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Synthesis of curcumin mimics with multidrug resistance reversal activities

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Abstract—In order to discover novel multidrug resistance (MDR) reversal agents for efficient cancer chemotherapy, the unsymmetrical curcumin mimics with various amide moieties (**6**–**19**) were synthesized and evaluated their MDR reversal activities in MDR cell line KBV20C. Among the tested compounds, **13**, **16**, and **17** showed potent MDR reversal activities by inhibiting drug efflux function of P-glycoprotein in KB20C cells, and almost recovered the cytotoxicity of vincristine and paclitaxel against KBV20C cell to the degree of potency against drug sensitive KB cells.

1. Introduction

Turmeric (*Curcuma longa* rhizomes) has been widely enjoyed as a spice in various foods in many Asian countries, and is also famous for the treatment of inflammatory related diseases in medicinal folklore.[1] Because its major component, curcumin (**1**), has a variety of biological activities, including antioxidant, antimutagenic, antiangiogenesis, antimicrobial, and immuno-modulation activity, many researchers have been interested in it[2–6] as well as its synthetic derivatives.[7–11] In particular, a number of studies of curcumin and its analogs were focused on their anti-angiogenesis activity, and it was discovered that curcumin is a promising lead compound in the discovery of novel anti-cancer agents through structural modification.[11]

In our previous reports, we reported that pyridine and thiophene linked symmetrical bis-alkynyl curcumin derivatives (**2**) effectively inhibited the proliferation and tube formation of human umbilical vein endothelial cells (HUVEC).[12] A preliminary study of the structure–activity relationship of symmetrical curcuminoids (**2**) explained that the feruloyl moiety plays a critical role in various biological functions, including inhibition upon tumorous angiogenesis.[12] This result led us to try to synthesize a type of unsymmetrical curcuminoids (**3**) that have just one

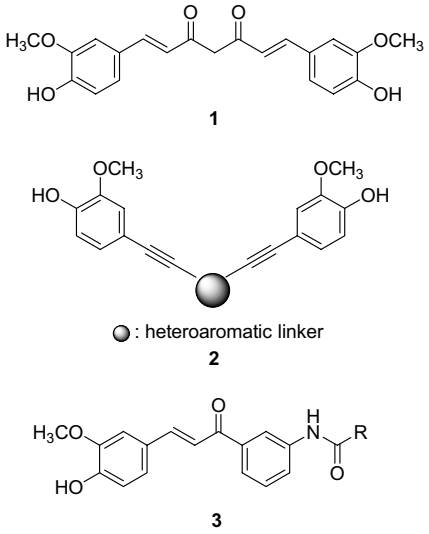

Figure 1.

Keywords: Curcumin; Curcumin mimics; Multidrug resistance; Multidrug resistance reversal activities; Anticancer.
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feruloyl group and other various functionalities for binding to active sites; these compounds also showed strong inhibitory activities against HUVEC proliferation and tube formation on Matrigel[13] (Fig. 1).

To date, chemotherapy is the most efficient tool to treat cancer and related diseases among the therapeutic methods, but the occurrence of drug resistance against clinically used anti-cancer drugs has become a significant obstacle in cancer treatment.[14] Because multidrug resistance (MDR) of cancer cells caused by prolonged administration of a certain drug can result in resistance toward multiple drugs, a number of studies have been aimed at discovering the mechanism of inhibition of MDR for improving therapeutic efficacy.[15–20]

Recently, there are some reports that dietary supplements, such as green tea polyphenol[21] and carotenoids,[22] have shown MDR reversal activity in cancer cells. In particular, widely used and studied curcuminoids were also reported to modulate the human *MDR1* gene expression.[23–26] Because the *MDR1* gene encoding P-glycoprotein (P-gp) is responsible for removing the structurally unrelated anti-cancer agents and maintaining an intracellular concentration within non-cytotoxic range,[27] it is necessary to find novel molecules that control the function of P-gp for the development of reversal agents of MDR. In our opinion, curcumin will be a good lead compound for recovering the therapeutic effect of anti-cancer drugs without unwanted side effects.

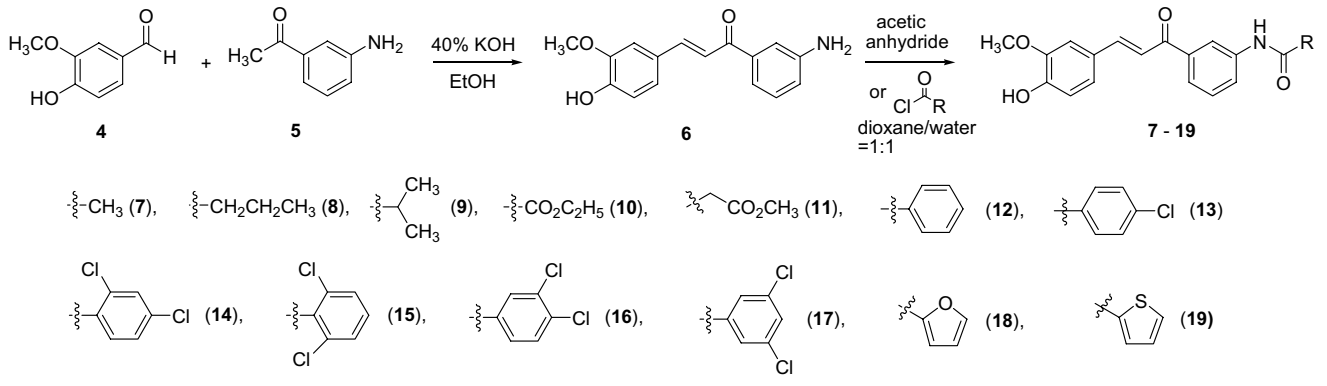
In this study, we report the synthetic details for unsymmetrical curcuminoids (**3**) and their reversal activities of MDR in multidrug resistant cancer cell line KBV20C.

