temperature until completion as monitored by TLC. The reaction mixture was diluted with EtOAc or with a mixture of MeOH/CH_2Cl_2 (10%) and 10% HCl, and the organic layer was separated, sequentially washed with brine, aqueous sodium bicarbonate, and water, and dried over anhydrous $MgSO_4$. The solvent was filtered and evaporated under reduced pressure to afford a crude solid, which was purified by silica gel column chromatography.

3-[2-(4-*tert*-Butyl-phenoxy)-acetylamino-benzoic Acid Methyl Ester (8d). Obtained as a yellowish solid (185 mg, quantitative yield) from **5d**. R_f = 0.57 (n-hexane:EtOAc:MeOH = 9:3:1); mp 76.6−77.8 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.40 (1H, s, NH), 7.99−8.08 (2H, m, aromatic-H), 7.82−7.84 (1H, m, aromatic-H), 7.45 (1H, ps-t, J = 7.8 Hz, aromatic-H), 7.34−7.38 (2H, m, aromatic-H), 6.9−6.96 (2H, m, aromatic-H), 4.61 (2H, s, CH_2), 3.93 (3H, s, CH_3), 1.32 (9H, s, CH_3); MS (ESI) m/z 364 $(M + Na)^+$, 340 $(M - H)^-$; Purity >99% (as determined by RP-HPLC, method B, t_R = 17.6 min).

3-[2-(4-Acetyl-phenoxy)-acetylamino]-benzoic Acid Methyl Ester (8e). Obtained as a white solid (158 mg, 97% yield) from **5e**. R_f = 0.40 (n-hexane:EtOAc:MeOH = 6:3:1); mp 130.2−130.9 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.32 (1H, s, NH), 8.07 (1H, m, aromatic-H), 7.97−8.01 (3H, m, aromatic-H), 7.83 (1H, d, J = 7.8 Hz, aromatic-H), 7.45 (1H, ps-t, J = 7.8 Hz, aromatic-H), 7.05 (2H, m, aromatic-H), 4.69 (2H, s, OCH_2CO), 3.92 (3H, s, OCH_3), 2.58 (3H, s, $COCH_3$); MS (ESI) m/z 350 $(M + Na)^+$, 326 $(M - H)^-$; Purity > 99% (as determined by RP-HPLC, method A, t_R = 13.5 min).

3-[2-(4-Fluoro-phenoxy)-acetylamino]-benzoic Acid Methyl Ester (8f). Obtained as a white solid (236.1 mg, 88.5% yield) from **5f**. R_f = 0.49 (n-hexane:EtOAc:MeOH = 6:3:1); mp 102.6−103.3 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.37 (1H, s, NH), 8.07 (1H, m, aromatic-H), 7.99−8.02 (1H, m, aromatic-H), 7.83 (1H, d, J = 7.8 Hz, aromatic-H), 7.44 (1H, ps-t, J = 7.8 Hz, aromatic-H), 7.02−7.08 (2H, m, aromatic-H), 6.93−6.97 (2H, m, aromatic-H), 4.59 (2H, s, CH_2), 3.92 (3H, s, CH_3); MS (ESI) m/z 326 $(M + Na)^+$, 302 $(M - H)^-$; purity > 99% (as determined by RP-HPLC, method C, t_R = 10.8 min).

3-[2-(4-Chloro-phenoxy)-acetylamino]-benzoic Acid Methyl Ester (8g). Obtained as a white solid (135.2 mg, 84.5% yield) from **5g**. R_f = 0.61 (n-hexane:EtOAc:MeOH = 6:3:1); mp 105.3−106.1 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.32 (1H, s, NH), 8.06 (1H, s, aromatic-H), 8.00 (1H, d, J = 8.4 Hz, aromatic-H), 7.83 (1H, d, J = 7.2 Hz, aromatic-H), 7.45 (1H, ps-t, J = 7.8 Hz, aromatic-H), 7.29−7.34 (2H, m, aromatic-H), 6.91−6.97 (2H, m, aromatic-H), 4.60 (2H, s, CH_2), 3.92 (3H, s, CH_3); MS (ESI) m/z 342 $(M + Na)^+$, 318 $(M - H)^-$; HPLC > 99% (as determined by RP-HPLC, method A, t_R = 16.4 min).

3-[2-(4-Bromo-phenoxy)-acetylamino]-benzoic Acid Methyl Ester (8h). Obtained as a white solid (138 mg, 76% yield) from **5h**. R_f = 0.73 (n-hexane:EtOAc:MeOH = 6:3:1); mp 109.1−109.6 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.32 (1H, s, NH), 8.06 (1H, m, aromatic-H), 7.99 (1H, m, aromatic-H), 7.84 (1H, m, aromatic-H), 7.42−7.47 (3H, m, aromatic-H), 6.89 (2H, m, aromatic-H), 4.59 (2H, s, OCH_2CO), 3.92 (3H, s, OCH_3); MS (ESI) m/z 386 $(M + Na)^+$, 362 $(M - H)^-$; Purity >96% (as determined by RP-HPLC, method D, t_R = 9.52 min).

3-[2-(4-Iodo-phenoxy)-acetylamino]-benzoic Acid Methyl Ester (8i). Obtained as a white solid (199.0 mg, 97% yield) from **5i**. $R_f = 0.66$ (n-hexane:EtOAc:MeOH = 6:3:1); mp 102.6−103.3 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.31 (1H, s, NH), 8.06 (1H, s, aromatic-H), 8.00 (1H, d, $J = 8.1$ Hz, aromatic-H), 7.83 (1H, d, $J = 7.8$ Hz, aromatic-H), 7.61−7.66 (2H, m, aromatic-H), 7.44 (1H, ps-t, $J = 7.8$ Hz, aromatic-H), 6.76−6.81 (2H, m, aromatic-H), 4.59 (2H, s, CH_2), 3.92 (3H, s, CH_3); MS (ESI) *m*/*z* 434 $(M + Na)^+$, 410 $(M - H)^-$; Purity >99% (as determined by RP-HPLC, method D, $t_R = 14.5$ min).

General Procedure for the Preparation of 9d−i. A mixture of appropriate (4-substituted phenoxy)-acetylamino benzoic acid methyl ester **8d−i** (1.0 mmol) and lithium hydroxide monohydrate (2.0 mmol) in THF/H_2O (1:1, 12 mL) was stirred at room temperature until completion, as monitored by TLC. Then the mixture was acidified with 10% HCl to pH 7 and partitioned between EtOAc and brine. The organic layer was separated washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography.

