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Synthesis and Biological Evaluation of Phenoxy-*N*-phenylacetamide Derivatives as Novel P-glycoprotein Inhibitors

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Overexpression of P-glycoprotein (Pgp) is associated with multidrug resistance (MDR) of tumor cells to a number of chemotherapeutic drugs. Pgp inhibitors have been shown to effectively reverse Pgp-mediated MDR. We prepared a series of phenoxy-*N*-phenylacetamide derivatives and tested for their ability to inhibit Pgp as potential MDR reversing agents, using a Pgp over-expressing MCF-7/ADR cell line. Some of the synthesized compounds exhibited moderate to potent reversal activity. Of note, compound **4o** showed a 3.0-fold increased inhibition compared with verapamil, a well-known Pgp inhibitor. In addition, co-treatment of the representative compound **4o** and a substrate anticancer agent doxorubicin resulted in a remarkable increase in doxorubicin's antitumor effect and inhibition of DNA synthesis in the MCF-7/ADR cell line. Taken together, these findings suggest that compound **4o** could be a useful lead for development of a novel Pgp inhibitor for treatment of MDR.

Key Words : Pgp, Chemotherapy, MDR reversal activity, Phenoxy-*N*-phenylacetamide derivatives

Introduction

Failure to respond to chemotherapy is a serious impediment in treatment of cancer. In this regard, development of multidrug resistance (MDR) is frequently observed, which leads to reduced sensitivity of cancer cells to a broad spectrum of cytostatics. The major mechanism of MDR is associated with overexpression of transporters of the ATP binding cassette (ABC) family. These efflux pumps are localized in the cell membrane and reduce the intracellular concentration of multiple structurally and functionally unrelated drugs by an active extrusion at the cost of ATP hydrolysis.[1-5]

P-glycoprotein (Pgp), the first discovered member of ABC efflux transporters, possesses their typical architecture, with two transmembrane domains consisting of six transmembrane helices and two cytoplasmic nucleotide-binding sites.[6] It can actively transport anticancer drugs out of the cancer cells and decrease their intracellular accumulation. Accordingly, Pgp has emerged as a promising target for cancer therapy and great efforts have been focused on the development of effective reversal agents to overcome Pgp-mediated MDR. A variety of compounds have been found to inhibit Pgp, including verapamil **1** (Fig. 1).[7,8] Several P-gp inhibitors have been featured in clinical studies, which showed that inhibiting ABC transporters for the purpose of overcoming MDR is a valid strategy, at least in haematological malignancies. However, due to the prevalence of severe side effects, Pgp inhibitors must be highly specific for successful application to the therapy of multiresistant tumors. Some other problems with MDR reversal agents include low inhibitory activity and high toxicity. As part of our program for development of Pgp inhibitors as MDR reversal agents, we recently reported new series of coumarin analogues and

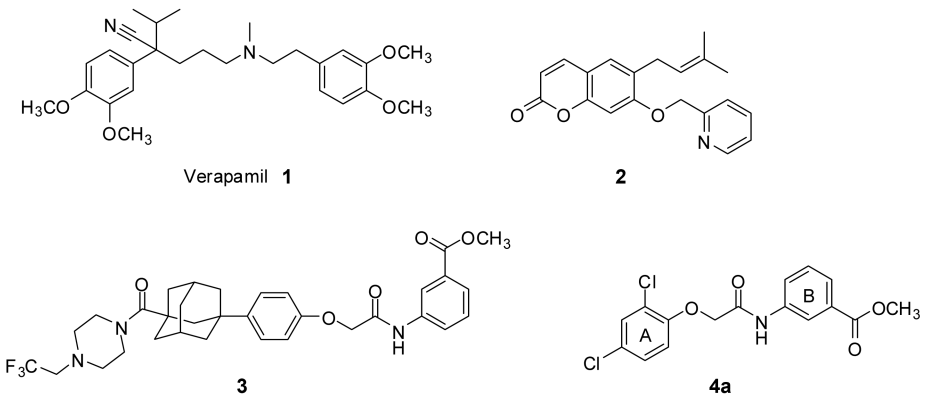


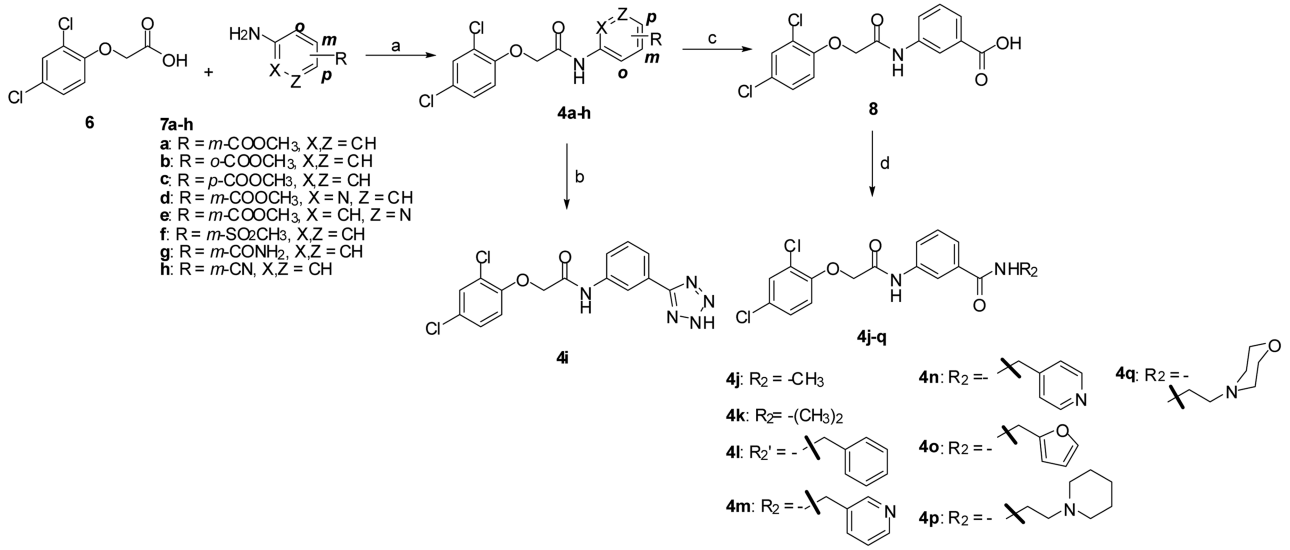
Figure 1. Structures of Pgp inhibitors.

