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Article

Bisphosphonylallenes as Suitable Scaffolds for Unprecedented 4,5-Diphosphonyldihydropyridazines and 3,4-Diphosphonylpyrroles Displaying Antimelanoma Activity

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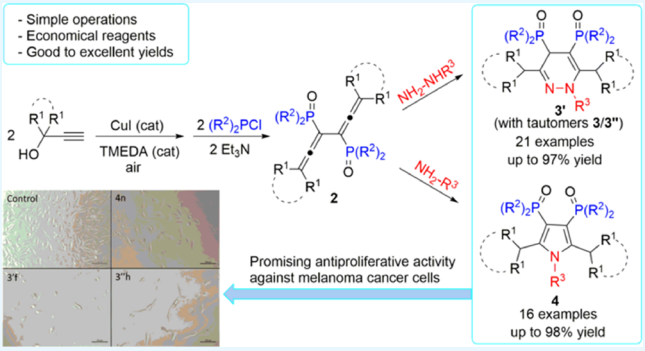
ABSTRACT: An efficient and simple approach has been developed for the synthesis of unprecedented 4,5-diphosphonyldihydropyridazines and 3,4-diphosphonylpyrroles, through the condensation of bisphosphonylallenes with hydrazines and primary amines, respectively. The reactions proceed under operationally simple, mild, and catalyst-free conditions, for a wide substrate scope. The synthesized compounds were screened for their antiproliferative activity against melanoma cancer cells, and they showed promising growth inhibition.



INTRODUCTION

Allenes and their derivatives are recognized as powerful building blocks for the synthesis of a wide variety of molecules of commercial significance, such as pharmaceuticals, agrochemicals, polymers, and other material molecules.[1] Over the past few years, allenes have been involved in diverse organic transformations like cycloadditions, cycloisomerizations, radical reactions, and transition-metal-catalyzed couplings,[2] showing the high synthetic flexibility of such molecular scaffolds. In particular, cyclization reactions of allenes have emerged as powerful tools for the construction of valuable carbocyclic and heterocyclic systems.[3]

Allenyl-phosphonates and -phosphine oxides, an important subclass of allenes, have also been used in many heterocyclization reactions, leading to a wide range of phosphorylated heterocycles, such as phosphono-benzofurans,[4] -pyrazoles,[5] -indoles,[6] and -isocoumarins.[6,7] However, bisallenyl-phosphonates and -phosphine oxides were much less studied and their reactivity remains underexplored, despite their unique structure which suggests the possibility of many heterocyclization reactions that could lead to novel diphosphonylated heterocycles with good therapeutic or metal-complexing potential. Typical reactions of bisphosphonylallenes involve their isomerization, on heating, to diphosphonylcyclobutenes, via intramolecular [2 + 2] cycloaddition.[8] More recently, we have described the double intramolecular cyclization of bisphosphonylallenes mediated by iodine or copper dibromide, leading to bis-1,2-oxaphospholenes.[9] In the continuation of these studies, we now report an efficient and simple approach to unprecedented 4,5-diphosphonyldihydropyridazines and 3,4-diphosphonylpyrroles, through the condensation of bisphosphonylallenes with hydrazines and primary amines, respectively. Our interest for these compounds is due to the well-known interesting biological properties of pyridazine[10] and pyrrole[11] derivatives, especially as anticancer agents. In addition, the presence of two phosphonyl pharmacophores that possess interesting biological effects and differential binding affinities to diverse biological targets[12] could improve the biological activity of these molecules, in a similar way to that reported for other pharmaceuticals.[13] Thus, the synthesized compounds were screened for their antiproliferative activity against melanoma cancer cells.

