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Design, synthesis, and preliminary biological evaluation of novel ethyl 1-(2′-hydroxy-3′-aroxypropyl)-3-aryl-1H-pyrazole-5-carboxylate

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Abstract—We synthesized a series of novel small molecules, ethyl 1-(2′-hydroxy-3′-aroxypropyl)-3-aryl-1H-pyrazole-5-carboxylate derivatives **3a**–**3o**, by the reaction of ethyl 3-aryl-1H-pyrazole-5-carboxylate with 2-aryloxymethylepoxide in the presence of potassium carbonate at refluxing in acetonitrile in moderate or excellent yields. We investigated the effects of all the compounds on A549 cell growth. The results showed that 15 compounds could suppress A549 lung cancer cell growth. Among them, compound **3i** was the most effective small molecule in inhibiting A549 cell growth. Compound **3f** might most effectively induce A549 cell differentiation. Compound **3g** remarkably induced cellular vacuolation.

Lung cancer is one of the most common causes of cancer death worldwide. Although recent advances in chemotherapy and radiation therapy have yielded modest improvements in patient outcomes, overall survival remains poor. Therefore, new therapeutic targets are needed. It has been reported that the antitumor efficacy of chemotherapeutic agents correlated with their growth-inhibiting, differentiation-inducing or apoptosis-inducing abilities.[1]

In our effort to discover and develop tumor growth inhibitors and apoptosis inducers as potential new anticancer agents, we have identified several classes of molecules as novel tumor growth inhibitors and apoptosis inducers, including safrole oxide, 1-alkoxy-3-(3′, 4′-methylenedioxy)phenyl-2-propanol, γ-lactone, morhpolinone derivatives, and 2,3-dihydro-3-hydroxymethyl-1,4-benzoxazine derivatives.[2–15] In an ongoing study in our laboratory on the design and synthesis of the small molecule, we are interested in extending our small molecules, library to meet the requirement of our research.

The pyrazole unit is the core structure in a number of natural products.[16] Many pyrazole derivatives are known to exhibit a wide range of biological properties such as anti-hyperglycemic, analgesic, anti-inflammatory, anti-pyretic, anti-bacterial, hypoglycemic, sedative–hypnotic activity,[17,18] and anticoagulant activity.[19] Particularly, arylpyrazoles are important in medicinal and pesticidal chemistry.[20] Recently, some arylpyrazoles were reported to have non-nucleoside HIV-1 reverse transcriptase inhibitory activity.[21] It is also reported that novel 5-substituted pyrazole analogs, which have CB1 binding affinities similar to SR 141716A have been synthesized and are presently undergoing pharmacological study as antagonists of CB1 receptors like SR 141716A. They may prove to be clinically useful for the treatment of obesity.[22] Extensive studies have been devoted to arylpyrazole derivatives such as Celecoxib, a well-known cyclooxygenase-2 inhibitor.[23–27] More recently, pyrazole derivatives as high affinity and

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selective A2B adenosine receptor antagonists have been reported.[28] But there were no reports on the synthesis and biological evaluation of ethyl 1-(2′-hydroxy-3′-aroxypropyl)-3-aryl-1H-pyrazole-5-carboxylate.

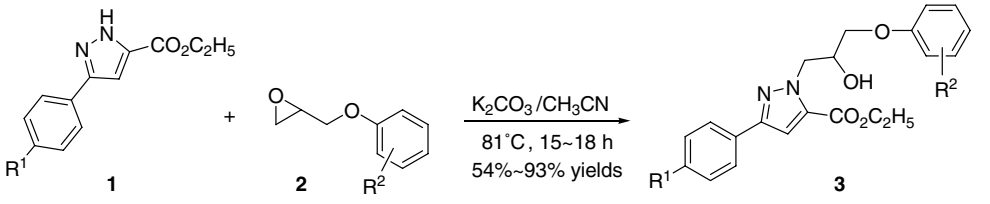
Herein, we would like to report the design and synthesis of novel ethyl 1-(2′-hydroxy-3′-aroxypropyl)-3-aryl-1H-pyrazole-5-carboxylate and the findings of their biological activities in inhibiting A549 cell growth.