2. Results and discussion

As shown in Scheme 1, the unsymmetrical curcuminoids (**3**), which have just one feruloyl group and amide functional groups for binding efficacy to active sites, were synthesized for evaluating the MDR reversal activity. Commercially available 4-hydroxy-3-methoxybenzaldehyde (Vanillin, **4**) was reacted with 3-acetylaniline (**5**) in the presence of a basic catalyst (40% KOH) in ethanol at room temperature for 10 h.[28] The crude product was isolated by silica gel chromatography ($CHCl_3$/CH_3OH = 97:3) to yield 1-(3-amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**6**). This amine (**6**), dissolved in a 1:1 mixture of dioxane and H_2O and then cooled to 0 °C in an ice bath, was reacted with acetic anhydride or one of a variety of acid chlorides at 0 °C for 5–7 h to obtain the amides (**7**–**19**).[29] Two alkyl amides, including butyramide (**8**), isobutyramide (**9**), and oxalamic acid ethyl ester (**10**), had slightly low yields. Compound **7** and other aromatic amide products (**11**–**19**) showed quantitative yields. ^{1}H- and ^{13}C NMR spectra, GC/MS spectra, and other instrumental analyses of the synthetic intermediate (**6**) and asymmetrical curcumin mimics (**7**–**19**) were used to identify their structure and test for MDR reversal activity.

To discover a promising initial candidate for MDR reversal agents, we evaluated cell viability for testing cytotoxicity of the asymmetrical curcumin mimic library (**6**–**19**) obtained from Scheme 1 against P-gp non-expressing KB and P-gp expressing KBV20C cells at a single concentration of 10 μM. As shown in Table 1, curcumin (**1**) and its synthetic mimics (**6**–**19**) did not display any cytotoxicity against either KB or KBV20C cells. The cytotoxicity of vincristine and paclitaxel against KB cells was significantly different from that against KBV20C cells; the IC_{50} of vincristine and paclitaxel against KB cells are 7.9 and 4.2 nM, respectively, whereas those in KBV20C cells are 5.72 and 1.44 μM, which means that KBV20C cells are multidrug resistant.

We next determined the MDR reversal effect of the synthetic curcumin mimics in KBV20C cells. When co-administering vincristine or paclitaxel to KBV20C cells with 10 μM of verapamil, a well known MDR reversal agent, their cytotoxicities were remarkably improved to 0.20 and 0.010 μM IC_{50}, respectively. In particular, the cytotoxicity of paclitaxel was almost recovered to the original strength in KB cells, a non-resistant cell line of KBV20C cells. This result proved that verapamil, already reported as a MDR reversal agent, can improve the cytotoxicity of vincristine and paclitaxel by inhibiting P-gp function without causing any cytotoxicity



Scheme 1. Synthesis of novel curcumin mimics with asymmetrical units including alkyl amide, chloro-substituted benzamide, or heteroaromatic amide moieties. Reagents and conditions: yield for **6**, 45%; **7**, 97%; **8**, 21%; **9**, 24%; **10**, 26%; **11**, 25%; **12**, 98%; **13**, 94%; **14**, 85%; **15**, 91%; **16**, 88%; **17**, 70%; **18**, 85%; **19**, 87%.

Table 1. Cancer cell viability after treatment of asymmetrical curcumin mimics produced via Scheme 1[a]

Compound	KB cell	KBV20C cell	Compound	KB cell	KBV20C cell
Curcumin	89.2 ± 6.1[b]	93.1 ± 6.5	**12**	89.5 ± 7.1	85.5 ± 10.5
Vincristine	7.9 nM[c]	5.72 μM[c]	**13**	95.7 ± 8.9	96.6 ± 7.3
Paclitaxel	4.2 nM[c]	1.44 μM[c]	**14**	98.3 ± 10.7	94.6 ± 4.3
6	97.6 ± 4.5	99.4 ± 3.2	**15**	93.7 ± 16.2	75.3 ± 11.3
7	98.2 ± 8.2	92.4 ± 2.2	**16**	78.3 ± 6.9	72.6 ± 5.3
8	77.1 ± 8.1	80.8 ± 4.6	**17**	68.7 ± 4.2	70.3 ± 7.8
9	67.5 ± 9.4	67.7 ± 15.1	**18**	60.2 ± 9.5	77.6 ± 7.3
10	84.7 ± 6.7	103.3 ± 8.5	**19**	74.7 ± 12.4	83.6 ± 8.7
11	72.9 ± 14.1	105.9 ± 12.3			

[a] After treatment of KB or KBV20C cells with 10 μM of each compound for 48 h, cell viability (%) was determined by using the MTS.
[b] Data are expressed as means ± standard deviation from three experiments.
[c] IC_{50}.

against cancer cells. In the same manner, in order to test the MDR reversal activity of the curcumin library (**6**–**19**), we have determined the proliferation inhibitory effect of vincristine or paclitaxel by treating KBV20C cells with 3 μM of each compound.

As expected, there was a great increase in cytotoxicity of the tested anticancer drugs, as shown in Table 2. In considering a preliminary structure–activity relationship, we found a consistent trend to explain this result. The precursor (**6**) for the synthetic curcumin mimics showed a low MDR reversal activity that is similar to the activity of curcumin. Although it has a disappointing potency, we thought it is possible to obtain potent curcuminoids by adding substituted amide groups for efficient binding affinity to the target. The MDR modulating effect of alkyl amide compounds (**7**–**9**), an ethyl carbamoyl compound (**10**), and a methyl carbamoyl acetate compound (**11**) increased slightly. In addition, a benzamide curcumin mimic (**12**) was also shown to have a weak change in MDR reversal effect.