2-substituted adamantyl-based compounds with potent Pgp inhibitory activities, including compounds **2** and **3**.[9,10]

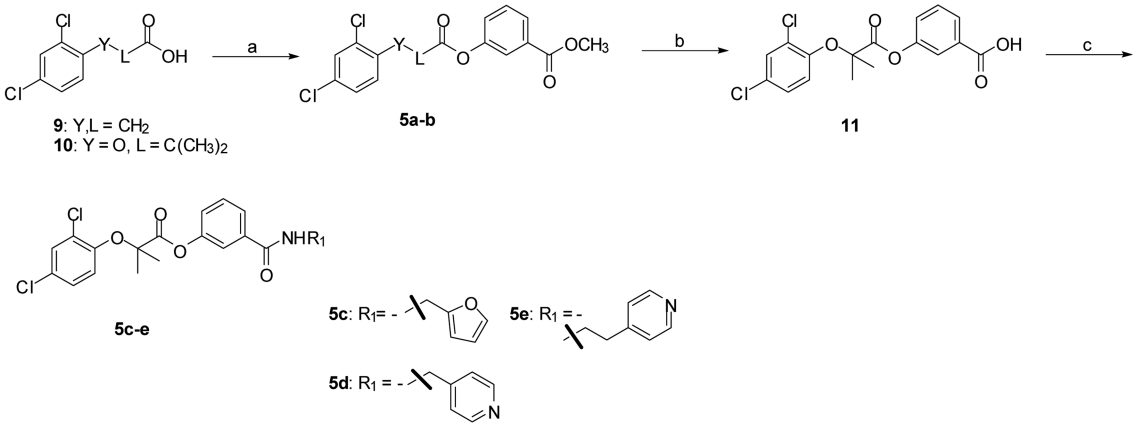
In order to develop novel inhibitors of Pgp with lower toxicity and higher efficacy, we carried out a high throughput screening from our in-house chemical library, which led to the discovery of 2-phenoxy-*N*-phenylacetamide **4a** as a promising inhibitor (Fig. 1). Herein, we report structure-activity relationships and biological evaluation of the titled compounds as potential Pgp inhibitors.

Results and Discussion

Chemistry. A series of phenoxy-*N*-phenylacetamide derivatives were prepared as shown in Scheme 1-2. Coupling of 2-(2,4-dichlorophenoxy)acetic acid **6** as the starting material with suitable substituted anilines **7a-h** (methoxycarbonyl, methanesulfonyl, aminocarbonyl, cyano) or hetero aromatic amines (isonicotinic, nicotinic) in the presence of PyBOP or EDC yielded the corresponding amide analogues **4a-h**. Carboxylic acid **8** coupling with a variety of amines in the presence of PyBOP or PPAA gave the corresponding amides **4i-q**. The amide **4h** further reacted with NaN_3 under TEA and *N*-methylpyrrolidone conditions provided the tetrazole derivative **4i**. As shown in scheme **2**, linker modified derivatives **5a-b** were also synthesized starting from the dichloro acid **9** and **10**. After coupling reaction the amide **5b** was further hydrolyzed using lithium hydroxide to give acid **11**. A variety of amide derivatives of compounds **12-17** in Table 4 were prepared according to methods in the literature.[11] Finally, acid **11** was reacted with a series of diverse amines to provide analogues **5c-e**. The structures of all the newly synthesized compounds were confirmed by ^{1}H NMR and mass spectral data which were in full agreement with their desired structures. All the synthesized compounds were readily dissolved in DMSO, and water solubility for the representative compound **4o** was around 0.1 mg/mL.



Scheme 1. Synthesis of 2-phenoxy-*N*-phenylacetamide derivatives. Reagents and Conditions: a) PyBOP, DIPEA, DMF, rt, 12 h for **4b** and **4c**; EDC, HOBt, DIPEA, DMF, rt, 12 h for **4a**, **4d-h**; b) **4h**, NaN_3, TEA, *N*-methylpyrrolidone, 150 °C, overnight; c) $LiOH{\cdot}H_2O$, THF, H_2O, rt, overnight; d) PPAA, Et_3N, CH_3CN, rt, 12 h for **4j**; EDC, HOBt, DIPEA, DMF, rt, 12 h for **4k-n**, **4p-q**; PyBOP, DIPEA, DMF, rt, 12 h for **4o**.



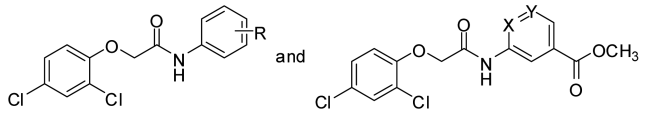
Scheme 2. Synthesis of linker modified derivatives. Reagents and Conditions: a) **7b**, EDC, HOBt, DIPEA, DMF, rt, 12 h for **5a-b**; b) **5b**, $LiOH{\cdot}H_2O$, THF, H_2O, rt, overnight; c) PPAA, Et_3N, CH_3CN, rt, 12 h for **5c-e**.

Biological Evaluation. The evaluation of the Pgp inhibiting properties of synthesized compounds was carried out by comparing the fluorescence uptake of the Pgp specific substrate rhodamine-123 (Rho-123) into inhibitor treated cells or untreated control cell lines by monitoring the fluorescence signal.

The breast cancer cell line of human origin, MCF7/ADR, was routinely cultured in RPMI 1640 supplemented with 10% fetal bovine serum, 2 mM glutamine, 100,000 U/mL penicillin, and 100 μg/mL streptomycin in a humidified incubator at 37 °C with a 5% CO_2 atmosphere. The cells were trypsinized twice a week with trypsin/ethylenediaminetetraacetic acid (EDTA) (0.02%/0.02%) and the medium was changed twice a week.

Increases in the efflux of drugs is the major feature of Pgp mediated MDR. Considering that Rho-123 efflux is a more sensitive measure than that of anticancer drugs, the efflux inhibitory activity of the synthesized compounds with Rho-123 as a substrate was chosen to quantify MDR reversal activity.[12] The intracellular accumulation ratio of Rho-123 in MCF-7/ADR cells over-expressing Pgp was lower than in wild-type MCF-7 cells[13] and Rho-123 fluorescence was 3.35 fold enhanced by treatment with 100 μM verapamil, a well-known Pgp inhibitor, as a reference drug. All the tested chemicals (10 microM) did not significantly affect the cell viability of MCF-7/ADR cells. The prepared compounds at the concentration of 10 mM were then evaluated for their ability to inhibit the Pgp protein. The initial investigation was focused on determining the importance of the *m*-carboxylic acid methyl ester on the B phenyl ring and changing the B phenyl ring to a pyridine ring (Table 1 and 2). Compounds with a carboxylic acid methyl ester substitution at the *ortho*- or *para*-positions (**4b** and **4c**) had a lower Pgp inhibitory activity than compounds with substitutions at the *meta*-position (the parent compound **4a**), which reversed the transport of Rho-123 up to 1.47-fold compared with that of vehicle. In addition, the introduction of a hetero atom on the B phenyl ring (**4d-e**) led to a significant loss in inhibitory activity. The substitution position on the B phenyl ring might constitute an important structural requirement for increasing Pgp inhibitory activity. We then examined the effects of substituents on the A phenyl ring as shown in Table 4. Substitution of the 2,4-dichloro moiety on the A phenyl ring of **4a** by lipophilic groups (such as 4-fluoro **12**, 4-chloro **13**, 4-bromo **14**, 4-*tert*-butyl and phenyl **16-17**), and hydrophilic groups (such as 4-nitro **15**) caused no increase in inhibition, while compound **13** (2.88-fold increase) was more potent with than compound **4a**. However, compound **13** showed significant cytotoxicity (48.7 ± 2.3% cell death at 30 μM), an undesirable property for a potential Pgp inhibitor. Based on that finding, more derivatization with *meta*- substitution on the B phenyl ring of **4a** was attempted in order to optimize the effect of compound **4a**. We found that replacement of the carboxylic acid methyl ester with sulfone (**4f**), tetrazole (**4i**) and carboxylic acid (**8**) led, surprisingly, to a decrease in Pgp