3-[2-(4-*tert*-Butyl-phenoxy)-acetylamino-benzoic Acid (9d). Obtained as a white solid (68.7 mg, 65.7% yield) from the corresponding ester **8d**. $R_f = 0.35$ (CH_2Cl_2:MeOH = 10:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.41 (1H, s, NH), 8.03−8.11 (2H, m, aromatic-H), 7.87 (1H, d, $J = 7.5$ Hz, aromatic-H), 7.45 (1H, m, aromatic-H), 7.36 (2H, d, $J = 8.7$ Hz, aromatic-H), 6.92 (2H, m, aromatic-H), 4.60 (2H, s, CH_2), 1.31 (9H, s, CH_3); MS (ESI) *m*/*z* 350 $(M + Na)^+$, 326 $(M - H)^-$; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{21}O_4NNa$ $[(M + Na)^+]$ 350.1363, found: 350.1397).

3-[2-(4-Acetyl-phenoxy)-acetylamino]-benzoic Acid (9e). Obtained as a white solid (73 mg, 67% yield) from the corresponding ester **8e**. $R_f = 0.41$ (CH_2Cl_2:MeOH = 15:1); mp 199.4−201.0 °C (dec); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.26 (1H, m, aromatic-H), 8.00 (2H, m, aromatic-H), 7.86 (1H, m, aromatic-H), 7.79 (1H, d, $J = 8.1$ Hz, aromatic-H), 7.43 (1H, ps-t, $J = 8.1$ Hz, aromatic-H), 7.14 (2H, m, aromatic-H), 4.79 (2H, s, OCH_2CO), 2.55 (3H, s, $COCH_3$); MS (ESI) *m*/*z* 336 $(M + Na)^+$, 312 $(M - H)^-$.

3-[2-(4-Fluoro-phenoxy)-acetylamino]-benzoic Acid (9f). Obtained as a white solid (108.3 mg, 83.24% yield) from the corresponding ester **8f**. $R_f = 0.18$ (n-hexane:EtOAc:MeOH = 6:3:1); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.31 (1H, s, NH), 8.27 (1H, s, aromatic-H), 7.84 (1H, d, $J = 8.7$ Hz, aromatic-H), 7.67 (1H, d, $J = 8.1$ Hz, aromatic-H), 7.41 (1H, ps-t, $J = 7.8$ Hz, aromatic-H), 7.12−7.18 (2H, m, aromatic-H), 7.01−7.05 (2H, m, aromatic-H), 4.71 (2H, s, CH_2); MS (ESI) *m*/*z* 312 $(M + Na)^+$, 288 $(M - H)^-$.

3-[2-(4-Chloro-phenoxy)-acetylamino]-benzoic Acid (9g). Obtained as a white solid (70.3 mg, 74.2% yield) from the corresponding ester **8g**. $R_f = 0.28$ (n-hexane:EtOAc:MeOH = 6:3:1); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.30 (1H, s, NH), 8.26 (1H, s, aromatic-H), 7.83 (1H, d, $J = 7.8$ Hz, aromatic-H), 7.66 (1H, d, $J = 7.2$ Hz, aromatic-H), 7.44 (1H, ps-t, $J = 7.8$ Hz, aromatic-H), 7.33−7.36 (2H, m, aromatic-H), 7.01−7.04 (2H, m, aromatic-H), 4.72 (2H, s, CH_2); MS (ESI) *m*/*z* 328 $(M + Na)^+$, 304 $(M - H)^-$).

3-[2-(4-Bromo-phenoxy)-acetylamino]-benzoic Acid (9h). Obtained as a white solid (44.6 mg, 51% yield) from the corresponding ester **8h**. $R_f = 0.22$ (n-hexane:EtOAc:MeOH = 6:3:1); mp 226.0−226.9 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.26 (1H, m, aromatic-H), 7.86 (1H, m, aromatic-H), 7.79 (1H, d, $J = 8.1$ Hz, aromatic-H), 7.41−7.46 (3H, m, aromatic-H), 6.99 (2H, m, aromatic-H), 4.68 (2H, s, OCH_2CO); MS (ESI) *m*/*z* 372 $(M + Na)^+$, 348 $(M - H)^-$.

3-[2-(4-Iodo-phenoxy)-acetylamino]-benzoic Acid (9i). Obtained as a white solid (64.4 mg, 67.7% yield) from the corresponding ester **8i**. $R_f = 0.16$ (n-hexane:EtOAc:MeOH = 6:3:1); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.25 (1H, s, aromatic-H), 7.85 (1H, d, $J = 8.1$ Hz, aromatic-H), 7.60−7.67 (3H, m, aromatic-H), 7.43 (1H, ps-t, $J = 8.1$ Hz, aromatic-H), 6.86 (2H, d, $J = 8.7$ Hz, aromatic-H), 4.72 (2H, s, CH_2); MS (ESI) *m*/*z* 420 $(M + Na)^+$, 396 $(M - H)^-$.

General Procedure for the Preparation of 10a−d,j. EDCI (1.5−2.0 equiv) and HOBt (1.5−2.0 equiv) were added to a solution of appropriate phenoxyacetic acid **5a-d,j** (1.0 equiv), 3-aminobenzamide **7** (1.5−2.0 equiv), and DIPEA (1.5−2.0 equiv) in DMF, and the resulting mixture was stirred at room temperature until completion as monitored by TLC. Reaction mixture was diluted with EtOAc or with a mixture of MeOH/CH_2Cl_2 (10%), sequentially washed with aqueous sodium bicarbonate, brine, and water, and dried over anhydrous $MgSO_4$. The solvent was filtered and evaporated under reduced pressure to afford a crude solid, which was purified by silica gel column chromatography (MeOH:CH_2Cl_2 = 1:9 to 3:9).

3-[2-(4-Adamantan-1-yl-phenoxy)-acetylamino]-benzamide (10a). Obtained as a colorless solid (145.0 mg, 89.6% yield) from **5a**. $R_f = 0.32$ (n-hexane:EtOAc:MeOH = 12:3:1); mp 150.6−151.4 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.08 (1H, m, aromatic-H), 7.80 (1H, m, aromatic-H), 8.57 (1H, d, $J = 8.4$ Hz, aromatic-H), 7.43 (1H, m, aromatic-H), 7.30 − 7.33 (2H, m, aromatic-H), 7.00 (2H, m, aromatic-H), 4.65 (2H, s, CH_2), 2.06 (3H, m, adamantyl-H), 1.90 (6H, m, adamantyl-H), 1.80 (6H, m, adamantyl-H); MS (ESI) *m*/*z* 427 $(M + Na)^+$, 403 $(M - H)^-$; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{32}O_3N_3$ $[(M + NH_4)^+]$ 422.2438, found: 422.2449.