Chemistry. Synthesis of ethyl 1-(2′-hydroxy-3′-aroxypropyl)-3-aryl-1H-pyrazole-5-carboxylate (**3**) is outlined in Scheme 1. Starting compounds, ethyl 3-aryl-1H-pyrazole-5-carboxylate (**1**), were readily prepared by the reaction of ethyl 2,4-dioxo-4-arylbutanoate (**5**), which can be obtained from commercially available 4-substituted acetophenone (**4**) and diethyl oxalate, with hydrazine in the presence of acetic acid at room temperature as shown in Scheme 2. The reaction of ethyl 3-aryl-1H-pyrazole-5-carboxylate (**1**) with 2-aryloxymethylepoxide (**2**) in the presence of potassium carbonate at refluxing in acetonitrile afforded ethyl 1-(2′-hydroxy-3′-aroxypropyl)-3-aryl-1H-pyrazole-5-carboxylate in moderate yields and completely regioselectivity. All of the compounds gave satisfactory spectral data. Representatively, the structures of **3i** and **3j** were confirmed by ^{1}H NMR and ^{13}C NMR data.[29]

Effects of the compounds on the viability of A549 lung cancer cells.[30] The data obtained by MTT assay showed that all the 15 compounds **3a**–**3o** had inhibitory effects on the growth of A549 cells in dosage- and time-dependent manners as shown in Fig. 1. Compounds **3f**, **3h**, and **3i** could inhibit the cell growth obviously at 12.5 μM after 48 h of the treatment. Compounds **3c**, **3d**, **3e**, **3f**, **3h**, and **3i** inhibited the cell growth obviously at 25 μM after 24 h of the treatment. At 25 μM after 48 h of the treatment, compounds **3a**, **3g**, **3j**, and **3k** could also suppress the growth of A549 cells except for **3c**, **3d**, **3e**, **3f**, **3h**, and **3i**. At 50 and 100 μM, all the compounds effectively inhibited the cell growth (Fig. 1). Taken altogether, compound **3i** was the most effective compound in suppressing A549 cell growth. The growth inhibitory properties (IC_{50}) for the compounds **3a**–**3o** are listed in Table 1.

Effects of the compounds on the morphology of A549 cells. The compounds induced the changes of A549 cell morphology concomitant with cell growth inhibition induced by them (Fig. 2). When exposed to compounds **3a**, **3f**, **3h** or **3j** 50 μM for 24 h, A549 cells became slender and longer, the effect of compound **3f** was most strong among these four compounds. The data suggested that the four compounds not only could inhibit A549 cell growth, but also might induce the cell differentiation. When A549 cells were treated with compounds **3b**, **3c**, **3d**, **3e**, **3i**, **3k**, **3l** or **3m**, the cells became round and detached from the bottom of cell culture dish, indicating that the compounds might induce A549 cell death. Compounds **3b**, **3c**, **3d**, **3e**, **3k**, **3l**, and **3m** might cause cell apoptosis, while compound **3i** might induce cell necrosis. When treated with compound **3g**, the cells vacuolated gradually as the concentration increased and the time elongated (Fig. 2). The result told us that compound **3g** might also induce cell death because vacuolation is a common event in many cell death processes including both apoptosis and necrosis.[31] More interestingly, we will use compound **3g** as a powerful tool to study the mechanism of cellular vacuolation during cell death and differentiation.

In summary, we have described a facile approach to prepare ethyl 1-(2′-hydroxy-3′-aroxypropyl)-3-aryl-1H-pyrazole-5-carboxylate **3a**–**3o** by the reaction of ethyl

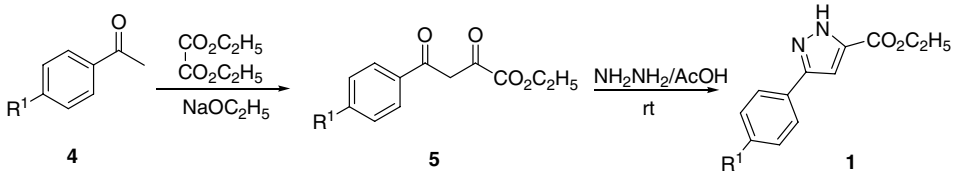


1a R^1 = H
1b R^1 = Cl
1c R^1 = OMe

2a R^2 = H
2b R^2 = 4-Cl
2c R^2 = 4-NO_2
2d R^2 = 2-NO_2
2e R^2 = 2-OMe

3a R^1 = R^2 = H
3b R^1 = H, R^2 = 4-Cl
3c R^1 = H, R^2 = 4-NO_2
3d R^1 = H, R^2 = 2-NO_2
3e R^1 = H, R^2 = 2-OMe
3f R^1 = Cl, R^2 = H
3g R^1 = Cl, R^2 = 4-Cl
3h R^1 = Cl, R^2 = 4-NO_2
3i R^1 = Cl, R^2 = 2-NO_2
3j R^1 = Cl, R^2 = 2-OMe
3k R^1 = OMe, R^2 = H
3l R^1 = OMe, R^2 = 4-Cl
3m R^1 = OMe, R^2 = 4-NO_2
3n R^1 = OMe, R^2 = 2-NO_2
3o R^1 = OMe, R^2 = 2-OMe

Scheme 1.



Scheme 2.

