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Identification of Diaryl 5-Amino-1,2,4-oxadiazoles as Tubulin Inhibitors: the Special Case of 3-(2-Fluorophenyl)-5-(4-methoxyphenyl)amino-1,2,4-oxadiazole

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Abstract

The combination of experimental (inhibition of colchicine binding) and computational (COMPARE, docking studies) data unequivocally identified diaryl 5-amino-1,2,4-oxadiazoles as potent tubulin inhibitors. Good correlation was observed between tubulin binding and cytostatic properties for all tested compounds with the notable exception of the lead candidate, 3-(3-methoxyphenyl)-5-(4-methoxyphenyl)amino-1,2,4-oxadiazole (DCP 10500078). This compound was found to be substantially more active in our *in vitro* experiments than the monofluorinated title compound, 3-(2-fluorophenyl)-5-(4-methoxyphenyl)amino-1,2,4-oxadiazole (DCP 10500067/ NSC 757486), which in turn demonstrated slightly better tubulin binding activity. Comparative SAR analysis of twenty five diaryl 5-amino-1,2,4-oxadiazoles with other known tubulin inhibitors, such as combretastatin A-4 (CA-4) and colchicine, provides further insight into the specifics of their binding as well as the plausible mechanism of action.

During the last 5 years, development of novel fluorinated anticancer drug candidates with rational single-molecule polypharmacy¹ potential (also known as multi-target ligands or designed multiple ligands)^{2–9} became one of the priority research areas within the Discovery Chemistry Project framework.^{10,11} Our initial interest in A-B-C heterocyclic systems^{12,13} was prompted by the success of two recently approved cytostatic drugs exploiting the single-molecule polypharmacy mode of action, the multi-kinase inhibitors sorafenib¹⁴ and its ring

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B fluorinated analog regorafenib¹⁵ (Figure 1). It was expected that the versatile nature of the A-B-C heterocyclic systems having three rigid heterocyclic or aromatic rings interconnected by conformationally flexible links would provide an attractive structural platform for the development of new anticancer drug candidates.

Our previous effort yielded several new families of compounds with anticancer potential based on this A-B-C platform.^{10,11} One of these families, diaryl 5-amino-1,2,4-oxadiazoles,¹¹ was of particular interest due to the demonstrated high potency (nanomolar IC₅₀ values against cancer cells in culture) of the lead compound, DCP 10500078 (see Figure 2 and Table 1). However, at that time we were unable to determine the exact mechanism of action of the lead compound. Here we report the results of subsequent biochemical and computational experiments which allowed us to identify diaryl 5-amino-1,2,4-oxadiazoles as tubulin inhibitors.

The Developmental Therapeutics Program (DTP) of the National Cancer Institute (NCI) developed a set of software solutions (COMPARE) which allows for the online comparative analysis of the 60-cell line screening tests performed at their facilities.¹⁶ Several diaryl 5-amino-1,2,4-oxadiazoles from the Discovery Chemistry Project (DCP) collection were submitted to the DTP (see Table 1), and the results of the tests of the most active C,H,N,O-only compounds (e.g., DCP 10500071/NSC 757489) were further analyzed using the online COMPARE tool. Unfortunately, the initial results of the COMPARE calculations for these initial compounds were inconclusive – analog compounds identified by COMPARE exhibited various modes of anticancer activity with no apparent pattern or tendency.

The original set of available diaryl 5-amino-1,2,4-oxadiazoles was re-evaluated with the aim of finding derivatives that would perform better within the COMPARE algorithm framework. Monofluorinated derivatives attracted our attention, since some of the fluorinated heteroaromatic compounds, such as 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole (NSC 721648),¹⁷ showed better selectivity against different cancer cell lines as compared with nonfluorinated analogs.¹⁸ Similar observations were also recently made for heterocyclic compounds containing simple fluoroaliphatic chains.¹⁹ A breakthrough in COMPARE analysis was eventually achieved with the title monofluorinated derivative, DCP 10500067/NSC 757486. This compound demonstrated good activity pattern correlation with another A-B-C heterocyclic system, 2,3-dihydro-2-(phenyl)-4(1*H*)-quinazolinone (Figure 3), which acts as a typical tubulin inhibitor.²⁰ Other A-B-C heterocyclic systems, such as 2-phenyl-4-quinolones,²¹ 2-aryl-4-benzoyl-imidazoles,²² 4-substituted methoxybenzoyl-aryl-thiazoles²³ and diaryl 1,2,4-triazoles,^{24,25} are known antimitotic agents interacting with tubulin.

