Turkish Journal of Chemistry

http://journals.tubitak.gov.tr/chem/

Research Article

Turk J Chem
(2018) 42: 1334 – 1343

doi:10.3906/kim-1803-25

Synthesis and cytotoxicity evaluation of [(2,4-dichlorophenoxy)methyl]-5-aryl-1,3,4-oxadiazole/4*H*-1,2,4-triazole analogues

Mohamed Jawed AHSAN*
Department of Pharmaceutical Chemistry, Maharishi Arvind College of Pharmacy, Jaipur, Rajasthan, India

Received: 09.03.2018 • **Accepted/Published Online:** 30.05.2018 • **Final Version:** 11.10.2018

Abstract: We report herein the synthesis, characterization, and cytotoxicity evaluations of some newer oxadiazole and triazole analogues (**5a**–**j**). The cytotoxicity of all the title compounds were evaluated as per the National Cancer Institute protocol in a one-dose assay (10 μM) on nine different panels of 59 cancer cell lines. 2-{5-[(2,4-Dichlorophenoxy)methyl]-1,3,4-oxadiazol-2-yl}phenol (**5e**) showed the maximum cytotoxicity among the series of ten compounds. The cytotoxicity of **5e** was comparable to that of the standard anticancer drug, 5-fluorouracil, and better than that of imatinib. The structure activity relationship was also discussed.

Key words: Anticancer activity, cancer cell lines, cytotoxicity, one dose assay, oxadiazole, triazole

1. Introduction

Cancer is uncontrolled growth of abnormal cells that grow outside their usual boundaries and then assault the adjoining parts of the body and spread to other organs. Cancer is the second leading cause of deaths worldwide and accounted for 8.8 million deaths in 2015.[1] In 2018, 1,735,350 new cancer cases and 609,640 cancer deaths are projected to occur in the United States.[2] There are many types of cancer treatment, and the treatment strategy depends upon cancer type and stage. The most important cancer treatments are chemotherapy, surgery, radiation therapy, immunotherapy, targeted therapy, and hormonal therapy. Stem cell transplant and precision medicine may also help during cancer treatment.[3] Chemotherapy is a major part of cancer therapeutics; however, it has its own limitations of limited efficacy, selectivity, high cost, genotoxicity, and drug resistance.[4] Extensive research and development, especially in the design and discovery anticancer agents, is the need of the present day.

Compounds containing heterocyclic rings are of great importance both in medicine and industry.[5] Oxadiazole is one among the heterocyclic rings and has fascinating diverse biological potentials. Oxadiazoles have a large impact on multiple drug discovery programs across a variety of therapeutic areas, including tuberculosis,[6] cancer,[7] HIV,[8] diabetes,[9] obesity,[10] inflammation,[11] and infection.[12] The carbonyl compounds of amides, ester, carbamates, and hydroxamic acids have been successfully replaced with oxadiazole rings for improved efficacy.[13–15] Similarly, triazole analogues are well reported anticancer agents.[16,17] The literature on oxadizoles and our previous published work[18] is a source of inspiration to continue research on further exploration of oxadiazole, and in the present investigation we report herein the synthesis and cytotoxicity evaluation of some new oxadiazole analogues. A few triazole analogues were also synthesized and are reported herein.

*Correspondence: jawedpharma@gmail.com

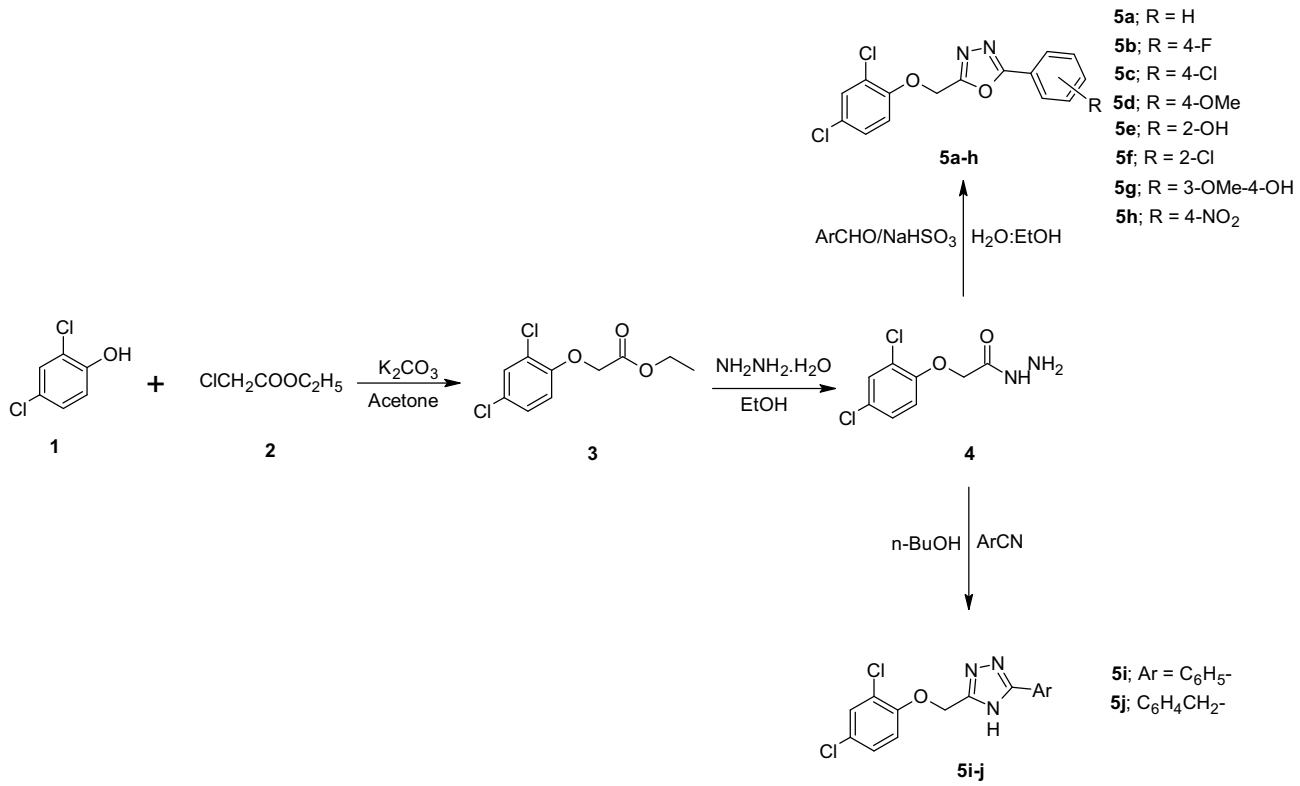
2. Results and discussion

2.1. Chemistry

As shown in the Scheme, ethyl(2,4-dichlorophenoxy)acetate (**3**) was synthesized by stirring a mixture of 2,4-dichlorphenol (**1**) and ethylchloroacetate (**2**) suspended in acetone and potassium carbonate for 24 h.[18,19] Ethyl(2,4-dichlorophenoxy)acetate (**3**) was further refluxed with hydrazine hydrate in ethanol for 6 h to synthesize 2-(2,4-dichlorophenoxy)acetohydrazide (**4**).[18,19] In the final step, an equimolar quantity of 2-(2,4-dichlorophenoxy)acetohydrazide (**4**) and aromatic aldehyde was refluxed in an ethanol/water system (1:2, v/v) solvent by adding 20 mol% $NaHSO_3$ for 10 h to obtain 2-[(2,4-dichlorophenoxy)methyl]-5-aryl-1,3,4-oxadiazole (**5a**–**h**).[12] The progress of the reaction was monitored throughout by thin-layer chromatography (TLC) using n-hexane:ethylacetate (1:1) as mobile phase. Base-catalyzed synthesis of 3-[(2,4-dichlorophenoxy)methyl]-5-aryl-4*H*-1,2,4-triazole (**5i**,**j**) was achieved by refluxing 2-(2,4-dichlorophenoxy)acetohydrazide (**4**) and nitrile in *n*-butanol for 2–3 h in the presence of K_2CO_3.[20] The progress of the reactions was monitored throughout by TLC (Silica gel 60 F_{254}) using mobile phase, chloroform–methanol (9:1), and benzene–acetone (9:1). The spots were visualized under either iodine vapor or UV light. All the compounds were obtained in satisfactory yield ranging between 52% and 81%. All the chemicals were procured from CDH (New Delhi, India), Merck (Kenilworth, NJ, USA), and SD Fine (Mumbai, India). The title compounds (**5a**–**j**) were further characterized by infrared (IR), nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR), and mass spectral data. IR, NMR, and mass spectra data were obtained on a Shimadzu 8201 PC (Kyoto, Japan), Bruker AC 400 MHz spectrometer (in DMSO-d_6) (Billerica, MA, USA), and Bruker Esquire LCMS using ESI, respectively. The purity of compounds was checked by elemental analyses (PerkinElmer 2400 elemental analyzer, Waltham, MA, USA). In the ^{1}H NMR, the prototype compound **5e** showed a singlet at δ 5.27 ppm corresponding to the protons of CH_2, a doublet at δ 6.85 ppm corresponding to one aromatic proton, a double doublet at δ 7.11 ppm corresponding to another aromatic proton of 2,4-dichlorophenyl, a multiplet at δ 7.23–7.70 ppm corresponding to the four aromatic protons, a singlet at δ 8.31 ppm corresponding to the one aromatic proton (2,4-dichlorophenyl), and a singlet at δ 10.03 ppm corresponding to the phenolic proton (ArOH). The ^{13}C NMR of compound **5e** showed δ ppm: 166.52, 155.61, 152.83, 142.18, 131.49, 130.51, 128.91, 128.20, 128.13, 124.09, 121.99, 117.17, 116.31, 112.22, and 67.0. The mass spectra showed $(M+H)^+$ and $(M+2)^+$ at 337 and 338, respectively.