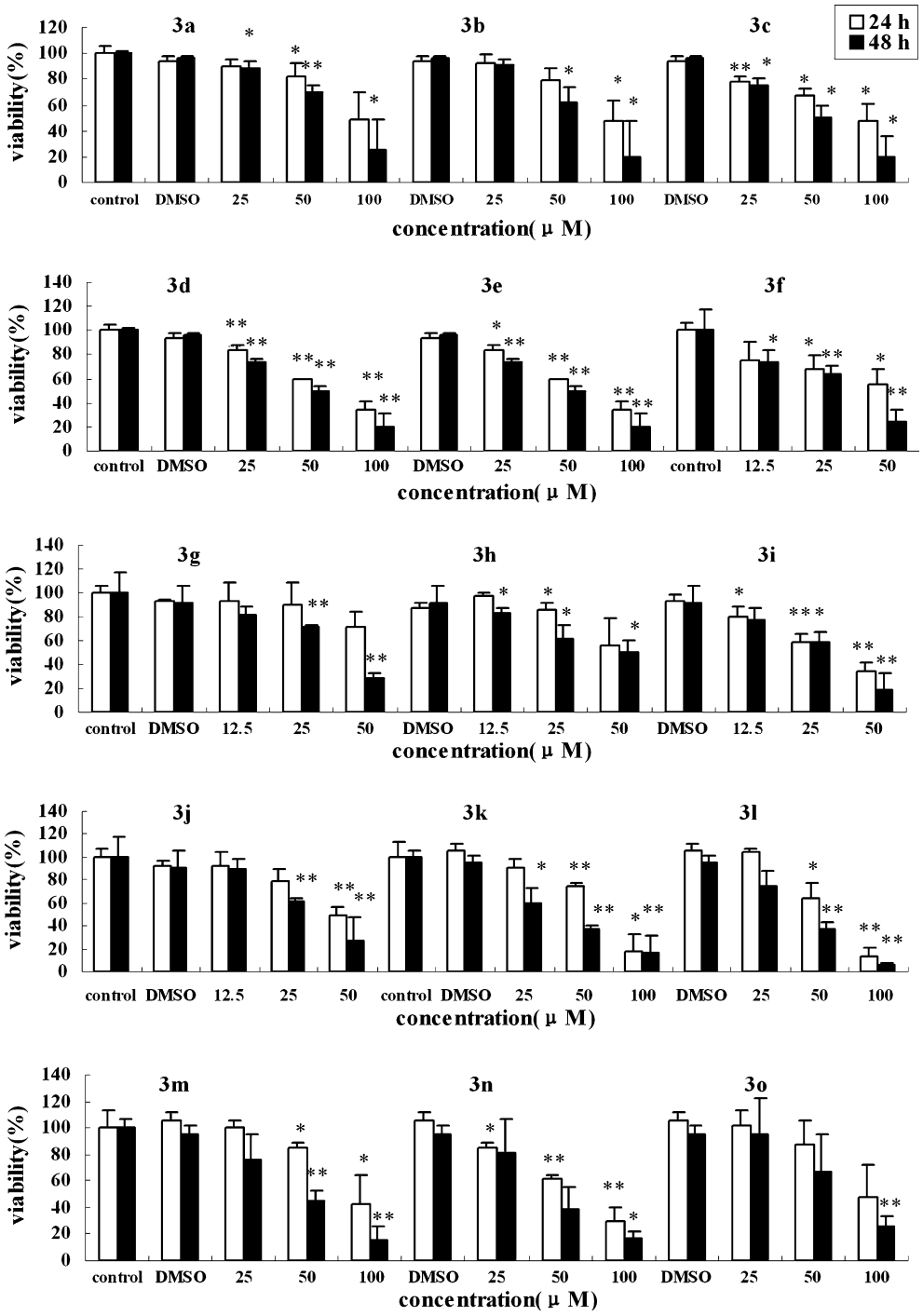


Figure 1. Effects of the 15 derivatives **3a**–**3o** on the viability of A549 lung cancer cells. Control, the viability of the cells cultured in the medium without any derivatives. DMSO, the viability of the cells cultured in the medium containing DMSO 0.1% (v/v) used as a vehicle control. Other bars show the viability of the cells treated with the 15 derivatives at the concentrations indicated for 24 or 48 h, respectively. Data are means ± SE from three independent experiments ($^{*}P < 0.05$, $^{**}P < 0.01$ vs the DMSO group).