On the other hand, the MDR reversal activity of mono- or di-chlorobenzamide curcuminoids (**13**–**17**) was dramatically improved. In comparison to the IC_{50} of vincristine and paclitaxel against both KB and KBV20C cells co-treated with verapamil, the cytotoxicities of the tested anticancer drugs were almost recovered to their original activities. Careful consideration of the structure–activity relationship of chlorobenzamide curcumin mimics (**13**–**17**) that showed strong MDR reversal activity indicated that one chloride group at the *meta*- or *para*-position on benzamide can increase the activity. However, a compound with 2,6-dichlorobenzamide (**15**) showed a similar activity as other weakly active compounds. Based on this result, we need to design and synthesize the curcumin structure with a bulkier binding group at the *meta*- or *para*-position on benzamide.

In order to disclose the effect of a heteroaromatic group on MDR reversal activity, we synthesized a furan carboxamide (**18**) and a thiophene carboxamide (**19**). However, they showed only mild MDR reversal activity.

Finally, to determine whether these MDR reversing activities were mediated by inhibiting drug efflux function of P-gp, we examined effects of compounds **13**, **16**, and **17** on the intracellular accumulation of Rhodamine 123 (Rh123), a fluorescent P-gp substrate, using flow cytometry. As shown in Figure 2, inhibition of P-gp with verapamil caused an increase in the accumulation of Rh123 by about 3.7 fold in KBV20C cells. Treatment of KBV20C cells with these compounds led to an enhanced accumulation of Rh123, indicating that treatment with these compounds was enough to inhibit P-gp function and lead to an intracellular accumulation of Rh123. Collectively, our results imply that P-gp function might be sufficiently abrogated by treatment with our established curcumin mimics, which

Table 2. Multidrug resistance (MDR) reversal activity against KBV20C cells[a]

Compound	IC_{50} (μM)		Compound	IC_{50} (μM)	
	Vincristine	Paclitaxel		Vincristine	Paclitaxel
Verapamil	0.20	0.010	**12**	3.82	0.42
Curcumin	0.82	0.42	**13**	**0.48**	**0.063**
6	1.26	0.83	**14**	0.72	0.045
7	1.26	0.72	**15**	1.23	0.10
8	2.89	0.21	**16**	**0.85**	**0.026**
9	2.92	0.24	**17**	**0.41**	**0.022**
10	3.31	1.09	**18**	1.44	0.21
11	3.81	0.32	**19**	1.41	0.18

[a] KBV20C cells were seeded at a density of 1×10^4/well in 96-well plates and co-treated with various concentrations of vincristine or paclitaxel in the presence of 10 μM verapamil or 3 μM curcumin mimics. Cell viability was determined using the MTS assay.

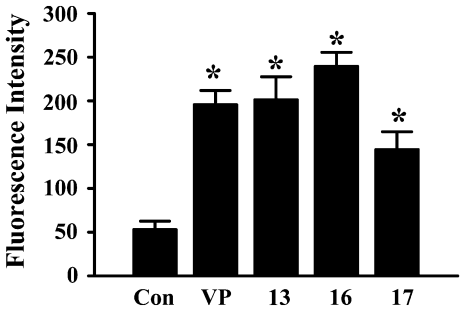


Figure 2. Effect of curcumin mimics on Rh123 accumulation in drug resistance cells. KBV20C cells were pre-treated with 10 μM of verapamil or curcumin mimics for 1 h. Following a treatment with 10 mM Rh123, the mean fluorescence intensity of intracellular Rh123 was determined as described in Section 4. Relative fluorescence intensity represents the means ± SD of three independent experiments. $^{*}p < 0.05$, compared to control group with Student's *t*-test.

leads to an accumulation of anticancer drugs enabling them to exert their cytotoxic effects.

3. Conclusion

As shown in Scheme 1, Tables 1 and 2, we have synthesized unsymmetrical curcuminoids with various amide groups (**7**–**19**) and tested the MDR reversal activity using the potent anticancer agents, vincristine and paclitaxel, against P-gp non-expressing KB and P-gp expressing KBV20C cells in comparison with verapamil as a positive control. Among the tested compounds, **13**, **16**, and **17** showed a potent MDR reversal activity by inhibiting drug efflux function of P-gp, and the others were moderately potent. From the study of a preliminary structure–activity relationship, it was considered that half of the curcumin structure, feruloyl benzamidobenzene, is a promising lead structure for a MDR reversal agent and, in particular, one or two chloride groups at the *meta*- or *para*-position on benzamide can increase MDR reversal activity. In order to discover novel MDR reversal agents for efficient cancer chemotherapy, it is necessary to design and synthesize an elaborate curcumin mimic library for further research.

4. Experimental

4.1. General

Melting points were determined on an Electrothermal IA9200 apparatus and were not corrected. IR spectra were recorded as thin films for solids and neat state for liquid on Mattson FTIR spectrometer. ^{1}H and ^{13}C NMR spectra recorded on a Bruker 400 MHz FT-NMR spectrometer at 400 and 100 MHz, respectively, in the indicated solvent using TMS as an internal standard. Chemical shifts are expressed in ppm (δ) and coupling constants (J) in Hz. Elemental analysis was carried out on a CE instruments EA1110 elemental analyzer. Thin-layer chromatography (TLC) was performed on precoated Merck silica gel 60 F254 plates. Column chromatography was performed over silica gel (230–400 mesh). All other reagents were commercially available.