RESULTS AND DISCUSSION

Chemistry. Bisphosphonylallenes **2** were readily obtained in two steps from terminal propargyl alcohols, as described earlier by our group.[9] The first step involved the synthesis of diynediols **1**, in 50−85% yields, from the CuI-catalyzed oxidative homocoupling of terminal propargyl alcohols performed in tetrahydrofuran (THF) at room temperature, under open air,

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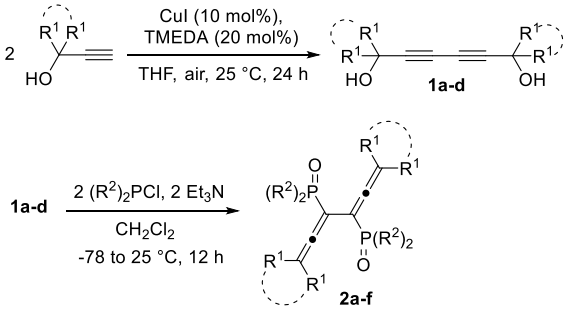
and in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine as a base (Table 1). In the second step, diyne-diols **1** were

Table 1. Synthesis of Diyne-diols 1a−d and Bisphosphonylallenes 2a−f



diyne-diol	R^1	yield (%)[a]	bis-allene	R^2	yield (%)[a]
1a	Me	85	**2a**	OEt	85
1b	Ph	71	**2b**	OEt	80
1c	$-(CH_2)_4-$	50	**2c**	OEt	44
1d	$-(CH_2)_5-$	80	**2d**	OEt	95
1a	Me	85	**2e**	Ph	82
1d	$-(CH_2)_5-$	80	**2f**	Ph	69

[a]Isolated yield.

reacted with either diethyl chlorophosphite or *P*-chlorodiphenylphosphine, in the presence of triethylamine, to provide bis-allenylphosphonates **2a−d** and bis-allenylphosphine oxides **2e,f** in multigram scales and yields up to 95% (Table 1). In addition to their physical and spectral data which were identical to those reported in the literature,[9] the structure of the synthesized bisphosphonylallenes was further investigated through the single-crystal X-ray diffraction analysis of compounds **2a,b,c,d,f**. These first reported X-ray structures of bisphosphonylallenes revealed that the two allenyl motifs adopt a twisted conformation in the crystal with a torsion angle of 180° (Figure 1 and Supporting Information).

With the bisphosphonylallenes **2a−f** in hand, their behavior toward hydrazine derivatives was investigated. At first, the reaction of bisphosphonylallene **2b** with methylhydrazine (2 equiv) was performed in a variety of solvents at different temperatures, in order to optimize the reaction conditions

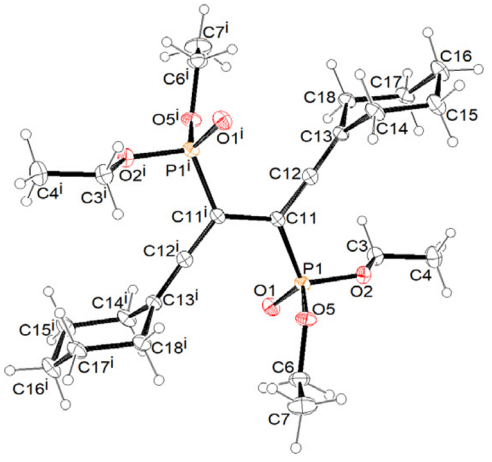


Figure 1. X-ray molecular structure of bisphosphonylallene **2d**, showing thermal displacement ellipsoids at the 30% probability level.

(Table 2). It was found that performing the reaction in nonpolar solvents such as toluene or 1,4-dioxane at reflux temperature gave the desired 4,5-diphosphonyldihydropyridazine **3b** in equilibrium with its tautomeric isomer **3′b**, in 91 and 96% overall yield, respectively (Table 2, entries 1 and 2). Switching to ethanol, as a protic solvent, provided a comparable overall yield of 92% of the tautomeric mixture (**3b** + **3′b**), after 2 h at 78 °C (Table 2, entry 3). Also tested was the use of fluorinated alcohols such as 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), but this left the starting materials intact even after prolonged heating at reflux temperature, presumably due to the high protic character of these fluorinated solvents which leads to a strong solvation of the hydrazine, thus preventing its reactivity (Table 2, entries 4 and 5). When using polar and aprotic solvents such as THF, MeCN, DMF, or CH_2Cl_2, the reaction furnished the desired product in moderate to high yields (Table 2, entries 6−9). The best results were recorded with CH_2Cl_2 which gave a 97% overall yield of the tautomeric mixture (**3b** + **3′b**) after 1 h at room temperature (Table 2, entry 9). Reducing the amount of methylhydrazine from 2 equiv to 1.5, 1.2, or 1.1 equiv led to a lower yield (Table 2, entries 10−12).

