Concerns the manuscript: **Ref. No.: TET-D-15-01916**
Title: Synthesis of derivatives of methoxy dibenzo[*b, f*]oxepine with sodium azide

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Dear Editor,

I would like to thank referees for their careful reading of our manuscript and for their remarks, which were very helpful to us. We have improved the manuscript according of reviewers' comments. We hope that the revised version of our paper, enclosed herein, properly fulfils all the recommendations.

First of all, we re-worked the part of the results and the discussion in the following manner:

- we begun this section with an overview of our previous study involving the reaction of dinitrostilbene derivatives with sodium azide,
- we included a scheme 2 outlining the transformation key intermediates,
- we used our previous work to introduce our hypothesis for the new work,
- we discussed the olefin isomerisation, and proposed role of azide in this reaction,
- we referred the calculations performed in DMSO, because the reaction proceeded in DMSO, and also NMR was measured in DMSO-d_6. The structures were investigated in DMSO. In the text we supplemented the information on the type of solvent,
- we summarized the methods of preparation of dibenzo[*b, f*]oxepine in figure 2,
- we corrected the NMR analysis of compounds and references according to the template of *Tetrahedron,*
- we did not include the mass (only mmol) in part of General procedure of synthesis of dibenzo[*b,f*]oxepines, because the same procedure applied for all products,

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We hope that the new revised version of our manuscript is now suitable for publication in the *Tetrahedron.*

Yours sincerely,

Hanna Krawczyk

Synthesis of derivatives of methoxydibenzo[*b, f*]oxepine in the presence of sodium azide

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Keywords: cyclization • methoxydibenzo[*b, f*]oxepines •heterocycles• DFT calculations• molecular modeling

Abstract:

Dibenzo[*b,f*]oxepin is an important scaffold in medicinal chemistry and its derivatives occur in several medicinally important plants. A new approach to methoxydibenzo[*b, f*]oxepines (**15-21**) proceeding under mild reaction conditions, has been developed. Notably, the use of sodium azide in reaction allow obtaining the new substituted dibenzo[*b, f*]oxepines. In order to study their shape and conformation, the optimum structures of the compounds were calculated using the DFT B3LYP/6-311++G(2d, p) method. A docking simulation was performed to insert compound **20** into the crystal structure of tubulin at the colchicine binding site to determine the probable binding model. The information of this work can be

helpful for the investigation of new tubulin polymerization inhibitors exhibiting stronger activity.

Introduction

The growth and development of most solid tumors require that they form their own functional vascular supply, which is produced from the host's normal vascular network in the process of angiogenesis. This neo-vasculature of tumors is, due to its significance, an excellent target in terms of annihilating cancer cells. Two forms of vascular targeting agents (VTAs) have evolved: those that inhibit the angiogenesis process (called angiogenesis inhibitors, AIs) and those that damage the already-established vessels (vascular disrupting agents, VDAs).[1,2] Combretastatins CA1P (OXi4503) and CA4P (a class of naturally occurring stilbene derivatives, Fig. 1) are new vascular disrupting agents and vascular targeting agents.[1,2] They exhibit remarkable abilities to inhibit gastric tumor metastasis and to enhance antitumor immune reactivity.[3] OXi4503 is the diphosphate prodrug of the stilbenoid combretastatin A1, originally isolated from the plant *Combretum caffrum*, with vascular-disrupting and antineoplastic activities.[4-7] Upon administration, combretastatin A1 diphosphate (CA1P) is dephosphorylated to afford the active metabolite combretastatin A1 (CA1), which promotes rapid microtubule depolymerization; endothelial cell mitotic arrest and apoptosis, destruction of the tumor vasculature, disruption of tumor blood flow and tumor cell necrosis may ensue.[8-10] The corresponding disodium phosphate prodrug of CA-4 (fosbretabulin, Fig.1) is currently of an advanced stage of clinical development, having recently entered phase II/III studies in combination with carboplatin or paclitaxel in patients with anaplastic thyroid cancer.[11-13] It is worth noting that these compounds contain numerous methoxy groups in the framework. Moreover, only the *Z*-isomer of the stilbenoid exhibits the properties of a drug, whereas the *E*-isomer does not.[14]