4.2. Synthesis of 1-(3-amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (6)

A mixture of 4-hydroxy-3-methoxybenzaldehyde (1.5 g, 10.0 mmol) and 3′-aminoacetophenon (1.4 g, 10.0 mmol) is dissolved in 15 mL of ethanol and allowed to stir for several minutes at 5 °C (ice bath). 10 mL of a 40% KOH solution in water is added dropwise to the flask over several minutes. The mixture is then allowed to stir at room temperature for approximately 10 h. After the reaction was complete, the reaction mixture was neutralized with a 2 N HCl. The solution was extracted three times with ether (10 mL). The organic layer was concentrated and purified by silica gel column chromatography (methylene chloride/methanol = 94:6). Yield 49%; mp 154–155 °C; TLC (methylene chloride/methanol = 94:6) $R_f = 0.39$; IR (KBr pellet) ν_{max} 3548, 3362, 3042, 1649, 1569, 1512 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (2H, s, NH_2), 3.97 (3H, s, OCH_3), 5.89 (1H, s, OH), 6.88–6.90 (1H, m, $NH_2C_6H_4$), 6.96 (1H, d, $J = 8.2$ Hz, $CH_3OC_6H_3$), 7.13 (1H, d, $J = 1.8$ Hz, $CH_3OC_6H_3$), 7.21 (1H, dd, $J = 8.2$ and 1.8 Hz, $CH_3OC_6H_3$), 7.28–7.39 (3H, m, $NH_2C_6H_4$), 7.33 (1H, d, $J = 15.6$ Hz, CH=C*H*Ar), 7.73 (1H, d, $J = 15.6$ Hz, C*H*=CHAr) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.0, 110.2, 114.4, 115.1, 118.7, 119.2, 119.9, 123.4, 127.3, 129.4, 139.6, 145.0, 146.9, 147.1, 148.6, 190.9 ppm; MS (EI+) (*m*/*z*) 269 (M^+); Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20; Found C, 70.56; H, 5.57; N, 5.12.

4.3. *N*-{3-[(*E*)-3-(4-hydroxy-3-methoxy-phenyl)acryloyl]-phenyl}acetamide (7)

To a solution of 1-(3-amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone (**6**) (0.1 g, 0.373 mmol) in 2.5 mL of dioxane/H_2O (50:50) was added acetic anhydride (0.038 g, 0.372 mmol) over a 20 min period at 0 °C followed by 5 h of vigorous stirring at room temperature. The solvent was removed in vacuo, and the resulting solid was purified by silica gel column chromatography to give **7** ($CHCl_3$/methanol = 94:6). Yield 97%; mp 119–120 °C; TLC (methylene chloride/methanol = 94:6) $R_f = 0.33$; IR (KBr pellet) ν_{max} 3533, 3330, 3049, 1676, 1649, 1574 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 2.20 (3H, s, CH_3), 3.97 (3H, s, OCH_3), 6.64 (1H, s, OH), 6.96 (1H, d, $J = 8.2$ Hz, $CH_3OC_6H_3$), 7.15 (1H, d, $J = 1.6$ Hz, $CH_3OC_6H_3$), 7.21 (1H, dd, $J = 8.2$ and 1.7 Hz, $CH_3OC_6H_3$), 7.36 (1H, d, $J = 15.7$ Hz, CH=C*H*Ar), 7.41–7.47 (1H, m, NHC_6H_4), 7.72 (1H, m, NHC_6H_4), 7.75 (1H, d, $J = 15.7$ Hz, C*H*=CHAr), 7.96 (1H, d, $J = 7.5$ Hz, NHC_6H_4), 8.04 (1H, s, NHC_6H_4), 8.31 (1H, br s, NH)ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 24.5, 56.1, 110.3, 115.1, 119.5, 119.6, 123.5, 123.9, 124.0, 127.3, 129.2, 138.8, 139.1, 145.5, 147.1, 148.7, 168.9, 190.3; MS (FAB+) (*m*/*z*) 311 (M^+); Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50; Found C, 68.78.56; H, 5.36; N, 4.31.

4.4. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}butyramide (8)

The same procedure described above was employed for the preparation of **8** by using **6** and butyryl chloride (0.045 g, 0.372 mmol) as a starting material. The resulting suspension was purified by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:1). Yield 21%; TLC (ethyl acetate/*n*-hexane = 1:1) $R_f = 0.20$; IR (neat) ν_{max} 3527, 3319, 2961, 1657, 1575, 1514 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (3H, t, $J = 14.8$ Hz, $CH_2CH_2CH_3$), 1.75–1.80 (2H, m, $CH_2CH_2CH_3$), 2.38 (2H, t, $J = 14.9$ Hz, $CH_2CH_2CH_3$), 3.94 (3H, s, OCH_3), 6.10 (1H, s, OH), 6.94 (1H, d, $J = 8.2$ Hz, $CH_3OC_6H_3$), 7.11 (1H, d, $J = 1.9$ Hz, $CH_3OC_6H_3$), 7.20 (1H, dd, $J = 8.2$ and 1.7 Hz, $CH_3OC_6H_3$), 7.34 (1H, d, $J = 15.6$ Hz, CH=CHAr), 7.44 (1H, t, $J = 15.8$ Hz, NHC_6H_4), 7.71 (1H, br s, NH), 7.71–7.72 (1H, m, NHC_6H_4), 7.74 (1H, d, $J = 15.6$ Hz, CH=CHAr), 7.96 (1H, d, $J = 7.7$ Hz, NHC_6H_4), 8.03 (1H, s, NHC_6H_4) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 19.0, 29.8, 39.6, 56.1, 110.2, 114.9, 119.5, 119.6, 123.5, 124.1, 127.3, 129.3, 138.6, 139.1, 145.7, 146.9, 148.5, 171.8, 190.4; MS (FAB+) (*m*/*z*) 339 (M^+); Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13; Found C, 71.26; H, 6.18; N, 4.22.