3. Cytotoxicity

All the title compounds (**5a**–**j**) were evaluated for their cytotoxicity at 10 μM drug concentrations as per the National Cancer Institute (NCI) protocol on nine different panels of 59 human cancer cell lines.[21–24] The results of cytotoxicity study are given in Table 1. All the tested compounds showed moderate or weaker cytotoxicity except for **5e**, which showed promising cytotoxicity among the series. The compounds **5a**, **5b**, **5f**, and **5g** showed higher sensitivity towards the UACC 257 (melanoma) [percent growth inhibitions (%GIs) = 43.11, 28.58, 45.05, and 40.58, respectively], NCI-H522 (non-small cell lung cancer) (%GIs = 39.29, 39.28, 36.14, and 40.83, respectively) and A549/ATCC (non-small cell lung cancer) (%GIs = 29.97, 23.44, 20.45, and 28.05, respectively). Compounds **5i** and **5j** showed higher sensitivity towards the UO-31 (renal cancer) with %GIs of 22.89 and 23.43, respectively. Similarly, compounds **5e** and **5h** showed higher sensitivity towards the NCI-H522 (non-small cell lung cancer) with %GIs of 98.03 and 36.89. Overall, excellent growth control (%GI of 98.03) regarding NCI-H522 (non-small cell lung cancer) was observed in compound **5e**. Compounds with GIs of $\geq$68%



Scheme. Protocol for the synthesis of 2-[(2,4-dichlorophenoxy)methyl]-5-aryl-1,3,4-oxadiazoles (**5a**–**h**) and 3-[(2,4-dichlorophenoxy)methyl]-5-aryl-4*H*-1,2,4-triazoles (**5i**,**j**).

were considered to be active towards that particular cell line.[25] Compound **5e** showed promising cytotoxicity (%GIs of $\geq$68%) against 15 different cancer cell lines (Figure 1). Figure 1 shows the %GIs of **5e** on 59 human cancer cell lines at 10 μM drug concentration. The cytotoxicity of **5e** [mean growth percent (MGP) = 46.12] and 5-fluorouracil (5-FU) (MGP = 42.21) was comparable. Compound **5e** showed far better %GIs on nearly 26 cancer cell lines having 50 cancer cell lines in common (Figure 2). Figure 2 shows the %GIs of **5e** and 5-FU on 50 human cancer cell lines in common at 10 μM drug concentrations. The average %GIs against the nine panels was also calculated for comparative study and **5e** showed higher sensitivity towards leukemia, non-small cell lung cancer, CNS cancer, and ovarian cancer (Table 2). The cytotoxicity data of imatinib and 5-FU were obtained from the NCI data warehouse index.

The structure activity relationship was established with cytotoxicity studies, and the 2-hydroxy substitution showed the maximum cytotoxicity. The 2-chloro substitution showed higher cytotoxicity than the 4-hydroxy-3-methoxy and nitro substitutions. The order of cytotoxicity in the present investigation was 2-OH > 2-Cl > 4-OH-3-OCH_3 > 4-NO_2, while the overall activity was 3,4-(OCH_3)$_2$ > 2-OH > 2-Cl > 4-OH-3-OCH_3 > 4-NO_2 > 4-Cl > 4-OCH_3.[18]

3.1. Conclusion

All the compounds were synthesized in satisfactory yield and evaluated for cytotoxicity on nine different panels of nearly 60 human cancer cell lines. Compound **5e** showed promising cytotoxicity among the series of compounds.

Table 1. The cytotoxicity evaluation of 2-[(2,4-dichlorophenoxy)methyl]-5-aryl-1,3,4-oxadiazoles (**5a**–**h**) and 3-[(2,4-dichlorophenoxy)methyl]-5-aryl-4*H*-1,2,4-triazoles (**5i**,**j**).

Compound	Cancer cell lines assay in single dose assay 10 μM concentration				
	Mean GP	GP range	The most sensitive cell lines	GP	% GI
5a	98.36	56.89 to 116.71	UACC 257 (Melanoma)	56.89	43.11
			NCI-H522 (Non-small cell lung cancer)	60.71	39.29
			A549/ATCC (Non-small cell lung cancer)	70.03	29.97
			HT29 (Colon cancer)	80.15	19.85
			PC-3 (Prostate cancer)	80.90	19.10
5b	98.78	60.72 to 117.88	NCI-H522 (Non-small cell lung cancer)	60.72	39.28
			UACC 257 (Melanoma)	71.42	28.58
			HT29 (Colon cancer)	72.64	27.36
			A549/ATCC (Non-small cell lung cancer)	76.56	23.44
			HL-60(TB) (Leukemia)	87.29	12.71
5c	97.75	72.06 to 126.71	HCT116 (Colon cancer)	72.06	27.94
			T-47D (Breast cancer)	77.06	22.94
			A549/ATCC (Non-small cell lung cancer)	77.21	22.79
			PC-3 (Prostate cancer)	77.25	22.75
5d	99.88	77.31 to 140.84	A549/ATCC (Non-small cell lung cancer)	77.31	22.69
			SNB-75 (CNS cancer)	81.46	18.54
			UACC 257 (Melanoma)	81.55	18.45
			HL-60(TB) (Leukemia)	85.24	14.76
5e	46.12	1.97 to 89.91	NCI-H522 (Non-small cell lung cancer)	1.97	98.03
			HL-60 (TB) (Leukemia)	3.89	96.11
			HCT-116 (Colon cancer)	8.59	91.41
			CCRF-CEM (Leukemia)	15.45	84.55
			HT29 (Colon cancer)	18.16	81.84
5f	93.33	54.95 to 116.65	UACC 257 (Melanoma)	54.95	45.05
			NCI-H522 (Non-small cell lung cancer)	63.86	36.14
			MOLT-4 (Leukemia)	65.29	34.71
			CCRF-CEM (Leukemia)	71.41	20.59
			A549/ATCC (Non-small cell lung cancer)	71.55	20.45
5g	94.97	59.17 to 115.61	NCI-H522 (Non-small cell lung cancer)	59.17	40.83
			UACC 257 (Melanoma)	59.42	40.58
			HL-60 (TB) (Leukemia)	61.28	38.72
			A549/ATCC (Non-small cell lung cancer)	71.95	28.05
			UO-31 (Renal cancer)	75.10	24.90
5h	96.73	63.11 to 120.45	NCI-H522 (Non-small cell lung cancer)	63.11	36.89
			HL-60 (TB) (Leukemia)	70.44	29.56
			PC-3 (Prostate cancer)	75.54	24.46
			CCRF-CEM (Leukemia)	77.09	22.91
			UO-31 (Renal cancer)	78.27	21.73
5i	98.01	77.11 to 121.90	UO-31 (Renal cancer)	77.11	22.89
			SK-OV-3 (Ovarian cancer)	80.91	19.09
			CCRF-CEM (Leukemia)	85.89	14.11
			PC-3 (Prostate cancer)	87.34	13.66
			HOP-62 (Non-small cell lung cancer)	86.76	13.24

Table 1. Continued.

Compound	Cancer cell lines assay in single dose assay 10 μM concentration				
	Mean GP	GP range	The most sensitive cell lines	GP	% GI
5j	97.14	76.57 to 112.18	UO-31 (Renal cancer)	76.57	23.43
			HL-60(TB) (Leukemia)	82.56	17.44
			MOLT-4 (Leukemia)	83.27	16.73
			SNB-75 (CNS cancer)	86.37	13.63
			T-47D (Breast cancer)	86.79	13.21
5-FU	42.21	−19.6 to 95.5	SF-539 (CNS cancer)	−19.6	119.6
			HCC-2998 (Colon cancer)	−17.8	117.8
			A498 (Renal cancer)	−16.3	116.3
			HS 578T (Breast cancer)	−10.8	110.8
			MCF7 (Breast cancer)	11.5	88.5

GP = growth percent; %GI = percent growth inhibition
The data of one-dose assay for 5-fluorouracil (5-FU) were taken from the NCI database compound ID NSC 19893 (https://dtp.cancer.gov/dtpstandard/servlet/MeanGraphSummary).

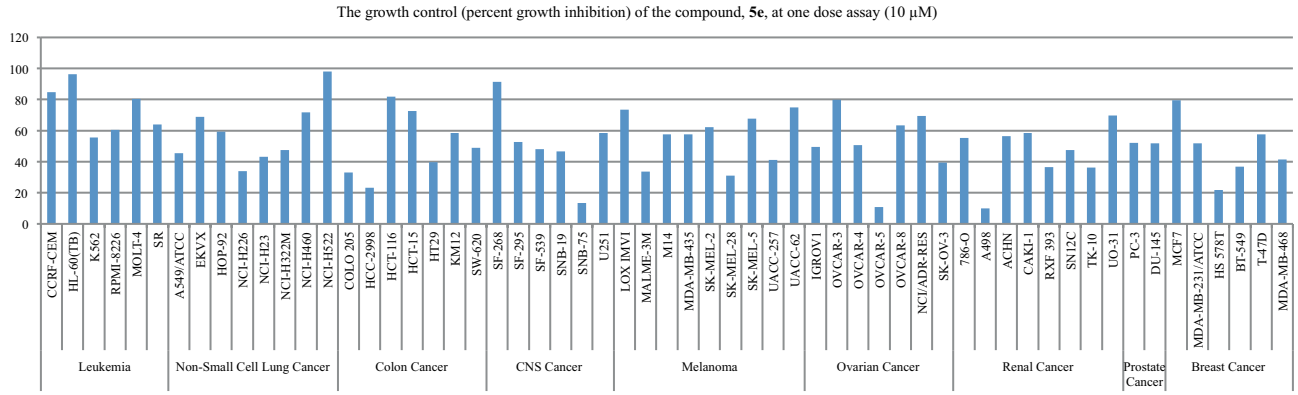


Figure 1. The percent growth inhibitions (%GIs) of the compound, **5e**, on 59 human cancer cell lines at 10 μM drug concentration.