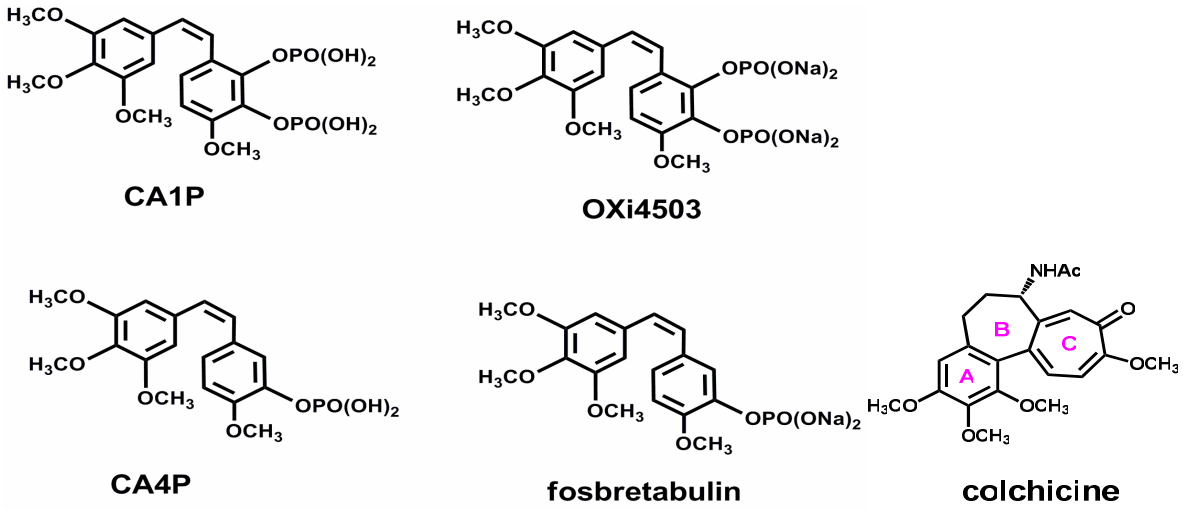


Figure 1. The structure of CA1P, CA4P and their sodium salts -OXi4503 and fosbretabulin, and structure of colchicine.

Continuing our study concerning the synthesis and search for biologically active stilbenes,[15-20] we have directed our attention to the dibenzo[*b,f*]oxepines. These compounds have in their skeleton a (*Z*)- stilbene motif, and additionally their aromatic rings are connected by the oxygen. Moreover, dibenzo[*b,f*]oxepin is an important scaffold in medicinal chemistry and its derivatives occur in several medicinally important plants.[21-26] Molecules with this skeleton exhibit antidepressive,[27,28] antipsychotic,[29-34] anti-estrogenic,[35] antitumor[25] and anti-inflammatory[36] properties. Their activity as VTAs has not been investigated.

Multiple synthetic pathways provide access to the dibenzo[*b,f*]oxepin scaffold (Fig.2).[27-60] One of these has focused primarily on the combination of Ullmann coupling and the Friedel-Crafts reaction.[27,28,32,36-38] An efficient synthesis is a two-step protocol that involves Ullmann coupling and ring-closing metathesis reactions.[28] Also the nucleophilic aromatic substitution reaction (SNAr) has been often used for the formation of biaryl ethers.[39-43] Expansion of a xanthene ring using a Wagner-Meerwein rearrangement or, a Mn (III)-based oxidative radical rearrangement has been an interesting method, too.[44-49] In the synthesis of dibenzo[*b,f*]oxepines a sequential Heck reaction and Pd-catalyzed etherification were adopted.[50,51]