The optimized reaction conditions involving the use of methylhydrazine (2 equiv) in CH_2Cl_2 at room temperature were also successfully applied to bis-allenylphosphonates **2a,c,d** bearing, respectively, methyl, tetramethylene, or pentamethylene groups on the allenic motifs. In analogy, the corresponding tautomeric mixtures of 4,5-diphosphonyldihydropyridazines (**3** + **3′**) were obtained in 87, 50, and 67% overall yield, respectively (Table 3, entries 1, 3, and 4). It can be noted that better yields were recorded with bis-allenes **2a,b** bearing methyl or phenyl substituents on the allenic motifs compared to those containing tetramethylene or pentamethylene substituents (**2c,d**). Similar results were obtained with bis-allenylphosphine oxides **2e,f**, affording analogous 4,5-diphosphonyldihydropyridazine tautomers in 75 and 72% overall yield, respectively (Table 3, entries 5 and 6).

To further extend the scope of this reaction, we examined the behavior of hydrazine hydrate. The reactions were incomplete at room temperature but proceeded efficiently at refluxing CH_2Cl_2 to afford the corresponding 4,5-diphosphonyldihydropyridazines as equilibrium mixtures of tautomers **3**, **3′**, and **3″**, in good to excellent overall yields (Table 3, entries 7−11). However, the reaction of phenylhydrazine failed to give the desired dihydropyridazine core but led to a complex mixture of unidentified products, whatever the reaction time in refluxing CH_2Cl_2. This could be attributed to the low nucleophilicity of the conjugated NHPh nitrogen, which prevents it from attacking the second allenic carbon to provoke cyclization.

It is worth noting that tautomers **3**, initially formed in the reactions, completely isomerize into tautomers **3′** at room temperature. The rate of this process is deeply affected by the nature of the substituents and could take from few hours to several days. In the case of compound **3b**, for example, isomerization to **3′b** needed approximately 26 days to be complete, as shown by ^{31}P NMR monitoring (see Figure S69 in the Supporting Information).

The promising results obtained with hydrazine derivatives prompted us to further investigate the behavior of primary amines toward bisphosphonylallenes **2**, which would allow a straightforward approach to unprecedented 3,4-diphosphonylpyrroles. Initially, the reaction of bisphosphonylallene **2a** with benzylamine (2 equiv) was tested in a large range of solvents,

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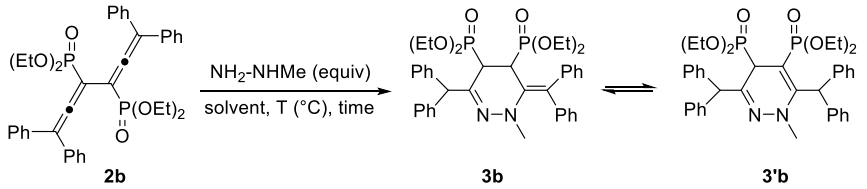
Table 2. Optimization of the Reaction Conditions for the Synthesis of 4,5-Diphosphonyldihydropyridazines[a]



entry	NH_2-NHMe (equiv)	solvent	temperature (°C)	time[b]	yield (%)[c]
1	2	toluene	110	2 h	91
2	2	1,4-dioxane	100	30 min	96
3	2	EtOH	78	2 h	92
4	2	TFE	80	24 h	0
5	2	HFIP	60	24 h	0
6	2	THF	65	20 min	95
7	2	MeCN	80	20 min	92
8	2	DMF	90	20 min	43
9	2	CH_2Cl_2	25	1 h	97
10	1.5	CH_2Cl_2	25	24 h	92
11	1.2	CH_2Cl_2	25	24 h	84
12	1.1	CH_2Cl_2	25	24 h	79

[a]Reaction conditions: **2b** (0.25 mmol), methylhydrazine, solvent (2 mL), in a sealed tube. [b]The progress of the reactions was monitored by ^{31}P NMR. [c]Isolated overall yield.