3-(2-Phenoxy-acetylamino)-benzamide (10b). Obtained as a colorless solid (146 mg, 82.2% yield) from **5b**. $R_f = 0.62$ (MeOH:MC = 1:9); mp 180.4−182.3 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.19 (1H, s, CONH), 8.09 (1H, s, aromatic-H), 7.93 (1H, s, $CONH_2$), 7.80 (1H, m, aromatic-H), 7.56 (1H, d, $J = 7.5$ Hz, aromatic-H), 7.35 (4H, m, aromatic-H, $CONH_2$), 6.98 (3H, m, aromatic-H), 4.70 (2H, s, OCH_2); MS (ESI) *m*/*z* 293 $(M + Na)^+$, 269 $(M - H)^-$; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{15}N_2O_3$ $[(M + H)^+]$ 271.1077, found: 271.1084.

3-(2-*p*-Tolyloxy-acetylamino)-benzamide (10c). Obtained as a colorless solid (133 mg, 77.8% yield) from **5c**. $R_f = 0.56$ (MeOH:MC = 1:9); mp 187−189.1 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.16 (1H, s, CONH), 8.09 (1H, s, aromatic-H), 7.93 (1H, s, $CONH_2$), 7.80 (1H, d, $J = 8.1$ Hz, aromatic-H), 7.56 (1H, d, $J = 8.1$ Hz, aromatic-H), 7.37 (2H, m, aromatic-H, $CONH_2$), 7.10 (2H, d, $J = 8.7$ Hz, aromatic-H), 6.9 (2H, d, $J = 8.4$ Hz, aromatic-H), 4.65 (2H, s, OCH_2), 2.23 (3H, s, CH_3); MS (ESI) *m*/*z* 307 $(M + Na)^+$, 283 $(M - H)^-$; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{20}N_3O_3$ $[(M + NH_4)^+]$ 302.1499, found: 302.1502.

3-[2-(4-*tert*-butyl-Phenoxy)-acetylamino]-benzamide (10d). Obtained as a colorless solid (168 mg, 85.8% yield) from **5d**. $R_f = 0.55$ (MeOH:MC = 1:9); mp 187−190 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.18 (1H, s, CONH), 8.10 (1H, s, aromatic-H), 7.93 (1H, s, $CONH_2$), 7.80 (1H, d, $J = 8.1$ Hz, aromatic-H), 7.56 (1H, d, $J = 8.1$ Hz, aromatic-H), 7.35 (4H, m, aromatic-H, $CONH_2$), 6.92 (2H, dd, $J = 3.0$, 12.3 Hz, aromatic-H), 4.67 (2H, s, OCH_2), 1.25 (9H, s, $C(CH_3)_3$); MS (ESI) *m*/ *z* 349 $(M + Na)^+$, 325 $(M - H)^-$.

3-[2-(4-Nitro-phenoxy)-acetylamino]-benzamide (10j). Obtained as a colorless solid (135 mg, 81% yield) from **5j**. $R_f = 0.52$ (MeOH:MC = 1:9); mp 205.1−207.4 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ10.32 (1H, s, CONH), 8.24 (2H, d, $J = 9.3$ Hz, aromatic-H), 8.08 (1H, s, aromatic-H), 7.94 (1H, s, $CONH_2$), 7.78 (1H, d, $J = 8.1$ Hz, aromatic-H), 7.58 (1H, d, $J = 7.2$ Hz, aromatic-H), 7.39 (2H, m, aromatic-H, $CONH_2$), 7.21 (2H, d, $J = 9.3$ Hz, aromatic-H), 4.92 (2H, s, OCH_2); MS (ESI) *m*/*z* 338 $(M + Na)^+$, 314 $(M - H)^-$; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{17}N_4O_5$ $[(M + NH_4)^+]$ 333.1193, found: 333.1166.

General Procedure for the Preparation of 11−14. EDCI (1.5 equiv) and HOBt (1.5 equiv) were added to a solution of 4-[2-(4-adamantan-1-yl-phenoxyl)-acetylamino]-benzoic acid **1** (1.0 equiv), appropriate amine (1.5 equiv), and DIPEA (1.5 equiv) in DMF (5 mL), and the resulting mixture was stirred at room temperature until completion as monitored by TLC. Reaction mixture was diluted with EtOAc, sequentially washed with aqueous sodium bicarbonate, brine, and water, and dried over anhydrous $MgSO_4$. The solvent was filtered and evaporated under reduced pressure to afford a crude solid, which was purified either by silica gel column chromatography or by preparative TLC.

3-[2-(4-Adamantan-1-yl-phenoxy)-acetylamino]-*N*-(4-chloro-phenyl)-benza mide (11). Obtained as a colorless solid (15 mg, 59% yield). $R_f = 0.29$ (EtOAc:n-hexane = 3:7); mp 247−250 °C;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.39 (1H, s, CONH), 10.27 (1H, s, CONH), 8.16 (1H, s, aromatic-H), 7.89 (1H, d, J = 8.7 Hz, aromatic-H), 7.80 (2H, d, J = 9.0 Hz, aromatic-H), 7.66 (1H, d, J = 7.8 Hz, aromatic-H), 7.45 (3H, m, aromatic-H), 7.28 (2H, d, J = 8.4 Hz, aromatic-H), 6.93 (2H, d, J = 8.4 Hz, aromatic-H), 4.69 (2H, s, OCH_2CO), 2.03 (3H, s, adamantyl-H), 1.83 (6H, s, adamantyl-H), 1.71 (6H, s, adamantyl-H); MS (ESI) m/z 513 (M − H)$^-$; HRMS (ESI) m/z calcd for $C_{31}H_{35}N_3O_3Cl$ [(M + NH_4)$^+$] 532.2361, found: 532.2372.