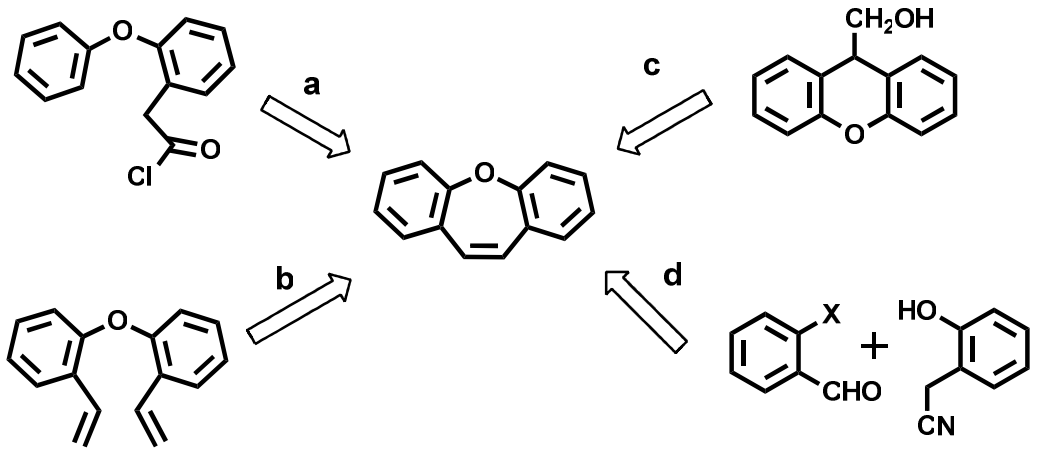


Figure 2. Examples of methods for the preparation of the dibenzo[*b,f*]oxepin scaffold: a) the combination of Ullmann coupling and the Friedel-Crafts reaction;[27,28,32, 36-38] b) the Ullmann coupling and ring-closing metathesis reactions;[28] c) the Wagner-Meerwein rearrangement; [44-47] d) one-pot transition-metal-free synthesis from 2-halobenzaldehydes.[52]

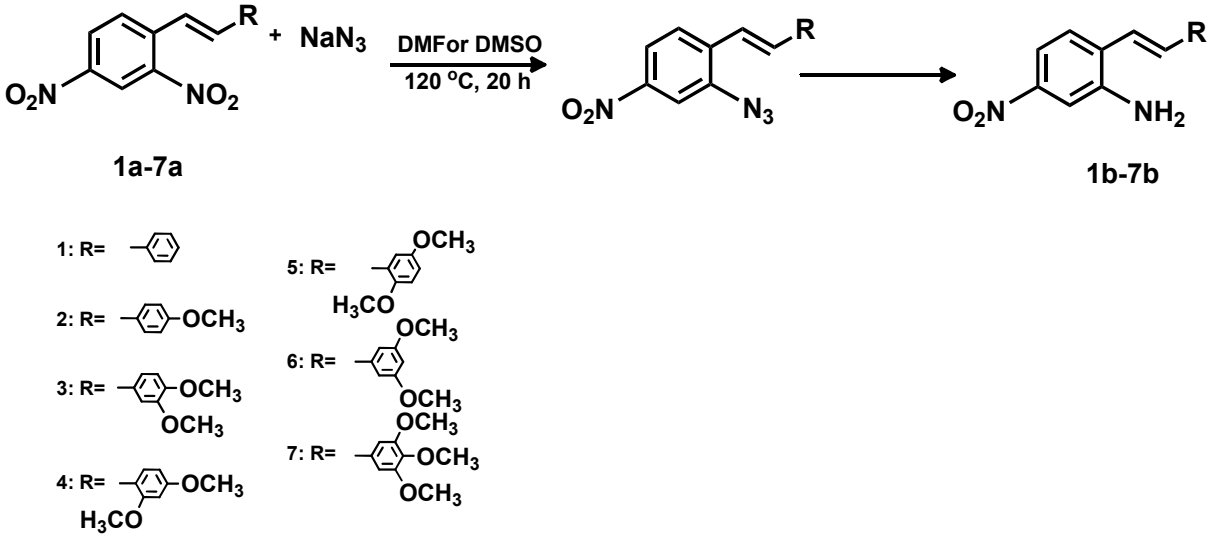
Another noteworthy approach has been to prepare dibenzo[*b,f*]oxepines with various functional groups via a one-pot cascade reaction[53] under Cu-assisted as well as Cu-free conditions.[52] Synthetic approaches to naturally occurring dibenzo[*b,f*]oxepins concerned mainly the preparation of various bauhinoxepins.[54-58] In 2001, Chernysheva *et al.*[59,60] reported a one-pot procedure to prepare NO_2-substituted dibenz[*b,f*]oxepines. However, this method involved explosive 2,4,6-trinitrotoluene as the starting reagent.

As part of a program to search for biologically active stilbenes we have sought to develop an efficient and easy synthesis of methoxydibenzo[*b,f*]oxepines.