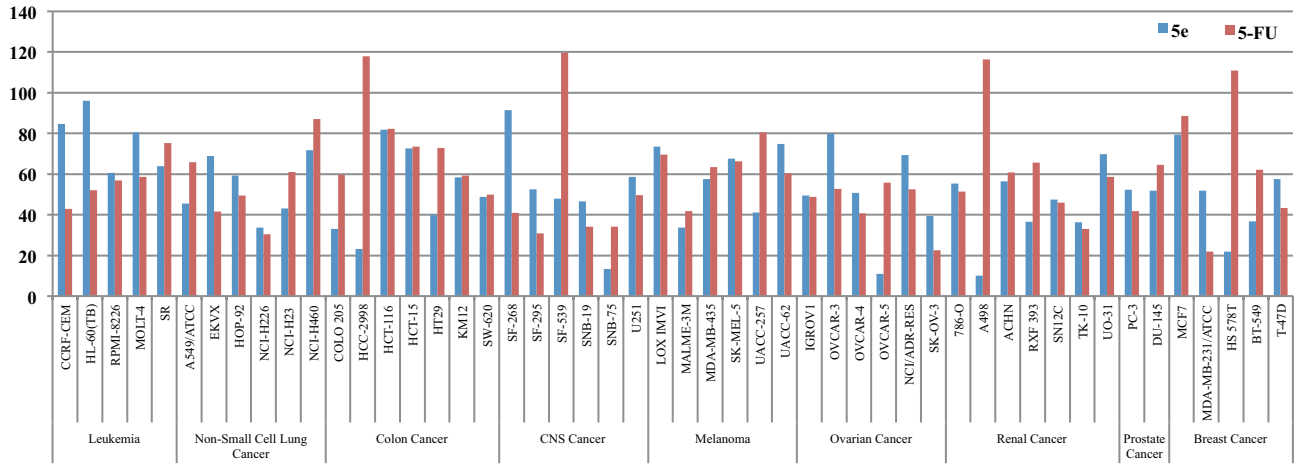


Figure 2. The percent growth inhibitions (%GIs) of the compound, **5e**, and 5-fluorouracil (5-FU) on 50 human cancer cell lines in common at 10 μM drug concentrations.

Table 2. The average percent growth inhibitions (GIs) of 2-[(2,4-dichlorophenoxy)methyl]-5-aryl-1,3,4-oxadiazoles, 3-[(2,4-dichlorophenoxy)methyl]-5-aryl-4*H*-1,2,4-triazoles, imatinib, and 5-FU.

Compound	Leukemia	Non-small cell lung cancer	Colon cancer	CNS cancer	Melanoma	Ovarian cancer	Renal cancer	Prostate cancer	Breast cancer
5a	5.81	8.69	0.43	–1.07	3.26	–5.82	–0.67	3.83	0.91
5b	2.86	6.88	–0.59	–0.75	3.50	–5.79	0.79	4.99	0.19
5c	108.88	91.81	95.58	99.56	95.72	101.36	100.53	91.4	95.28
5d	112.31	94.41	99.67	97.64	97.92	99.38	102.30	106.86	98.15
5e	**73.57**	**58.45**	51.09	**51.72**	52.96	**51.84**	46.31	52.02	48.07
5f	23.47	11.64	2.17	1.00	6.65	0.15	2.73	11.27	5.52
5g	15.27	11.97	0.46	2.61	4.01	–1.06	4.27	–0.79	4.91
5h	19.55	9.99	1.64	0.77	1.41	–8.59	0.47	7.31	3.49
5i	3.11	5.69	1.54	2.98	–1.05	2.56	–1.90	0.74	3.58
5j	8.65	3.61	–3.71	5.68	2.50	4.36	0.75	3.39	1.87
Imatinib	9	15.68	5.34	5.80	2.02	–7.15	3.86	12.50	12.15
5-FU	57.23	51.23	**73.63**	51.57	**55.2**	45.44	**61.69**	**53.15**	**65.34**

GP = growth percent; %GI = percent growth inhibition. Bold figure shows higher activity.

The cytotoxicity of **5e** was higher than that of imatinib and comparable to that of 5-FU. The cytotoxicity studies reported herein may provide an insight into the design of other anticancer agents with improved antiproliferative activity.

4. Experimental

4.1. Method for the synthesis of ethyl(2,4-dichlorophenoxy)acetate (3)

Equimolar amounts of 2,4-dichlorophenol (0.05 mol; 5.91 mL) and ethyl chloroacetate (0.05 mol; 5.35 mL) in 50–60 mL acetone, and 5 g anhydrous potassium carbonate were refluxed for 24 h with continuous stirring to obtain ethyl(2,4-dichlorophenoxy)acetate (**3**).[19]

4.2. Method for the synthesis of 2-(substitutedphenoxy)acetohydrazide (4)

A solution of substituted ethyl(2,4-dichlorophenoxy)acetate (0.03 mol; 7.01 mL) (**3**) and hydrazine hydrate (0.045 mol; 2.18 mL) was refluxed in ethanol for 5–6 h to obtain 2-(2,4-dichlorophenoxy)acetohydrazide (**4**). The solid thus obtained was recrystallized with an absolute ethanol.[19]

4.3. General procedure for the synthesis of 2-[(2,4-dichlorophenoxy)methyl]-5-aryl-1,3,4-oxadiazole (5a–h)

2-(2,4-Dichlorophenoxy)acetohydrazide (**4**) (0.001 mol; 0.235 g) and aromatic aldehydes (0.001 mol) were refluxed in an ethanol–water (1:2, v/v) solvent system for 10–12 h, using 20 mol% solution of $NaHSO_3$ to obtain the title compounds [(2,4-dichlorophenoxy)methyl]-5-aryl-1,3,4-oxadiazole (**5a**–**h**).

4.3.1. 2-[(2,4-Dichlorophenoxy)methyl]-5-phenyl-1,3,4-oxadiazole (5a)

Creamy solid; mp 112–114 °C; ^{1}H NMR (DMSO d_6, 400 MHz) δ ppm: 5.30 (2H, s, CH_2), 7.07 (1H, dd, J = 8.8, 8.9 Hz, ArH), 7.31 (1H, d, J = 7.4 Hz, ArH), 7.41–7.96 (5H, m, ArH), 8.02 (1H, s, ArH); ^{13}C NMR (DMSO d_6, 100 MHz) δ ppm: 168.74, 163.98, 153.30, 134.36, 129.69, 129.20, 128.98, 128.27, 127.62, 127.42, 124.98, 115.53, 66.17; Mass (m/z) 321 $(M+H)^+$, 322 $(M+2)^+$; Calcd/Anal. [C (56.10) 56.06, H (3.14) 3.16, N (8.72) 8.75].

4.3.2. 2-[(2,4-Dichlorophenoxy)methyl]-5-(4-fluorophenyl)-1,3,4-oxadiazole (5b)

Creamy solid; mp 118–120 °C; ^{1}H NMR (DMSO d_6, 400 MHz) δ ppm: 5.32 (2H, s, CH_2), 7.11 (1H, d, J = 8.7 Hz, ArH), 7.15–7.57 (4H, m, ArH), 7.71 (1H, d, J = 7.3 Hz, ArH), 7.98 (1H, s, ArH); ^{13}C NMR (DMSO d_6, 100 MHz) δ ppm: 166.40, 152.98, 142.27, 132.24, 129.80, 129.73, 128.41, 126.09, 125.57, 122.96, 115.83, 115.32, 67.00; Mass (m/z) 339 $(M+H)^+$, 340 $(M+2)^+$; Calcd/Anal. [C (53.12) 53.10, H (2.67) 2.69, N (8.26) 8.24].

4.3.3. 2-[(2,4-Dichlorophenoxy)methyl]-5-(4-chlorophenyl)-1,3,4-oxadiazole (5c)

White solid; mp 122–124 °C; ^{1}H NMR (DMSO d_6, 400 MHz) δ ppm: 5.31 (2H, s, CH_2), 6.99 (1H, dd, J = 8.0, 7.9 Hz, ArH), 7.12 (1H, d, J = 8.0 Hz, ArH), 7.27 (1H, s, ArH), 7.43 (2H, d, J = 7.3 Hz, ArH), 7.78 (2H, d, J = 7.3 Hz, ArH); ^{13}C NMR (DMSO d_6, 100 MHz) δ ppm: 166.52, 152.91, 142.44, 134.27, 131.41, 129.40, 128.93, 128.11, 128.09, 124.57, 124.31, 117.13, 67.11; Mass (m/z) 354 $(M+H)^+$, 355 $(M+2)^+$; Calcd/Anal. [C (50.66) 50.63, H (2.55) 2.59, N (7.88) 7.85].

4.3.4. 2-[(2,4-Dichlorophenoxy)methyl]-5-(4-methoxyphenyl)-1,3,4-oxadiazole (5d)

Light yellow solid; mp 102–104 °C; ^{1}H NMR (DMSO d_6, 400 MHz) δ ppm: 3.81 (3H, s, OCH_3), 5.32 (2H, s, CH_2), 6.97 (1H, d, J = 8.1 Hz, ArH), 7.02 (2H, d, J = 8.0 Hz, ArH), 7.12 (1H, dd, J = 8.1, 8.0 Hz, ArH), 7.19 (1H, s, ArH), 7.39 (2H, d, J = 8.0 Hz, ArH); ^{13}C NMR (DMSO d_6, 100 MHz) δ ppm: 166.52, 160.67, 152.81, 142.48, 131.47, 128.51, 128.40, 128.13, 124.01, 118.99, 117.57, 114.31, 67.11, 55.62; Mass (m/z) 351 $(M+H)^+$, 352 $(M+2)^+$; Calcd/Anal. [C (54.72) 54.69, H (3.44) 3.47, N (7.98) 7.95].

4.3.5. 2-{5-[(2,4-Dichlorophenoxy)methyl]-1,3,4-oxadiazol-2-yl}phenol (5e)

Light brown solid; mp 152–154 °C; ^{1}H NMR (DMSO d_6, 400 MHz) δ ppm: 5.27 (2H, s, CH_2), 6.85 (1H, d, J = 7.3 Hz, ArH), 7.11 (1H, dd, J = 7.1, 7.2 Hz, ArH), 7.23–7.70 (4H, m, ArH), 8.31 (1H, s, ArH), 10.03 (1H, s, ArOH); ^{13}C NMR (DMSO d_6, 100 MHz) δ ppm: 166.52, 155.61, 152.83, 142.18, 131.49, 130.51, 128.91, 128.20, 128.13, 124.09, 121.99, 117.17, 116.31, 112.22, 67.01; Mass (m/z) 337 $(M+H)^+$, 338 $(M+2)^+$; Calcd/Anal. [C (53.44) 53.49, H (2.99) 2.97, N (8.31) 8.29].

