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Diaryl α-nitrostilbenes as nitro-substituted analogues of combretastatins: synthesis and biological evaluation in the sea urchin embryo model

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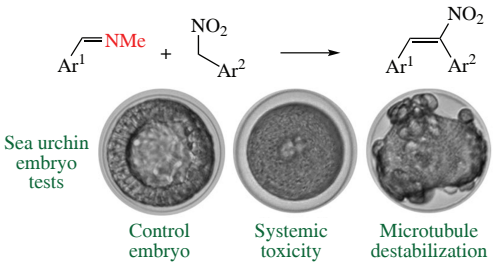
A series of nitro analogues of potent antimitotic combretastatin A-4 (diaryl α-nitrostilbenes, DNSs) was synthesized by the Knoevenagel condensation of arylnitromethanes with methylamine Schiff bases of benzaldehydes. The obtained stilbenes featured only *cis*-diaryl topology irrespective of substitution pattern in the aryl fragments. The evaluation on a sea urchin embryo model suggested that DNSs exhibited both antitubulin and tubulin-unrelated effects similar to those of corresponding monoaryl nitrostyrenes.



Keywords: α-nitrostilbenes, arylnitromethanes, Knoevenagel condensation, combretastatin, tubulin, microtubule, sea urchin embryo.

1,2-Diaryl-1-nitroethylenes **1** (diaryl α-nitrostilbenes, DNSs, Figure 1) are widely used as synthetic intermediates for the preparation of various chemically and biologically important molecules.[1–8] As Michael acceptors, DNSs play a crucial role in stereoselective sulfa-Michael addition between nitroalkenes and thiols to afford biologically active sulfur-containing compounds.[9,10] A replacement of NO_2-substituted ethene bridge in DNSs with 5-membered *N*-containing heterocycle afforded a family of *vic*-diarylated azoles[2,6,7,11–13] being analogues of natural mitostatics combretastatins CA2 and CA4 (see Figure 1) possessing potent antimitotic microtubule destabilizing effect. Structural similarity of DNSs and combretastatins suggests that DNSs may effectively interact with tubulin/microtubules and, as a result, display antiproliferative effect. Indeed, benzyl nitrostyrenes **2** (see Figure 1) were found to exhibit both *in vitro* cytotoxicity at low micromolar concentration range and *in vivo* anticancer activity, along with inhibition of purified tubulin polymerization.[14] Furthermore, introduction of electron-acceptor groups, such as CN or C(O)Me into ethene linker of combretastatins yielded potent cytotoxic compounds that inhibited tubulin polymerization.[15–18] Hence, DNSs, structurally similar to cyanostilbenes, could also exhibit antiproliferative antitubulin effect. Considering these data, in the present work, a facile effective metal-free method for preparation of DNSs featuring aryl or hetaryl fragments with varying substitution pattern was applied. The biological activity of the targeted compounds was further assessed in a sea urchin embryo model, which allows for identification of antimitotic microtubule-destabilizing mode of action, non-tubulin antiproliferative activity, specific effects on sea urchin embryonic morphogenesis, and overall systemic toxicity.[8]

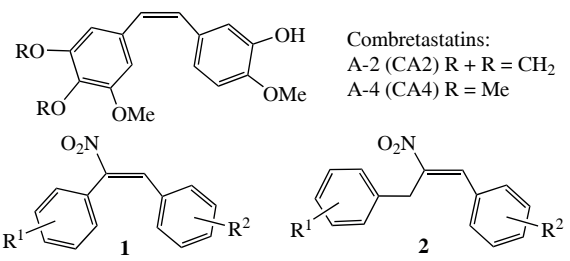
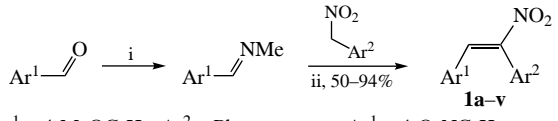


Figure 1 Structure of combretastatins A-2 and A-4 (CA2, CA4) and their nitro-substituted analogues.