Results and Discussion

In our previous study we found that the reaction between a derivative of 2,4-dinitrostilbene and sodium azide always gave the corresponding (*E*)-2-amino-4-nitrostilbene as the sole product (Scheme 1).[15-20] The reaction was regiospecific with only the *ortho*-NO_2 group replaced. We have shown that the transformation proceeds *via* an intermediate azide

product which after about 1 h gradually disappears with simultaneous formation of the final amine product.[16-20] On the basis of our investigations, we hypothesize that the strongly electron-withdrawing nitro group at position 4 in the substrates makes the nitro group at position 2 more prone to substitution by the azide group and subsequently to reduction into an amine group. Because the *ortho*-nitro group is more prone to substitution we suppose that 2-hydroxy-2',4'- dinitrostilbenes can undergo intramolecular nucleophilic substitution and can finally give dibenzo[*b,f*]oxepines scaffold.

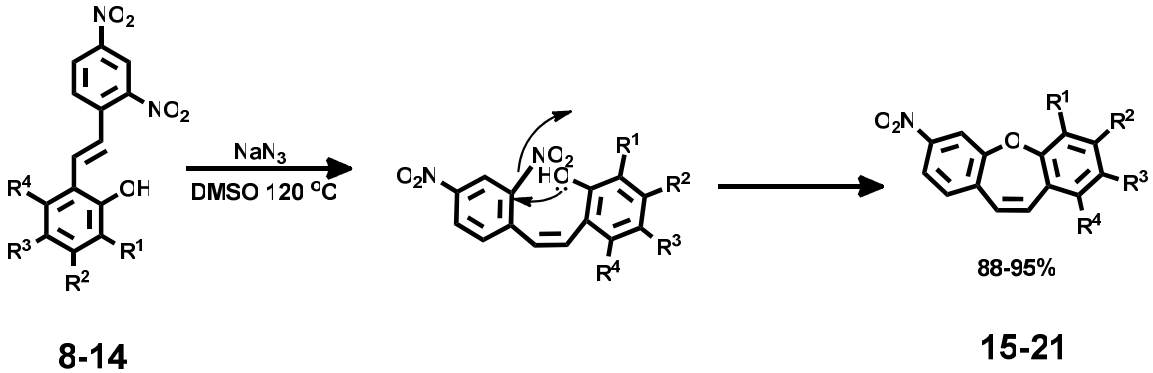


Scheme 1. The unanticipated formation of aminostilbenes **1b-7b** from nitrostilbenes **1a-7a** under azidation conditions.

Herein, we report a two-step synthesis of dibenzo[*b,f*]oxepin that involves the condensation of 2,4-dinitrotoluene with various substituted methoxyaldehydes[61] and subsequent cyclization of the obtained stilbenes. The cyclization reactions were made both without and with sodium azide, to assess if azide was formed before there was isomerization to form *Z* and cyclization to dibenzo[*b,f*]oxepin. Serendipitously, the addition of sodium azide influenced the yield of these reactions. In our investigation we conducted studies of the cyclization reaction of (*E*)-2-hydroxy-2',4'-dinitrostilbene (**8**) and the methoxy derivatives of

(*E*)-2-hydroxy-2',4'-dinitrostilbene (**9-13**) and the nitro derivative of (*E*)-2-hydroxy-2',4'-dinitrostilbene (**14**) in the presence of sodium azide (Table 1). In all cases we obtained the scaffold of dibenzo[*b*,*f*]oxepine (**15-21**). Just like with the derivatives of 2,4-dinitrostilbene without a hydroxyl group, only the *ortho*-NO_2 group in position 2' was replaced. We can assume that a stilbene substituted with two electron-withdrawing NO_2 groups located in one of the rings, reduces the electron density in the system. As a result, nucleophilic substitution of one of the nitro groups by the hydroxyl oxygen from the 2-position derived from the other aryl ring is possible. In the case of derivative (*E*)-2-hydroxy-2',4'-dinitrostilbenes, the azide intermediate products have not been observed.

Table 1. Synthesis of dibenzo[*b*,*f*]oxepines **(15-21).**



Compound number	R^1	R^2	R^3	R^4	yield (%)[a]
8,15	H	H	H	H	92
9,16	OCH_3	H	H	H	88
10,17	H	OCH_3	H	H	95
11,18	H	H	OCH_3	H	95
12,19	H	H	H	OCH_3	95
13,20	OCH_3	H	OCH_3	H	95
14,21	NO_2	H	H	H	90

[a] Isolated yield.