4.3.6. 2-[(2,4-Dichlorophenoxy)methyl]-5-(2-chlorophenyl)-1,3,4-oxadiazole (5f)

White solid; mp 152–154 °C; ^{1}H NMR (DMSO d_6, 400 MHz) δ ppm: 5.32 (2H, s, CH_2), 6.85 (1H, d, J= 7.9 Hz, ArH), 7.05 (1H, dd, J= 7.9, 7.8 Hz, ArH), 7.19 (1H, s, ArH), 7.23-7.46 (4H, m, ArH); ^{13}C NMR (DMSO d_6, 100 MHz) δ ppm: 166.51, 155.60, 152.81, 142.18, 139.49, 132.31, 131.91, 130.22, 129.44, 128.90, 128.43,

128.09, 127.21, 124.11, 117.56, 67.12; Mass (m/z) 354 $(M+H)^+$, 355 $(M+2)^+$; Calcd/Anal. [C (50.66) 50.65, H (2.55) 2.57, N (7.88) 7.86].

4.4. 4-{5-[(2,4-Dichlorophenoxy)methyl]-1,3,4-oxadiazol-2-yl}-2-methoxyphenol (5g)

Creamy solid; mp 160–162 °C; ^{1}H NMR (DMSO d_6, 400 MHz) δ ppm: 3.73 (3H, s, OCH_3), 5.20 (2H, s, CH_2), 7.09 (1H, s, ArH), 7.31–8.15 (4H, m, ArH), 8.39 (1H, s, ArH), 11.86 (1H, s, ArOH); ^{13}C NMR (DMSO d_6, 100 MHz) δ ppm: 168.93, 164.23, 153.26, 142.16, 140.47, 133.45, 131.86, 130.31, 129.69, 128.29, 127.54, 125.00, 122.65, 115.60, 67.59, 66.20; Mass (m/z) 367 $(M+H)^+$, 368 $(M+2)^+$; Cacld/Anal. [C (52.34) 52.38, H (3.29) 3.33, N (7.63) 7.65].

4.4.1. 2-[(2,4-Dichlorophenoxy)methyl]-5-(4-nitrophenyl)-1,3,4-oxadiazole (5h)

Light yellow solid; mp 220–222 °C; ^{1}H NMR (DMSO d_6, 400 MHz) δ ppm: 5.35 (2H, s, CH_2), 7.10 (1H, d, J = 8.75 Hz, ArH), 7.31 (1H, dd, J = 7.0, 6.7 Hz, ArH), 7.96 (2H, d, J = 8.2 Hz, ArH), 8.09 (1H, s, ArH), 8.25 (2H, d, J = 8.5, ArH); ^{13}C NMR (DMSO d_6, 100 MHz) δ ppm: 169.20, 153.22, 148.37, 142.07, 132.64, 131.40, 128.54, 128.35, 128.27, 124.38, 121.98, 115.79, 67.52; Mass (m/z) 365 $(M+H)^+$, 366 $(M+2)^+$; Calcd/Anal. [C (49.20) 49.18, H (2.48) 2.50, N (11.48) 11.43].

4.5. General method for the synthesis of 3-[(2,4-dichlorophenoxy)methyl]-5-aryl-4H-1,2,4-triazoles (5i,j).

2-(2,4-Dichlorophenoxy)acetohydrazide (**4**) (0.001 mol; 0.235 g) and nitriles (0.001 mol) were refluxed in n-butanol and K_2CO_3 for 2–3 h to obtain the 3-[(2,4-dichlorophenoxy)methyl]-5-aryl-4H-1,2,4-triazoles (**5i,j**).[20]

4.5.1. 3-[(2,4-Dichlorophenoxy)methyl]-5-phenyl-4H-1,2,4-triazole (5i)

Creamy solid; mp 182–184 °C; ^{1}H NMR (DMSO d_6, 400 MHz) δ ppm: 4.55 (1H, s, NH), 4.82 (2H, s, CH_2), 7.01 (1H, d, J =8.3 Hz, ArH), 7.33–7.57 (5H, m, ArH), 7.85 (1H, dd, J = 6.9, 7.0 Hz, ArH), 7.93 (1H, s, ArH); ^{13}C NMR (DMSO d_6, 100 MHz) δ ppm: 157.20, 152.08, 148.37, 131.07, 130.64, 129.31, 128.84, 128.35, 128.27, 127.55, 124.08, 117.79, 71.82; Mass (m/z) 320 $(M+H)^+$, 321 $(M+2)^+$; Calcd/Anal. [C (56.27) 56.23, H (3.46) 3.48, N (13.12) 13.15].

4.5.2. 3-Benzyl-5-[(2,4-dichlorophenoxy)methyl]-4H-1,2,4-triazole (5j)

Creamy solid; mp 172–174 °C; ^{1}H NMR (DMSO d_6, 400 MHz) δ ppm: 3.33 (2H, s, CH_2), 4.14 (1H, s, NH), 4.82 (2H, s, CH_2), 6.80 (1H, d, J = 8.1 Hz, ArH), 7.23 (1H, dd, J = 8.1, 8.0 Hz, ArH), 7.43–7.50 (5H, m, ArH), 7.80 (1H, s, ArH); ^{13}C NMR (DMSO d_6, 100 MHz) δ ppm: 157.25, 152.18, 141.37, 136.37, 131.14, 129.41, 128.81, 128.05, 128.01, 125.85, 124.18, 117.09, 71.82, 36.22; Mass (m/z) 334 $(H)^+$, 335 $(M+2)^+$; Calcd/Anal. [C (57.50) 57.55, H (3.92) 3.89, N (12.57) 12.54].

4.6. Cytotoxicity

The new synthesized compounds were evaluated for their cytotoxicity at 10 μM drug concentrations as per the NCI protocol on nine different panels of 59 human cancer cell lines.[21–24] The human tumor cell lines were

grown in RPMI 1640 medium. The cell lines were inoculated into 96-well microtiter having cell densities 5000–40,000 cells/well and further incubated for 24 h at 37 °C (5% CO_2, 95% air, and 100% relative humidity) prior the addition of test compounds. The microtiter plates were incubated for 48 h after addition of test compounds (solution in DMSO) and finally the assay was terminated by addition of trichloroacetic acid (10%). Sulforhodamine B (SRB) was added and excess SRB was removed washing 5 times with 1% acetic acid, and finally absorbance was recorded on an automated plate reader at a wavelength of 515 nm. Using the seven absorbance measurements [time zero (T_i), control growth (C), and test growth in the presence of drug at the five concentration levels (T_f)], the percentage growth was calculated at each of the drug concentrations levels as $\frac{Tf-Ti}{C-Ti} \times 100$ for concentrations for which $T_f \geq T_i$, and $\frac{Tf-Ti}{Ti} \times 100$ for concentrations for which $T_f < T_i$.

Acknowledgments

The author thankfully acknowledges the National Cancer Institute, USA, and Maharishi Arvind College of Pharmacy, India, for in vitro anticancer data and research facility, respectively.

References

1. Siegel, R. L.; Miller, K. D.; Jemal, A. *CA Cancer J. Clin.* **2017**, *67*, 7-30.
2. Siegel, R. L.; Miller, K. D.; Jemal, A. *CA Cancer J. Clin.* **2018**, *68*, 7-30.
3. Arruebo, M.; Vilaboa, N.; Saez-Gutierrez, B.; Lambea, J.; Tres, A.; Valladares, M.; Gonzalez-Fernandez, A. *Cancers* **2011**, *3*, 3279-3330.
4. Aydemir, N.; Bilaloglu, R. Genotoxicity of two anticancer drugs, gemcitabine and topotecan, in mouse bone marrow in vivo. *Mutat. Res.* **2003**, *537*, 43-51.
5. Bostrom, A.; Hogner, A.; Llinas, A.; Wellner, E.; Plowright, A. T. *J. Med. Chem.* **2012**, *55*, 1817-1830.
6. Ahsan, M. J.; Samy, G. J.; Habibullah, K.; Nomani, M. S.; Saraswat, P.; Gaur, R.; Singh, A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7246-7250.
7. Zhang, K.; Wang, P.; Xuan, L.; Fu, X.; Jing, F.; Li, S,; Liu, Y.; Chen, B. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5154-5156.
8. Khan, M. U.; Akhtar, T.; Al-Masoudi, N. A.; Stoeckli-Evans, H.; Hameed, S. *Med. Chem.* **2012**, *8*, 1190-1197.
9. Jones, R. M.; Leonard, J. N.; Buzard, D. J.; Lehmann, J. *Expert Opin. Ther. Pat.* **2009**, *19*, 1339-1359.
10. Lee, S. H.; Seo, H. J.; Lee, S. H.; Jung, M. E.; Park, J. H.; Park, H. J.; Yoo, J.; Yun, H.; Na, J.; Kang, S. Y.; et al. *Med. Chem.* **2008**, *51*, 7216-7233.
11. Rathore, A.; Sudhakar, R.; Ahsan, M. J.; Ali, A.; Subbarao, N.; Jadav, S. S.; Umar, S.; ShaharYar, M. *Bioorg. Chem.* **2017**, *70*, 107-117.
12. Sangshetti, J. N.; Chabukswar, A. R.; Shinde, B. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 444-448.
13. Patani, G. A.; LaVoie, E. J. *Chem. Rev.* **1996**, *96*, 3147-3176.
14. Warmus, J. S.; Flamme, C.; Zhang, L. Y.; Barrrett, S.; Bridges, A.; Kaufman, M.; Tecle, H.; Gowan, R.; Sebolt-Leopold, J.; Leopold, W.; et al. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6171-6174.
15. McBriar, M. D.; Clader, J. W.; Chu, I.; Del Vecchio, R. A.; Favreau, L.; Greenlee, W. J.; Hyde, L. A.; Nomeir, A. A.; Parker, E. M.; Pissarnitski, D. A.; et al. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 215-219.
16. Ouyang, X.; Chen, X.; Piatnitski, E. L.; Kiselyov, A. S.; He, H. Y.; Mao, Y.; Pattaropong, V.; Yu, Y.; Kim, K. H.; Kincaid, J.; et al. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5154-9.
17. Kaur, R.; Dwivedi, A. R.; Kumar, B.; Kumar, V. *Anticancer Agents Med. Chem.* **2016**, *16*, 465-489.