Table 1. Growth inhibitory properties for the compounds **3a**–**3o** at 48 h

Compound	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	**3j**	**3k**	**3l**	**3m**	**3n**	**3o**
IC_{50} (μM)	65	59	48	30	58	27	33	45	26	32	33	38	44	45	68

3-aryl-1H-pyrazole-5-carboxylate with 2-aryloxymethylepoxide, and we found 15 interesting compounds that could suppress A549 lung cancer cell growth. Compound **3i** was the most effective small molecule in inhibiting A549 cell growth. Compound **3f** might most effectively induce A549 cell differentiation. Compound **3g** remarkably

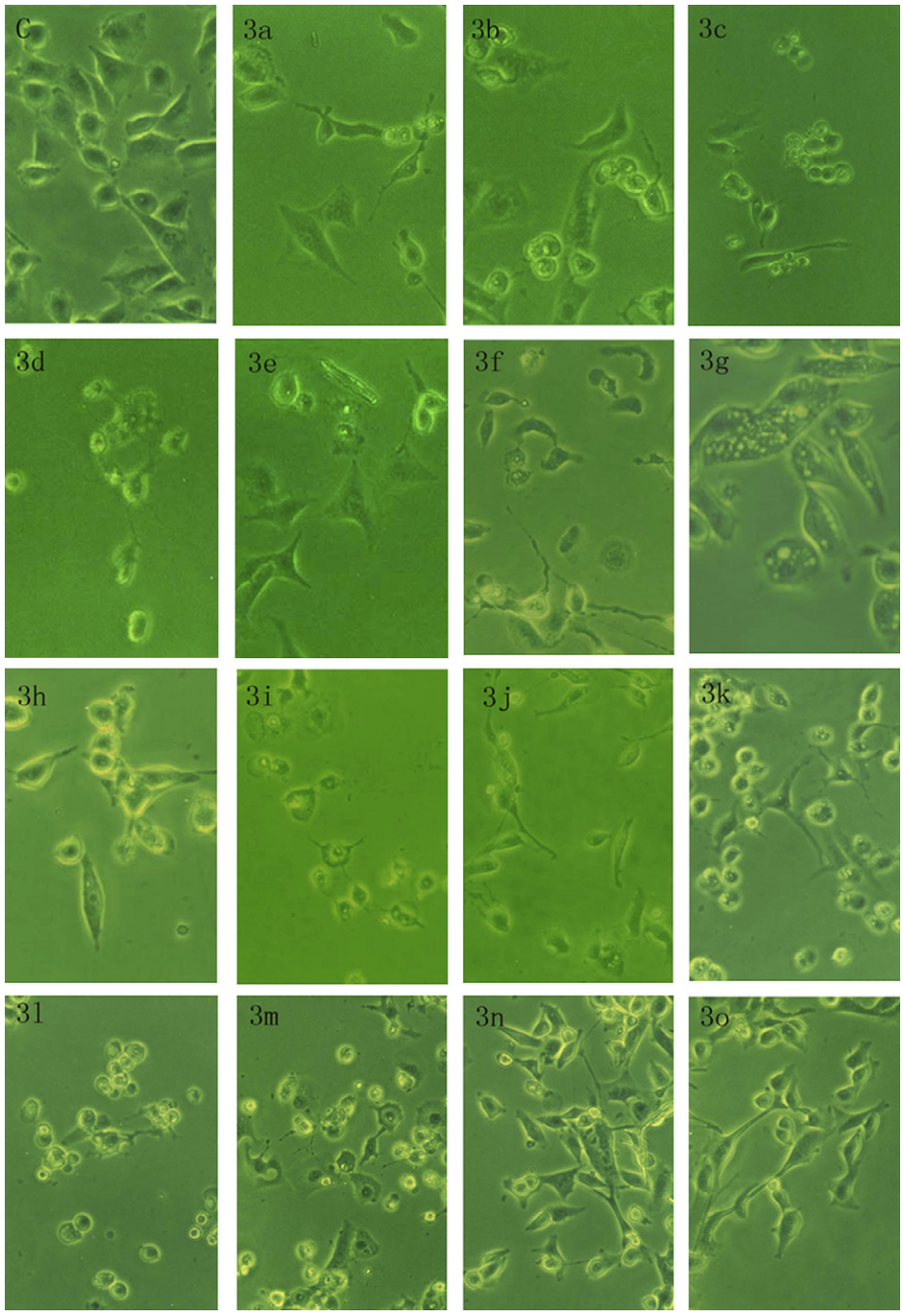


Figure 2. Morphology image of A549 cells treated with the 15 compounds **3a**–**3o** (50 μM) for 48 h. C, the cells treated with DMSO 0.1% (v/v) as a vehicle control; **3a**–**3o**, the cells treated with the corresponding compound, respectively.

induced cellular vacuolation. The findings suggested that these compounds would be very useful for investigating the mechanisms of cell proliferation, differentiation, and apoptosis in our next research project and some of them may be a powerful drug against lung cancer.