During our examination we have investigated reaction formation of dibenzo[*b*,*f*]oxepines without sodium azide. We observed far lower yield in products (**15-20**) and, surprisingly, the absence of **21**. The relative rates were about 50% higher for reactions with sodium azide than the reactions without sodium azide. We concluded that to get high yield of oxepines there should be sodium azide.

In order to explain the selectivity of cyclization we calculated energy minima of the reactants in DMSO solution. The optimum structure of **8-14** using the DFT B3LYP/6-311++G(2d, p) method was calculated (see Supplementary Information). It appeared that the *ortho*-nitro group of 2' was rotated around the C–N axis by 30.8^{o} and 36.9^{o} for (**8-14**) (Table 2) and that the *para*-nitro group was coplanar with respect to the aromatic ring (see Supplementary Information). On the basis of our calculations, we have hypothesized that the coupling of *p* electrons of the nitro group from position 2' with π electrons in the aromatic ring is less effective than in the case of the nitro group at position 4' and makes the nitro group at position 2' more prone to substitution.

Table 2. The calculation angles between the *ortho*-nitro group in position 2 and ring of **8-14** stilbenes.

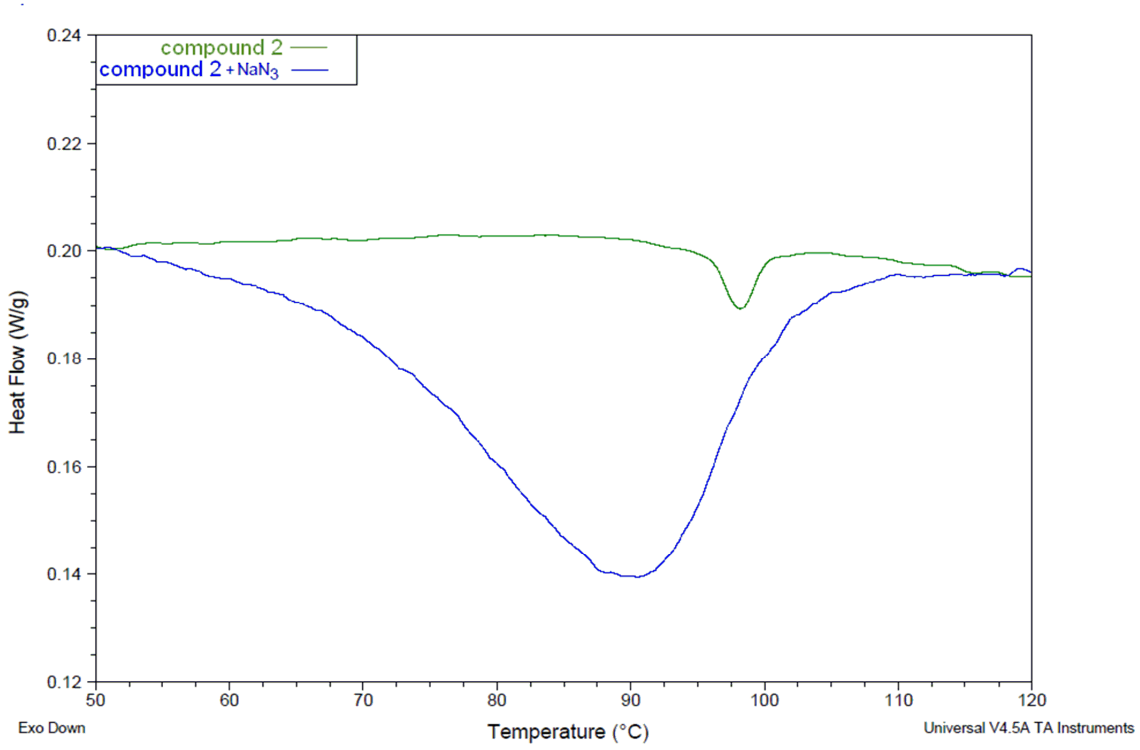
Compound	**Angles (^{o})**
8	36.4 / 34.9
9	31.6 / 31.5
10	34.1 / 34.4
11	31.4 / 31.4
12	30.8 / 30.8
13	31.3 / 31.3
14	33.7 / 34