3-[2-(4-Adamantan-1-yl-phenoxy)-acetylamino]-*N*-naphthalen-2-yl-benzamide (12). Obtained as a colorless solid (16 mg, 61.5% yield). R_f = 0.30 (EtOAc:n-hexane = 3:7); mp 201.3−203.7 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.47 (1H, s, CONH), 8.32 (1H, s, CONH), 8.19 (1H, s, aromatic-H), 8.12 (1H, s, aromatic-H), 7.82 (4H, m, aromatic-H), 7.68 (1H, d, J = 8.1 Hz, aromatic-H), 7.61 (1H, dd, J = 1.8, 9.0 Hz, aromatic-H), 7.45 (3H, m, aromatic-H), 7.33 (2H, d, J = 8.7 Hz, aromatic-H), 6.93 (2H, d, J = 9.3 Hz, aromatic-H), 4.6 (2H, s, OCH_2CO), 2.1 (3H, brs, adamantyl-H), 1.89 (6H, d, J = 1.8 Hz, adamantyl-H), 1.77 (6H, m, adamantyl-H); MS (ESI) m/z 553 (M + Na)$^+$, 529 (M − H)$^-$; HRMS (ESI) m/z calcd for $C_{35}H_{35}N_2O_3$ [(M + H)$^+$] 531.2641, found: 531.2611.

3-[2-(4-Adamantan-1-yl-phenoxyl)-acetylamino-*N*-furan-2-yl-methyl-benzamide (13). Obtained as a yellowish solid (79 mg, quantitative yield). R_f = 0.45 (n-hexane:EtOAc:MeOH = 6:3:1); mp 188.8−189.7 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.42 (1H, s, NH), 7.96 (1H, m, aromatic-H), 7.83−7.84 (1H, m, aromatic-H), 7.56 (1H, d, J = 7.8 Hz, aromatic-H), 7.26−7.44 (4H, m, aromatic-H), 6.92−6.95 (2H, m, aromatic-H), 6.53 (1H, m, NH), 6.30−6.35 (4H, m, aromatic-H), 4.64 (2H, dd, J = 5.4 Hz, CH_2), 4.60 (2H, s, CH_2), 2.10 (3H, m, adamantyl-H), 1.90 (6H, m, adamantyl-H), 1.77 (6H, m, adamantyl-H); MS (ESI) m/z 507 (M + Na)$^+$, 483 (M − H)$^-$; HRMS (ESI) m/z calcd for $C_{30}H_{36}O_4N_3$ [(M + NH_4)$^+$] 502.27003, found: 502.26852.

3-[2-(4-Adamantan-1-yl-phenoxy)-acetylamino]-*N*-(2-pyridin-4-yl-ethyl)-benzamide (14). Obtained as a colorless solid (25 mg, 40% yield). R_f = 0.52 (MeOH:MC = 1:9); mp 78.3−80.4 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.47 (3H, m, 2xCONH, aromatic-H), 7.97 (1H, s, aromatic-H), 7.75 (1H, d, J = 8.1 Hz, aromatic-H), 7.48 (1H, d, J = 7.2 Hz, aromatic-H), 7.33 (3H, m, aromatic-H), 7.13 (2H, d, J = 5.4 Hz, aromatic-H), 6.90 (2H, d, J = 9.0 Hz, aromatic-H), 6.78 (1H, brs, aromatic-H), 4.55 (2H, s, O*CH*$_2$CO), 3.68 (2H, q, J = 6.75 Hz, NH*CH*$_2$CH$_2$), 2.91 (2H, t, J = 6.9 Hz, NHCH$_2$*CH*$_2$), 2.08 (3H, s, adamantyl-H), 1.87 (6H, s, adamantyl-H), 1.75 (6H, m, adamantyl-H); MS (ESI) m/z 510 (M + H)$^+$, 508 (M − H)$^-$; HRMS (ESI) m/z calcd for $C_{32}H_{36}N_3O_3$ [(M + H)$^+$] 510.2750, found: 510.2738.

4-[2-(3′-Nitro-biphenyl-4-yl-oxy)-acetylamino]-benzoic Acid (15). To a mixture of 3-[2-(3′-bromo-phenoxy)-acetylamino]-benzoic acid methyl ester **8h** (100 mg, 0.27 mmol) and Pd(PPh_3)$_4$ (16.2 mg, 0.014 mmol) in 1,2-dimethoxyethane (7.0 mL) was added 3-nitrophenylboronic acid (68.4 mg, 0.41 mmol) followed by the addition of sodium hydrogen carbonate (68.9, 0.82 mmol) in H_2O (3 mL). The reaction mixture was refluxed with vigorous stirring for 18 h. The organic solvent was removed under reduced pressure and then partitioned between EtOAc and brine. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (n-hexane:EtOAc:MeOH = 15:3:1) gave 4-[2-(3′-nitro-biphenyl-4-yl-oxy)-acetylamino]-benzoic acid methyl ester, as a greenish solid (81 mg, 73.8% yield). R_f = 0.38 (n-hexane:EtOAc:MeOH = 9:3:1); mp 162.8−165.5 °C (dec); MS (ESI) m/z 429 (M + Na)$^+$, 405 (M − H)$^-$. To a solution of 4-[2-(3′-nitro-biphenyl-4-yl-oxy)-acetylamino]-benzoic acid methyl ester (124 mg, 0.31 mmol) in THF/H_2O (1:1, 10 mL) was added lithium hydroxide monohydrate (25.7 mg, 0.61 mmol) at room temperature. The resulting mixture was stirred overnight and then acidified with 10% HCl to pH 7. EtOAc was added and the organic layer was separated. After concentration, the residue was purified by crystallization from CH_2Cl_2/MeOH/n-hexane to give 4-[2-(3′-nitro-biphenyl-4-yl-oxy)-acetylamino]-benzoic acid as a light green solid (55.9 mg, 44.9% yield). R_f = 0.26 (CH_2Cl_2:MeOH = 15:1); mp 254.8−255.7 °C (dec); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.38 (1H, s, aromatic-H), 8.29 (1H, s, aromatic-H), 8.10 (2H, m, aromatic-H), 7.86 (1H, d, J = 7.8 Hz, aromatic-H), 7.65−7.76 (4H, m, aromatic-H), 7.44 (1H, ps-t, J = 7.8 Hz, aromatic-H), 7.14 (2H, m, aromatic-H), 4.79 (2H, s, OCH_2CO); MS (ESI) m/z 391 (M − H)$^-$; HRMS (ESI) m/z calcd for $C_{21}H_{20}N_3O_6$ [(M + NH_4)$^+$] 410.1346, found: 410.1355.