Acknowledgments

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29. Spectral data of compounds **3a**–**3o**.
Ethyl 1-(2′-hydroxy-3′-phenoxypropyl)-3-phenyl-1H-pyrazole-5-carboxylate. Compound **3a**: Pale yellowish oil; IR (film) *v*: 3443 (OH), 3062, 2981, 2935, 1720 (C=O), 1599 (C=C), 1496 (C=N), 1244, 1213, 1044, 756, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.41 (t, J = 7.1 Hz, 3H, CH_3), 2.99 (br s, OH), 3.81 (dd, J = 6.0, 9.4 Hz, 1H, CH_2), 3.97 (dd, J = 4.6, 9.4 Hz, 1H, CH_2), 4.40 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.44–4.51 (m, 3H, 2′-H and 3′-H), 6.74 (d, J = 7.8 Hz, 2H, ArH), 6.84 (s, 1H, 4-H), 6.95 (t, J = 7.9 Hz, 1H, ArH), 7.27 (t, J = 7.5 Hz, 2H, ArH), 7.37–7.44 (m, 5H, ArH); HRMS (EI) calcd for $C_{21}H_{22}N_2O_4$ (M^+) 366.1580, found 366.1584.
Ethyl 1-(3′-(4′-chlorophenoxy)-2′-hydroxypropyl)-3-phenyl-1H-pyrazole-5- carboxylate. Compound **3b**: Pale yellowish oil; IR (film) *v*: 3426 (OH), 3064, 2978, 2931, 1723 (C=O), 1596 (C=C), 1492 (C=N), 1245, 1214, 1094, 1035, 824, 700, 671 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.41 (t, J = 7.1 Hz, 3H, CH_3), 2.89 (br s, OH), 3.75 (dd, J = 5.8, 9.4 Hz, 1H, CH_2), 3.97 (dd, J = 4.5, 9.4 Hz, 1H, CH_2), 4.39 (q, J = 7.1 Hz, 2H, OCH_2), 4.41–4.47 (m, 3H, 2-H and 3-H), 6.65 (d, J = 8.9 Hz, 2H, ArH), 6.86 (s, 1H, 4-H), 7.19 (d, J = 8.9 Hz, 2H, ArH), 7.36 (t, J = 6.9 Hz, 3H, ArH), 7.42 (d, J = 6.9 Hz, 2H, ArH); HRMS (EI) calcd for $C_{21}H_{21}ClN_2O_4$ (M^+) 400.1190, found 400.1179.
Ethyl 1-(2′-hydroxy-3′-(4′-nitrophenoxy)propyl)-3-phenyl-1H-pyrazole-5-carboxylate. Compound **3c**: Pale greenish oil; IR (film) *v*: 3425 (OH), 3079, 2929, 1720 (C=O), 1593 (NO_2), 1512 (C=N), 1343 (NO_2), 1261, 1214, 1028, 845, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.41 (t, J = 7.2 Hz, 3H, CH_3), 3.13 (br s, OH), 3.86 (dd, J = 5.8, 9.6 Hz, 1H, CH_2), 4.04 (dd, J = 4.5, 9.6 Hz, 1H, CH_2), 4.42 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 4.46–4.52 (m, 3H, 2′-H and 3′-H), 6.78 (d, J = 9.2 Hz, 2H, ArH), 6.85 (s, 1H, 4-H), 7.35–7.46(m, 5H, ArH), 8.15 (d, J = 9.2 Hz, 2H, ArH); HRMS (EI) calcd for $C_{19}H_{16}N_3O_5$ [(M-OEt)$^+$] 366.1090, found 366.1131.
Ethyl 1-(2′-hydroxy-3′-(2′-nitrophenoxy)propyl)-3-phenyl-1H-pyrazole-5-carboxylate. Compound **3d**: Pale yellowish oil; IR (film) *v*: 3426 (OH), 3057, 2981, 2931, 1716 (C=O), 1608 (C=C), 1525 (N=O), 1350 (N=O), 1245, 1213, 1026, 859, 746, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.41 (t, J = 7.1 Hz, 3H, CH_3), 3.45 (br s, OH), 3.99 (dd, J = 5.4, 9.4 Hz, 1H, CH_2), 4.09 (dd, J = 4.6, 9.6 Hz, 1H, CH_2), 4.42 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.48–4.54 (m, 3H, 2′-H and 3′-H), 6.83 (s, 1H, 4-H), 7.00 (d, J = 8.4 Hz, 1H, ArH), 7.04 (t, J = 8.2 Hz, 1H, ArH), 7.35–7.41 (m, 5H, ArH), 7.51 (t, J = 8.2 Hz, 1H, ArH), 7.85 (d, J = 8.2 Hz, 1H, ArH); HRMS (EI) calcd for $C_{21}H_{21}N_3O_6$ (M^+) 411.1430, found 411.1426.
Ethyl 1-(2′-hydroxy-3′-(2′-methoxyphenoxy)propyl)-3-phenyl-1H-pyrazole-5-carboxylate. Compound **3e**: Pale yellowish oil; IR (film) *v*: 3457 (OH), 3064, 2980, 2937, 1731 (C=O), 1593 (C=C), 1506 (C=N), 1254, 1212, 1125, 10278, 838, 766, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.40 (t, J = 7.1 Hz, 3H, CH_3), 3.51 (br s, OH), 3.74 (s, 3H, OCH_3), 3.92 (dd, J = 5.5, 9.9 Hz, 1H, CH_2), 4.02 (dd, J = 5.3, 9.9 Hz, 1H, CH_2), 4.40 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.42–4.51 (m, 3H, 2′-H and 3′-H), 6.78–6.85 (m, 3H, ArH, 4-H), 6.87 (t, J = 7.8 Hz, 1H, ArH), 6.94 (t, J = 7.8 Hz, 1H, ArH), 7.41–7.45 (m, 5H, ArH); HRMS (EI) calcd for $C_{22}H_{24}N_2O_5$ (M^+) 396.1685, found 396.1696.
Ethyl 3-(4′-chlorophenyl)-1-(2′-hydroxy-3′-phenoxypropyl)-1H-pyrazole-5-carboxylate Compound **3f**: Pale yellowish oil; IR (film) *v*: 3432 (OH), 3063, 2981, 2935, 1719 (C=O), 1599 (C=C), 1496 (C=N), 1245, 1212, 1093, 1029, 839, 755,692 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.40 (t, J = 7.0 Hz, 3H, CH_3), 3.15 (br s, OH), 3.80 (dd, J = 5.7, 9.0 Hz, 1H, CH_2), 3.95 (dd, J = 3.6, 9.0 Hz, 1H, CH_2), 4.41 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 4.42–4.50 (m, 3H, 2′-H and 3′-H), 6.74 (d, J = 7.8 Hz, 2H, ArH), 6.82 (s, 1H, 4-H), 6.96 (t, J = 7.8 Hz, 1H, ArH), 7.25 (t, J = 7.8 Hz, 2H, ArH), 7.32 (d, J = 8.1 Hz, 2H, ArH), 7.38 (d, J = 8.1 Hz, 2H, ArH); HRMS (EI) calcd for $C_{21}H_{21}ClN_2O_4$ (M^+) 400.1190, found 400.1187.