Several synthetic protocols to obtain DNSs were reported: (i) the nitration of stilbenes[19–21] and unsaturated carboxylic acids;[22] (ii) cross-coupling reaction[23] involving Grignard reagents;[3] and (iii) Knoevenagel condensation of arylnitromethanes with benzaldehydes.[24] We chose Knoevenagel method using in most cases readily available polyalkoxy benzaldehydes Ar^1CHO and arylnitromethanes $Ar^2CH_2NO_2$ (Scheme 1). The arylnitromethanes were synthesized according to an amended procedure described previously.[25,26]

Diverse modifications of condensation of arylnitromethanes with aromatic aldehydes catalyzed by amines were published.[6,24,27] Condensation of arylnitromethanes with butylamine Schiff bases of benzaldehydes afforded DNSs in good yields.[27,28] However, the isolation of the targeted DNSs by crystallization was challenging due to the partial solubility of butylammonium acetate in organic solvents.[27] To avoid this drawback, herein, butylamine Schiff bases were replaced with methylamine Schiff bases $Ar^1CH{=}NMe$ that were synthesized in ~100% yield using 2.5-fold excess of methylamine hydrochloride and equivalent amount of $NaHCO_3$ in methanol.[29] Under these conditions, the formed methylammonium acetate did not



1a–v

a Ar^1 = 4-$MeOC_6H_4$, Ar^2 = Ph
b Ar^1 = 3-$MeOC_6H_4$, Ar^2 = Ph
c Ar^1 = 2-$MeOC_6H_4$, Ar^2 = Ph
d Ar^1 = 4-$EtOC_6H_4$, Ar^2 = Ph
e Ar^1 = 2,3-$(MeO)_2C_6H_3$, Ar^2 = Ph
f Ar^1 = 2,4-$(MeO)_2C_6H_3$, Ar^2 = Ph
g Ar^1 = 2,5-$(MeO)_2C_6H_3$, Ar^2 = Ph
h Ar^1 = 3,4-$(MeO)_2C_6H_3$, Ar^2 = Ph
i Ar^1 = 2,5-$(MeO)_2$-3,4-$(OCH_2O)C_6H$, Ar^2 = Ph
j Ar^1 = 3-O_2N-4-$MeOC_6H_3$, Ar^2 = Ph
k Ar^1 = Ph, Ar^2 = 4-$MeOC_6H_4$
l Ar^1 = 3,4,5-$(MeO)_3C_6H_2$, Ar^2 = 4-$MeOC_6H_4$
m Ar^1 = 4-$O_2NC_6H_4$, Ar^2 = 4-$MeOC_6H_4$
n Ar^1 = 3-$O_2NC_6H_4$, Ar^2 = 4-$MeOC_6H_4$
o Ar^1 = 2-$O_2NC_6H_4$, Ar^2 = 4-$MeOC_6H_4$
p Ar^1 = 2-thienyl, Ar^2 = 4-$MeOC_6H_4$
q Ar^1 = 1-methylpyrazol-4-yl, Ar^2 = 4-$MeOC_6H_4$
r Ar^1 = Ph, Ar^2 = 4-$EtOC_6H_4$
s Ar^1 = 4-$MeOC_6H_4$, Ar^2 = 3,4,5-$(MeO)_3C_6H_2$
t Ar^1 = 4-$MeOC_6H_4$, Ar^2 = 3-O_2N-4-$MeOC_6H_3$
u Ar^1 = 4-$MeOC_6H_4$, Ar^2 = 4-BrC_6H_4
v Ar^1 = 2,5-$(MeO)_2$-3,4-$(OCH_2O)C_6H$, Ar^2 = 4-$O_2NC_6H_4$

Scheme 1 *Reagents and conditions*: i, $MeNH_2 \cdot HCl$, $NaHCO_3$, MeOH, room temperature, overnight; ii, MeCN–AcOH, room temperature, overnight (molar ratio $[Ar^2CH_2NO_2]$: $[Ar^1CH{=}NMe]$ = 1 : 1.1).

Table 1 Effects of DNSs **1a–v**, nitrostyrenes **3**, **4**, isoapiol **5a**, and isodillapiol **5b** on the sea urchin *Paracentrotus lividus* embryos.