3-[2-(4-Thiophen-2-yl-phenoxy)-acetylamino]-benzoic Acid (16). To a mixture of 3-[2-(3′-bromo-phenoxy)-acetylamino]-benzoic acid methyl ester **8h** (100 mg, 0.27 mmol) and Pd(PPh_3)$_4$ (16.2 mg, 0.014 mmol) in 1,2-dimethoxyethane (7.0 mL) was added thiophene-2-boronic acid (23.2 mg, 0.19 mmol) followed by the addition of sodium hydrogen carbonate (42.85 mg, 0.51 mmol) in H_2O (0.68 mL). The reaction mixture was refluxed with vigorous stirring until completion as monitored by TLC. The organic solvent was removed under reduced pressure and then partitioned between EtOAc and brine. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (CH_2Cl_2:MeOH = 5:1) gave 3-[2-(4-thiophen-2-yl-phenoxy)-acetylamino]-benzoic acid as a white solid (19.8 mg, 33% yield). R_f = 0.25 (CH_2Cl_2:MeOH = 10:1); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.31 (1H, s, NH), 8.23 (1H, s, aromatic-H), 7.85 (1H, d, J = 8.1 Hz, aromatic-H), 7.59−7.67 (3H, m, aromatic-H), 7.38−7.47 (3H, m, aromatic-H), 7.04−7.11 (3H, m, aromatic-H), 4.76 (2H, s, CH_2); MS (ESI) m/z 376 (M + Na)$^+$, 352 (M − H)$^-$; HRMS (ESI) m/z calcd for $C_{19}H_{15}NO_4S$ [(M + NH_4)$^+$] 354.07946, found: 354.08151.

3-[2-(4′-Methyl-biphenyl-4-yloxy)- acetylamino]-benzoic acid (17). 3-[2-(3′-Bromo-phenoxy)-acetylamino]-benzoic acid methyl ester **8h** (150 mg, 0.41 mmol) was added to a suspension of Pd(PPh_3)$_4$ (23.8 mg, 0.021 mmol) in degassed [bmim][BF_4] (0.5 mL) at ambient temperature. The mixture was stirred overnight at 110 °C. The solution was cooled to ambient temperature and sequentially added 4-tolyl boronic acid (112 mg, 0.82 mmol) and a solution of sodium hydrogen carbonate (68.9 mg, 0.82 mmol) in water (1.0 mL). The mixture was reheated overnight at 110 °C with vigorous stirring and then cooled and extracted with EtOAc. The combined extracts were washed with brine and water, dried over anhydrous $MgSO_4$, and concentrated under vacuo. Purification by silica gel column chromatography (n-hexane:EtOAc:MeOH = 15:3:1) gave 4-[2-(4′-methy-biphenyl-4-yloxy)- acetylamino]-benzoic acid methyl ester as a white solid (70.2 mg, 45.6% yield). R_f = 0.45 (n-hexane:EtOAc:MeOH = 9:3:1). To a solution of 4-[2-(4′-methy-biphenyl-4-yloxy)- acetylamino]-benzoic acid methyl ester (60 mg, 0.16 mmol) in THF/H_2O (1:1, 10 mL) was added lithium hydroxide monohydrate (13.4 mg, 0.32 mmol) at room temperature. The resulting mixture was stirred overnight and then acidified with 10% HCl to pH 7. EtOAc was added and the organic layer was separated. After concentration, the residue was purified by crystallization from CH_2Cl_2/MeOH/n-hexane to give 3-[2-(4′-methyl-biphenyl-4-yloxy)-acetylamino]-benzoic acid as a white solid (17.5 mg, 30.3% yield). R_f = 0.22 (CH_2Cl_2:MeOH = 15:1); mp 251−252.4 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.25 (1H, s, aromatic-H), 7.85 (1H, m, aromatic-H), 7.65 (1H, m, aromatic-H), 7.55 (2H, m, aromatic-H), 7.46 (2H, m, aromatic-H), 7.39 (1H, ps-t, J = 8.1 Hz, aromatic-H), 7.19 (2H, m, aromatic-H), 7.06 (2H, m, aromatic-H), 4.71 (2H, s, OCH_2CO), 2.30 (3H, s, CH_3); MS (ESI) m/z 384 (M + Na)$^+$, 360 (M − H)$^-$.

3-[2-(3′-Methoxy-biphenyl-4-yl)-acetylamino]-benzoic acid (18). 3-[2-(3′-Bromo-phenoxy)-acetylamino]-benzoic acid methyl ester **8h** (100 mg, 0.27 mmol) was added to a suspension of Pd(PPh_3)$_4$ (15.9 mg, 0.014 mmol) in degassed [bmim][BF_4] (0.1 mL) at ambient temperature. The mixture was heated overnight at 110 °C. The solution was cooled to ambient temperature and sequentially added 3-methoxylphenyl boronic acid (83.4 mg, 0.55 mmol), and a solution of sodium hydrogen carbonate (46.2 mg, 0.55 mmol) in H_2O (0.5 mL). The mixture was reheated overnight at 110 °C with vigorous stirring, then cooled and extracted with EtOAc. The combined extracts were washed by brine. The organic phase was dried over anhydrous $MgSO_4$, and concentrated under vacuo. Purification by silica gel column chromatography (n-hexane:EtOAc:MeOH = 15:3:1) gave 3-[2-(3'-methoxy-biphenyl-4-yl-xyl)-acetyl-

amino]-benzoic acid methyl ester as a white solid (78.1 mg, 73.9% yield). $R_f = 0.46$ (n-hexane:EtOAc:MeOH = 9:3:1). To a solution of 3-[2-(3′-methoxy-biphenyl-4-yl-xyl)-acetylamino]-benzoic acid methyl ester (117 mg, 0.3 mmol) in THF/H_2O (1:1, 20 mL) was added lithium hydroxide monohydrate (25.2 mg, 0.6 mmol) at room temperature. The resulting mixture was stirred overnight, and then acidified with 10% HCl to pH 7. EtOAc was added and the organic layer was separated. After concentration, the residue was purified by recrystallization from CH_2Cl_2/MeOH/n-hexane) to give 3-[2-(3′-methoxy-biphenyl-4-yl)-acetylamino]-benzoic acid as a white solid (63.7 mg, 56.1% yield). $R_f = 0.38$ (CH_2Cl_2:MeOH = 15:1); mp 184.5−187.4 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.32 (1H, s, NH), 8.30 (1H, s, aromatic-H), 7.89 (1H, d, J = 8.4 Hz, aromatic-H), 7.62−7.68 (3H, m, aromatic-H), 7.46 (1H, ps-t, J = 8.1 Hz, aromatic-H), 7.34 (1H, ps-t, J = 8.1 Hz, aromatic-H), 7.08−7.19 (3H, m, aromatic-H), 6.88 (1H, dd, J = 8.1, 2.7 Hz, aromatic-H), 4.78 (2H, s, OCH_2CO), 3.81 (3H, s, OCH_3); MS (ESI) m/z 400 (M + Na)$^+$, 376 (M − H)$^-$; HRMS (ESI) m/z calcd for $C_{22}H_{23}N_2O_5$ [(M + NH_4)$^+$] 395.1601, found: 395.1598.