Table 1. MDR reversal activities for compounds **4a-e** in MCF-7/ADR cells

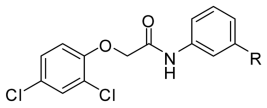


4a-c **4d-e**

No	Structure			Fold increase
	R	X	Y	
4a	*m*-$COOCH_3$			1.47
4b	*o*-$COOCH_3$			1.11
4c	*p*-$COOCH_3$			1.17
4d		N	CH	0.90
4e		CH	N	1.30
Verapamil (100 μM)				3.35

[a]Values are means of three experiments.

Table 2. MDR reversal activities for compounds **4a-4q** and **8** in MCF-7/ADR cells



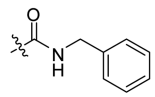
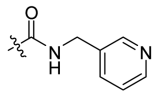
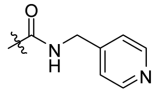
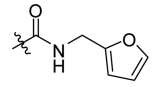
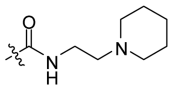
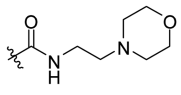
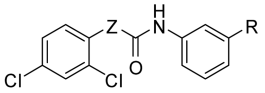
No	Structure R	Fold increase
4a	$COOCH_3$	1.47
4f	SO_2CH_3	1.47
4g	$CONH_2$	0.85
4i		1.18
8	COOH	0.97
4j	$CONHCH_3$	1.10
4k	$CON(CH_3)_2$	1.03
4l		1.07
4m		1.14
4n		1.77
4o		3.00
4p		1.54
4q		1.10

Table 3. MDR reversal activities for compounds **5a-e** in MCF-7/ADR cells



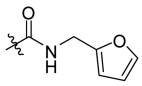
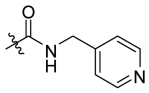
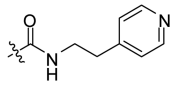
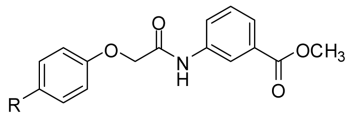
No	Structure		Fold Increase
	R	Z	
5a	OCH_3		1.27
5b	OCH_3		2.12
5c			1.34
5d			1.07
5e			1.45

Table 4. MDR reversal activities for compounds**12-17** in MCF-7/ADR cells



No	Structure	Fold increase
	R	
12[11]	F	1.17
13[11]	Cl	2.89
14[11]	Br	1.17
15[11]	NO_2	1.13
16[11]		1.21
17[11]		1.08

inhibition. Of interest, amongst the amide analogues, the amides with a one-carbon spacer showed an increase in potency. For example, the benzylamide and *N*-(pyridin-3-ylmethyl) amide (**4m**) showed no inhibitory activity, the *N*-(pyridin-4-ylmethyl)amide (**4n**) had a moderate potency, and the furfurylamide (**4o**) showed greater potency (3.0-fold increase) than that of **4a**. Compounds with a free amide, a methyl amide, a dimethyl amide (**4g** and **4j-k**) and amides with two-carbon spacer heterocycles (**4p-q**) showed no increase in Pgp inhibition.

Next we modified the linker between the two phenyl rings (Table 3). Replacement of oxygen atom (**5a**) by a carbon atom, which should generate a more flexible conformation, resulted in significant loss of inhibitory activity. On the contrary, introduction of a dimethyl group (**5b**) linking the oxygen to an amide creating a rigid conformation of the

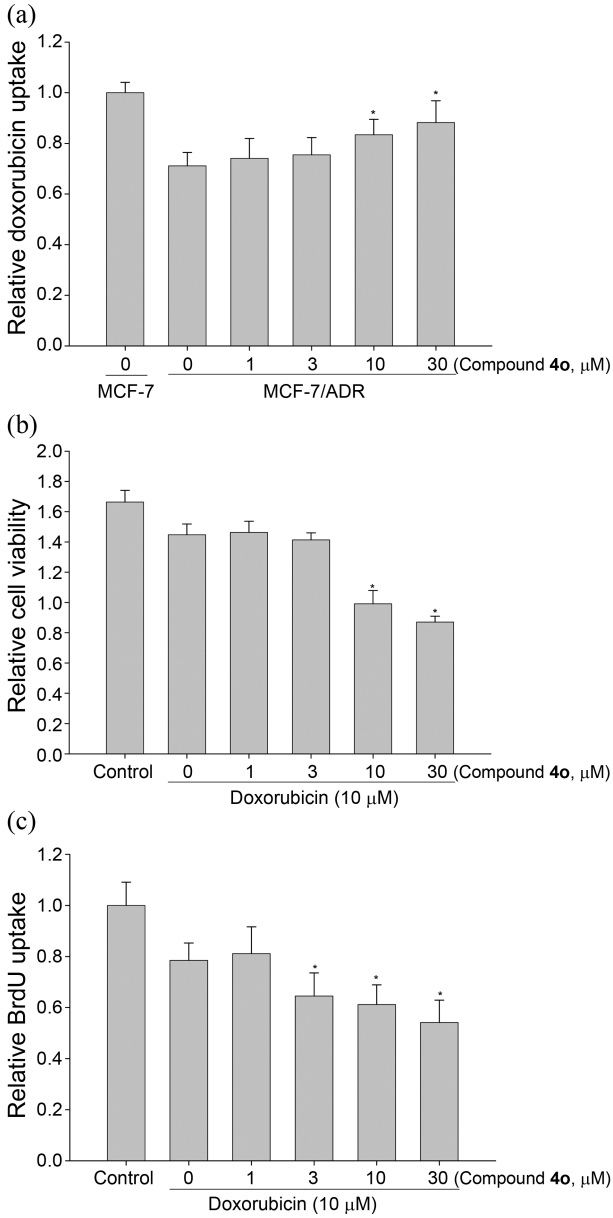


Figure 2. The overcoming of resistance to doxorubicin in MCF-7/ADR cells by compound **4o**. (a) Cellular doxorubicin uptake. After incubation of MCF-7/ADR cells with or without compound **4o** (1-30 μM) for 1 h, cells were treated with doxorubicin (30 μM) for 60 min. Doxorubicin fluorescence intensities retained in cell lysates of MCF-7 and MCF-7/ADR cells were measured using excitation and emission wavelengths of 470 and 590 nm, respectively. The values were divided by the total protein content of each sample. Data are presented as means ± SD of 4 different samples (significant versus untreated MCF-7/ADR cells, $*p < 0.05$; MCF-7 control level = 1). (b) Synergistic cytotoxicity by compound **4o** and doxorubicin in MCF-7/ADR cells. MCF-7/ADR cells were exposed to doxorubicin (10 μM) in the presence or absence of compound **4o** (1-30 μM) for 24 h. Cell viabilities were determined by crystal violet assay. Data represent the means ± SD of 8 different samples (significant versus doxorubicin alone-treated MCF-7/ADR cells, $*p < 0.05$). (c) Potentiation of doxorubicin-mediated DNA synthesis inhibition by compound **4o**. MCF-7/ADR cells were treated as described in panel B, and BrdU assays were performed. Data represent the mean ± SD of 6 different samples (significant versus doxorubicin alone-treated MCF-7/ADR cells, $*p < 0.05$).