Compound	Minimum effective concentration (MEC, μM)[a]				
	Fertilized egg treatment		Hatched blastula treatment		
	Cleavage alteration	Cleavage arrest	Embryo spinning	Morphological anomalies	Embryo mortality
1a	2	4 TE[b]	4	1	4
1b	1	2 TE[b]	>4	1	2
1c	2	>4	>4	2	>4
1d[c]	~2	~4	~2	~1	~2
1e	2	>4	>4	2	4
1f	2	>4	>4	2	4
1g	2	>4	>4	2	4
1h	1	4	>5	1	2
1i[c]	~2	~4	~1	~1	~2
1j	1	2	>4	0.5	1
1k	2	4	>4	2	4
1l	1	4	>4	1	4
1m	1	2	>4	0.5	1
1n	1	2	>4	0.5	1
1o	0.2	1 TE[b]	1	1	2
1p	0.2	2	2	0.2	4
1q	2	>4	>4	1	>4
1r	1	2 TE[b]	>4	1	2
1s	1	2	2	1	2
1t	4	>4	>4	0.5	4
1u[c]	~2	>4	>4	~1	~2
1v	2	>4	>4	2	2
3	2	4	4	1	>4
4a	2	4	4	2	4
4b	2	4	4	2	5
5a	2	8	>10	>10	>10
5b	20	80	>100	40	100
CA2	0.002	0.01 TE[b]	0.05	0.01	0.04[d]
CA4	0.002	0.01 TE[b]	0.05	0.005	0.05[d]

[a]The sea urchin embryo assay was conducted as described previously.[8] Fertilized eggs and hatched blastulae were exposed to 2-fold decreasing concentrations of compounds. Duplicate measurements showed no differences in MEC values. [b]TE: tuberculate arrested eggs typical for microtubule destabilizing agents. [c]MEC values were approximate due to compound precipitation in seawater. [d]Embryo mortality was observed after 25 h of exposure.

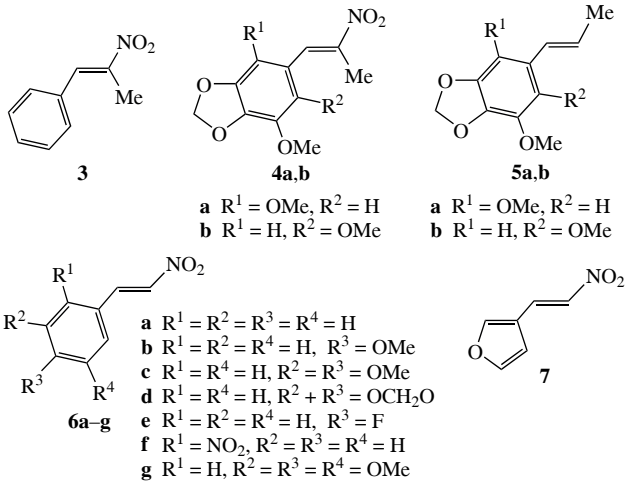


Figure 2 Structure of styrenes **3**, **4**, **6**, **7**, and their natural analogues isoapiol **5a** and isodillapiol **5b**.

interfere with DNSs crystallization, resulting in obtaining the targeted molecules **1a–v** with high yields (Scheme 1, Table 1, and Table S1 of Online Supplementary Materials). This method made it possible to improve the yield of DNSs by 15–30% on average compared to literature data. The lower (20–44%) yields were obtained for only compounds **1e**, **1f**, **1q**, and **1v**.

Methylnitrostyrenes **4a** and **4b** were synthesized from isoapiol **5a** and isodillapiol **5b** (Figure 2), respectively, according to published protocol.[30] Compounds **1a**,**i**,**m**,**l**,**p**,**q** and **5a**,**b** were previously published elsewhere (see references in Table S2, Online Supplementary Materials).

Alike combretastatins, biological activity of DNSs should depend on their spatial configuration, namely, the isomers with *cis*-diaryl topology were anticipated to be significantly more potent than the corresponding *trans*-isomers. According to the literature, *cis*-stilbenes are converted to more stable *trans*-isomers in the light, at heating, and in the living organism.[31] Therefore, elucidation of spatial configuration and stability of the targeted DNSs was of paramount importance. The single-crystal X-ray diffraction analysis of compounds **1i** and **4a** was executed (Figure 3).† The *cis*-configuration for aryl rings (**1i**) as well as for aryl/methyl substituents (**4a**) was retained even in the presence of the bulky 2,5-dimethoxy-3,4-methylenedioxy-benzene fragment. Specifically, in compound **1i** the 2,5-dimethoxy-3,4-methylenedioxybenzene ring and nitro group were found to be within the plane of the double bond, whereas

† *Crystal data for* **1i**. $C_{17}H_{15}NO_6$, M_r = 329.30, monoclinic, space group *C*2/*c*, synchrotron radiation (λ = 0.96260 Å), at 100 K, a = 21.841(4), b = 6.7692(14) and c = 21.035(4) Å, β = 90.50(3)°, V = 3109.8(10) Å^3, Z = 8, d_{calc} = 1.407 g cm^{-3}, μ = 0.227 mm^{-1}, F(000) = 1376. Total of 22356 reflections were measured and 3377 independent reflections (R_{int} = 0.1136) were used. The refinement converged to wR_2 = 0.1373 and GOF = 1.069 for all independent reflections [R_1 = 0.0546 was calculated for 2775 observed reflections with $I > 2\sigma(I)$].