The DSC analysis of cyclization reaction of compound **9** with and without azide has been done and is presented in Fig.3 (in this process the product **16** was obtained). The DSC

analysis provides information on the transformation of an analyte, which depends on the heat exchange conditions in the analyzer–sample system (see Supplementary Information). Measurements were taken at 0.1 ^{o}C/min heating rate. The analysis showed only one exothermic transition above 88 ^{o}C in cyclization with azide and above 98 ^{o}C in the reaction without azide. Based on Ozawa–Flynn–Wall analysis, conversion vs. the activation energy were estimated. It could be observed that, e.g. for 0.1 conversion, the activation energy in cyclization with azide was lower than without azide (about 6.59 kJ/mol, see Supplementary Information). Therefore, one can conclude that the sodium azide decreases the activation energy of cyclization reaction and, probably for compound **14**, allows the reaction to proceed.

The results of calculations show the *para*-nitro substituent aligning in conjugation with the benzene ring whilst the *ortho*-nitro substituent twists out of conjugation, presumably for steric reasons. The coplanarity of the *para*-nitro group may be important for an intramolecular S_NAr mechanism. We have hypothesized that the phenoxide attacks the electron-deficient ring to form a spiro intermediate, which then undergoes ring expansion with expulsion of a leaving group (Table 1). The process proceeds for all stilbenes (**8-13**) but only in the case **14** (phenoxide ring is bonded with EWG group) with sodium azide. The addition of sodium azide could influence the process of isomerization of stilbenes from *E* to *Z*, because the relative rates were about 50% higher for reactions with sodium azide than for the reactions without sodium azide (**15-20**) (the azide intermediate products have not been observed). In the literature there are examples of compounds investigated as *E*/*Z* catalysts of stilbene.[62] NO was tested as an *E*/*Z* catalyst of stilbene in solution.[62] However, C=C bonded molecule investigated showed slight increase in the rate of isomerization, but the experiment was performed at room temperature. The *E*/*Z* isomerization of stilbene in the presence of NaN_3 has not been previously described.

Figure 3. DSC curves of the cyclization of compound **9** with (-) and without azide (-).



In order to determine the structure of reaction products (**15-21**) in solution, ^{1}H and ^{13}C NMR spectra of all the products have been measured (complete data shown in Supplementary Information). The ^{1}H and ^{13}C NMR resonances were assigned unequivocally, based on the combined information from 1D to 2D NMR (gCOSY, gHSQC and gHMBC) experiments. Coupling constants (^{1}H–^{1}H) were measured directly from resolution-enhanced 1D spectra and confirmed, when necessary, by homo-decoupling. gHSQC and gHMBC analysis allowed the assignment of the dibenzo[*b,f*]oxepines regiochemistry.

Additionally, the optimum structure of **15-21** was calculated using the DFT B3LYP/6-311++G(2d,p) method (and with polarizable continuum model–PCM) [see Supplementary Information]. Calculations have shown that the scaffold of dibenzo[*b,f*]oxepine is not planar and that it creates a basket. The dihedral angles between aromatic rings connected with oxygen and double bound for **15-21** dibenzooxepines are 64.9°-68.8° (Table 3).

As we previously mentioned, upon administration, combretastatin A1 diphosphate (CA1P) is dephosphorylated to the active metabolite combretastatin A1 (CA1) (Fig.1), which promotes rapid microtubule depolymerization.[63-66] Microtubules are highly dynamic polymers and their essential element is the α/β-tubulin heterodimer. The tubulin heterodimer contains at least three distinct drug binding sites: the paclitaxel, vinblastine, and colchicine binding sites. [67] For the first two of these sites, drugs are in current use in clinical oncology.[68] Over the last decades, a large number of compounds able to interact with the colchicines binding site have been investigated.[69] However, no colchicine site inhibitor has found clinical application in anticancer therapy. Colchicine (Fig.1) itself binds to tubulin very tightly, but its severe toxicity to normal tissues has hampered its use in the clinic.[70] Colchicine is known to bind the non-polymerized tubulin.[70] The C ring of colchicine interacts establishing van der Waals contacts with Valα181, Serα178, and Valβ315. The carbonyl group behaves as a hydrogen bond acceptor, interacting with Valα181. The A ring is buried in a hydrophobic pocket delimited by Lysβ352, Asnβ350, Leuβ378, Alaβ316, Leuβ255, Lysβ254, Alaβ250 and Leuβ242, and the methoxy group at position 3 is involved in a hydrogen bond interaction within the thiol group of Cysβ241. Currently, combretastatin A-4 (CA-4) is one of the most promising *anti*-tubulin agents that targets the colchicines site.[71]