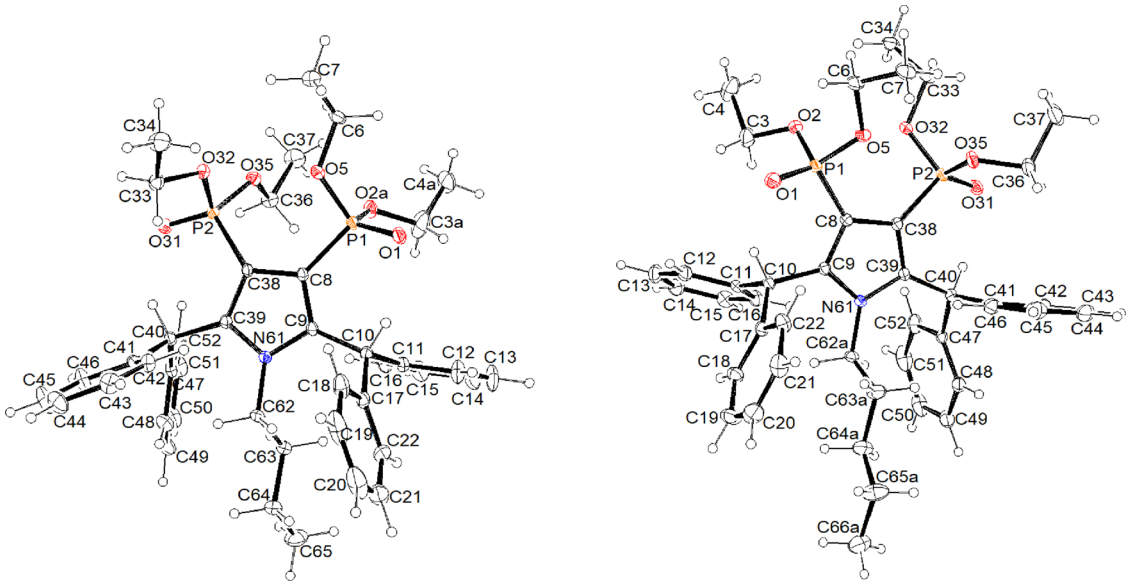


Figure 2. X-ray molecular structures of **4f** (left) and **4j** (right), showing thermal displacement ellipsoids at the 30% probability level.

including polar, protic, and nonpolar ones. As shown in Table 4, the best results were recorded with toluene which gave a 95% yield of the desired product **4a** after 24 h at 110 °C (Table 4, entry 8). Reducing the amount of benzylamine from 2 equiv to 1.5 or 1.2 equiv led to a diminished yield (Table 4, entries 9, 10). Accordingly, the optimized conditions were set as follows: benzylamine (2 equiv), toluene as the solvent, at 110 °C for 24 h.

With the optimized conditions in hand, we next studied the scope of this methodology. A variety of structurally diverse primary amines were found to react smoothly with bisphosphonylallenes **2** and provided a series of 3,4-diphosphonylpyrroles of type **4** in good to excellent yields (Table 5). The reactions proceeded efficiently with bis-allenylphosphonates **2a−d**, with bis-allenes **2a**,**b** bearing methyl or phenyl substituents on the allenic motifs giving better yields, as with our previous results with hydrazines. However, bis-allenylphosphine oxides **2e**,**f** did not give the desired 3,4-diphosphonylpyrroles. With regard to the amines, benzylamine as well as alkylamines, namely, *n*-butylamine, amylamine, and caprylamine, can be successfully used, leading to the corresponding diphosphonylpyrroles in up to 98% yield (Table 5), whereas the less-reactive aromatic amines such as aniline and *para*-anisidine and ammonia failed to afford any products.