Encouraged by these computational results, we performed subsequent direct binding experiments that unequivocally demonstrated that DCP 10500067/NSC 757486 was indeed a potent tubulin inhibitor. Other diaryl 5-amino-1,2,4-oxadiazoles, including our lead compound, DCP 10500078, also demonstrated strong inhibitory effects on tubulin, although not as high as DCP 10500067/NSC 757486 (see Table 1). The results of these experiments allowed us to identify several key parameters affecting the ability of diaryl 5-amino-1,2,4-oxadiazoles to interact with tubulin. This identification was facilitated by the abundance of available data regarding the structure of tubulin^{26,27} and its inhibitors,²⁸ including colchicine site ligands.^{29,30}

One of the key parameters determining potency of inhibitory effects on tubulin was the presence of an alkyl- (or alkoxy-) substituent in the para-position of the PhNH – fragment. Diaryl 5-amino-1,2,4-oxadiazoles without this substituent were inactive (e.g., DCP 10500035, DCP 10500060, DCP 10500070). A methoxy group was the best substituent,

followed by methyl, ethoxy, and ethyl (DCP 10500067/NSC 757486, DCP 10500068/NSC 757487, DCP 10500065, and DCP 10500064, respectively). It appears that the addition of electron-withdrawing groups to the PhNH – fragment reduced interactions with tubulin, albeit only moderately (DCP 10500068/NSC 757487 and DCP 10500066/NSC 757485). These observations were in general agreement with the previously reported antiproliferative activity data.¹¹

Unlike the PhNH group in the 5-position, the 3-aryl group was quite tolerant in regard to substitution (Table 1). No strict requirements were observed, to the extent that even a plain phenyl ring provided adequate antitubulin activity (e.g., DCP 10500063, Table 1). This was not a very intuitive conclusion, given the fact that both colchicine and CA-4 have three methoxy groups involved in ligand-protein interactions in the colchicine site^{26,29} (see also the results of the docking studies below). We did observe enhanced anticancer cell activity (but not antitubulin activity) for our lead compound DCP 10500078, which has the (3-methoxy)phenyl group in the 5 position of the 1,2,4-oxadiazole ring. However, adding additional methoxy groups did not improve either antitubulin or antiproliferative activity. This differentiates diaryl 5-amino-1,2,4-oxadiazoles from other tubulin inhibitors with a similar mechanism of action, such as CA-4, which is required to have three adjacent “colchicine-like” methoxy groups for optimal activity. In this respect, diaryl 5-amino-1,2,4-oxadiazoles are somewhat unique, given the fact that they satisfy fewer structural criteria required for a significant interaction with tubulin (Figure 4).²⁹

Docking studies were used to delineate the binding interactions of the most efficient compound, DCP 10500067/NSC 757486 (Figure 4, right) at the colchicine site. The models showed that binding by DCP 10500067/NSC 757486 at the colchicine site was largely driven by hydrophobic contacts. DCP 10500067/NSC 757486 occupied similar conformational space as colchicine (Figure 5), and, accordingly, its binding was characterized by common pharmacophoric features with colchicine. As previously described,²⁹ the methoxytropolone moiety of colchicine contains two hydrophobic centers, one contained in its methoxy carbon and the second in the tropolone ring. Similarly, the 4-methoxyaryl group of DCP 10500067/NSC 757486 mapped onto these two hydrophobic centers. As the docked model shows, this 4-methoxy group is superimposable with the methoxy substituent on the colchicinoid tropolone, and, concomitantly, the adjoining aromatic ring functioned as the bioisostere of the tropolone ring of colchicine. At the opposite end of the colchicine site, the trimethoxyaryl group of colchicine is characterized by a hydrophobic center that also contains a weak hydrogen bond acceptor in its 1-methoxy oxygen atom.²⁹ As depicted in Figure 5, the 2-fluorophenyl group of DCP 10500067/NSC 757486 mapped onto the trimethoxy moiety of colchicine. The aromatic ring of the 2-fluorophenyl group encompasses the hydrophobic center. Additionally, an electronegative fluorine atom may be a bioisostere of the 1-methoxy oxygen atom, potentially forming a weak and unconventional hydrogen bond to the Cys239 thiol group in the same fashion as the 1-methoxy oxygen of colchicine.