Crystal data for **4a**. $C_{12}H_{13}NO_6$, M_r = 267.23, triclinic, space group $P\bar{1}$, CuK_α-radiation, at 100 K, a = 7.0546(3), b = 7.4861(3) and c = 11.6392(5) Å, α = 106.729(4)°, β = 91.932(4)°, γ = 97.698(4)°, V = 581.67(4) Å^3, Z = 2, d_{calc} = 1.526 g cm^{-3}, μ = 1.061 mm^{-1}, F(000) = 280. Total of 13644 reflections were measured and 2509 independent reflections (R_{int} = 0.0268) were used. The refinement converged to wR_2 = 0.0895 and GOF = 1.068 for all independent reflections [R_1 = 0.0329 was calculated for 2336 observed reflections with $I > 2\sigma(I)$].

CCDC 2160706 (**1i**) and 2384701 (**4a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk.

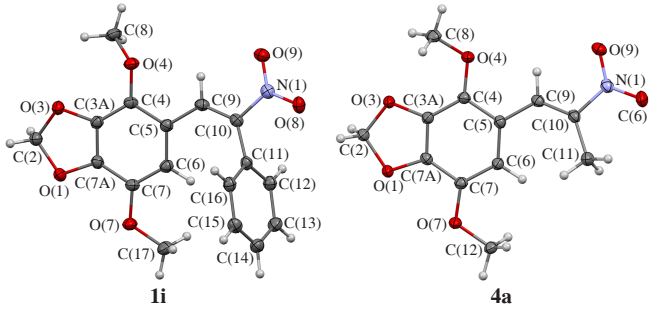


Figure 3 Molecular structure of *E*-1-phenyl-2-(2,5-dimethoxy-3,4-methylenedioxyphenyl)-1-nitroethylene **1i** and *E*-1-(2,5-dimethoxy-3,4-methylenedioxyphenyl)-2-nitropropene **4a**.

the phenyl ring was rotated relative to the double bond with the angle of 81.3°. The *cis*-arrangement of the aryl substituents in DNSs **1a–v** was also proved by their vinyl proton chemical shifts in the same range of 8.13–8.48 ppm in the ^{1}H NMR spectra. The *cis*-diaryl topology for aryl rings in DNSs suggested the ability of these molecules to exhibit antimitotic activity, in particular, to interact with tubulin/microtubules.

Antiproliferative effect of a CA4 nitroethylene analogue **1l** with $Ar^1 = 3,4,5\text{-}(MeO)_3C_6H_2$ and $Ar^2 = 4\text{-}MeOC_6H_4$ was first described in 1950. This compound at 87 μM concentration inhibited growth of chick embryo fibroblasts.[32] Subsequently, cytotoxic tubulin-targeting benzyl nitrostilbenes **2** (see Figure 1) were identified. However, no correlation between cytotoxicity and inhibition of tubulin polymerization was observed, suggesting another mode of action in addition to antitubulin effect.[15] With this in mind, DNSs **1a–v** were evaluated for antimitotic antitubulin activity and other toxic effects using a phenotypic sea urchin embryo assay.[8] Antimitotic/anti-proliferative activity was assessed by cell division (cleavage) alteration/arrest after fertilized eggs exposure to tested molecules. Figure 4 illustrates the typical cleavage defects caused by DNSs.