18. Ahsan, M. J.; Choupra, A.; Sharma, R. K.; Jadav, S. S.; Hassan, M. Z.; Bakht, M. A.; Padmaja, P.; Al-Tamini, A. B. S.; Geesi, M. H. *Anticancer Agents Med. Chem.* **2017**, *18*, 121-138.

19. Ahsan, M. J.; Ansari, M. Y.; Kumar, P.; Soni, M.; Yasmin, S.; Jadav, S. S.; Sahoo, G. C. *Beni-Seuf Univ. J. Basic Appl Sci.* **2016**, *5*, 119-125.

20. Yeung, K. S.; Farkas, M. E.; Kadow, J. F.; Meanwell, N. A. *Tetrahedron Lett.* **2005**, *46*, 3429-3432.

21. Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. *J. Natl. Cancer Inst.* **1990**, *83*, 1107-11012.

22. Boyd, M. R.; Paull, K. D. *Drug Dev. Res.*, **1995**, *34*, 91-109.

23. Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigro-Wolff, A.; et al. *J. Nat. Cancer Inst.* **1991**, *83*, 757-766.

24. Shoemaker, R. H. *Nat. Rev. Cancer* **2006**, *6*, 813-823.

25. Corona, P.; Carta, A.; Loriga, M.; Vitale, G.; Paglietti, G. *Eur. J. Med. Chem.* **2009**, *44*, 1579-1591.

Supplementary material

Cytotoxicity data of 2-[(2,4-dichlorophenoxy)methyl]-5-phenyl-1,3,4-oxadiazole (**5a)**

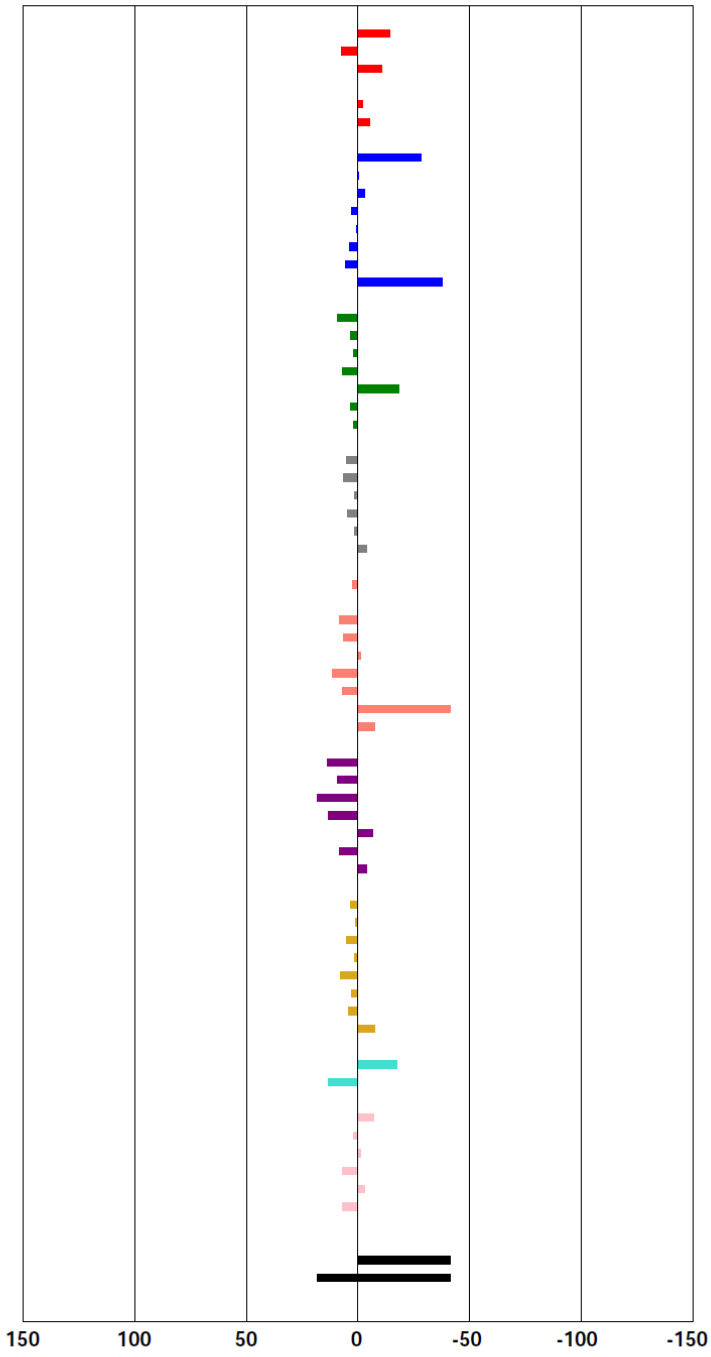
Developmental Therapeutics Program

One Dose Mean Graph

NSC: D-799017 / 1	Conc: 1.00E-5 Molar	Test Date: Jul 10, 2017
Experiment ID: 1707OS32		Report Date: Aug 03, 2017

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	84.25
HL-60(TB)	105.76
K-562	87.55
MOLT-4	98.45
RPMI-8226	96.12
SR	93.03
Non-Small Cell Lung Cancer	
A549/ATCC	70.03
EKVX	98.19
HOP-62	95.31
NCI-H226	101.35
NCI-H23	99.00
NCI-H322M	101.97
NCI-H460	103.89
NCI-H522	60.71
Colon Cancer	
COLO 205	107.54
HCC-2998	101.90
HCT-116	100.22
HCT-15	105.17
HT29	80.15
KM12	101.69
SW-620	100.35
CNS Cancer	
SF-268	103.62
SF-295	105.00
SF-539	100.03
SNB-19	103.01
SNB-75	100.08
U251	94.70
Melanoma	
LOX IMVI	100.84
MALME-3M	98.53
M14	106.50
MDA-MB-435	104.63
SK-MEL-2	97.17
SK-MEL-28	109.75
SK-MEL-5	105.47
UACC-257	56.89
UACC-62	90.88
Ovarian Cancer	
IGROV1	111.91
OVCAR-3	107.59
OVCAR-4	116.71
OVCAR-5	111.72
OVCAR-8	91.91
NCI/ADR-RES	106.44
SK-OV-3	94.49
Renal Cancer	
786-0	101.64
A498	99.62
ACHN	103.35
CAKI-1	99.84
RXF 393	106.08
SN12C	101.40
TK-10	102.60
UO-31	90.83
Prostate Cancer	
PC-3	80.90
DU-145	111.64
Breast Cancer	
MCF7	91.42
MDA-MB-231/ATCC	100.44
HS 578T	97.04
BT-549	105.12
T-47D	95.40
MDA-MB-468	105.17
Mean	98.36
Delta	41.47
Range	59.82

Mean Growth Percent - Growth Percent



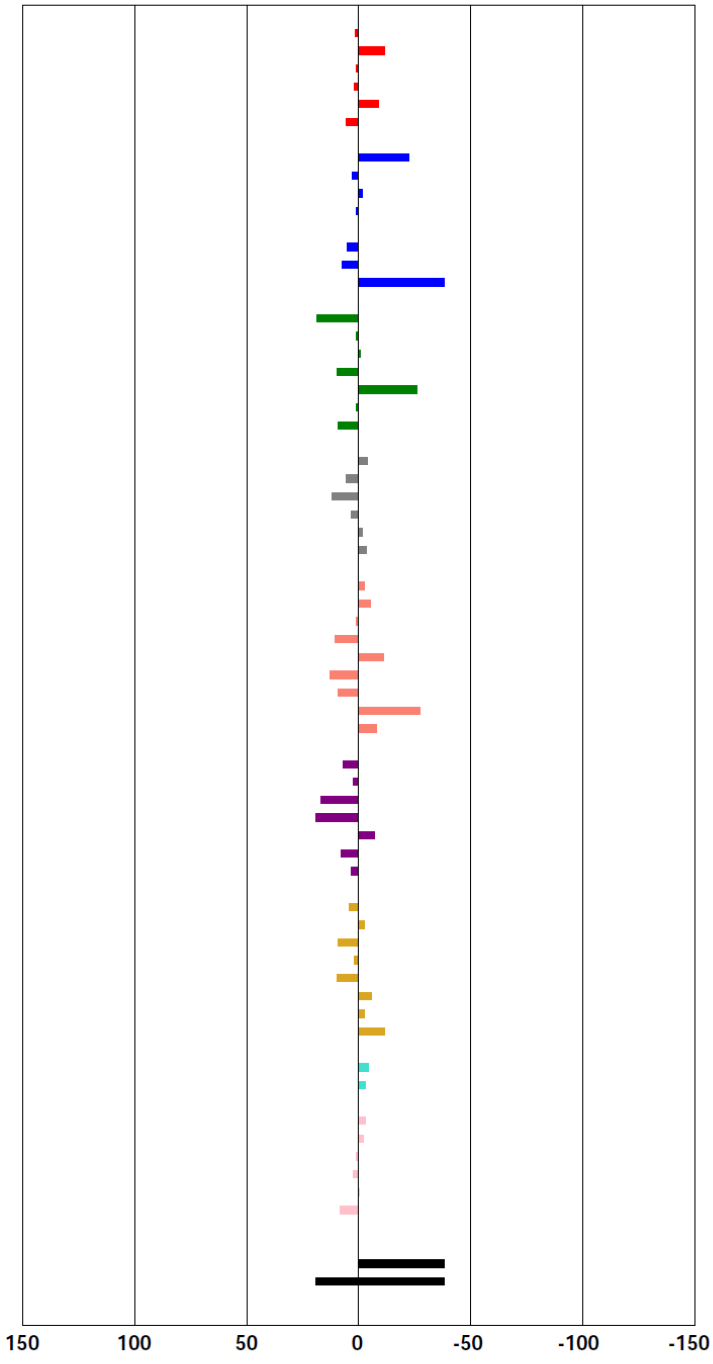
Cytotoxicity data of 2-[(2,4-dichlorophenoxy)methyl]-5-phenyl-1,3,4-oxadiazole (**5a)**

Developmental Therapeutics Program

One Dose Mean Graph

NSC: D-799016 / 1	Conc: 1.00E-5 Molar	Test Date: Jul 10, 2017
Experiment ID: 1707OS32		Report Date: Aug 03, 2017