We were particularly interested in determining the role of fluorine in tubulin binding, being intrigued by the fact that monofluorinated diaryl 5-amino-1,2,4-oxadiazole DCP 10500067/NSC 757486 had the highest antitubulin activity among all diaryl 5-amino-1,2,4-oxadiazoles tested so far, including our lead compound, DCP 10500078. Several other fluorinated diaryl 5-amino-1,2,4-oxadiazoles were evaluated (DCP 10500056, DCP 10500064, DCP 10500065, DCP 10500066/NSC 757485, DCP 10500067/NSC 757486, DCP 10500068/NSC 757487, see Table 1), but it does not appear that the introduction of fluorine automatically improves antitubulin activity.¹⁸ Similar conclusions can be drawn from the results of our docking studies, where only marginally specific interactions involving the fluorine atom in DCP 10500067/NSC 757486 were observed (Figure 5). We also found that

the accumulation of more than one fluorine atom does not provide any further improvement in activity (compare, for example, DCP 10500068/NSC 757487 and DCP 10500066/NSC 757485).

It may be speculated that tubulin-binding selectivity rather than the strength of the interaction was positively affected by the introduction of fluorine, which in turn resulted in a better correlation with other known tubulin inhibitors in the COMPARE database. Similar conclusions can be made by the analysis of other monofluorinated A-B-C heterocyclic systems that act as tubulin inhibitors (Figure 6).²⁴ Further tests are required to confirm this hypothesis.

Finally, we observed reasonably good correlation between tubulin binding capacity and overall growth inhibition activity for all tested compounds (Figure 7). This observation tentatively leads us to postulate that the anticancer activity of diaryl 5-amino-1,2,4-oxadiazoles is predominantly related to their tubulin inhibition potential, with some notable exceptions. For example, the activities of the lead compound, DCP 10500078, and its analog, DCP 10500071/NSC 757489, containing one additional methoxy group (red symbols, Figure 7), are somewhat high in relation to its tubulin inhibition potential, and this may warrant additional investigation.

It is prudent to note that some of the poly(methoxy)-substituted diaryl 5-amino-1,2,4-oxadiazoles with poor tubulin binding – growth inhibition activity correlations (e.g., Figure 7, right) also exhibited poor correlations with “classical” tubulin inhibitors in the COMPARE analysis mentioned earlier. These poor correlations combined with elevated activity might indicate an additional biological target worth pursuing further in our quest towards rational single-molecule polypharmacy. Another poly(methoxy)aryl compound, chlorotrianisene (1,1',1''-(2-chloroethene-1,1,2-triyl)tris(4-methoxy)benzene), was recently identified as a potent polypharmacy agent.³¹

In summary, the combination of experimental binding experiments and computational COMPARE and docking studies unequivocally identified diaryl 5-amino-1,2,4-oxadiazoles as potent tubulin inhibitors. The presence of an alkyl(alkoxyl) group in the 4 position of the PhNH fragment was found to be critical for antitubulin activity, whereas the presence of these groups in the opposite phenyl ring provided only a marginal effect on antitubulin activity. Good correlation was observed between tubulin binding and anticancer properties for all tested compounds with the notable exception of the lead candidate, DCP 10500078, and its analog with one additional methoxy group, DCP 10500071/NSC 757489. The lead compound was found to be substantially more active in our *in vitro* antiproliferative activity experiments compared with the monofluorinated derivative DCP 10500067/NSC 757486, which, however, had slightly better antitubulin activity. The search for novel anticancer compounds with rational single-molecule polypharmacy potential for prostate cancer chemotherapy in the framework of the Discovery Chemistry Project continues.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Multi-kinase inhibitors sorafenib (left) and regorafenib (right).

DCP 10500078

Figure 2.
The structure of the lead diaryl 5-amino-1,2,4-oxadiazole compound, DCP 10500078.

NSC 113764

Figure 3.
2,3-dihydro-2-(phenyl)-4(1*H*)-quinazolinone (NSC 113764, a known tubulin inhibitor).²⁰

Figure 4.

Binding requirements for colchicine (left),²⁹ CA-4 (middle)²⁹ and the most efficient diaryl 5-amino-1,2,4-oxadiazole, DCP 10500067/NSC 757486 (right). Purple and orange spheres represent small hydrophobic pharmacophore centers that are important to activity. Green and cyan colored bonds demark larger hydrophobic centers that provide a common structural framework for ligand binding at the colchicine site.

Figure 5.

(Left) Docked pose of DCP 10500067/NSC 757486 at the colchicine site of 1SA0 αβ-tubulin. β-tubulin is depicted in purple ribbon. Binding site residues in α- and β-tubulin are rendered in stick models, with carbon atoms for α- and β-tubulin colored orange and tan, respectively. DCP 10500067/NSC 757486 is depicted as a thick stick with its carbon atoms colored green. Nitrogen, oxygen and fluorine are colored blue, red, and pale cyan, respectively. (Right) Superimposition of DCP 10500067/NSC 757486 with colchicine at the colchicine binding site, rendered the same as above. Colchicine has its carbon atoms colored light blue.