linker, displayed a 2.12 fold increase in activity. The carboxylic acid methyl ester on the B phenyl ring of **5b** was then modified by amides substituted with one-carbon spacer heterocyclic rings, for which *N*-(pyridin-4-ylmethyl) amide (**5d**) displayed no increase in Pgp inhibitory activity, while furfuryl amide (**5c**) and *N*-(pyridin-4-ylethyl)amide (**5e**) had moderate potency with 1.34 and 1.45 fold increase, respectively.

In order to test whether cellular uptake of doxorubicin was enhanced by the inhibitors in doxorubicin resistant cancer cells, we evaluated the biological activities of the representative derivative **4o**. Of note, doxorubicin was accumulated in MCF-7/ADR cells to a lesser extent than in MCF-7 cells. Doxorubicin uptake in MCF-7/ADR cells was significantly increased by treatment of cells with compound **4o** at 10 and 30 μM, respectively (Fig. 2(a)). To assess whether cytotoxicity of doxorubicin on MCF-7/ADR cells can be reversed by compound **4o**, we determined cell viability and DNA synthesis intensity after pre-incubation of the cells with vehicle or compound **4o** (1-30 μM). Compound **4o** significantly enhanced both the cytotoxicity and the DNA synthesis inhibition of doxorubicin, as indicated by crystal violet assays (Fig. 2(b)) and BrdU uptake (Fig. 2(c)) assays. These results suggested that inhibition of MDR1 by compound **4o** could restore cell sensitivity to doxorubicin. Furthermore, we determined the possible synergy of compound **4o** on paclitaxel-mediated inhibition of cell proliferation in MCF-7/ADR cells, since paclitaxel is a known Pgp substrate. Compound **4o** potentiated paclitaxel-mediated cytotoxicity in a concentration-dependent manner (Fig. 3(a)). Several Pgp inhibitors were reported to block the function of MDR transporter via down-regulation of Pgp expression.[14,15] In the case of **4o**, however, Pgp expression was not altered in the concentration range of 1-10 ìM, and there was a marginal reduction at 30 μM in MCF-7/ADR cells (Fig. 3(b)). Hence, the mechanistic basis for Pgp inhibition by compound **4o** may not result from transcriptional inhibition of the *mdr1* gene, a finding that now warrants more studies on mechanism.

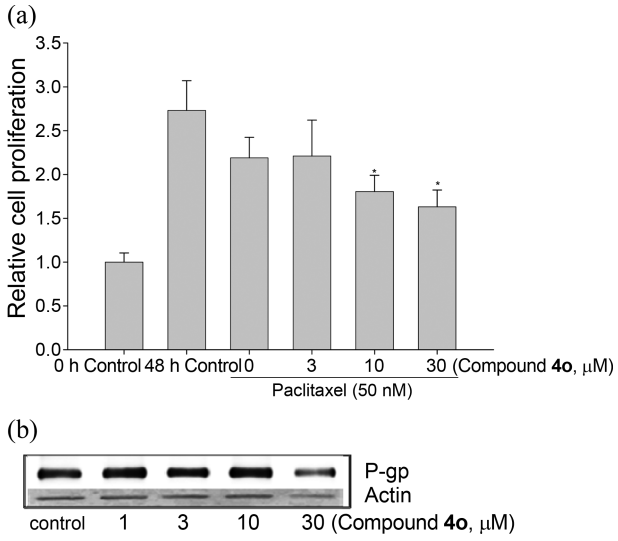


Figure 3. Effects of compound **4o** on paclitaxel-induced cell proliferation inhibition and Pgp expression. (a) Synergistic cell proliferation inhibition by compound **4o** and paclitaxel in MCF-7/ADR cells. Compound **4o** (3-30 μM) was preincubated for 1 h and MCF-7/ADR cells were exposed to paclitaxel (50 nM) for an additional 48 h in 10% FBS-containing medium. Relative cell number was determined by crystal violet assay. Data represent the means ± SD of 8 different samples (significant versus paclitaxel alone-treated MCF-7/ADR cells, $*p < 0.05$). (b) Effect of compound **4o** on Pgp expression in MCF-7/ADR cells. MCF-7/ADR cells were incubated with or without compound **4o** (1-30 μM) for 18 h and total cell lysates were subjected to immunoblotting for MDR1 and actin.

In summary, a series of phenoxy-*N*-phenylacetamide derivatives were synthesized and evaluated for their Pgp reversal activity in the Pgp over-expressing MCF-7/ADR cell line. Some of the synthesized compounds showed moderate to potent reversal activity, among which compound **4o** showed a 3.0-fold increase compared with verapamil, a well-known Pgp inhibitor. In addition, co-treatment of compound **4o** with doxorubicin resulted in a remarkable antitumor effect and inhibition of DNA synthesis in MCF-7/ADR cells. Compound **4o** may be a promising candidate for development of an novel MDR reversal drug. Further biological evaluation studies, pharmacokinetics studies, and mechanistic studies on this new compound are currently in progress and will be reported in due course.

Experimental Section

All of the commercial chemicals and solvents were of reagent grade and were used without further purification. All reactions were carried out under an atmosphere of dried argon, in flame-dried glassware. Proton NMR spectra were recorded on a Varian 300 (300 MHz) spectrometer at ambient temperature. Chemical shifts are reported as ppm (δ) downfield from an internal standard tetramethylsilane. Mass spectrometric data were determined using an Agilent 6890 series instrument and a JEOL, JMS-600M Gas Chromatograph/Mass Spectrometer. Products were purified by flash column chromatography using silica gel 60 (230-400 mesh Kieselgel 60). The purity of the products was checked by reversed phase high-pressure liquid chromatography (RP-HPLC) to a minimum purity of 95%, which was done using either a Dionex Corp. HPLC or a 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 (5 μ particle size, 12 nm pore size), 4.6 mm dia. × 150 mm with a flow rate of 1.0 mL/min. Compound purity was assessed using one of the following methods – **Method A:** a gradient of 50% to 100% B in 30 min; **Method B:** a gradient of 25% to 100% B in 30 min; **Method C:** a gradient of 60% B to 100% B in 30 min.

