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Discovery of 3-aryl-5-aryl-1,2,4-oxadiazoles as a new series of apoptosis inducers. 2. Identification of more aqueous soluble analogs as potential anticancer agents

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ABSTRACT

As a continuation of our efforts to discover and develop the 3-aryl-5-aryl-1,2,4-oxadiazole series of apoptosis inducers as potential anticancer agents, we explored substitutions at the 2- and 3-positions of the 3-aryl group to improve the aqueous solubility properties and identify development candidates. A small substitution such as methyl or hydroxymethyl at the 2-position was well tolerated. This modification, in combination with a 3-substituted furan ring as the 5-aryl group, resulted in **4g** and **4h,** which have improved solubility properties. Compound **4g** was found to have good in vivo efficacy in animal studies via intravenous administration.

Currently, cancer is the second leading cause of death in the United States and in developed countries.[1] Tremendous progress has been made in the war against cancer with the development of many novel chemotherapy agents,[2] including paclitaxel, docetaxel[3] and ixabepilone,[4] as well as small molecule targeted therapies[5] such as imatinib[6] and sorafenib.[7] However, due to toxicity and drug-resistance problems with many currently available treatments, it remains a great challenge to discover and develop more effective drugs to conquer cancer.[1]

Since it is known that the anti-tumor efficacy of many chemotherapeutic agents are correlated with their ability to induce apoptosis,[8] novel approaches to promote apoptosis in cancer cells via targeting regulators of apoptosis[9] could lead to the development of new anticancer treatments.[10] In addition, these new agents may overcome tumor resistance to conventional anti-cancer drugs.[11] We therefore have developed a cell-based, high throughput screening technology using our novel caspase-3 substrates,[12] termed Apoptosis Screening and AntiCancer Platform (ASAP), for the identification of apoptosis inducers as potential new anticancer agents. Since the screening technology measures the activation of downstream caspase-3 in the cells, our assay can discover apoptosis inducers that interact with either known or novel targets upstream of caspase-3.

Applying this HTS assay, we have reported the discovery and structure–activity relationship (SAR) studies of several novel series of apoptosis inducers interacting with known or novel molecular targets (Chart 1).[13] These include *N*-phenyl nicotinamides (**1a**),[14] 4-aryl-4*H*-chromenes (**1b**),[15] gambogic acid (**1c**),[16] 4-anilino-2-(2-pyridyl)pyrimidines (**1d**),[17] *N*-methyl-*N*-phenylnaphthalen-1-amines (**1e**),[18] 4-anilinoquinazolines (**1f**),[19] *N*-phenyl-1*H*-pyrazolo[3,4-*b*]quinolin-4-amines (**1g**),[20] 1-benzoyl-3-cyanopyrrolo[1,2-*a*]quinolines (**1h**),[21] and *N*-aryl-9-oxo-9*H*-fluorene-1-carboxamides (**1i**).[22] We also have reported the discovery of 3-(4-chlorophenyl)-5-(3-chlorothiophen-2-yl)-1,2,4-oxadiazole (**1j**) as a novel apoptosis inducer with tumor selective properties,[23] and the identification of TIP47, an insulin-like growth factor II (IGF II) receptor binding protein, as its molecular target.[24] SAR study of 3-aryl-5-aryl-1,2,4-oxadiazoles indicated that a 3-substituted thiophen-2-yl or a furan-2-yl in the 5-position of 1,2,4-oxadiazole is essential for the apoptosis inducing activity. In the 3-position of the 1,2,4-oxadiazole, a substituted phenyl or pyridyl is important for activity.[23] Due to the three aryl ring structure of 3-aryl-5-aryl-1,2,4-oxadiazoles, these molecules are relatively planar, resulting in low aqueous solubility and our initial in vivo studies were done by ip administration.[24] Herein we wish to report additional SAR studies to improve the aqueous solubility properties of 3-aryl-5-aryl-1,2,4-oxadiazoles and identify potential clinical development candidates.