GI50 (average) = 464 nM
StdDev = 270

GI50 (average) = 556 nM
StdDev = 523

Figure 6. Average activity (HCT-116, ZR-75-1, HeLa, KB-3-1, and KB-V1a cell lines) and StdDev of fluorinated (right) and nonfluorinated (left) 1,5-diphenyl-1,2,4-triazole derivatives.²⁴

DCP 10500078 **DCP 10500071**

Figure 7. (Left) Correlation between inhibition of colchicine binding at 5 μ M inhibitor and growth inhibition of diaryl 5-amino-1,2,4-oxadiazole. (Right) The structures of the two polymethoxy-substituted derivatives with relatively high growth inhibition activity (red symbols).

Table 1

Tubulin binding, IC₅₀ and GI₅₀ data of some diaryl 5-amino-1,2,4-oxadiazoles and CA-4.

Compound name, DCP or (NSC number), if applicable	Chemical Formula	Inhibition of tubulin assembly (IC ₅₀ (μM) ±SD)	Inhibition of colchicine binding (% inhibition ± SD) at 5 μM inhibitor	Average <i>in vitro</i> growth inhibition (-Log GI ₅₀), NCI data, (unless noted)
CA-4 (NSC 613729), a reference compound		1.2 ± 0.007	99 ± 0.7	7.83
DCP 10500035			inactive	
DCP 10500056		3.5 ± 0.4	53 ± 2	
DCP 10500057		3.5 ± 0.04	50 ± 2	
DCP 10500058 (NSC 757477)		2.5 ± 0.3	52 ± 5	5.19
DCP 10500059 (NSC 757478)		1.8 ± 0.1	65 ± 1	6.24
DCP 10500060			inactive	

Compound name, DCP or (NSC number), if applicable	Chemical Formula	Inhibition of tubulin assembly (IC_{50} (μ M) $\pm$ SD)	Inhibition of colchicine binding (% inhibition $\pm$ SD) at 5 μ M inhibitor	Average <i>in vitro</i> growth inhibition (-Log GI_{50}), NCI data, (unless noted)
DCP 10500061		1.2 ± 0.1	82 ± 3	
DCP 10500062		1.7 ± 0.06	80 ± 0.3	
DCP 10500063		1.4 ± 0.2	88 ± 1	
DCP 10500064		2.7 ± 0.1	73 ± 3	
DCP 10500065		1.7 ± 0.1	76 ± 0.2	
DCP 10500066 (NSC 757485)		1.6 ± 0.3	81 ± 3	6.07
DCP 10500067 (NSC 757486)		1.1 ± 0.1	91 ± 0.4	6.69

Compound name, DCP or (NSC number), if applicable	Chemical Formula	Inhibition of tubulin assembly (IC_{50} (μ M) $\pm$ SD)	Inhibition of colchicine binding (% inhibition $\pm$ SD) at 5 μ M inhibitor	Average <i>in vitro</i> growth inhibition (-Log GI_{50}), NCI data, (unless noted)
DCP 10500068 (NSC 757487)		1.6 $\pm$ 0.05	85 $\pm$ 2	6.22
DCP 10500069		1.8 $\pm$ 0.08	56 $\pm$ 2	
DCP 10500070			inactive	
DCP 10500071 (NSC 757489)		2.6 $\pm$ 0.2	68 $\pm$ 3	6.61
DCP 10500072 (NSC 757490)		3.6 $\pm$ 0.04	52 $\pm$ 3	5.58
DCP 10500073		1.6 $\pm$ 0.007	81 $\pm$ 1	
DCP 10500074 (NSC 757491)		1.6 $\pm$ 0.04	78 $\pm$ 3	6.07

Compound name, DCP or (NSC number), if applicable	Chemical Formula	Inhibition of tubulin assembly (IC_{50} (μ M) $\pm$ SD)	Inhibition of colchicine binding (% inhibition $\pm$ SD) at 5 μ M inhibitor	Average <i>in vitro</i> growth inhibition (-Log GI_{50}), NCI data, (unless noted)
DCP 10500075 (NSC 757492)		2.2 ± 0.04	76 ± 3	5.91
DCP 10500076		1.9 ± 0.3	76 ± 3	
DCP 10500077 (NSC 757493)		2.3 ± 0.05	73 ± 0.7	6.25
DCP 10500078		1.9 ± 0.09	90 ± 2	8.01 (HCT-116, DU-145, PC-3, MDA-MB-231, and PANC-1 cell lines) ¹¹
DCP 10500079		1.5 ± 0.2	85 ± 0.4	