The structure of 3,4-diphosphonylpyrroles **4** was unambiguously confirmed through the X-ray crystal analysis of compounds **4f** and **4j**, as depicted in Figure 2.

Antimelanoma Activity. The antiproliferative activity of eleven 4,5-diphosphonyldihydropyridazines **3′a−f**, **3″g**, **3′h**, **3″h**, **3′i**, and **3′k** and sixteen 3,4-diphosphonylpyrroles **4a−p** was evaluated on A2058 (ATCC CRL-11147) cells which are highly invasive human epithelial adherent melanoma cells that contain the V600E BRAF mutation and considered as highly

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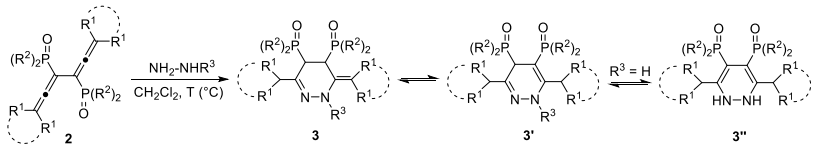
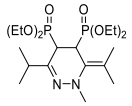
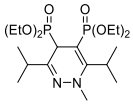
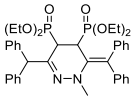
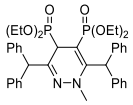
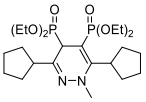
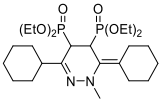
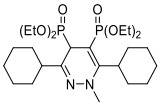
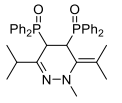
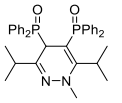
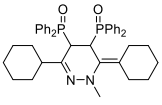
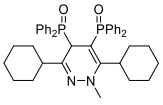
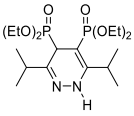
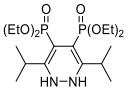
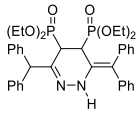
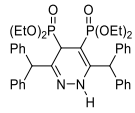
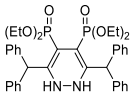
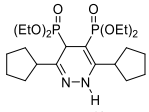
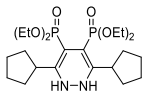
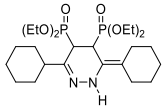
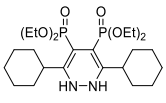
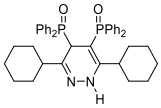
Table 3. Substrate Scope Studies in the Synthesis of 4,5-Diphosphonyldihydropyridazines[ab]



entry	tautomer 3	tautomer 3'	tautomer 3"	T (°C)	time (h)[c]
1	 **3a, 64%**	 **3'a, 23%**	-	25	3
2	 **3b, 71%**	 **3'b, 26%**	-	25	1
3	-	 **3'c, 50%**	-	25	2
4	 **3d, 62%**	 **3'd, 5%**	-	25	3
5	 **3e, 52%**	 **3'e, 23%**	-	25	4
6	 **3f, 54%**	 **3'f, 18%**	-	25	24
7	-	 **3'g, 45%**	 **3"g, 37%**	40	24
8	 **3h, 63%**	 **3'h, 5%**	 **3"h, 26%**	40	24
9	-	 **3'i, 42%**	 **3"i, 18%**	40	9
10	 **3j, 14%**	-	 **3"j, 42%**	40	16
11	-	 **3'k, 85%**	-	40	24

[a]Reaction conditions: **2** (0.25 mmol), hydrazine derivative (0.50 mmol), CH_2Cl_2 (2 mL), in a sealed tube. [b]Isolated yields. [c]The progress of the reactions was monitored by ^{31}P NMR.