4.5. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-isobutyramide (9)

The same procedure described above was employed for the preparation of **9** by using **6** and isobutyryl chloride (0.040 g, 0.372 mmol) as a starting material. The resulting suspension was purified by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:1). Yield 24%; TLC (ethyl acetate/*n*-hexane = 1:1) $R_f = 0.23$; IR (neat) ν_{max} 3525, 3319, 3011, 2962, 1657, 1575, 1514 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (6H, d, $J = 6.9$ Hz, CH_3), 2.55–2.58 (1H, m, CH), 3.96 (3H, s, OCH_3), 5.99 (1H, br s, OH), 6.95 (1H, d, $J = 8.2$ Hz, $CH_3OC_6H_3$), 7.13 (1H, d, $J = 1.6$ Hz, $CH_3OC_6H_3$), 7.22 (1H, dd, $J = 8.2$ and 1.7 Hz, $CH_3OC_6H_3$), 7.36 (1H, d, $J = 15.6$ Hz, CH=CHAr), 7.46 (1H, t, $J = 15.9$ Hz, NHC_6H_4), 7.49 (1H, br s, NH), 7.72 (1H, s, NHC_6H_4), 7.76 (1H, d, $J = 15.6$ Hz, CH=CHAr), 7.87 (1H, d, $J = 7.5$ Hz, NHC_6H_4), 8.04 (1H, s, NHC_6H_4) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 36.7, 56.0, 110.2, 114.9, 119.5, 119.6, 123.5, 124.0, 124.1, 127.3, 129.3, 138.7, 139.1, 145.7, 146.9, 148.5, 175.8, 190.4; MS (FAB+) (*m*/*z*) 339 (M^+); Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13; Found C, 71.13; H, 6.15; N, 4.26.

4.6. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-oxalamic acid ethyl ester (10)

The same procedure described above was employed for the preparation of **10** by using **6** and ethyl oxalyl chloride (0.051 g, 0.372 mmol) as a starting material. The resulting suspension was purified by silica gel column chromatography (chloroform/methanol = 95:5). Yield 26%; TLC (chloroform/methanol = 95:5) $R_f = 0.35$; IR (neat) ν_{max} 3335, 3006, 1701, 1654, 1577, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, t, $J = 14.1$ Hz, CH_2CH_3), 3.97 (3H, s, OCH_3), 4.45 (2H, q, $J = 7.1$ Hz, CH_2CH_3), 5.98 (1H, s, OH), 6.96 (1H, d, $J = 8.1$ Hz, $CH_3OC_6H_3$), 7.14 (1H, s, $CH_3OC_6H_3$), 7.25 (1H, t, $J = 15.7$ Hz, $CH_3OC_6H_3$), 7.36 (1H, d, $J = 15.6$ Hz, CH=CHAr), 7.53 (1H, t, $J = 15.8$ Hz, NHC_6H_4), 7.78 (1H, d, $J = 15.6$ Hz, CH=CHAr), 7.84 (1H, d, $J = 7.7$ Hz, NHC_6H_4), 7.99 (1H, d, $J = 8.0$ Hz, NHC_6H_4), 8.19 (1H, s, NHC_6H_4), 9.04 (1H, s, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$)δ 14.0, 56.1, 64.0, 110.1, 114.9, 119.2, 119.7, 123.6, 123.7, 125.4, 127.3, 129.6, 136.8, 139.4, 145.9, 146.8, 148.5, 154.2, 160.7, 189.7; MS (FAB+) (*m*/*z*) 369 (M^+); Anal. Calcd. for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79; Found C, 65.79; H, 5.15; N, 3.92.

4.7. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-malonamic acid methyl ester (11)

The same procedure described above was employed for the preparation of **11** by using **6** and acetoxyacetyl chloride (0.051 g, 0.372 mmol) as a starting material. The resulting suspension was purified by silica gel column chromatography (chloroform/methanol = 97/3). Yield 25%; TLC (chloroform/methanol = 97/3) $R_f = 0.11$; IR (neat) ν_{max} 3411, 1742, 1655, 1578, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 2.23 (3H, s, CH_3), 3.95 (3H, s, OCH_3), 4.72 (2H, s CH_2), 6.94 (1H, d, $J = 8.1$ Hz, $CH_3OC_6H_3$), 7.16 (1H, d, $J = 1.6$ Hz, $CH_3OC_6H_3$), 7.18 (1H, dd, $J = 8.2$ and 1.7 Hz, $CH_3OC_6H_3$), 7.36 (1H, d, $J = 15.6$ Hz, CH=CHAr), 7.46 (1H, t, $J = 15.8$ Hz, NHC_6H_4), 7.74 (1H, d, $J = 15.6$ Hz, CH=CHAr), 7.75 (1H, d, $J = 8.0$ Hz, NHC_6H_4), 8.00 (1H, d, $J = 8.0$ Hz, NHC_6H_4), 8.12 (1H, s, NHC_6H_4), 8,12 (1 H, s, OH), 9.38 (1H, s, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 20.8, 56.0, 63.0, 110.7, 115.5, 119.1, 119.8, 123.5, 124.1, 124.2, 126.8, 129.2, 138.2, 139.1, 145.7, 147.7, 149.4, 165.9, 170.1, 190.2; MS (FAB+) (*m*/*z*) 369 (M^+); Anal. Calcd. for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79; Found C, 65.51; H, 5.08; N, 3.75.