4-Benzyloxy-3-nitro-benzoic Acid (20). A suspension of 4-hydroxy-3-nitrobenzoic acid **19** (1.50 g) and K_2CO_3 (11.32 g) in acetone (160 mL) was refluxed overnight under argon. After filtration, the solution was concentrated in vacuo to give the crude product as a yellow solid, which was taken up in methanol (350 mL) and treated with an aqueous solution of NaOH (24.57 g, in 80 mL of H_2O). The mixture was stirred at room temperature for 3 h, concentrated under reduced pressure, acidified with 10% HCl to pH 7, and partitioned between EtOAc and water. The organic layer was separated, washed with brine and water, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (CH_2Cl_2:MeOH = 10:1) to give 4-benzyloxy-3-nitro-benzoic acid as a yellow solid (2.05 mg, 91.5% yield). $R_f = 0.17$ (CH_2Cl_2:MeOH = 10:1∼6:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.58 (1H, d, J = 2.4 Hz, aromatic-H), 8.23 (1H, dd, J = 2.4, 8.7 Hz, aromatic-H), 7.36−7.48 (5H, m, aromatic-H), 7.20 (1H, d, J = 9.0 Hz, aromatic-H), 5.34 (2H, s, CH_2); Purity >99% (as determined by RP-HPLC, method A, t_R = 13.3 min).

3-Amino-4-hydroxy-benzoic acid 2-trimethylsilanyl-ethyl Ester (22). To a mixture of 4-benzyloxy-3-nitro-benzoic acid **20** (1.87 g, 6.86 mmol) and HBTU (3.31 g, 10.30 mmol) in DMF (25 mL) was added 2-(trimethylsilyl)ethanol (1.22 g, 10.30 mmol) and DIPEA (1.29 g, 1.73 mL, 10.30 mmol). The reaction mixture was stirred overnight at room temperature, and then partitioned between ethyl acetate and 10% HCl. The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (n-hexane:EtOAc = 10:1) to give 4-benzyloxy-3-nitro-benzoic acid 2-trimethylsilylethyl ester as a yellow solid (1.97 g, 96.9% yield). $R_f = 0.3$ (n-hexane:EtOAc:MeOH =15:3:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.51 (1H, d, J = 2.7 Hz, aromatic-H), 8.17 (1H, dd, J = 1.8, 9.0 Hz, aromatic-H), 7.34−7.47 (5H, m, aromatic-H), 7.16 (1H, d, J = 8.4 Hz, aromatic-H), 4.39−4.45 (2H, m, CH_2), 1.10−1.16 (2H, m, CH_2), 0.08 (9H, s, CH_3). 4-Benzyloxy-3-nitro-benzoic acid 2-trimethylsilyl-ethyl ester (1.97 g, 5.27 mmol) was taken up in methanol and treated with 5% Pd−carbon (5% w/w), and stirred at room temperature under 1 psi hydrogen gas pressure. After completion of the reaction as monitored by TLC, the mixture was filtered through a Celite bed and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (CH_2Cl_2:EtOAc = 10:1) to give 3-amino-4-hydroxy-benzoic acid 2-trimethylsilyl-ethyl ester as a yellow solid (988.7 mg, 74.1% yield). $R_f = 0.2$ (n-hexane:EtOAc:MeOH =15:3:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39−7.44 (2H, m, aromatic-H), 6.78 (1H, d, J = 8.1 Hz, aromatic-H), 4.34−4.39 (2H, m, CH_2), 1.08−1.13 (2H, m, CH_2), 0.08 (9H, s, CH_3); MS (ESI) m/z 252 (M − H)$^-$.

3-[2-(4-Adamantan-1-yl-phenoxy)-acetylamino]-4-hydroxy-benzoic Acid methyl Ester (23). Oxalyl chloride (178.5 mg, 0.11 mL, 1.5 mmol) was added to a solution of **5a** (143.2 mg, 0.5mmol) and one drop of DMF in THF (5 mL), and the mixture was stirred for 1 h at room temperature. Then, 3-amino-4-hydroxybenzoic acid methyl ester (125.4 mg, 0.75 mmol) and pyridine (0.05 mL) were added, and the reaction was stirred overnight at room temperature. The reaction mixture was diluted with EtOAc and 10% HCl. The organic layer was sequentially washed with brine and water, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude solid was purified by flash column chromatography (n-hexane:EtoAc:MeOH = 6:3:1) to give **23** as a white solid (183.2 mg, 84.10% yield). $R_f = 0.68$ (n-hexane:EtOAc:MeOH = 6:3:1). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.10 (1H, s, OH), 9.24 (1H, s, NH), 8.69 (1H, m, aromatic-H), 7.60−7.64 (1H, m, aromatic-H), 7.30 (2H, d, J = 8.4 Hz, aromatic-H), 6.94−6.99 (3H, m, aromatic-H), 4.74 (2H, s, CH_2), 3.79 (3H, s, CH_3), 2.04 (3H, m, adamantyl-H), 1.83 (6H, m, adamantyl-H), 1.72 (6H, m, adamantyl-H); MS (ESI) m/z 434 (M − H)$^-$; HRMS (ESI) m/z calcd for $C_{26}H_{29}O_5NNa$ [(M + Na)$^+$] 458.1943, found: 458.1942.