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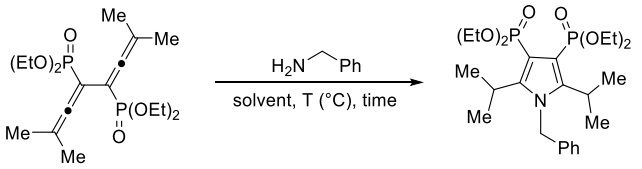
Table 4. Optimization of the Reaction Conditions for the Synthesis of 3,4-Diphosphonylpyrroles[a]



2a 4a

entry	solvent	temperature (°C)	time (h)[b]	yield (%)[c]
1	CH_2Cl_2	40	48	70
2	$CHCl_3$	60	24	84
3	THF	65	72	89
4	MeCN	80	30	83
5	DMF	90	24	23
6	EtOH	78	144	84
7	1,4-dioxane	100	24	88
8	toluene	110	24	95
9	toluene	110	24	89[d]
10	toluene	110	24	81[e]

[a]Reaction conditions: **2a** (0.25 mmol), benzylamine (0.50 mmol), solvent (2 mL), in a sealed tube. [b]The progress of the reactions was monitored by ^{31}P NMR. [c]Isolated yield. [d]Benzylamine (0.40 mmol). [e]Benzylamine (0.30 mmol).

resistant to anticancer drugs.[14] All tested compounds except **3′a** exerted an antiproliferative activity in A2058 melanoma cells (Figure 3), ranging from 5 to 72% growth inhibition. The best results were obtained with **4n**, **3′f**, and **3″h** that exerted more than 55% growth inhibition.

In general, the 4,5-bis(diphenylphosphoryl)-dihydropyridazines were found to be more active than the corresponding 4,5-bis(diethoxyphosphoryl) derivatives, as shown by the respective growth inhibitions of compounds **3′f** and **3′d**. Among the 4,5-bis(diphenylphosphoryl)-dihydropyridazines tested, the *N*-methylated compounds are more active than the corresponding *N*−H analogues, as exemplified with **3′f** and **3′k**. In addition, when compared with isopropyl groups (compound **3′e**), cyclohexyl groups at C3 and C5 (compound **3′f**) considerably increase the efficiency of the growth inhibitor.

As for the 4,5-bis(diethoxyphosphoryl)dihydropyridazines, the *N*-methylated compounds are this time less active than the corresponding *N*−H analogues, as exemplified with **3′b** and **3″h**, **3′i** and **3′c**, and **3″g** and **3′a**. For most of the compounds studied, substituents at C3 and C5 impact the activity in the following order: diphenylmethyl > cyclohexyl > cyclopentyl > isopropyl.

Regarding the 3,4-diphosphonylpyrroles, for a given substituent onto the pyrrole nitrogen, the best substituent at C2 and C5 for the activity is often diphenylmethyl, followed by cyclohexyl, then cyclopentyl, and finally isopropyl. For given substituents at C2 and C5, octyl is the most promising group to fix to pyrrolic nitrogen.

However, the cytotoxicity of the molecules **4n**, **3′f**, and **3″h** was low according to the weak morphological modifications observed in the cell cultures (Figure 4). Appearance of rounded