General Synthetic Procedures of the Coupling Reaction by using EDC (4a, 4d-h, 4k-n, 4p-q). EDC (1.5 eqv.) and HOBT (1.5 eqv.) were added to a solution of acid (1 eqv.), amine (1.5 eqv.), and DIPEA (1.5 eqv.) in DMF, 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.

3-[2-(2,4-Dichloro-phenoxy)-acetylamino]-benzoic Acid Methyl Ester (4a): Yield = 30.6%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.6 (1H, s, NH), 8.14 (1H, m, aromatic-H), 7.93-7.96 (1H, m, aromatic-H), 7.85 (1H, d, J = 7.8 Hz, aromatic-H), 7.43-7.48 (2H, m, aromatic-H), 7.25-7.29 (1H, m, aromatic-H), 6.91 (1H, d, J = 9.0 Hz, aromatic-H), 4.66 (2H, s, CH_2), 3.93 (3H, s, CH_3); MS (EI) *m/z* 353 (M^+); HRMS (EI) *m/z* calcd for $C_{16}H_{13}Cl_2NO_4$ [M^+] 353.0222, found: 353.0208; Purity > 99% (as determined by RP-HPLC, method A, t_R = 16.6 min).

2-(2-(2,4-Dichlorophenoxy)acetamido)isonicotinic Acid Methyl Ester (4d): Yield = 69.8%; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 10.88 (1H, s, NH), 8.54 (2H, m, aromatic-H), 7.58 (2H, m, aromatic-H), 7.34-7.38 (1H, m, aromatic-H), 7.11 (1H, d, J = 8.4 Hz, aromatic-H), 4.99 (2H, s, CH_2), 3.89 (3H, s, CH_3); MS (EI) *m/z* 354 (M^+); HRMS (EI) *m/z* calcd for $C_{15}H_{12}Cl_2N_2O_4$ [M^+] 354.0174, found: 354.0171; Purity > 99% (as determined by RP-HPLC, method B, t_R = 18.2 min).

5-(2-(2,4-Dichlorophenoxy)acetamido)nicotinic Acid Methyl Ester (4e): Yield = 59.7%; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 9.01 (1H, s, aromatic-H), 8.96 (1H, s, aromatic-H), 8.75 (1H, s, NH), 8.66 (1H, s, aromatic-H), 7.45 (1H, d, J = 2.4 Hz, aromatic-H), 7.45 (1H, dd, J = 2.4 & 8.4 Hz, aromatic-H), 6.91 (1H, d, J = 8.4 Hz, aromatic-H), 4.68 (2H, s, CH_2), 3.97 (3H, s, CH_3); MS (EI) *m/z* 354 (M^+); HRMS (EI) *m/z* calcd for $C_{15}H_{12}Cl_2N_2O_4$ [M^+] 354.0174, found: 354.0175; Purity > 99% (as determined by RP-HPLC, method A, t_R = 13.5 min).

2-(2,4-Dichloro-phenoxy)-N-(3-methanesulfonyl-phenyl)-acetamide (4f): Yield = 55.0%; ^{1}H-NMR (CD_3OD and DMSO-d_6, 300 MHz) δ 8.41 (1H, m, aromatic-H), 7.99-8.03 (1H, m, aromatic-H), 7.66-7.79 (3H, m, aromatic-H), 7.45 (1H, dd, J = 2.4 & 9.0 Hz, aromatic-H), 7.24 (1H, d, J = 9.0 Hz, aromatic-H), 4.30 (2H, s, CH_2), 3.27 (3H, s, CH_3); MS (EI) *m/z* 373 (M^+); HRMS (EI) *m/z* calcd for $C_{15}H_{13}Cl_2NO_4S$ [M^+] 372.9942, found: 372.9945; Purity > 99% (as determined by RP-HPLC, method A, t_R = 10.9 min).

3-(2-(2,4-dichlorophenoxy)acetamido)benzamide (4g): Yield = 86.4%, ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 10.30 (1H, s, NH), 8.05 (1H, s, aromatic-H), 7.95 (1H, s, NH_2), 7.76 (1H, d, J = 7.8 Hz, aromatic-H),), 7.60 (1H, d, J = 2.4 Hz, aromatic-H), 7.57 (1H, d, J = 7.5 Hz, aromatic-H), 7.35-7.42 (3H, m, aromatic-H, NH_2), 7.11 (1H, d, J = 9.0 Hz, aromatic-H), 4.87 (2H, s, CH_2); MS (EI) *m/z* 338 (M^+); HRMS (EI) *m/z* calcd for $C_{15}H_{12}Cl_2N_2O_3$ [M^+] 338.0225, found: 338.0227; Purity > 99% (as determined by RP-HPLC, method B, t_R = 13.2 min).

***N*-(3-Cyano-phenyl)-2-(2,4-dichloro-phenoxy)-acetamide (4h):** Yield = 81.3%; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.90 (1H, s, NH), 7.26 (1H, s, aromatic-H), 6.97-7.01 (1H, m, aromatic-H), 6.65-6.71 (3H, m, aromatic-H), 6.47-6.50 (1H, m, aromatic-H), 6.12 (1H, d, J = 8.7 Hz, aromatic-H), 4.86 (2H, s, CH_2); MS (EI) *m/z* 320 (M^+); HRMS (EI) *m/z* calcd for $C_{15}H_{10}Cl_2N_2O_2$ [M^+] 320.0119, found: 320.0121; Purity > 99% (as determined by RP-HPLC, method A, t_R = 10.2 min).

3-[2-(2,4-Dichloro-phenoxy)-acetylamino]-*N*,*N*-dimethyl-benzamide (4k): Yield = 56%; ^{1}H-NMR (CD_3OD, 300 MHz) δ 7.74 (1H, ps-t, J = 1.8 Hz, aromatic-H), 7.64 (1H, m, aromatic-H), 7.45 (2H, m, aromatic-H), 7.28 (1H, dd, J = 2.4 & 9.0 Hz, aromatic-H), 7.18 (1H, m, aromatic), 7.09 (1H, d, J = 9.3 Hz, aromatic), 4.77 (2H, s, CH_2), 3.09 (3H, s, NCH_3), 3.00 (3H, s, NCH_3); MS (EI) *m/z* 366 (M^+); HRMS (EI) *m/z* calcd for $C_{17}H_{16}Cl_2N_2O_3$ [M^+] 366.0538, found: 366.0535; Purity > 99% (as determined by RP-HPLC, method A, t_R = 14.8 min).