3-[2-(4-Adamantan-1-yl-phenoxy)-acetylamino]-4-hydroxy-benzoic Acid (25): EDCI (500.4 mg, 2.61 mmol) and HOBt (352.6 mg, 2.61 mmol) were added to a mixture of (4-adamantan-1-yl-phenoxy)acetic acid (**5a**, 496.5 mg, 1.74 mmol), 3-amino-4-hydroxy-benzoic acid 2-trimethylsilyl-ethyl ester (**22**, 527.0 mg, 2.08 mmol), and DIPEA (337.3 mg, 0.45 mL, 2.61mmol) in DMF (17.5 mL). The resulting reaction mixture was stirred overnight at 50 °C and then partitioned between EtOAc and 10% HCl. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (n-hexane:EtOAc = 3:1) to give 3-[2-(4-adamantan-1-yl-phenoxy)acetylamino]-4-hydroxybenzoic acid 2-trimethylsilyl-ethyl ester **24** as a white solid (521.5 mg, 51.0% yield). $R_f = 0.5$ (n-hexane:EtOAc = 5:1); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.24 (1H, s, NH), 8.67 (1H, m, aromatic-H), 7.57−7.61 (1H, m, aromatic-H), 7.30 (2H, d, J = 9.3 Hz, aromatic-H), 6.92−6.96 (3H, m, aromatic-H), 4.73 (2H, s, CH_2), 4.32 (2H, t, J = 8.1 Hz, CH_2), 2.04 (3H, m, adamantyl-H), 1.83 (6H, m, adamantyl-H), 1.72 (6H, m, adamantyl-H), 1.08−1.13 (2H, t, J = 7.81 Hz, CH_2); MS (ESI) m/z 544 (M + Na)$^+$, 520 (M − H)$^-$. To an ice-cooled solution of **24** (516.5 mg, 0.99 mmol) in dry THF (30 mL) was added n-Bu_4NF (14.86 mL, 1 M in THF), the mixture was stirred overnight at room temperature, and then the mixture was partitioned between EtOAc and 10% HCl. The organic layer was sequentially washed with brine and water, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel flash column chromatography (CH_2Cl_2:MeOH = 10:1) to give **25** as a white solid (330.2 mg, 79.1% yield). $R_f = 0.4$ (n-hexane:EtOAc = 10:1); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.26 (1H, s, NH), 8.64 (1H, s, aromatic-H), 7.56 (1H, d, J = 8.7 Hz, aromatic-H), 7.29 (2H, d, J = 8.4 Hz, aromatic-H), 6.90−6.96 (3H, m, aromatic-H), 4.71 (2H, s, CH_2), 2.03 (3H, m, adamantyl-H), 1.72−1.82 (12H, m, adamantyl-H); MS (ESI) m/z 420 (M − H)$^-$; HRMS (ESI) m/z calcd for $C_{25}H_{27}O_5NNa$ [(M + Na)$^+$] 444.1784, found: 444.1787.

3-[2-(4-Adamantan-1-yl-phenoxy)-acetylamino]-4-hydroxy-benzamide (26). A solution of NH_4Cl (6.5 mg, 0.12 mmol) in dry toluene (2 mL) was treated with trimethylaluminium (2.0 M in hexane) (0.26 mL. 0.51 mmol) and stirred for 0.25 h at room temperature. To the mixture was added a solution of 3-[2-(4-adamantan-1-yl-phenoxy)-acetylamino]-4-hydroxy-benzoic acid methyl ester (50.1 mg, 0.12 mmol) in toluene (4 mL), and it was stirred at 80 °C for 3 h. Then the reaction mixture was allowed to cool and was treated with dilute HCl, until no more effervescense was observed. The reaction mixture was then partitioned between EtOAc and saturated $NaHCO_3$ solution. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2:MeOH = 15:1) to give 3-[2-(4-adamantan-1-yl-phenoxy)-acetylamino]-4-hydroxy-benzamide as a white solid (12.9 mg, 25.6% yield). $R_f = 0.16$ (n-hexane:EtOAc:MeOH = 6:3:1); ^{1}H NMR ($CDCl_3$ + CD_3OD, 300 MHz) δ 8.26 (1H, d, J = 2.4 Hz, aromatic-H), 7.23 (1H, d, J = 2.1 Hz, aromatic-H), 6.99 (2H, d, J = 9.3 Hz, aromatic-H), 6.64 (2H, d, J = 9.3 Hz, aromatic-H), 6.59

(1H, d, $J = 8.7$ Hz, aromatic-H), 4.25 (2H, s, CH_2), 1.75 (3H, m, adamantyl-H), 1.56 (6H, m, adamantyl-H), 1.44 (6H, m, adamantyl-H); MS (ESI) *m*/*z* 443 $(M + Na)^+$, 419 $(M - H)^-$; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{28}O_4N_2Na$ $[(M + Na)^+]$ 443.1947, found: 443.1944.

3-[2-(4-Adamantan-1-yl-phenoxy)-acetylamino]-4-hydroxy-*N*,*N*-dimethyl-benzamide (27). A solution of dimethylamine (0.06 mL, 0.12 mmol) in dry toluene (2 mL) was treated with trimethylaluminium (2.0 M in hexane) (0.15 mL. 0.31 mmol) and stirred for 0.25 h at room temperature. To the mixture was added a solution of the 3-[2-(4-adamantan-1-yl-phenoxy)-acetylamino]-4-hydroxy-benzoic acid methyl ester (30.1 mg, 0.07 mmol) in toluene (8 mL), and it was stirred at 80 °C for 3 h. The reaction mixture was allowed to cool and was treated with dilute HCl, until no more effervescense was observed. The reaction mixture was then partitioned between EtOAc and water. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (n-hexane: EtOAc:MeOH = 15:3:1) to give 3-[2-(4-adamantan-1-yl-phenoxy)-acetylamino]-4-hydroxy-*N*,*N*-dimethyl-benzamide as a white solid (10.4 mg, 23.2% yield). $R_f = 0.25$ (n-hexane:EtOAc:MeOH = 6:3:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.85 (1H, s, NH), 7.70 (1H, s, aromatic-H), 7.32 (2H, d, $J = 8.4$ Hz, aromatic-H), 7.03−7.05 (1H, m, aromatic-H), 6.93 (2H, d, $J = 8.7$ Hz, aromatic-H), 6.85 (1H, d, $J = 7.2$ Hz, aromatic-H), 4.61 (2H, s, CH_2), 3.07 (6H, s, CH_3), 2.09 (3H, m, adamantyl-H), 1.89 (6H, m, adamantyl-H), 1.76 (6H, m, adamantyl-H); MS (ESI) *m*/*z* 471 $(M + Na)^+$, 447 $(M - H)^-$; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{32}O_4N_2Na$ $[(M + Na)^+]$ 471.2260, found: 471.2261.