Ethyl 1-(3′-(4′-chlorophenoxy)-2′-hydroxypropyl)-3-(4′-chlorophenyl)-1H-pyrazole-5-carboxylate Compound **3g**: Pale yellowish oil; IR (film) *v*: 3431 (OH), 3068, 2981, 2935, 1723 (C=O), 1597 (C=C), 1492(C=N), 1244, 1213, 1093 (C–Cl), 1029, 823, 779, 671 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ:1.41 (t, J = 7.1 Hz, 3H, CH_3), 2.93 (br s, OH), 3.75 (dd, J = 6.1, 9.5 Hz, 1H, CH_2), 3.91 (dd, J = 4.8, 9.5 Hz, 1H, CH_2), 4.38 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.41–4.49 (m, 3H, 2′-H and 3′-H), 6.65 (d, J = 8.9 Hz, 2H, ArH), 6.82 (s, 1H, 4-H), 7.20 (d, J = 8.9 Hz, 2H, ArH), 7.31 (d, J = 8.5 Hz, 2H, ArH), 7.39 (d, J = 8.5 Hz, 2H, ArH); HRMS (EI) calcd for $C_{21}H_{20}Cl_2N_2O_4$ $(M)^+$ 434.0800, found 434.0782.

Ethyl 3-(4′-chlorophenyl)-1-(2′-hydroxy-3′-(4′-nitrophenoxy)propyl)-1H-pyrazole-5-carboxylate. Compound **3h**: Pale yellowish oil; IR (film) *v*: 3425 (OH), 3085, 2936, 1714 (C=O), 1593 (C=C), 1513 (N=O), 1343 (N=O), 1261, 1215, 1093, 1029, 845, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ:1.40 (t, J = 7.1 Hz, 3H, CH_3), 2.96 (br s, OH), 3.88 (dd, J = 6.0, 9.6 Hz, 1H, CH_2), 4.03 (dd, J = 4.9, 9.6 Hz, 1H, CH_2), 4.40 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.42–4.54 (m, 3H, 2′-H and 3-H), 6.79 (d, J = 9.2 Hz, 2H, ArH), 6.83 (s, 1H, 4-H), 7.32 (d,J = 8.5 Hz, 2H, ArH), 7.39 (d, J = 8.5 Hz, 2H, ArH), 8.22 (d, J = 9.2 Hz, 2H, ArH); HRMS (EI) calcd for $C_{21}H_{20}ClN_3O_6$ $(M)^+$ 445.1041, found 445.1057.