Consequently, the ability of compound **20**, which is structurally the closest to combretastatin A1, to interact with the tubulin (crystal structure from PDB code: 1SA0)[72] has been analyzed by computer molecular modeling. The molecular docking was performed by simulation of compound **20** into the colchicine binding site in tubulin. All docking runs were applied the Broyden-Fletcher-Goldfarb-Shanno (BFGS) method of AutoDock Vina program.[73,74]

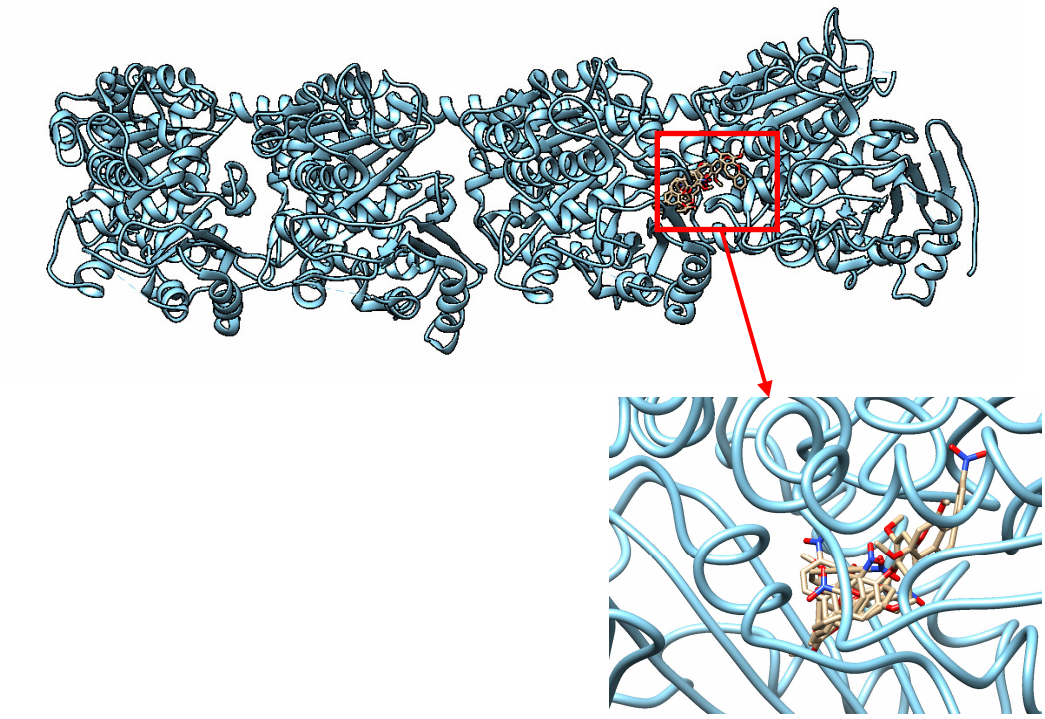
Table 3. The calculation dihedral angles aromatic rings connected with oxygen and double bound for **15-21.**

Compound	Angles (°)
15	66.1 / 66.9
16	67.6 /68.2
17	64.9 / 66.8
18	66.7 /66.5
19	66.1 /68.8
20	68.4 / 68.6
21	66.7 /66.3