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	100.35
HL-60(TB)	87.29
K-562	100.04
MOLT-4	100.69
RPMI-8226	90.09
SR	104.38
Non-Small Cell Lung Cancer	
A549/ATCC	76.56
EKVX	101.57
HOP-62	97.13
NCI-H226	99.65
NCI-H23	99.15
NCI-H322M	103.85
NCI-H460	106.31
NCI-H522	60.72
Colon Cancer	
COLO 205	117.41
HCC-2998	99.85
HCT-116	97.87
HCT-15	108.59
HT29	72.64
KM12	99.95
SW-620	107.85
CNS Cancer	
SF-268	95.00
SF-295	104.20
SF-539	110.67
SNB-19	101.95
SNB-75	97.18
U251	95.47
Melanoma	
LOX IMVI	96.04
MALME-3M	93.77
M14	99.76
MDA-MB-435	109.53
SK-MEL-2	87.50
SK-MEL-28	111.49
SK-MEL-5	108.07
UACC-257	71.42
UACC-62	90.95
Ovarian Cancer	
IGROV1	105.67
OVCAR-3	101.09
OVCAR-4	115.50
OVCAR-5	117.88
OVCAR-8	91.89
NCI/ADR-RES	106.54
SK-OV-3	101.93
Renal Cancer	
786-0	103.24
A498	96.37
ACHN	108.01
CAKI-1	100.55
RXF 393	108.38
SN12C	93.26
TK-10	96.45
UO-31	87.42
Prostate Cancer	
PC-3	94.25
DU-145	95.77
Breast Cancer	
MCF7	95.91
MDA-MB-231/ATCC	96.56
HS 578T	99.92
BT-549	101.26
T-47D	98.29
MDA-MB-468	106.97
Mean	98.78
Delta	38.06
Range	57.16



Cytotoxicity data of 2-{5-[(2,4-dichlorophenoxy)methyl]-1,3,4-oxadiazol-2-yl}phenol (**5e**)

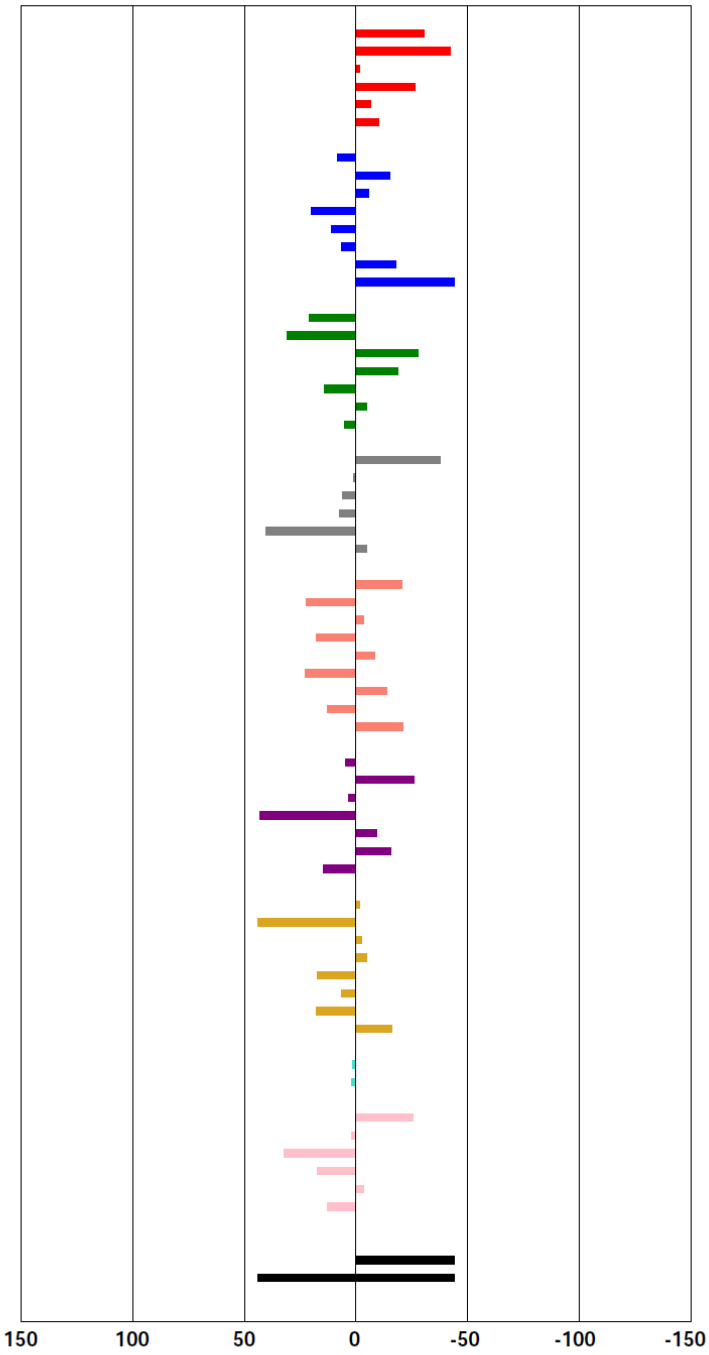
Developmental Therapeutics Program

One Dose Mean Graph

NSC: D-799014 / 1	Conc: 1.00E-5 Molar	Test Date: Jul 10, 2017
Experiment ID: 1707OS32		Report Date: Aug 03, 2017

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	15.45
HL-60(TB)	3.89
K-562	44.49
MOLT-4	19.54
RPMI-8226	39.43
SR	36.04
Non-Small Cell Lung Cancer	
A549/ATCC	54.51
EKVX	31.12
HOP-62	40.63
NCI-H226	66.22
NCI-H23	57.00
NCI-H322M	52.64
NCI-H460	28.34
NCI-H522	1.97
Colon Cancer	
COLO 205	67.03
HCC-2998	76.76
HCT-116	18.16
HCT-15	27.36
HT29	60.28
KM12	41.54
SW-620	51.21
CNS Cancer	
SF-268	8.59
SF-295	47.41
SF-539	52.07
SNB-19	53.52
SNB-75	86.64
U251	41.46
Melanoma	
LOX IMVI	25.53
MALME-3M	68.33
M14	42.49
MDA-MB-435	63.86
SK-MEL-2	37.87
SK-MEL-28	68.89
SK-MEL-5	32.35
UACC-257	58.89
UACC-62	25.13
Ovarian Cancer	
IGROV1	50.66
OVCAR-3	20.16
OVCAR-4	49.26
OVCAR-5	89.06
OVCAR-8	36.76
NCI/ADR-RES	30.59
SK-OV-3	60.66
Renal Cancer	
786-0	44.69
A498	89.91
ACHN	43.50
CAKI-1	41.51
RXF 393	63.45
SN12C	52.59
TK-10	63.66
UO-31	30.25
Prostate Cancer	
PC-3	47.83
DU-145	48.13
Breast Cancer	
MCF7	20.59
MDA-MB-231/ATCC	48.18
HS 578T	78.20
BT-549	63.28
T-47D	42.58
MDA-MB-468	58.73
Mean	46.12
Delta	44.15
Range	87.94

Mean Growth Percent - Growth Percent



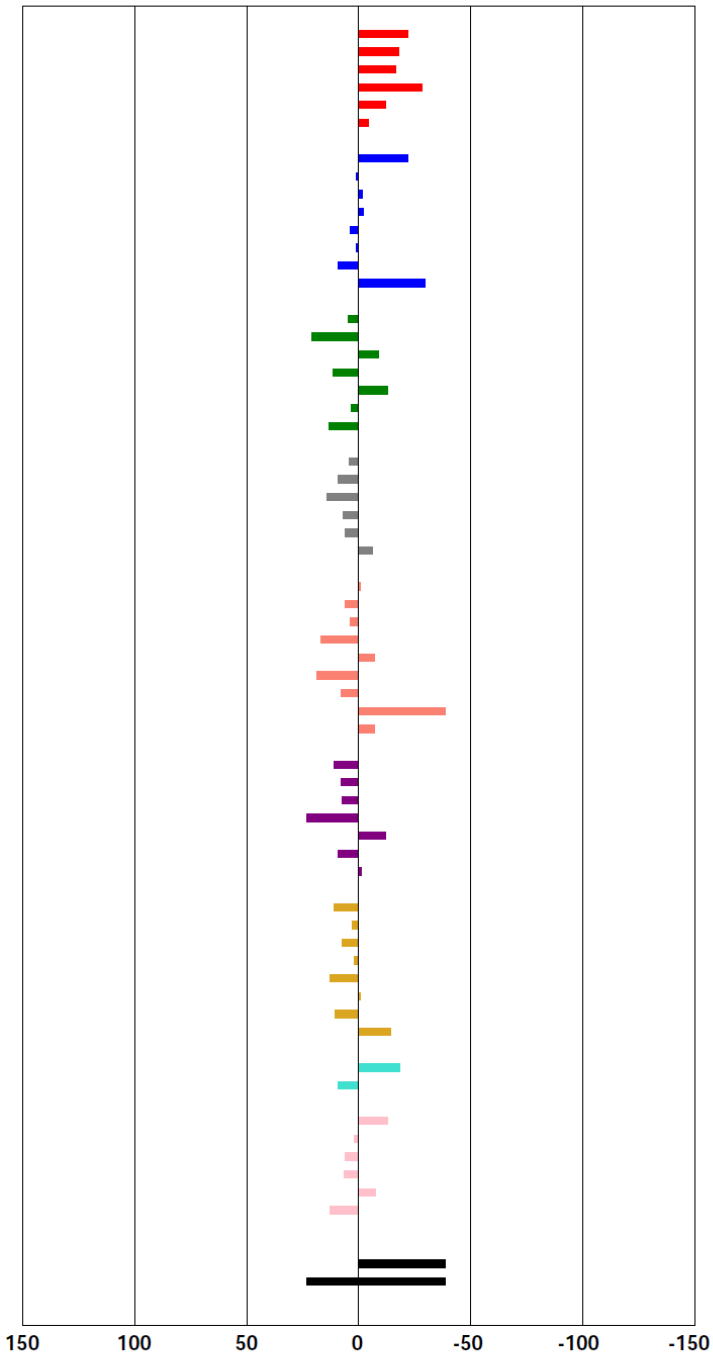
Cytotoxicity data of 2-[(2,4-dichlorophenoxy)methyl]-5-(2-chlorophenyl)-1,3,4-oxadiazole (**5f**)