Ethyl 3-(4′-chlorophenyl)-1-(2′-hydroxy-3′-(2′-nitrophenoxy)propyl)-1H-pyrazole-5-carboxylate. Compound **3i**: White solid, mp 121–124 °C; IR (KBr) *v*: 3342 (OH), 3130, 2988, 2947, 1727 (C=O), 1610 (C=C), 1534 (N=O), 1364 (N=O), 1250, 1212, 1092, 1035, 823, 745, 672 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ:1.38 (t, J = 7.2 Hz, 3H, CH_3), 3.26 (br s, OH), 4.00 (dd, J = 5.8, 9.4 Hz, 1H, CH_2), 4.08 (dd, J = 4.7, 9.4 Hz, 1H, CH_2), 4.39 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 4.44–4.54 (m, 3H, 2′-H and 3′-H), 6.80 (s, 1H, 4-H), 6.97 (d, J = 8.3 Hz, 1H, ArH), 7.04 (t, J = 8.3Hz, 1H, ArH), 7.31 (d, J = 8.5 Hz, 2H, ArH), 7.36 (d, J = 8.5 Hz, 2H, ArH), 7.50 (t, J = 8.3 Hz, 1H, ArH), 7.85 (d, J = 8.3 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ:14.4, 51.7, 61.1, 69.1, 69.9, 109.1, 114.6, 121.1, 126.1, 127.3, 129.3, 130.3, 134.5, 135.7, 139.4, 143.7, 145.4, 151.6, 162.0; HRMS (EI) calcd for $C_{21}H_{20}ClN_3O_5$ $[(M\text{-}O)^+]$ 429.1091, found 429.0859.

Ethyl 3-(4′-chlorophenyl)-1-(2′-hydroxy-3′-(2′-methoxyphenoxy)propyl)-1H- pyrazole-5-carboxylate. Compound **3j**: White solid, mp 96–99 °C; IR (KBr) *v*: 3447 (OH), 3063, 2935, 2835, 1720 (C=O), 1593 (C=C), 1506(C=N), 1254, 1210, 1124, 1092, 1027, 837, 743 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ:1.40 (t, J = 7.1 Hz, 3H, CH_3), 3.27 (br s, OH), 3.76 (s, 3H, OCH_3), 3.86 (dd, J = 5.8, 9.9 Hz, 1H, CH_2), 3.99 (dd, J = 5.2, 9.9 Hz, 1H, CH_2), 4.41 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.42–4.53 (m, 3H, 2′-H and 3′-H), 6.80 (d, J = 7.6 Hz, 2H, ArH), 6.82 (s, 1H, 4-H), 6.88 (t, J = 7.6 Hz, 1H, ArH), 6.97 (t, J = 7.6 Hz, 1H, ArH), 7.34–7.39 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ:14.4, 51.9, 55.6, 61.1, 69.4, 70.3, 109.0, 111.8, 114.7, 120.9, 122.3, 127.7, 129.0, 130.6, 135.3, 143.6, 145.2, 147.6, 149.7, 162.1; HRMS (EI) calcd for $C_{22}H_{23}ClN_2O_5$ $(M)^+$ 430.1295, found 430.1282.

Ethyl 1-(2′-hydroxy-3′-phenoxypropyl)-3-(4′-methoxyphenyl)-1H-pyrazole-5-carboxylate Compound **3k**: Pale yellowish oil; IR (film) *v*: 3444 (OH), 3063, 2980, 2936, 1721 (C=O), 1599 (C=C), 1499 (C=N), 1251, 1211, 1035, 839, 755, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ:1.40 (t, J = 7.1 Hz, 3H, CH_3), 3.33 (br s, OH), 3.80 (dd, J = 6.0, 9.6 Hz, 1H, CH_2), 3.85 (s, 3H, OCH_3), 3.96 (dd, J = 4.8, 9.6 Hz, 1H, CH_2), 4.38 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.41–4.49 (m, 3H, 2′-H and 3′-H), 6.75 (d, J = 8.8 Hz, 2H, ArH), 6.79 (s, 1H, 4-H), 6.92 (d, J = 7.4 Hz, 2H, ArH), 6.95 (t, J = 7.4 Hz, 1H, ArH), 7.24 (t, J = 7.4 Hz, 2H, ArH), 7.30 (d, J = 8.8 Hz, 2H, ArH); HRMS (EI) calcd for $C_{22}H_{24}N_2O_5$ $(M)^+$ 396.1685, found 396.1685.

Ethyl 1-(3′-(4′-chlorophenoxy)-2′-hydroxypropyl)-3-(4′-methoxyphenyl)-1H-pyrazole-5-carboxylate. Compound **3l**: Pale yellowish oil; IR (film) *v*: 3425 (OH), 3068, 2975, 2936, 1720 (C=O), 1613 (C=C), 1492 (C=N), 1250, 1212, 1093, 1034, 824, 779,671 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ:1.40 (t, J = 7.1 Hz, 3H, CH_3), 3.74 (dd, J = 5.7, 9.4 Hz, 1H, CH_2), 3.85 (s, 3H, OCH_3), 3.90 (dd, J = 4.5, 9.4 Hz, 1H, CH_2), 4.11 (br s, OH), 4.39 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.41–4.48 (m, 3H, 2′-H and 3′-H), 6.66 (d, J = 9.0 Hz, 2H, ArH), 6.78 (s, 1H, 4-H), 6.92 (d, J = 8.7 Hz, 2H, ArH), 7.12 (d, J = 9.0 Hz, 2H, ArH), 7.28 (d, J = 8.7 Hz, 2H, ArH); HRMS (EI) calcd for $C_{22}H_{23}ClN_2O_5$ $(M)^+$ 430.1295, found 430.1287.