***N*-Benzyl-3-[2-(2,4-dichloro-phenoxy)-acetylamino]-benzamide (4l):** Yield = 14%; ^{1}H-NMR (CD_3OD, 300 MHz) δ 7.99 (1H, t, J = 1.8Hz, aromatic-H), 8.08 (1H, dd, J = 1.2 & 7.5 Hz, aromatic-H), 7.61 (2H, m, aromatic-H), 7.19-7.44 (7H, m, aromatic-H), 7.01 (1H, d, J = 1.8 Hz, aromatic-H), 4.56 (2H, s, CH_2), 3.34 (2H, s, $NHCH_2Ph$); MS (EI) *m/z* 428 (M^+); HRMS (EI) *m/z* calcd for $C_{22}H_{18}Cl_2N_2O_3$ [M^+] 428.0694, found: 428.0692; Purity > 99% (as determined by reverse phase HPLC, method A, t_R = 17.3 min).

3-[2-(2,4-Dichloro-phenoxy)-acetylamino]-*N*-pyridin-3-ylmethyl-benzamide (4m): Yield = 55%; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 10.34 (1H, s, NH), 9.09 (1H, t, J = 6.0 Hz, NH), 8.54 (1H, d, J = 2.1 Hz, aromatic-H), 8.45 (1H, m, aromatic-H), 8.09 (1H, s, aromatic-H), 7.72 (2H, m, aromatic-H), 7.60 (2H, m, aromatic-H), 7.33-7.45 (3H, m, aromatic-H), 7.11 (1H, d, J = 9.0 Hz, aromatic-H), 4.88 (2H, s, CH_2), 4.48 (2H, d, J = 6.0 Hz, CH_2); MS (EI) *m/z* 429 (M^+); HRMS (EI) *m/z* calcd for $C_{21}H_{17}Cl_2N_3O_3$ [M^+] 429.0647, found: 429.0656; Purity > 99% (as determined by reverse phase HPLC, method A, t_R = 10.7 min).

3-[2-(2,4-Dichloro-phenoxy)-acetylamino]-*N*-pyridin-4-ylmethyl-benzamide (4n): Yield = 70%; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 10.35 (1H, s, NH), 9.12 (1H, t, J = 5.4 Hz, NH), 8.50 (2H, m, aromatic-H), 8.11 (1H, m, aromatic-H), 7.78 (1H, dd, J = 1.2 & 8.1 Hz aromatic-H), 7.61 (2H, m, aromatic-H), 7.44 (1H, ps-t, J = 7.8 Hz, aromatic-H), 7.38 (1H, dd, J = 2.4 & 8.6 Hz aromatic-H), 7.29 (2H, m, aromatic-H), 7.12 (1H, d, J = 9.0 Hz, aromatic-H), 4.88 (2H, s, CH_2), 4.49 (2H, d, J = 5.4 Hz, CH_2); MS (EI) *m/z* 429 (M^+); HRMS (EI) *m/z* calcd for $C_{21}H_{17}Cl_2N_3O_3$ [M^+] 429.0647, found: 429.0654; Purity > 99% (as determined by HPLC, method A, t_R = 10.7 min).

3-[2-(2,4-Dichloro-phenoxy)-acetylamino]-*N*-(2-piperidin-1-yl-ethyl)-benzamide (4p): Yield = 70%; ^{1}H-NMR (CD_3OD, 300 MHz) δ 8.09 (1H, t, J = 1.8 Hz, aromatic-H), 7.75 (1H, dd, J = 1.2 & 7.8 Hz, aromatic-H), 7.58 (1H, d, J = 7.8 Hz, aromatic-H), 7.45 (2H, m, aromatic-H), 7.28 (1H, dd, J = 2.4 & 8.7 Hz, aromatic-H), 7.09 (1H, d, J = 8.7 Hz, aromatic-H), 4.78 (2H, s, CH_2), 3.59 (2H, m, CH_2), 2.73-2.80 (6H, m, CH_2), 1.65-1.73 (4H, m, CH_2), 1.55 (2H, m, CH_2); MS (EI) *m/z* 449 (M^+); HRMS (EI) *m/z* calcd for $C_{22}H_{25}Cl_2N_3O_3$ [M^+] 449.1273, found: 449.1270; Purity > 99% (as determined by reverse phase HPLC, method A, t_R

= 11.1 min).

3-[2-(2,4-Dichloro-phenoxy)-acetylamino]-*N*-(2-morpholin-4-yl-ethyl)-benzamide (4q): Yield = 38%; ^{1}H-NMR (CD_3OD, 300 MHz) δ 8.02 (1H, m, aromatic-H), 7.78 (1H, m, aromatic-H), 7.57 (1H, m, aromatic-H), 7.41 (2H, m, aromatic-H), 7.24 (1H, dd, J = 2.4 & 9.0 Hz, aromatic-H), 7.05 (1H, d, J = 8.4 Hz, aromatic-H), 4.74 (2H, s, CH_2), 3.70-3.73 (4H, m, CH_2), 3.54 (2H, t, J = 6.6 Hz, CH_2), 2.57-2.66 (6H, m, CH_2); MS (EI) *m/z* 451 (M^+); HRMS (EI) *m/z* calcd for $C_{21}H_{23}Cl_2N_3O_4$ [M^+] 451.1066, found: 451.1064; Purity > 96% (as determined by HPLC, method A, t_R = 10.6 min).

3-[3-(2,4-Dichloro-phenoxy)-propionylamino]-benzoic Acid Methyl Ester (5a): Yield = 51.8%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.97 (1H, m, aromatic-H), 7.86 (1H, d, J = 8.1 Hz, aromatic-H), 7.76 (1H, d, J = 8.1 Hz, aromatic-H), 7.54 (1H, s, NH), 7.36-7.40 (2H, m, aromatic-H), 7.13-7.24 (2H, m, aromatic-H), 3.89 (3H, s, CH_3), 3.13 (2H, t, J = 7.2 Hz, aromatic-H), 2.67 (2H, t, J = 7.2 Hz, aromatic-H); MS (EI) *m/z* 351 (M^+); HRMS (EI) *m/z* calcd for $C_{17}H_{15}Cl_2NO_3$ [M^+] 351.0429, found: 351.0429; Purity > 99% (as determined by RP-HPLC, method A, t_R = 18.1 min).

3-[2-(2,4-Dichloro-phenoxy)-2-methyl-propionylamino]-benzoic Acid Methyl Ester (5b): Yield = 99.9 %; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.30 (1H, s, NH), 7.40 (1H, m, aromatic-H), 7.11-7.15 (1H, m, aromatic-H), 7.01-7.04 (1H, m, aromatic-H), 6.62-6.67 (2H, m, aromatic-H), 6.41 (1H, dd, J = 2.4 & 8.7 Hz, aromatic-H), 6.26 (1H, d, J = 9.0 Hz, aromatic-H), 3.12 (3H, s, CH_3), 0.84 (6H, s, CH_3); MS (EI) *m/z* 381 (M^+); HRMS (EI) *m/z* calcd for $C_{18}H_{17}Cl_2NO_4$ [M^+] 381.0535, found: 381.0535; Purity > 99% (as determined by RP-HPLC, method A, t_R = 14.1 min).