Developmental Therapeutics Program
One Dose Mean Graph

NSC: D-799012 / 1	Conc: 1.00E-5 Molar	Test Date: Jul 10, 2017
Experiment ID: 1707OS32		Report Date: Aug 03, 2017

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	71.41
HL-60(TB)	75.28
K-562	76.62
MOLT-4	65.29
RPMI-8226	81.41
SR	89.18
Non-Small Cell Lung Cancer	
A549/ATCC	71.55
EKVX	94.32
HOP-62	91.86
NCI-H226	91.19
NCI-H23	97.23
NCI-H322M	94.53
NCI-H460	102.31
NCI-H522	63.86
Colon Cancer	
COLO 205	97.88
HCC-2998	114.07
HCT-116	84.52
HCT-15	104.60
HT29	80.60
KM12	96.53
SW-620	106.64
CNS Cancer	
SF-268	97.53
SF-295	102.40
SF-539	107.49
SNB-19	100.21
SNB-75	99.33
U251	87.07
Melanoma	
LOX IMVI	92.79
MALME-3M	99.48
M14	96.99
MDA-MB-435	110.34
SK-MEL-2	86.16
SK-MEL-28	112.15
SK-MEL-5	101.17
UACC-257	54.95
UACC-62	86.13
Ovarian Cancer	
IGROV1	104.46
OVCAR-3	101.00
OVCAR-4	100.79
OVCAR-5	116.65
OVCAR-8	81.39
NCI/ADR-RES	102.33
SK-OV-3	92.32
Renal Cancer	
786-0	104.53
A498	96.13
ACHN	100.94
CAKI-1	95.11
RXF 393	105.94
SN12C	92.53
TK-10	103.89
UO-31	79.08
Prostate Cancer	
PC-3	74.93
DU-145	102.52
Breast Cancer	
MCF7	80.26
MDA-MB-231/ATCC	95.38
HS 578T	99.21
BT-549	100.03
T-47D	86.04
MDA-MB-468	105.99
Mean	93.33
Delta	38.38
Range	61.70

Mean Growth Percent - Growth Percent

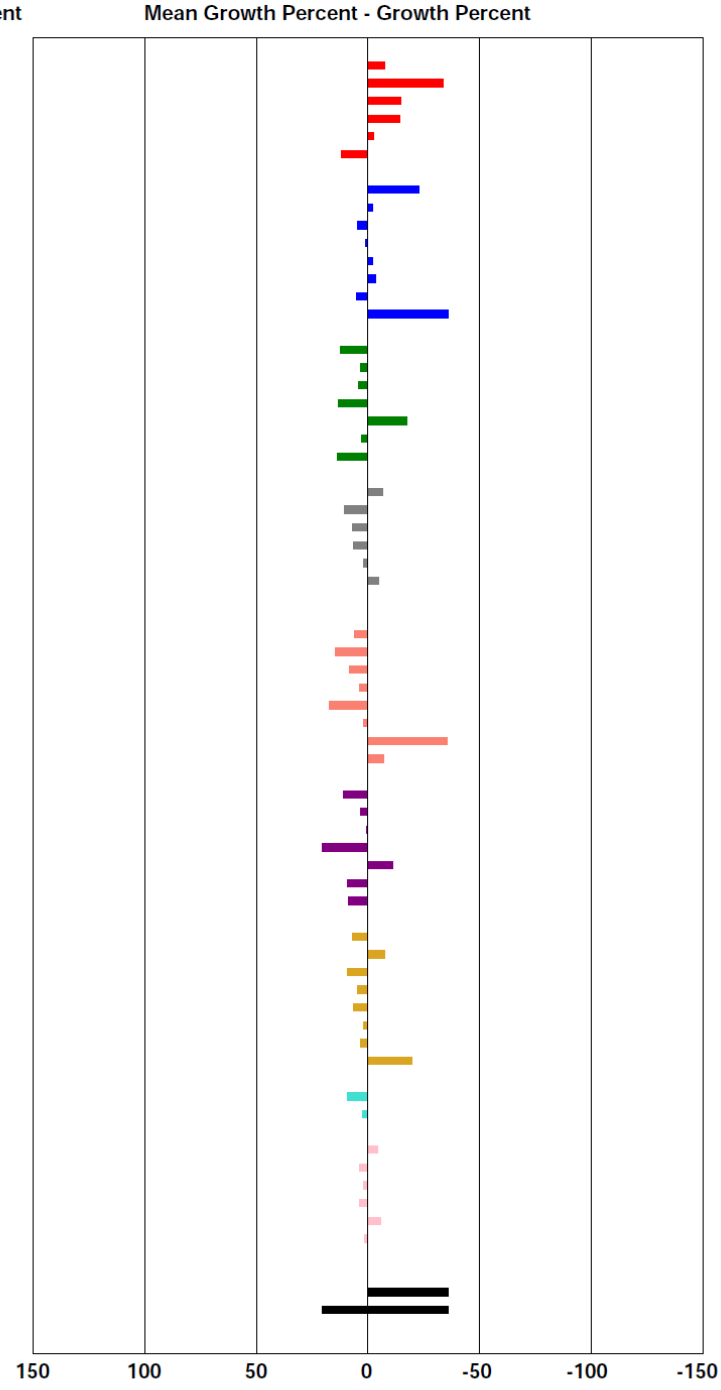


Cytotoxicity data of 4-{5-[(2,4-dichlorophenoxy)methyl]-1,3,4-oxadiazol-2-yl}-2-methoxyphenol (**5g**)

Developmental Therapeutics Program
One Dose Mean Graph

NSC: D-799015 / 1	Conc: 1.00E-5 Molar	Test Date: Jul 10, 2017
Experiment ID: 1707OS32		Report Date: Aug 03, 2017

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	87.27
HL-60(TB)	61.28
K-562	80.09
MOLT-4	80.54
RPMI-8226	92.47
SR	106.74
Non-Small Cell Lung Cancer	
A549/ATCC	71.95
EKVX	93.03
HOP-62	99.50
NCI-H226	95.94
NCI-H23	93.01
NCI-H322M	91.49
NCI-H460	100.13
NCI-H522	59.17
Colon Cancer	
COLO 205	107.25
HCC-2998	98.25
HCT-116	99.19
HCT-15	108.04
HT29	77.34
KM12	97.83
SW-620	108.90
CNS Cancer	
SF-268	88.60
SF-295	105.32
SF-539	101.82
SNB-19	101.40
SNB-75	97.05
U251	90.18
Melanoma	
LOX IMVI	95.22
MALME-3M	101.06
M14	109.37
MDA-MB-435	103.26
SK-MEL-2	98.59
SK-MEL-28	112.09
SK-MEL-5	97.09
UACC-257	59.42
UACC-62	87.80
Ovarian Cancer	
IGROV1	106.10
OVCAR-3	98.17
OVCAR-4	95.82
OVCAR-5	115.61
OVCAR-8	84.08
NCI/ADR-RES	104.15
SK-OV-3	103.54
Renal Cancer	
786-0	102.07
A498	87.52
ACHN	104.17
CAKI-1	99.79
RXF 393	101.67
SN12C	97.00
TK-10	98.49
UO-31	75.10
Prostate Cancer	
PC-3	104.00
DU-145	97.58
Breast Cancer	
MCF7	90.59
MDA-MB-231/ATCC	98.71
HS 578T	96.77
BT-549	98.57
T-47D	89.42
MDA-MB-468	96.50
Mean	94.97
Delta	35.80
Range	56.44

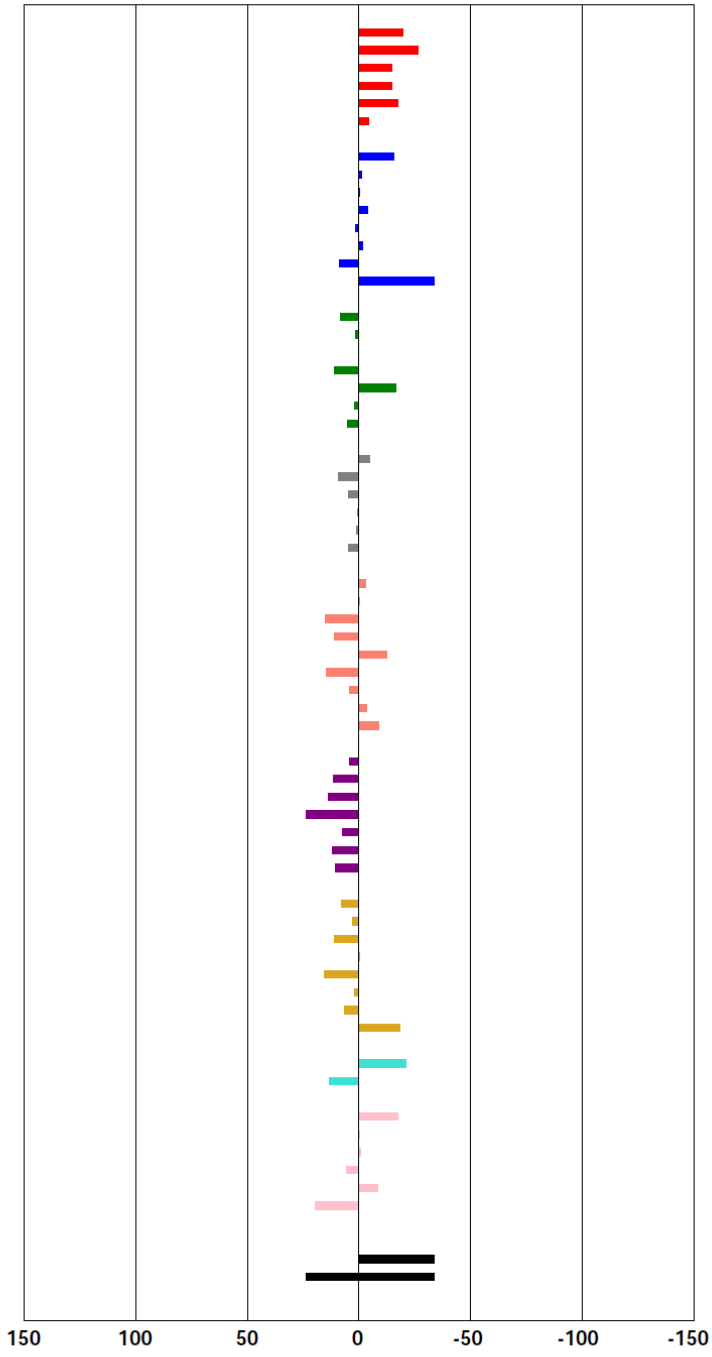


Cytotoxicity data of 2-[(2,4-dichlorophenoxy)methyl]-5-(4-nitrophenyl)-1,3,4-oxadiazole (**5h**)