Ethyl 1-(2′-hydroxy-3′-(4′-nitrophenoxy)propyl)-3-(4′-methoxyphenyl)-1H-pyrazole-5-carboxylate. Compound **3m**: Pale yellowish oil; IR (film) *v*: 3408 (OH), 3083, 2936, 2839, 1714 (C=O), 1593 (C=C), 1513 (N=O), 1343 (N=O), 1254, 1215, 1033, 845, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ:1.40 (t, J = 7.2 Hz, 3H, CH_3), 2.96 (br s, OH), 3.84 (s, 3H, OCH_3), 4.02 (dd, J = 5.2, 9.8 Hz, 1H, CH_2), 4.08 (dd, J = 4.5, 9.8 Hz, 1H, CH_2), 4.36 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 4.41–4.51 (m, 3H, 2′-H and 3′-H), 6.79 (s, 1H, 4-H), 6.80 (d, J = 9.2 Hz, 2H, ArH), 6.92 (d, J = 8.6 Hz, 2H, ArH), 7.27 (d, J = 8.6 Hz, 2H, ArH), 8.15 (d, J = 9.2 Hz, 2H, ArH); HRMS (EI) calcd for $C_{15}H_{17}N_2O_4$ $[(M\text{-}CH_2OC_6H_4NO_2)^+]$ 289.1190, found 289.0764.

Ethyl 1-(2′-hydroxy-3′-(2′-nitrophenoxy)propyl)-3-(4′-methoxyphenyl)-1H-pyrazole-5-carboxylate. Compound **3n**: Pale yellowish oil; IR (film) *v*: 3426 (OH), 3074, 2939, 2839, 1717 (C=O), 1609 (C=C), 1525 (N=O), 1350 (N=O), 1254, 1212, 1032, 840, 746 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.40 (t, J = 7.2 Hz, 3H, CH_3), 3.61 (br s, OH), 3.85 (s, 3H, OCH_3), 3.96 (dd, J = 5.8, 9.4 Hz, 1H, CH_2), 4.10 (dd, J = 4.1, 9.4 Hz, 1H, CH_2), 4.41 (q, J = 7.2 Hz, 2H, OCH_2),4.47–4.54 (m, 3H, 2′-H and 3′-H), 6.79 (s, 1H, 4-H), 6.91 (d, J = 8.8 Hz, 2H, ArH), 6.97 (d, J = 8.3 Hz, 1H, ArH), 7.04 (t, J = 8.3 Hz, 1H, ArH), 7.26 (d, J = 8.8 Hz, 2H, ArH), 7.51 (t, J = 8.3 Hz, 1H, ArH), 7.86 (d, J = 8.3 Hz, 1H, ArH); HRMS (EI) calcd for $C_{22}H_{23}N_3O_7$ $(M)^+$ 441.1536, found 441.1542.

Ethyl 1-(2′-hydroxy-3′-(2′-methoxyphenoxy)propyl)-3-(4′-methoxyphenyl)-1H-pyrazole-5-carboxylate. Compound **3o**: Pale yellowish oil; IR (film) *v*: 3445 (OH), 3052, 2934, 2836, 1719 (C=O), 1613 (C=C), 1505 (C=N), 1254, 1211, 1029, 838, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ:1.41 (t, J = 7.1 Hz, 3H, CH_3), 3.48 (br s, OH), 3.75 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.90 (dd, J = 5.6, 9.9 Hz, 1H, CH_2), 4.00 (dd, J = 5.3, 9.9 Hz, 1H, CH_2), 4.39 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.42–4.50 (m, 3H, 2′-H and 3′-H), 6.79 (s, 1H, 4-H), 6.84 (d, J = 9.1 Hz, 2H, ArH), 6.87 (d, J = 9.1 Hz, 2H, ArH), 6.93 (d, J = 8.8 Hz, 2H, ArH), 7.34 (d, J = 8.8 Hz, 2H, ArH); HRMS (EI) calcd for $C_{23}H_{26}N_2O_6$ $(M)^+$ 426.1791, found 426.1786.

30. A549 cells were cultured in the medium with or without the compounds **3a**–**3o** 12.5–100 μM for 24 or 48 h, respectively. Then, the morphological changes of the cells were observed under phase contrast microscope (Nikon, Japan).
31. Ono, K.; Wang, X.; Han, J. *Mol. Cell. Biol.* **2001**, *21*, 8276.