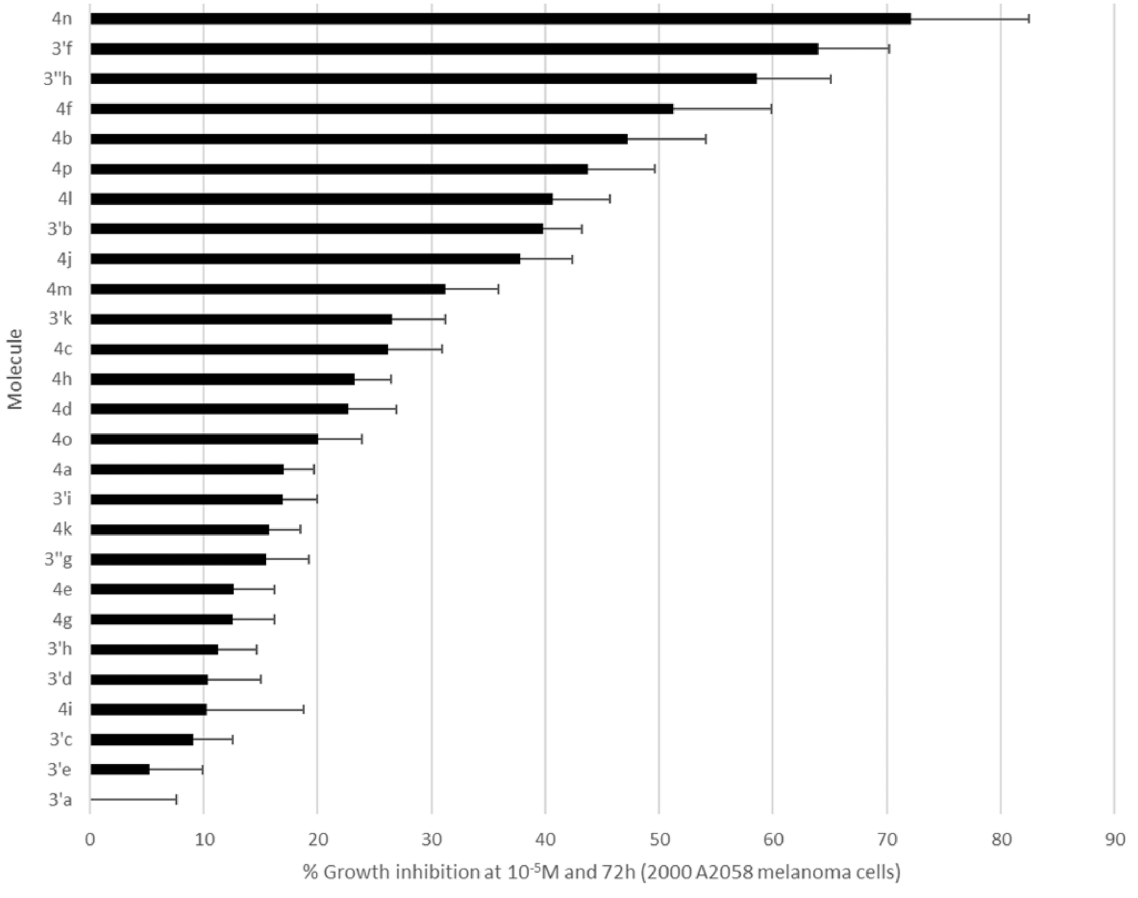


Figure 3. Percentage growth inhibition ± standard error of the mean (72 h treatment with 10^{-5} M in 2000 A2058 melanoma cells).

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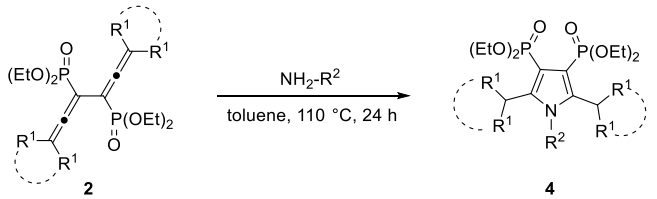
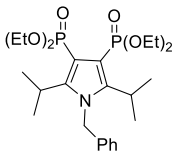
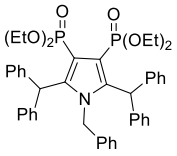
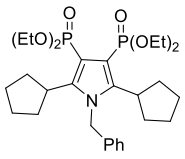
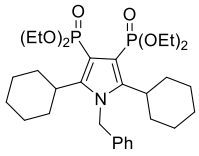
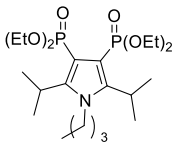
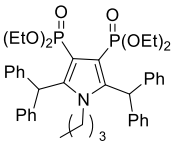
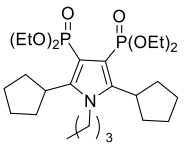
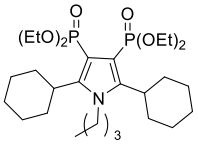
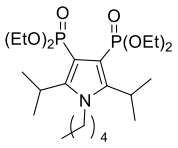
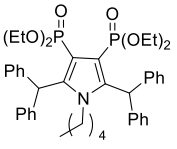
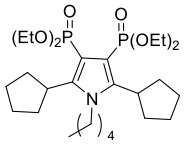
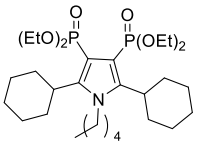
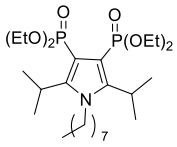
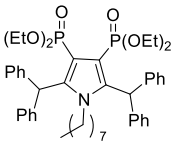
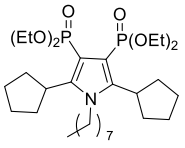
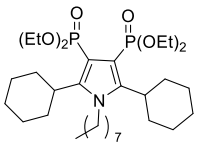
ACS Omega 2022, 7, 38894−38901