4.8. *N*-{3-[3-(4-Hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-benzamide (12)

The same procedure described above was employed for the preparation of **12** by using **6** and benzoyl chloride (0.052 g, 0.372 mmol) as a starting material. The resulting solid was purified by silica gel column chromatography (chloroform/methanol = 95/5). Yield 98%; mp 80–82 °C; TLC (chloroform/methanol = 95/5) $R_f = 0.33$; IR (KBr pellet) ν_{max} 3518, 3368, 3049, 1652, 1590, 1544, 1514 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 3.93 (3H, s, OCH_3), 6.93 (1H, d, $J = 8.0$ Hz, $CH_3OC_6H_3$), 7.15–7.18 (2H, m, $CH_3OC_6H_3$), 7.39 (1H, d, $J = 16.0$ Hz, CH=CHAr), 7.45–7.49 (3H, m, benzoyl-*H*), 7.52 (1H, t, $J = 14.5$ Hz, NHC_6H_4), 7.74 (1H, d, $J = 16.0$ Hz, CH=CHAr), 7.75 (1H, m, NHC_6H_4), 8.00 (2H, d, $J = 7.3$ Hz, benzoyl-*H*), 8.16 (1H, d, $J = 8.2$ Hz, NHC_6H_4), 8.19 (1H, s, OH), 8.35 (1H, s, NHC_6H_4), 9.69 (1H, s, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 56.0, 110.8, 115.5, 119.3, 120.5, 123.4, 123.9, 124.7, 126.8, 127.7, 128.4, 129.0, 131.7, 135.0, 139.0, 139.3, 145.5, 147.6, 149.3,

166.5, 190.4; MS (FAB+) (*m*/*z*) 373 (M^+); Anal. Calcd. for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13; N, 3.75; Found C, 73.25; H, 5.25; N, 3.89.

4.9. 4-Chloro-*N*-{3-[3-(4-hydroxy-3-methoxy-phenyl)-acryloyl]- phenyl}-benzamide (13)

The same procedure described above was employed for the preparation of **13** by using **6** and 4-chlorobenzoyl chloride (0.065 g, 0.372 mmol) as a starting material. The resulting solid was purified by silica gel column chromatography (chloroform/methanol = 95/5). Yield 94%; mp 212–215 °C; TLC (chloroform/methanol = 95/5) R_f = 0.31; IR (KBr pellet) ν_{max} 3484, 3374, 1668, 1652, 1583, 1514 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 4.04 (3H, s, OCH_3), 6.87 (1H, d, J = 7.8 Hz, $CH_3OC_6H_3$), 7.11–7.13 (2H, m, $CH_3OC_6H_3$), 7.31–7.40 (2H, m, 4-chlorobenzoyl-*H*), 7.43 (1H, t, J = 17.2 Hz, NHC_6H_4), 7.39 (1H, d, J = 16.0 Hz, CH=C*H*Ar), 7.68 (1H, d, J = 16.0 Hz, C*H*=CHAr), 7.69 (1H, m, NHC_6H_4), 7.94 (2 H, d, J = 8.5 Hz, 4-chlorobenzoyl-*H*), 8.10 (1H, d, J = 7.6 Hz, NHC_6H_4), 8.26 (1H, s, NHC_6H_4), 8.40 (1 H, s, OH), 9.89 (1H, s, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 56.3, 111.2, 116.0, 119.5, 120.9, 123.8, 124.3, 125.1, 127.1, 128.8, 129.3, 129.7, 133.7, 138.0, 139.3, 139.7, 145.9, 148.1, 149.8, 165.7, 190.6. MS (FAB+) (*m*/*z*) 407 (M^+); Anal. Calcd. for $C_{23}H_{18}ClNO_4$: C, 67.73; H, 4.45; N, 3.43; Found C, 66.37; H, 4.58; N, 3.19.

4.10. 2,4-Dichloro-*N*-{3-[3-(4-hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-benzamide (14)

The same procedure described above was employed for the preparation of **14** by **6** and using 2,4-dichlorobenzoyl chloride (0.091 g, 0.372 mmol) as a starting material. The resulting solid was purified by silica gel column chromatography (chloroform/methanol = 95/5). Yield 85%; mp 170–172 °C; TLC (chloroform/methanol = 95/5) R_f = 0.34; IR (KBr pellet) ν_{max} 3302, 1656, 1580, 1550, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 3.96 (3H, s, OCH_3), 6.94 (1H, d, J = 8.0 Hz, $CH_3OC_6H_3$), 6.95 (1H, s, OH), 7.15 (1H, d, J = 1.7 Hz, $CH_3OC_6H_3$), 7.22 (1H, dd, J = 8.2 and 1.7 Hz, $CH_3OC_6H_3$), 7.36–7.40 (1H, m, 2,4-dichlorobenzoyl-*H*), 7.38 (1H, d, J = 15.0 Hz, CH=C*H*Ar), 7.49 (1H, d, J = 1.7 Hz, 2,4-dichlorobenzoyl-*H*), 7.52 (1H, t, J = 15.9 Hz, NHC_6H_4), 7.67 (1H, d, J = 8.3 Hz, 2,4-dichlorobenzoyl-*H*), 7.76 (1H, d, J = 15.0 Hz, C*H*=CHAr), 7.76–7.80 (1H, m, NHC_6H_4), 8.08 (1H, d, J = 7.3 Hz, NHC_6H_4), 8.22 (1H, s, NHC_6H_4), 9.08 (1H, s, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 56.1, 110.4, 115.2, 119.4, 120.0, 123.5, 124.2, 124.6, 127.2, 127.5, 129.3, 130.0, 131.0, 131.9, 134.2, 136.9, 138.4, 139.3, 145.8, 147.2, 148.9, 164.2, 190.2; MS (FAB+) (*m*/*z*) 442 (M^+); Anal. Calcd. for $C_{23}H_{17}Cl_2NO_4$: C, 62.46; H, 3.87; N, 3.17; Found C, 61.81; H, 3.91; N, 2.96.