General Synthetic Procedures of the Coupling Reaction by using PyBOP (4b-c, 4o). To a mixture of benzoic acid (1 eqv.) and PyBOP (1.5 eqv.) in DMF was added amine (1.5 eqv.) and DIPEA (1.5 eqv.). 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.

2-[2-(2,4-dichloro-phenoxy)-acetylamino]-benzoic Acid Methyl Ester (4b): Yield = 66.6%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 11.84 (1H, s, NH), 8.73 (1H, d, J = 8.1 Hz, aromatic-H), 8.05 (1H, dd, J = 1.8 & 8.1 Hz, aromatic-H), 7.57 (1H, m, aromatic-H), 7.44 (1H, d, J = 2.4 Hz, aromatic-H), 7.13-7.22 (2H, m, aromatic-H), 6.92 (1H, d, J = 8.4 Hz, aromatic-H), 4.69 (2H, s, CH_2), 3.90 (3H, s, CH_3); MS (EI) *m/z* 353 (M^+); HRMS (EI) *m/z* calcd for $C_{16}H_{13}Cl_2NO_4$ [M^+] 353.0222, found: 353.0219; Purity > 99% (as determined by RP-HPLC, method B, t_R = 20.1 min).

4-[2-(2,4-Dichloro-phenoxy)-acetylamino]-benzoic Acid Methyl Ester (4c): Yield = 95.8%; ^{1}H-NMR (CD_3OD, 300 MHz) δ 7.96-7.99 (2H, m, aromatic-H), 7.64-7.71 (2H, m, aromatic-H), 7.41 (1H, d, J = 2.4 Hz, aromatic-H), 7.21-7.25 (1H, m, aromatic-H), 7.01 (1H, d, J = 8.4 Hz, aromatic-H), 4.71 (2H, s, CH_2), 3.87 (3H, s, CH_3); MS (EI) *m/z* 353 (M^+); HRMS (EI) *m/z* calcd for $C_{16}H_{13}Cl_2NO_4$ [M^+] 353.0222, found: 353.0220; Purity > 99% (as determined by RP-HPLC, method B, t_R = 18.6 min).

3-[2-(2,4-Dichloro-phenoxy)-acetylamino]-*N*-furan-2-ylmethyl-benzamide (4o): Yield = 99.9%; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 10.34 (1H, s, NH), 8.97 (1H, t, J = 5.4 Hz, N<u>H</u>CH_2), 8.05 (1H, s, aromatic-H), 7.73-7.76 (1H, m, aromatic-H), 7.55-7.59 (3H, m, aromatic-H), 7.34-7.43 (2H, m, aromatic-H), 7.10 (1H, d, J = 9.3 Hz, aromatic-H), 6.37-6.39 (1H, m, aromatic-H), 6.26 (1H, d, J = 3.0 Hz, aromatic-H), 4.86 (2H, s, CH_2), 4.86 (2H, d, J = 5.7 Hz, CH_2); MS (EI) *m/z* 418 (M^+); HRMS (EI) *m/z* calcd for $C_{20}H_{16}Cl_2N_2O_4$ [M^+] 418.0487, found: 418.0485; Purity > 99% (as determined by RP-HPLC, method B, t_R = 16.3 min).

General Synthetic Procedures of the Coupling Reaction by using PPAA (4j, 5c-e). The benzoic acid (1 eqv.) was dissolved in acetonitrile and PPAA (1.2 eqv.), Et_3N (4.0 eqv.) were added. The mixture was stirred at room temperature for 30 min and amine (1.2 eqv.) was added. The reaction solution was stirred overnight and evaporated under reduced pressure. The residue was purified by flash column chromatography.

3-(2-(2,4-dichlorophenoxy)acetamido)-*N*-methylbenzamide (4j): Yield = 24.8%; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 10.31 (1H, s, NH), 8.40 (1H, m, NH), 8.04 (1H, m, aromatic-H), 7.72-7.75 (1H, m, aromatic-H), 7.61 (1H, d, J = 2.4 Hz, aromatic-H), 7.52 (1H, d, J = 7.8 Hz, aromatic-H), 7.36-7.42 (2H, m, aromatic-H), 7.11 (1H, d, J = 8.7 Hz, aromatic-H), 4.87 (2H, s, CH_2), 1.56 (3H, d, J = 5.1 Hz, NCH_3); MS (EI) *m/z* 352 (M^+); HRMS (EI) *m/z* calcd for $C_{16}H_{14}Cl_2N_2O_3$ [M^+] 352.0381, found: 352.0381; Purity > 99% (as determined by RP-HPLC, method C, t_R = 12.9 min).

3-(2-(2,4-dichlorophenoxy)-2-methylpropanamido)-*N*-(furan-2-ylmethyl)benzamide (5c): Yield = 44.5%; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 10.22 (1H, s, NH), 8.93 (1H, t, J = 6.0 Hz, NH), 8.17 (1H, s, aromatic-H), 7.84-7.86 (1H, m, aromatic-H), 7.66 (1H, d, J = 2.4 Hz, aromatic-H), 7.57-7.59 (2H, m, aromatic-H), 7.42 (1H, d, J = 8.1 Hz, aromatic-H), 7.36 (1H, dd, J = 2.4 & 9.0 Hz, aromatic-H), 6.99 (1H, d, J = 8.7 Hz, aromatic-H), 6.39 (1H, m, aromatic-H), 6.26 (1H, d, J = 3.0 Hz, aromatic-H), 4.45 (2H, d, J = 6.0 Hz, CH_2), 1.56 (6H, s, CH_3); MS (EI) *m/z* 446 (M^+); HRMS (EI) *m/z* calcd for $C_{22}H_{20}Cl_2N_2O_4$ [M^+] 446.0800, found: 446.0802; Purity > 99% (as determined by RP-HPLC, method C, t_R = 9.2 min).

3-(2-(2,4-dichlorophenoxy)-2-methylpropanamido)-*N*-(pyridin-4-ylmethyl)benzamide (5d): Yield = 34.0%; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 10.25 (1H, s, NH), 9.10 (1H, t, J = 6.0 Hz, NH), 8.50 (2H, d, J = 5 Hz, aromatic-H), 8.22 (1H, m, aromatic-H), 7.86-7.89 (1H, m, aromatic-H), 7.65 (1H, d, J = 2.4 Hz, aromatic-H), 7.63 (1H, d, J = 7.2 Hz, aromatic-H), 7.44 (1H, t, J = 10.8 Hz, aromatic-H), 7.36 (1H, dd, J = 2.4 & 8.7 Hz, aromatic-H), 7.29 (2H, d, J = 6.3 Hz, aromatic-H), 6.99 (1H, d, J = 8.7 Hz, aromatic-H), 4.49 (2H, d, J = 5.7 Hz, CH_2), 1.56 (6H, s, CH_3); MS (EI) *m/z* 457 (M^+); HRMS (EI) *m/z* calcd for $C_{23}H_{21}Cl_2N_3O_3$ [M^+]

457.0960, found: 457.0962; Purity > 99% (as determined by RP-HPLC, method C, t_R = 18.6 min).