3-Aryl-5-aryl-1,2,4-oxadiazoles **4a–4b**, **4e** and **4g–4h** were prepared in two steps according to reported procedures (Scheme 1).[23]

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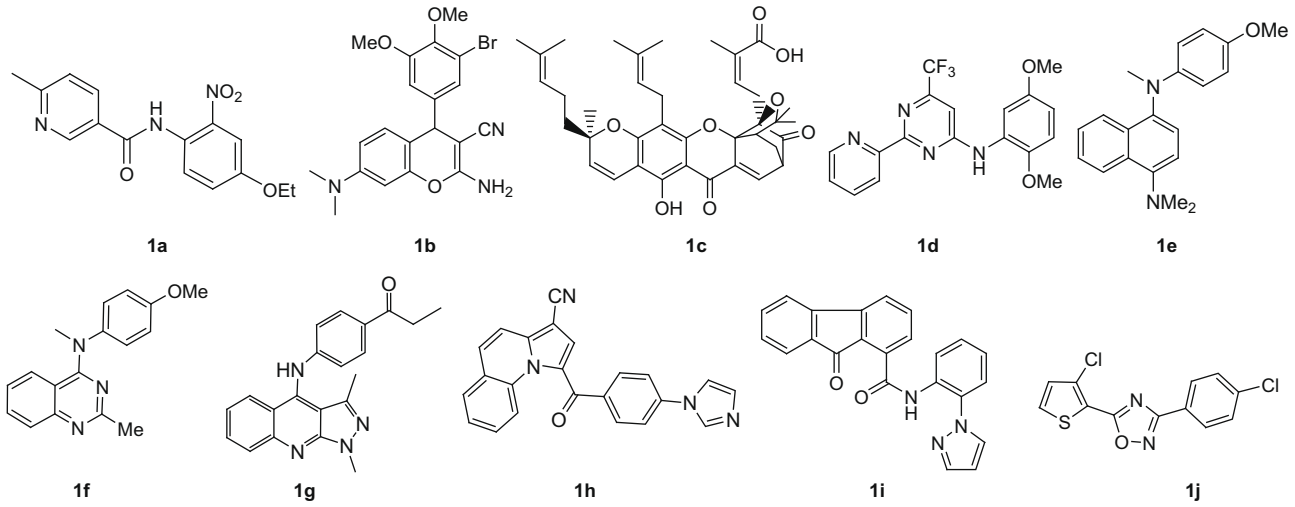
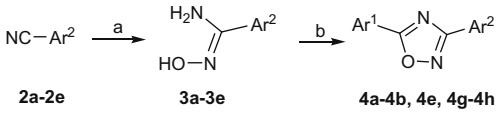
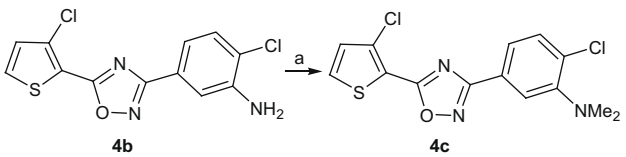


Chart 1.

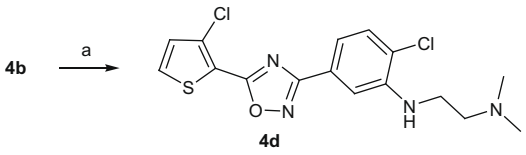


Scheme 1. Reagents: (a) $H_2NOH/EtOH/THF$; (b) Ar^1COCl/dioxane/pyridine.

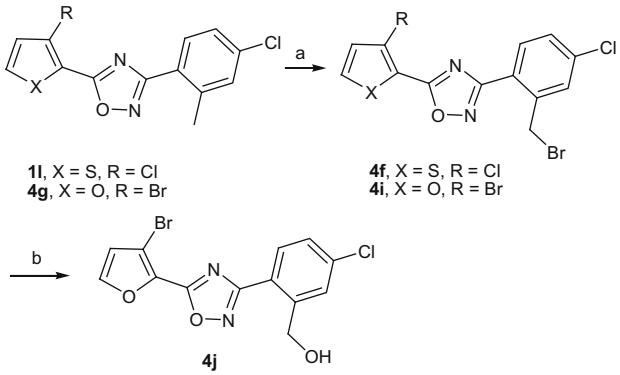
Reaction of substituted arylnitriles **2a–2e** with hydroxylamine in ethanol and THF[25] produced *N*-hydroxy-arylamidines **3a–3e**, which reacted with substituted aryl-2-carbonyl chloride in a one-pot reaction to produce the 3-aryl-5-aryl-1,2,4-oxadiazoles.[26] Dimethylamino analog **4c** was prepared from methylation of the amino compound **4b** (Scheme 2). The dimethylaminoethylamino analog **4d** was synthesized from alkylation of **4b** (Scheme 3). The bromomethyl analogs **4f** and **4i** were prepared from bromination of **1l** and **4g**, respectively. Reaction of **4i** with sodium hydroxide in water/dioxane produced the hydroxymethyl analog **4j** (Scheme 4). The phosphate prodrug was synthesized using procedures similar to what was reported for the preparation of combretastatin A-4 phosphate prodrug and other prodrugs.[27,28] Reaction of the bromomethyl analog **4i** with di-*tert*-butylphosphate in CH_3CN with cesium fluoride produced the phosphate ester **4k**, which was treated with HCl in dioxane to produce the acid **4l**. The disodium salt **4m** was synthesized by reaction of the acid **4l** with sodium methoxide in methanol (Scheme 5).