4.11. 2,6-Dichloro-*N*-{3-[3-(4-hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-benzamide (15)

The same procedure described above was employed for the preparation of **15** by using **6** and 2,6-dichlorobenzoyl chloride (0.091 g, 0.372 mmol) as a starting material. The resulting solid was purified by silica gel column chromatography (chloroform/methanol = 95/5). Yield 91%; mp 157–160 °C; TLC (chloroform/methanol = 95/5) R_f = 0.29; IR (KBr pellet) ν_{max} 3302, 1660, 1582, 1556, 1515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.96 (3H, s, OCH_3), 6.87 (1H, s, OH), 6.95 (1H, d, J = 8.2 Hz, $CH_3OC_6H_3$), 7.16 (1H, d, J = 1.5 Hz, $CH_3OC_6H_3$), 7.22 (1H, dd, J = 8.1 and 1.5 Hz, $CH_3OC_6H_3$), 7.29–7.39 (3H, m, 2,6-dichlorobenzoyl-*H*), 7.39 (1H, d, J = 16.0 Hz, CH=C*H*Ar), 7.52 (1H, t, J = 15.7 Hz, NHC_6H_4), 7.76 (1H, d, J = 16.0 Hz, C*H*=CHAr), 7.79 (1H, m, NHC_6H_4), 8.10 (1H, d, J = 7.9 Hz, NHC_6H_4), 8.25 (1H, s, NHC_6H_4), 9.24 (1H, s. NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 56.1, 110.4, 115.2, 119.6, 120.0, 123.5, 124.3, 124.6, 127.2, 128.0, 129.3, 130.7, 132.5, 136.3, 138.4, 139.3, 145.6, 147.2, 148.8, 162.9, 190.2; MS (FAB+) (*m*/*z*) 442 (M^+); Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 62.46; H, 3.87; N, 3.17; Found C, 62.11; H, 3.95; N, 3.25.

4.12. 3,4-Dichloro-*N*-{3-[3-(4-hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-benzamide (16)

The same procedure described above was employed for the preparation of **16** by using **6** and 3,4-dichlorobenzoyl chloride (0.091 g, 0.372 mmol) as a starting material. The resulting solid was purified by silica gel column chromatography (chloroform/methanol = 95/5). Yield 88%; mp 208–210 °C; TLC (chloroform/methanol = 95/5) R_f = 0.32; IR (KBr pellet) ν_{max} 3492, 3368, 3072, 1671, 1652, 1579, 1513, 1429 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.87 (3H, s, OCH_3), 6.85 (1H, d, J = 8.0 Hz, $CH_3OC_6H_3$), 7.30 (1H, d, J = 7.9 Hz, $CH_3OC_6H_3$), 7.51 (1H, s, $CH_3OC_6H_3$), 7.59 (1H, t, J = 7.6 Hz, NHC_6H_4), 7.71 (2H, s, 3,4-dichlorobenzoyl-*H*), 7.85 (1H, d, J = 8.3 Hz, CH=C*H*Ar), 7.96–8.00 (1H, m, NHC_6H_4), 7.99 (1H, d, J = 8.3 Hz, C*H*=CHAr), 8.11 (1H, d, J = 7.7 Hz, NHC_6H_4), 8.28 (1H, s, 3,4-dichlorobenzoyl-*H*), 8.38 (1H, s, NHC_6H_4), 9.73 (1H, br s, OH), 10.60 (1H, s, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 56.2, 112.2, 116.0, 119.0, 120.3, 124.4, 124.6, 125.0, 126.5, 128.5, 129.5, 130.0, 131.2, 131.7, 134.9, 135.2, 138.9, 139.5, 145.6, 148.3, 150.2, 163.7, 189.2. MS (FAB+) (*m*/*z*) 442 (M^+); Anal. Calcd. for $C_{23}H_{17}C_{l2}NO_4$: C, 62.46; H, 3.87; N, 3.17; Found C, 62.28; H, 3.63; N, 3.20.

4.13. 3,5-Dichloro-*N*-{3-[3-(4-hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-benzamide (17)

The same procedure described above was employed for the preparation of **17** by using **6** and 3,5-dichlorobenzoyl chloride (0.091 g, 0.372 mmol) as a starting material. The resulting solid was purified by silica gel column chromatography (chloroform/methanol = 95/5). Yield 70%; mp 202–206 °C; TLC (chloroform/methanol = 95/5) R_f = 0.36; IR (KBr pellet) ν_{max} 3483, 3310, 3076, 2912, 1660, 1651, 1588, 1569, 1513, 1435 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 3.95 (3H, s, OCH_3), 6.93 (1H, d, J = 8.3 Hz, $CH_3OC_6H_3$), 7.17–7.19 (2H, m, $CH_3OC_6H_3$), 7.40 (1H,

d, J = 15.6 Hz, CH=C*H*Ar), 7.50 (1H, t, J = 16.0 Hz, NHC_6H_4), 7.52 (1H, s, 3,5-dichlorobenzoyl-*H*), 7.74 (1H, d, J = 15.6 Hz, C*H*=CHAr), 7.77 (1H, m, NHC_6H_4), 8.02 (2H, d, J = 1.5 Hz, 3,5-dichlorobenzoyl-H), 8.18 (1H, d, J = 8.0 Hz, NHC_6H_4), 8.35 (1 H, s, NHC_6H_4), 8.88 (1H, s, OH), 10.32 (1H, s, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 56.3, 111.2, 116.0, 119.3, 120.8, 123.7, 124.3, 124.9, 126.9, 129.3, 131.4, 134.2, 135.2, 138.0, 139.2, 139.4, 145.8, 148.2, 150.0, 163.8, 190.3. MS (FAB+) (*m*/*z*) 442 (M^+); Anal. Calcd. for $C_{23}H_{17}C_{l2}NO_4$: C, 62.46; H, 3.87; N, 3.17; Found C, 62.29; H, 3.74; N, 3.27.