3-(2-(2,4-dichlorophenoxy)-2-methylpropanamido)-*N*-(2-(pyridin-4-yl)ethyl)benzamide (5e): Yield = 22.6%, ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 10.21 (1H, s, NH), 8.54 (1H, t, J = 6.3 Hz, NH), 8.46 (2H, d, J = 4.8 Hz, aromatic-H), 8.13 (1H, s, aromatic-H), 7.81-7.83 (1H, m, aromatic-H), 7.67 (1H, d, J = 2.4 Hz, aromatic-H), 7.50 (1H, d, J = 7.8 Hz, aromatic-H), 7.34-7.42 (2H, m, aromatic-H), 7.27 (2H, d, J = 5.4 Hz, aromatic-H), 6.99 (1H, d, J = 8.7 Hz, aromatic-H), 3.52 (2H, m, CH_2), 2.87 (2H, t, J = 7.5 Hz, CH_2), 1.56 (6H, s, CH_3); MS (EI) *m/z* 471 (M^+); HRMS (EI) *m/z* calcd for $C_{24}H_{23}Cl_2N_3O_3$ [M^+] 471.1116, found: 471.1116; Purity > 99% (as determined by RP-HPLC, method C, t_R = 9.1 min).

2-(2,4-Dichloro-phenoxy)-*N*-[3-(1*H*-tetrazol-5-yl)-phenyl]-acetamide (4i): A mixture of *N*-(3-cyano-phenyl)-2-(2,4-dichloro-phenoxy)-acetamide (70.0 mg, 0.22 mmol), sodium azide (42.9 mg, 0.66 mmol) and triethylamine hydrochloride (45.4 mg, 0.33 mmol) in *N*-methylpyrrolidone (5 mL) (NMP) was stirred at 150 °C under nitrogen overnight. After cooling, the reaction mixture was diluted with water, acidified to pH 1 with 10% v/v hydrochloric acid, and extracted with ethyl acetate. The organic phase was washed with brine, dried (using anhydrous $MgSO_4$), and concentrated. The residue was purified by silica gel flash column chromatography (CH_2Cl_2:MeOH = 3:1) to give **4i** as a purple solid (57.2 mg, 71.6% yield). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 10.31 (1H, s, NH), 8.21 (1H, s, aromatic-H), 7.64-7.72 (2H, m, aromatic-H), 7.61 (1H, d, J = 2.4 Hz, aromatic-H), 7.34-7.40 (2H, m, aromatic-H), 7.13 (1H, d, J = 9.0 Hz, aromatic-H), 4.89 (2H, s, CH_2); MS (EI) *m/z* 363 (M^+); HRMS (EI) *m/z* calcd for $C_{15}H_{11}Cl_2N_5O_2$ [M^+] 363.0290, found: 363.0294; Purity > 98% (as determined by RP-HPLC, method A, t_R = 6.8 min).

General Procedure for Hydrolysis (8, 11). To a solution of ester (1 eqv.) in THF/H_2O (3:1) was added LiOH·H_2O (2 eqv.) at room temperature. The reaction mixture was stirred overnight then partitioned between ethyl acetate and 10% HCl. The organic phase was washed with brine, dried ($MgSO_4$ anh.) and concentrated. The residue was washed with ethyl acetate to give acid as a white solid.

3-[2-(2,4-Dichloro-phenoxy)-acetylamino]-benzoic Acid (8): White solid, 85.8% yield; ^{1}H-NMR (CD_3OD, 300 MHz) δ 8.25 (1H, s, aromatic-H), 7.84 (1H, d, J = 8.7 Hz, aromatic-H), 7.79 (1H, d, J = 8.1 Hz, aromatic-H), 7.47 (1H, t, J = 2.4 Hz, aromatic-H), 7.42 (1H, d, J = 7.8 Hz, aromatic-H), 7.29 (1H, dd, J = 2.4 & 9.04 Hz, aromatic-H), 7.10 (1H, d, J = 9.3 Hz, aromatic-H), 4.77 (2H, s, CH_2); MS (EI) *m/z* 339 (M^+); HRMS (EI) *m/z* calcd for $C_{15}H_{11}Cl_2NO_4$ [M^+] 339.0065, found: 339.0064; Purity > 99% (as determined by RP-HPLC, method A, t_R = 13.8 min).

3-(2-(2,4-dichlorophenoxy)-2-methylpropanamido)benzoic acid (11): White solid, 66.8% yield; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 10.28 (1H, s, NH), 8.36 (1H, s, aromatic-H), 7.93 (1H, d, J = 8.4 Hz, aromatic-H), 7.66-7.68 (2H, m, aromatic-H), 7.44 (1H, t, J = 7.8 Hz, aromatic-H), 7.34 (1H, dd, J = 3.0 & 9.0 Hz, aromatic-H), 6.98 (1H, d, J = 8.4 Hz, aromatic-H), 1.56 (6H, s, CH_3); MS (EI) *m/z* 367 (M^+); HRMS (EI) *m/z* calcd for $C_{17}H_{15}Cl_2NO_4$ [M^+] 367.0378, found: 367.0376.

Pgp Reversal Assay. MCF-7/ADR cells were seeded in 24-well plates. At 80% confluence, the cells were incubated in FBS-free DMEM for 18 h. The culture medium was changed to Hanks' balanced salt solution and the cells were incubated at 37 °C for 30 min. After incubation of the cells with 20 μM rhodamine-123 for 90 min, the medium was completely removed. The cells were then washed three times with an ice-cold phosphate buffer (pH 7.0) and lysed in EBC lysis buffer. The rhodamine-123 fluorescence in the cell lysates was measured in a microplate spectrofluorometer using excitation and emission wavelengths of 480 and 540 nm, respectively. Fluorescence values were normalized to the total protein content of each sample and are presented as a ratio to controls.

Crystal Violet Assay. Doxorubicin- or paclitaxel-induced decreases in cell viability was determined by crystal violet staining of non-viable cells. Cells were stained with 0.4% crystal violet in methanol for 30 min at room temperature and then washed with tap water. Stained cells were extracted with 50% methanol and dye extracts were measured at 550 nm using a microtiter plate reader (Berthold Technologies, Bad Wildbad, Germany).

5-Bromo-2'-deoxy-uridine (BrdU) Assay. Viable adherent cells were incubated with BrdU (5-bromo-2'-deoxy-uridine) labeling solution (10 μM) for 2 h. Cells were fixed with fixation solution for 30 min at room temperature and incubated with 100 μL *anti*-BrdU peroxidase-labeled antibody for 90 min. After three washings, substrate solution for colorimetric quantification was added at a final concentration of 100 μL/mL and left at room temperature for 5-30 min until color development was sufficient for photometric detection. The absorbance was assayed at 405 nm.

Statistical Methods. For all results we calculated the mean and S. D. Statistical analysis was performed using Student *t*-test. Differences were considered significant at $p < 0.05$.

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