Scheme 2. Reagents: (a) $HCHO/NaBH_4/THF/H_2SO_4$.



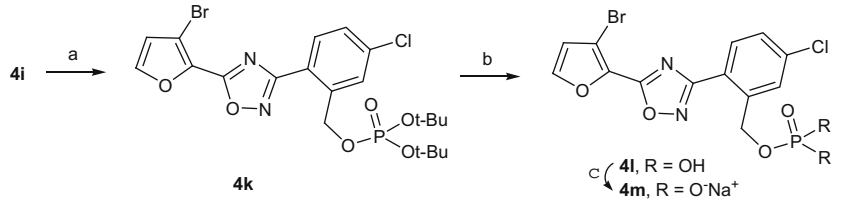
Scheme 3. Reagents: (a) $BrCH_2CH_2NMe_2{\cdot}HBr/NEt_3/EtOH$.



Scheme 4. Reagents: (a) NBS/AIBN/$Br_2/CCl_4/h\nu$; (b) $NaOH/H_2O$/dioxane.

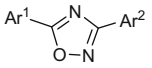
The apoptosis inducing activity of these 3-aryl-5-aryl-1,2,4-oxadiazoles was measured by our cell- and caspase-based HTS assay[14] against three cell lines, T47D breast cancer cells, DLD-1 colon cancer cells, and H-1299 non-small cell lung cancer cells, and the results are summarized in Table 1. It was previously reported that the 3,4-dichlorophenyl analog **1k** maintained the activity of the 4-substituted analog **1j**.[23] We therefore explored introduction of other groups at the 3-position. Encouragingly, the 3-methyl analog **4a** was found to have activity similar to that of **1k,** while introduction of an amino (**4b**) or dimethylamino (**4c**) group at the 3-position only lowered slightly the activity. Introduction of a dimethylaminoethylamino group (**4d**) in an effort to increase aqueous solubility resulted in an inactive compound up to 10 μM, indicating that a large group is not tolerated at the 3-position.

As an alternate approach for increasing solubility, we reasoned that a substitution at the 2-position would force the phenyl ring out of the plane of the 1,2,4-oxadiazole ring and might improve solubility properties. Based on ChemDraw3D models after energy minimizations, the phenyl group was found to lie out of the plane of the 1,2,4-oxadiazole ring by about 30° for compound **1j**, but increased to about 40° for the 2-methyl analog **1l** and about 50° for the 2-bromomethyl analog **4f** (Fig. 1), suggesting that a substitution in the 2-position of the phenyl does make the molecule less planar. The 2-methyl analog **1l** was equipotent to **1j**[23] while the 2-amino (**4e**) and 2-bromomethyl (**4f**) analogs were found to be 3–4-fold less active.



Scheme 5. Reagents: (a) CsF/KOP(O)–(O*t*-Bu)$_2$/CH_3CN; (b) 4.0 M HCl/dioxane; (c) NaOMe/MeOH.

Table 1
Activity of 3-aryl-5-aryl-1,2,4-oxadiazoles in the caspase activation assay



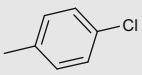
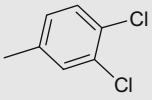
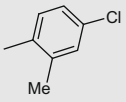
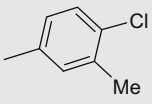
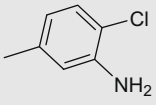
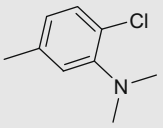
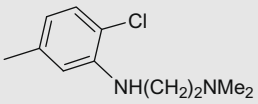
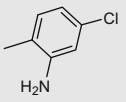
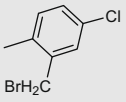
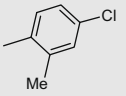
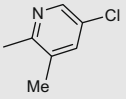
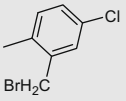
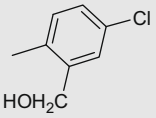
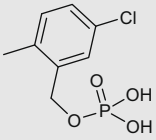
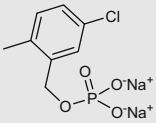
Compound #	Ar^1	Ar^2	EC_{50} (μM)[a]		
			T47D	DLD1	H1299
1j[b]			1.2 ± 0.1	0.44 ± 0.06	>10
1k[b]			1.4 ± 0.2	0.37 ± 0.05	>10
1l[b]			0.91 ± 0.09	0.38 ± 0.06	>10
4a			1.7 ± 0.1	0.59 ± 0.01	>10
4b			2.4 ± 1.1	0.58 ± 0.10	>10
4c			2.1 ± 0.4	0.54 ± 0.16	>10
4d			>10	>10	>10
4e			3.1 ± 0.3	1.1 ± 0.1	>10
4f			4.5 ± 0.1	1.1 ± 0.04	8.6 ± 0.7