4.14. Furan-2-carboxylic acid {3-[3-(4-hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-amide (18)

The same procedure described above was employed for the preparation of **18** by **6** and using 2-furoyl chloride (0.049 g, 0.372 mmol) as a starting material. The resulting solid was purified by silica gel column chromatography (chloroform/methanol = 95/5). Yield 85%; mp 82–84 °C; TLC (chloroform/methanol = 95/5) R_f = 0.30; IR (KBr pellet) ν_{max} 3308, 3011, 2951, 1652, 1578, 1541, 1512, 1429 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (3H, s, OCH_3), 6.01 (1H, s, OH), 6.58–6.59 (1H, m, furan-*H*), 6.96 (1H, d, J = 8.2 Hz, furan-*H*), 7.14 (1H, s, $CH_3OC_6H_3$), 7.23 (1H, d, J = 8.3 Hz, $CH_3OC_6H_3$), 7.27 (1H, t, J = 7.1 Hz, $CH_3OC_6H_3$), 7.37 (1H, d, J = 15.7 Hz, CH=C*H*Ar), 7.51 (1H, t, J = 15.9 Hz, NHC_6H_4), 7.54 (1H, d, J = 0.7 Hz, furan-*H*), 7.78 (1H, d, J = 15.7 Hz, C*H*=CHAr), 8.05 (1H, d, J = 7.7 Hz, NHC_6H_4), 8.16 (1H, s, NHC_6H_4), 8.26 (1H, s, NH) ppm. ^{13}C NMR (400 MHz, $CDCl_3$) δ 56.1, 110.2, 112.7, 114.9, 115.7, 119.5, 119.7, 123.6, 124.1, 124.4, 127.4, 129.4, 137.9, 139.3, 144.5, 145.7, 146.9, 147.5, 148.5, 156.3, 190.2. MS (FAB+) (*m*/*z*) 363 (M^+); Anal. Calcd. for $C_{21}H1_7NO_5$: C, 69.41; H, 4.72; N, 3.85; Found C, 67.96; H, 4.80; N, 3.70.

4.15. Thiophene-2-carboxylic acid {3-[3-(4-hydroxy-3-methoxy-phenyl)-acryloyl]-phenyl}-amide (19)

The same procedure described above was employed for the preparation of **19** by using **6** and 2-thiophenecarbonyl chloride (0.055 g, 0.372 mmol) as a starting material. The resulting solid was purified by silica gel column chromatography (chloroform/methanol = 95:5). Yield 87%; mp 193–195 °C; TLC (chloroform/methanol = 95:5) R_f = 0.28; IR (KBr pellet) ν_{max} 3349, 3066, 1649, 1580, 1542, 1514, 1430 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 3.97 (3H, s, OCH_3), 6.79 (1H, s, OH), 6.95 (1H, d, J = 8.3 Hz, $CH_3OC_6H_3$), 7.13–7.15 (2H, m, $CH_3OC_6H_3$), 7.21–7.23 (1H, m, thiophene-*H*), 7.39 (1H, d, J = 15.7 Hz, CH=C*H*Ar), 7.48–7.52 (1H, t, J = 7.8 Hz, NHC_6H_4), 7.57 (1H, d, J = 5.0 Hz, thiophene-*H*), 7.75–7.79 (1H, m, NHC_6H_4), 7.77 (1H, d, J = 15.9 Hz, C*H*=CHAr), 7.83 (1H, d, J = 3.7 Hz, thiophene-*H*), 8.13 (1H, d, J = 7.8 Hz, NHC_6H_4), 8.20 (1H, s, NHC_6H_4), 8.90 (1H, s, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 56.1, 110.4, 115.1, 119.5, 120.1, 123.5, 124.1, 124.5, 127.2, 127.8, 128.8, 129.3, 131.1, 138.7, 139.1, 139.6, 145.6, 147.1, 148.8, 160.5, 190.3. MS (FAB+) (*m*/*z*) 379 (M^+); Anal. Calcd. for $C_{21}H_{17}NO_4S$: C, 66.47; H, 4.52; N, 3.69, S, 8.45; Found C, 63.36; H, 4.50; N, 3.55, S, 7.72.

4.16. Cell culture and cytotoxicity test

P-gp non-expressing KB cells and P-gp expressing KBV20C cells were cultured in RPMI 1640 (Invitrogen, Carlsbad, CA) with 10% fetal bovine serum (HyClone Laboratories, Logan, UT) and 1% penicillin/streptomycin (Invitrogen). KBV20C cells were grown in the presence of 20 nM vincristine (Sigma Chemical, St. Louis, MO) as described previously.[30] Cytotoxicity was determined by the MTS assay (Promega, Madison, WI) according to our published paper.[30]

4.17. Rh123 accumulation assay

Fluorescence intensity of intracellular Rh123 was determined by flow cytometry.[30] Briefly, after pre-treatment of KBV20C cells with 10 μM of each compounds for 1 h, the cells were further incubated for 3 h in the presence of Rh123. Then, the cells were washed with phosphate buffered saline and the mean fluorescence intensity of intracellular Rh123 was detected using flow cytometry.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2008.02.012.

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