To identify targeting tubulin/microtubules, the compounds effect was examined on hatched blastulae (8–10 h post-fertilization). A specific change of embryo swimming pattern, namely, spinning on the bottom of the culture vessel instead of forward swimming near the surface, served as an evidence for microtubule destabilizing mechanism of action. Quick destruction of arrested eggs that prevented acquisition of tuberculate shape typical of microtubule destabilizers, as well as pronounced developmental defects and mortality after hatching in the absence of embryo spinning, suggested systemic toxicity of a compound. The results are presented in Tables 1 and S2. Generally, microtubule destabilizing agents can cause embryo mortality not only due to mitotic alteration/arrest at cleavage stage, but also when applied to post-hatched blastulae at a considerably higher concentration, resulting in embryo death after several hours of rapid spinning. For example, CA4 cleavage alteration MEC value was 2 nM, whereas embryo death after hatching was observed only at 50 nM concentration (see Table 1). In contrast, all tested DNSs caused cleavage abnormalities and post-hatching impairments at a concentration range of 0.2–4 μM irrespectively of embryo spinning, suggesting their systemic toxicity. In addition, compounds **1a**, **1d**, **1i**, **1o**, **1p**, and **1s** exhibited microtubule destabilizing activity as well, since they induced embryo spinning. The most potent DNSs **1o** and **1p** featuring 2-nitrobenzene ring and thienyl heterocycle, respectively, showed cleavage alteration MEC value of 0.2 μM. Molecules **1b** and **1r**, albeit failed to generate embryo spinning, could be considered as weak antitubulin agents due to their ability to induce formation of tuberculate arrested eggs typical for microtubule destabilizers. The activity of compounds **1d**, **1i**, and **1u** was estimated only approximately due to their precipitation in seawater. Specifically, crystals in seawater were observed at the concentration of 2 μM (**1d**) and 0.5 μM (**1u**), and **1i** formed oily spots on the surface of seawater at 2 μM concentration. The structure–activity relationship details are presented in Online Supplementary Materials. The impact of nitroethylene fragment into biological effect was assessed in a series of styrenes **3**, **4a**,**b**, and their activity was compared with that of isoapiol **5a** and isodillapiol **5b** (see Figure 2, Tables 1 and S2). DNSs **1a**, **1f**, and **1i** were selected for NCI60 cytotoxicity screen on sixty human cancer cell lines. These molecules inhibited growth of cancer cells with GI_{50} value of 1.38, 1.41, and 1.46 μM concentration, respectively (Figures S1–S6), which correlated well with sea urchin embryo assay results.

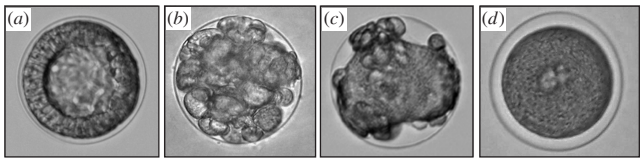


Figure 4 Typical effects of DNSs on the sea urchin *Paracentrotus lividus* eggs and embryos. (*a*) Intact early blastula. (*b*), (*c*) Effects of **1o** at 0.5 μM (*b*, aberrant cleavage) and 1 μM (*c*, arrested tuberculate egg) concentration. (*d*) Round-shaped arrested egg caused by **1s** at 2 μM concentration. Fertilized egg treatment. Incubation temperature: 22 °C. The images were made at 5.5 h postfertilization. The average egg/embryo diameter is 115 μm.

Our data were in a good correlation with the reported effects of nitroalkenes **6a–f** and **7**.[33] These molecules were found to suppress growth of HeLa cells with GI_{50} values of 2–25 μM. Furyl derivative **7** inhibited purified tubulin polymerization and affected both mitotic and interphase microtubule arrangement, most probably due to tubulin conformation disorder, suggesting both antitubulin and tubulin-unrelated mode of action. Similarly, 1-(3,4,5-trimethoxyphenyl)-2-nitroethylene **6g** (see Figure 2) suppressed cancer cells growth with GI_{50} values of 4.6–17.3 μM, inhibited both tubulin polymerization and colchicine binding to tubulin, although much weaker than CA4, suggesting additional tubulin-unrelated mechanism of **6g** effect.[34]

In summary, an efficient method for the preparation of DNSs by the Knoevenagel condensation of arylnitromethanes with methylamine Schiff bases of benzaldehydes has been developed. The synthetic protocol excluded column chromatography and allowed for the preparation of DNSs in high yields including previously inaccessible polymethoxybenzene-containing derivatives. The synthesized DNSs featured only *cis*-topology for two aryls and aryl/methyl substituent pairs irrespectively of the substitution pattern in the aryl rings. The DNSs exhibited both antitubulin and tubulin-unrelated effects in the phenotypic sea urchin embryo assay. Non-tubulin activity of DNSs could be related to the high reactivity of nitroethylene fragment towards SH-, NH-, OH-groups[10,35,36] that are widely abundant in living systems.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7633.

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