Developmental Therapeutics Program
One Dose Mean Graph

NSC: D-799013 / 1	Conc: 1.00E-5 Molar	Test Date: Jul 10, 2017
Experiment ID: 1707OS32		Report Date: Aug 03, 2017

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	77.09
HL-60(TB)	70.44
K-562	81.93
MOLT-4	81.85
RPMI-8226	79.19
SR	92.22
Non-Small Cell Lung Cancer	
A549/ATCC	81.34
EKVX	95.42
HOP-62	96.45
NCI-H226	92.77
NCI-H23	98.44
NCI-H322M	95.14
NCI-H460	105.44
NCI-H522	63.11
Colon Cancer	
COLO 205	104.82
HCC-2998	98.27
HCT-116	96.91
HCT-15	107.53
HT29	80.22
KM12	98.71
SW-620	102.05
CNS Cancer	
SF-268	91.79
SF-295	105.79
SF-539	101.38
SNB-19	97.37
SNB-75	97.80
U251	101.48
Melanoma	
LOX IMVI	93.90
MALME-3M	96.64
M14	111.68
MDA-MB-435	107.72
SK-MEL-2	84.34
SK-MEL-28	111.27
SK-MEL-5	100.78
UACC-257	93.18
UACC-62	87.83
Ovarian Cancer	
IGROV1	100.75
OVCAR-3	108.18
OVCAR-4	110.60
OVCAR-5	120.45
OVCAR-8	104.22
NCI/ADR-RES	108.85
SK-OV-3	107.12
Renal Cancer	
786-0	104.52
A498	99.47
ACHN	107.63
CAKI-1	96.33
RXF 393	112.28
SN12C	98.55
TK-10	103.19
UO-31	78.27
Prostate Cancer	
PC-3	75.54
DU-145	109.84
Breast Cancer	
MCF7	79.30
MDA-MB-231/ATCC	96.35
HS 578T	96.03
BT-549	102.40
T-47D	88.53
MDA-MB-468	116.47
Mean	96.73
Delta	33.62
Range	57.34



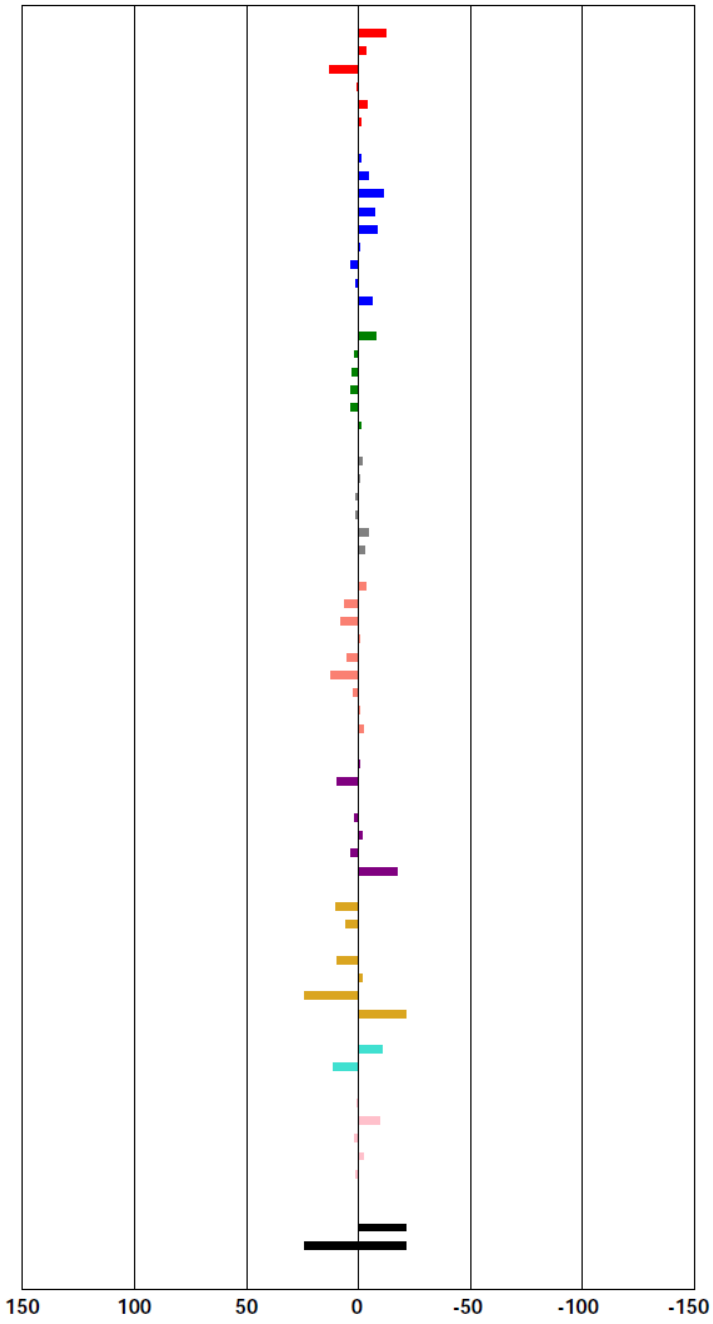
Cytotoxicity data of 3-[(2,4-dichlorophenoxy)methyl]-5-phenyl-4H-1,2,4-triazole (**5i**)

Developmental Therapeutics Program
One Dose Mean Graph

NSC: D-793125 / 1	Conc: 1.00E-5 Molar	Test Date: Sep 12, 2016
Experiment ID: 1609OS82		Report Date: Sep 29, 2016

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	85.89
HL-60(TB)	94.91
K-562	110.80
MOLT-4	98.69
RPMI-8226	94.00
SR	97.07
Non-Small Cell Lung Cancer	
A549/ATCC	97.12
EKVX	93.79
HOP-62	86.76
HOP-92	90.84
NCI-H226	89.94
NCI-H23	97.65
NCI-H322M	101.37
NCI-H460	99.29
NCI-H522	92.05
Colon Cancer	
COLO 205	90.52
HCC-2998	99.78
HCT-15	100.77
HT29	101.22
KM12	101.48
SW-620	97.00
CNS Cancer	
SF-268	96.61
SF-295	97.77
SF-539	99.42
SNB-19	99.26
SNB-75	93.57
U251	95.51
Melanoma	
LOX IMVI	94.59
MALME-3M	104.07
M14	105.80
MDA-MB-435	97.67
SK-MEL-2	103.33
SK-MEL-28	110.17
SK-MEL-5	100.35
UACC-257	97.83
UACC-62	95.64
Ovarian Cancer	
IGROV1	97.56
OVCAR-3	107.89
OVCAR-4	98.14
OVCAR-5	99.65
OVCAR-8	96.51
NCI/ADR-RES	101.39
SK-OV-3	80.91
Renal Cancer	
786-0	108.05
A498	103.96
ACHN	98.01
RXF 393	107.74
SN12C	96.56
TK-10	121.90
UO-31	77.11
Prostate Cancer	
PC-3	87.34
DU-145	109.18
Breast Cancer	
MDA-MB-231/ATCC	98.78
HS 578T	88.64
BT-549	99.95
T-47D	95.63
MDA-MB-468	99.08
Mean	98.01
Delta	20.90
Range	44.79

Mean Growth Percent - Growth Percent



Cytotoxicity data of 3-benzyl-5-[(2,4-dichlorophenoxy)methyl]-4H-1,2,4-triazole (**5j**)

Developmental Therapeutics Program

One Dose Mean Graph

NSC: D-794025 / 1	Conc: 1.00E-5 Molar	Test Date: Nov 28, 2016
Experiment ID: 1611OS18		Report Date: Dec 16, 2016

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	100.78
HL-60(TB)	82.56
K-562	91.04
MOLT-4	83.27
RPMI-8226	98.27
SR	92.19
Non-Small Cell Lung Cancer	
A549/ATCC	100.05
EKVX	94.93
HOP-62	94.87
HOP-92	88.64
NCI-H226	103.90
NCI-H23	93.74
NCI-H322M	90.42
NCI-H460	106.65
NCI-H522	94.34
Colon Cancer	
COLO 205	109.96
HCC-2998	101.89
HCT-116	104.17
HCT-15	104.86
HT29	105.99
KM12	97.62
SW-620	101.54
CNS Cancer	
SF-268	92.77
SF-295	98.06
SF-539	95.57
SNB-19	93.14
SNB-75	86.37
U251	100.02
Melanoma	
LOX IMVI	94.30
MALME-3M	95.99
M14	96.71
MDA-MB-435	101.40
SK-MEL-2	90.81
SK-MEL-28	97.25
SK-MEL-5	104.36
UACC-257	99.53
Ovarian Cancer	
IGROV1	88.82
OVCAR-3	102.51
OVCAR-4	96.04
OVCAR-5	88.63
OVCAR-8	100.65
NCI/ADR-RES	100.74
SK-OV-3	92.10
Renal Cancer	
786-0	92.83
A498	103.92
ACHN	93.87
RXF 393	112.18
SN12C	103.98
TK-10	111.41
UO-31	76.57
Prostate Cancer	
PC-3	87.22
DU-145	105.99
Breast Cancer	
MCF7	104.66
MDA-MB-231/ATCC	91.99
HS 578T	101.32
BT-549	93.24
T-47D	86.79
MDA-MB-468	110.80
Mean	97.14
Delta	20.57
Range	35.61