Table 5. Reagent Scope in the Synthesis of 3,4-Diphosphonylpyrroles[ab]



 4a, 95%	 4b, 98%	 4c, 89%	 4d, 91%
 4e, 92%	 4f, 84%	 4g, 79%	 4h, 72%
 4i, 84%	 4j, 88%	 4k, 73%	 4l, 70%
 4m, 90%	 4n, 93%	 4o, 97%	 4p, 88%

[a]Reaction conditions: **2** (0.25 mmol), amine (0.50 mmol), toluene (2 mL), at 110 °C for 24 h in a sealed tube. [b]Isolated yields.

cells suggested that the molecules exerted a cytostatic effect but had no pro-apoptotic activity.

Although preliminary, these results open the way for further molecular assays to confirm the capacity of these molecules to act as cell cycle blockers and interact with pharmacological targets relevant to the treatment of melanoma, such as kinases.[15]

CONCLUSIONS

In summary, we have successfully developed a simple and efficient methodology for the synthesis of unprecedented 4,5-diphosphonyldihydropyridazines and 3,4-diphosphonylpyrroles, through the condensation of bisphosphonylallenes with hydrazines and primary amines, respectively. The salient features of these syntheses include high yields, simple operations, mild and catalyst-free conditions, and broad substrate scope, which make these protocols more amenable for high throughput library synthesis. The synthesized compounds showed promising efficacy when screened for their antiproliferative activity against melanoma cancer cells.

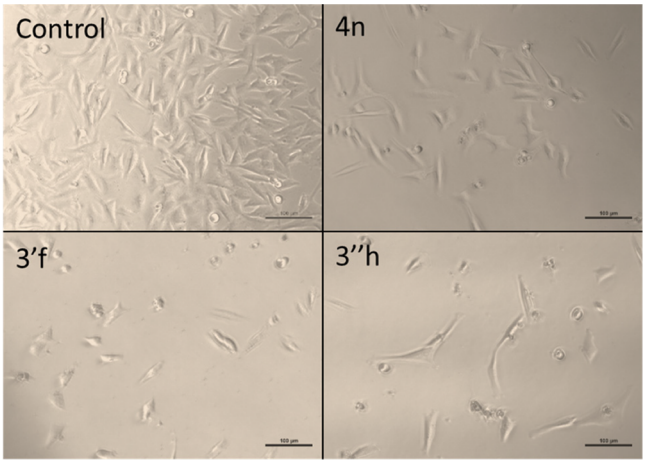


Figure 4. Microphotography of A2058 melanoma cells after 72 h growth in the control cell culture medium containing 1% DMSO (control) or the cell culture medium containing 10^{-5} M molecule (**4n**, **3′f**, or **3″h**).

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c04619.

Supplemental data containing full experimental details, spectral and crystal data, and copies of NMR (^{1}H, ^{31}P, and ^{13}C) spectra (PDF), together with CIF files.

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All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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