Table 1 (*continued*)

Compound #	Ar^1	Ar^2	EC_{50} (μM)[a]		
			T47D	DLD1	H1299
4g			1.1 ± 0.1	0.71 ± 0.11	>10
4h			0.94 ± 0.06	1.2 ± 0.1	>10
4i			2.2 ± 0.2	ND[c]	2.3 ± 1.5
4j			2.9 ± 0.5	ND[c]	>10
4l			>10	ND[c]	>10
4m			>10	ND[c]	>10
Vinblastine	NA[d]	NA	0.032 ± 0.006	0.16 ± 0.04	0.082 ± 0.016
Colchicine	NA	NA	0.014 ± 0.003	0.18 ± 0.04	0.05 ± 0.01
Taxol	NA	NA	0.037 ± 0.003	0.054 ± 0.007	0.098 ± 0.015

[a] Cells were treated with the test compounds for 48 h, data are the mean of three or more experiments and are reported as mean ± standard error of the mean (SEM).
[b] Data from Ref. 23.
[c] ND, not determined.
[d] NA, not applied.

To further improve the solubility properties, we replaced the thiophene ring in **1l** with a less hydrophobic furan ring. Compound **4g** has a *C* log *P* value of 4.56 compared to 4.98 for **1l** and was found to have activity similar to that of **1l**. The 2-pyridyl analog **4h** retained the activity of **4g** while decreasing the *C* log *P* value to 3.40. Several compounds were tested in a variety of solvents and mixtures of solvents to determine the maximal solubility. Compound **4g** was found to be soluble in a solution (DMSO/ethanol/Cremophor EL/D5W = 11.5:2.25:11.25:75) at 4.8 mg/mL, while compound **4h** was soluble in a solution (ethanol/Cremophor EL/D5W = 6.0:11.3:82.7) at 3.8 mg/mL. Both solutions are suitable for intravenous (iv) administration in animal studies. The bromomethyl analog **4i** and hydroxymethyl analog **4j** were about 2–3-fold less active than **4g**. Compound **4j** (*C* log *P* = 3.02) also had good solubility in a solution (ethanol/Cremophor EL/D5W = 4.0:10.0:86.0) at 4.0 mg/mL. The disodium salt phosphate prodrug **4m** was found to have good aqueous solubility (10 mg/mL in D5W), similar to what has been reported for the combretastatin A-4 phosphate prodrug.[27] However, the phosphate prodrugs **4l** and **4m** were found to be inactive in the caspase activation assay up to 10 μM, suggesting that the conversion of **4l** and **4m** to the active drug **4j** might be slow under the assay conditions.

The activities of these 3-aryl-5-aryl-1,2,4-oxadiazoles against the human colorectal cancer cell line DLD-1 roughly paralleled the activity towards T47D cells. Similar to compound **1j**, all the 3-aryl-5-aryl-1,2,4-oxadiazoles tested were either inactive, or much less active against non-small cell lung cancer cell line H1299, indicating that modifications at the 2 and 3-positions of the phenyl group did not change the selectivity profile of these compounds. In comparison, vinblastine, colchicine and taxol, three known cytotoxic compounds, had similar EC_{50} values in the caspase activation assay in all the three cell lines.

Selected compounds as well as control compounds were tested by the traditional inhibition of cell proliferation (GI_{50}) assay to confirm that the active compounds can inhibit tumor cell growth, as well as to confirm the tumor selectivity as observed from the caspase assay. The growth inhibition assays in T47D and H1299 cells were run in a 96-well microtiter plate as described previously[14] and the data are summarized in Table 2. Compound **4g** had activity similar to **1j** as an inhibitor of T47D cancer cell growth, and was not active in H1299 cells up to 10 μM. This is comparable to what was observed in the caspase activation assay, confirming that compound **4g** is selective against certain tumor types. Compounds **4h** and **4j** also had good activity against T47D cells and were inactive in H1299 cells. In comparison colchicine and taxol had similar GI_{50} values in both cell lines tested.