3-[2-(4-Adamantan-1-yl-phenoxy)-acetylamino]-*N*-furan-2-ylmethyl-4-hydroxy-benzamide (28). A solution of furfurylamine (6.8 mg, 0.07 mmol, 0.07 mL) in dry toluene (1 mL) was treated with trimethylaluminium (2.0 M in hexane) (0.15 mL. 0.31 mmol) and stirred for 0.25 h at room temperature. To the mixture was added a solution of the 3-[2-(4-adamantan-1-yl-phenoxy)-acetylamino]-4-hydroxy-benzoic acid methyl ester (30.1 mg, 0.07 mmol) in toluene (8 mL), and it was stirred at 80 °C for 3 h. The reaction mixture was allowed to cool and was treated with dilute HCl, until no more effervescense was observed. The reaction mixture was then partitioned between EtOAc and water. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2:MeOH = 15:1) to give 3-[2-(4-adamantan-1-yl-phenoxy)-acetylamino]-*N*-furan-2-ylmethyl-4-hydroxy-be nzamide as a white solid (15.4 mg, 44.0% yield). $R_f = 0.34$ (n-hexane:EtOAc:MeOH = 6:3:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.71 (1H, s, NH), 7.76 (1H, s, aromatic-H), 7.48 (1H, d, $J = 9.0$ Hz, aromatic-H), 7.33−7.38 (3H, m, aromatic-H), 7.04 (1H, d, $J = 8.1$ Hz, aromatic-H), 6.95 (2H, d, $J = 9.0$ Hz, aromatic-H), 6.44 (1H, s, NH), 6.32 (2H, d, $J = 8.7$ Hz, aromatic-H), 4.62−4.69 (4H, m, CH_2), 2.10 (3H, m, adamantyl-H), 1.90 (6H, m, adamantyl-H), 1.77 (6H, m, adamantyl-H); MS (ESI) *m*/*z* 523 $(M + Na)^+$, 499 $(M - H)^-$; HRMS (ESI) *m*/*z* calcd for $C_{30}H_{32}O_5N_2Na$ $[(M + Na)^+]$ 523.2209, found: 523.2214.

3-[2-(4-Adamantan-1-yl-phenoxy)-acetylamino]-*N*-(2-dimethylamino-ethyl) -4-hydroxy-benzamide (29). A solution of 3-[2-(4-adamantan-1-yl-phenoxy)-acetylamino]-4-hydroxy-benzoic acid **25** (70.1 mg, 0.17 mmol), *N*,*N*-dimethyl-ethylenediamine (22.1 mg, 0.25 mmol, 0.03 mL), EDCI (48.0 mg, 0.25 mmol), HOBT (34.0 mg, 0.25 mmol), and DIPEA (0.05 mL, 0.25 mmol) in DMF (5 mL) was stirred overnight at 60 °C. The mixture was cooled to room temperature and partitioned between EtOAc and water. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2:MeOH = 20:1) to give 3-[2-(4-adamantan-1-yl-phenoxy)-acetylamino]-*N*-(2-dimethylamino-ethyl)-4-hydr oxy-benzamide as a colorless solid (9.7 mg, 11.6% yield). $R_f = 0.16$ (CH_2Cl_2:MeOH = 10:1); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.26 (1H, m, aromatic-H), 7.85 (1H, dd, $J = 1.8$ and 9.0 Hz, aromatic-H), 7.45−7.47 (1H, m, aromatic-H), 7.36 (2H, d, $J = 9$ Hz, aromatic-H), 7.02 (2H, d, $J = 6.6$ Hz, aromatic-H), 4.73 (2H, s, CH_2), 3.63 (2H, t, $J = 6.6$ Hz, CH_2), 2.93 (2H, t, $J = 6.6$ Hz, CH_2), 2.60 (6H, s, CH_3), 2.08 (3H, m, adamantyl-H), 1.91 (6H, m, adamantyl-H), 1.81 (6H, m, adamantyl-H); MS (ESI) *m*/*z* 492 $(M + H)^+$, 490 $(M - H)^-$; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{37}O_4N_3Na$ $[(M + Na)^+]$ 514.2682, found: 514.2689.

3-[2-(4-Adamantan-1-yl-phenoxy)-acetylamino]-4-hydroxy-*N*-(3-morpholin-4-yl-propyl)-benzamide (30). 3-Morpholin-4-yl-propylamine (0.03 mL, 0.18 mmol) and DIPEA (0.03 mL, 0.18 mmol) were added to a solution of 3-[2-(4-adamantan-1-yl-phenoxy)-acetylamino]-4-hydroxy-benzoic acid **25** (50 mg, 0.12 mmol) and HATU (68.5 mg, 0.18 mmol) in DMF (3 mL), and the resulting reaction mixture was stirred overnight at room temperature. The mixture was partitioned between EtOAc and brine. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by preparative TLC (CH_2Cl_2:MeOH = 15:1) gave 3-[2-(4-adamantan-1-yl-phenoxy)-acetylamino]-4-hydroxy-*N*-(3-morpholin-4-yl-propyl)-benzamide, as a colorless solid (9.5 mg, 14.5% yield). $R_f = 0.35$ (CH_2Cl_2:MeOH = 10:1); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.57 (1H, d, $J = 2.4$ Hz, aromatic-H), 7.51 (1H, dd, $J = 2.4$, 8.7 Hz, aromatic-H), 7.33 (2H, d, $J = 8.7$ Hz, aromatic-H), 6.98 (2H, d, $J = 8.7$ Hz, aromatic-H), 6.92 (1H, d, $J = 8.7$ Hz, aromatic-H), 4.67 (2H, s, CH_2), 3.76−3.81 (4H, m, aliphatic-H), 6.92 (2H, t, $J = 6.9$ Hz, aliphatic-H), 2.71−2.79 (6H, m, aliphatic-H), 2.07 (3H, m, adamantyl-H), 1.91 (8H, m, adamantyl-H and aliphatic-H), 1.80 (6H, m, adamantyl-H); MS(ESI) *m*/*z* 548 $(M + H)^+$, 546 $(M - H)^-$; HRMS (ESI) *m*/*z* calcd for $C_{32}H_{42}O_5N_3$ $[(M + H)^+]$ 548.3124, found: 548.3121.

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Supporting Information Available: A table listing HPLC retention times and purities for **1**, **8a**, **9d**−**i**, **10a**−**j**, **11**−**18**, **23**, and **25**−**30**, and biological procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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