Compound **4g** was selected for in vivo tumor efficacy testing. The MX-1 human breast cancer xenograft in vivo experiment

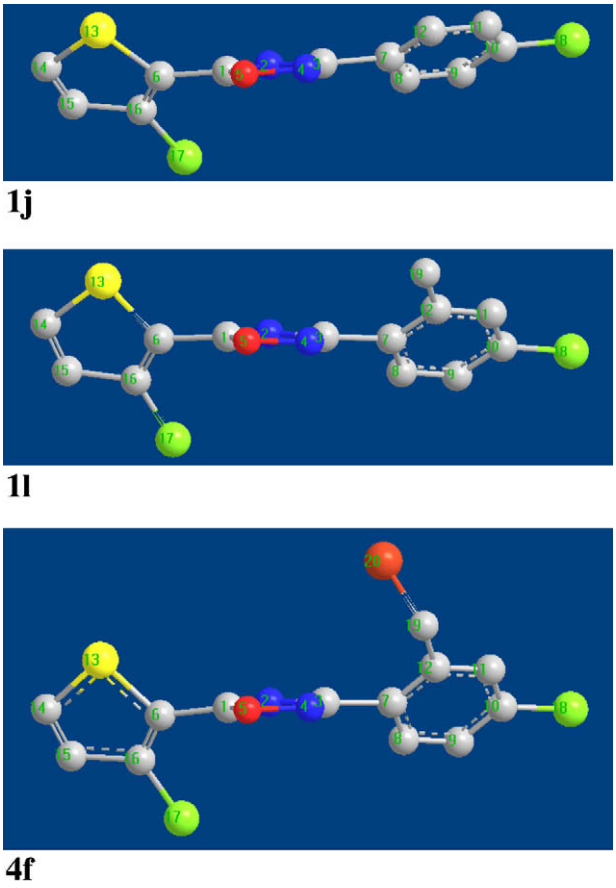


Figure 1. ChemDraw3D models of compounds **1j**, **1l** and **4f** after MM2 energy minimizations.

Table 2
Cell growth inhibition of 3-aryl-5-aryl-1,2,4-oxadiazoles

Compound #	GI_{50} (μM)[a]	
	T47D	H1299
1j[b]	0.19 ± 0.03	>10
4g	0.13 ± 0.04	>10
4h	0.66 ± 0.23	>10
4j	0.50 ± 0.01	>10
Colchicine	0.14 ± 0.03	0.063 ± 0.016
Taxol	0.026 ± 0.003	0.023 ± 0.003

[a] Cells were treated with the test compounds for 48 h, data are the mean of three or more experiments and are reported as mean ± standard error of the mean (SEM).
[b] Data from Ref. 23.

was performed as described previously.[24] Compound **4g**, dosed iv at 20 mg/kg once per day for 5 days for two weeks in combination with paclitaxel, was found to be active in the MX-1 human breast cancer xenograft model in mice, resulting in 80% tumor growth inhibition (Fig. 2), and is well tolerated with maximum body weight decrease of <10%.

In conclusion, we have explored the synthesis of compounds with substitutions at the 2- or 3-positions of the phenyl group of 3-aryl-5-aryl-1,2,4-oxadiazoles with the aim of improving aqueous solubility properties. It was found that a small substitution at the 2-position is well tolerated. This substitution also forces rotation of the phenyl ring out of the plane of the oxadiazole, making the molecule less planar. Together with replacing the thiophene ring by a furan ring, this study led to several potent compounds, such as **4g** and **4h,** with improved solubility that can be formulated

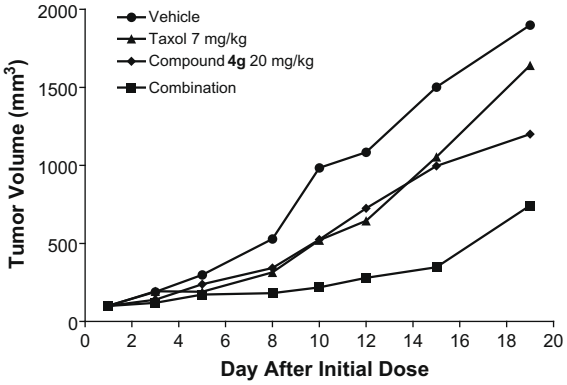


Figure 2. Compound **4g** inhibited the growth of established (~100 mm^3) MX-1 tumor xenografts in Crl:Nu/Nu-nuBR mice. Compound **4g** and paclitaxel were dosed intravenous at 20 and 7 mg/kg, respectively, days 1–5 and 8–12. *P* value as calculated by Student's *t*-test is <0.01 for the combination.

for iv administration in animal studies as potential anticancer agents. In addition, the phosphate prodrug **4m** also had good aqueous solubility.

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