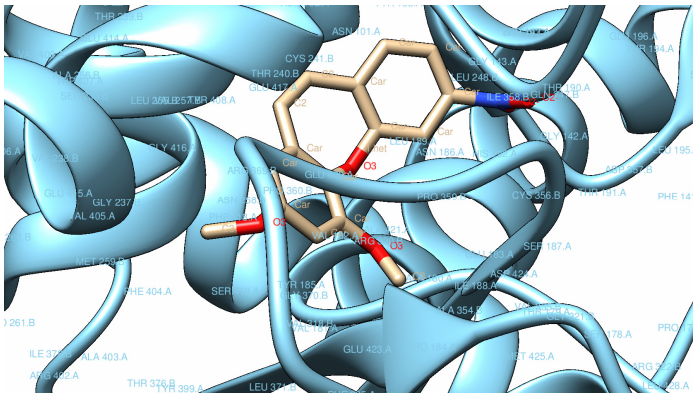
The binding model of compound **20** and tubulin is depicted in Figure 4. The amino acid residue of α and β tubulin (crystal structure from PDB code: 1SA0)[72] was labeled. In the binding mode, compound **20** was bound to the colchicine binding site of tubulin *via* hydrophobic interaction and binding was stabilized by a hydrogen bond. The nitro group behaves as a hydrogen bond acceptor, interacting with Valα181. The calculated binding energies were used as parameters for the selection of the cluster of docking posed to be evaluated (Fig.4a,b), in which the binding mode of the lowest energy structure was located (selection of the cluster in docking for the lowest energy structure (pose) of investigated molecule). The selected pose of **20** had an estimated binding free energy of -7.2 kcal/mol (binding free energy of control compounds colchicine and CA-4 are -8.6 kcal/mol and -7.62 kcal/mol, respectively[71]). The model was similar to the models between colchicine, CA-4 and the colchicine binding site.[75,76] In the **20** binding model, more details revealed that there were some key roles of the interaction between **20** and tubulin (Fig. 4b). The compound **20** was embedded in the hydrophobic pocket occupied by the A ring of colchicine (van der Waals contact with Valα181, Cysβ241, Leuβ248 and Glyα 142). Overall, these results suggested that compound **20** could be well inserted into tubulin, similar to colchicine and CA-4.[75,76]

Figure 4. a) 3D model of the interaction between compound **20** and the colchicine binding site of α and β tubulin (crystal structure from PDB code: 1SA0);[72] b) the selected pose of **20** -an estimated binding free energy of -7.2 kcal/mol.

a)



b)



Conclusions

In summary, we have developed a new, easy synthesis of dibenzo[*b,f*]oxepine from substituted 2-hydroxy-2',4'-dinitrostilbene with high yield. Notably, the addition of sodium azide

decreases the activation energy in a cyclization reaction and, therefore, the cyclization reaction with EWG group in the ring may be performed. Calculations show that the scaffold of dibenzo[*b,f*]oxepine is not planar and that it creates a basket, which may be significant in further application of this method for the synthesis of medicinally useful compounds. Molecular docking was further performed to study compound **20** and tubulin protein interactions. After analysis of the binding model of compound **20** with tubulin, it was found that several interactions with the protein residues in the colchicine binding site are present. This information can be helpful for the investigation of new tubulin polymerization inhibitors exhibiting stronger activitiy. The biological activity of our products (**15-21**) will be investigated in the near future.

Materials and methods

All the spectra were recorded using a Varian VNMRS spectrometer operating at 11.7 T magnetic field. Measurements were performed for ca. 1.0 M solutions of all the compounds in DMSO-d_6. The residual signals of DMSO-d_6 (2.54 ppm) in ^{1}H NMR and the DMSO-d_6 signal (40.45 ppm) in ^{13}C NMR spectra were used as the chemical shift references. All the proton spectra were recorded using the standard spectrometer software and parameters set: acquisition time 3 s, pulse angle 30^0. The standard measurement parameter set for ^{13}C NMR spectra was: pulse width 7 μs (the 90 o pulse width was 12.5 μs), acquisition time 1 s, spectral width 200 ppm, 1000 scans of 32 K data point were accumulated and after zero-filling to 64 K; and the FID signals were subjected to Fourier transformation after applying a 1 Hz line broadening. The ^{1}H–^{13}Cgs-HSQC and ^{1}H–^{13}Cgs-HMBC spectra were also recorded using the standard Varian software. All (*E*)-2'-hydroxy-2,4-dinitrostilbenes used in dibenzo[*b,f*]oxepines synthesis were obtained according H. Hoyer, M. Vogel procedure. [61]

General procedure of synthesis of dibenzo[*b,f*]oxepines 15-21 (Table 1): (*E*)-2'-Hydroxy-2,4-dinitrostilbene (1.70 mmol), and NaN_3 (190 mg, 2.95 mmol) in DMSO (15 ml), were sequentially added to a three-necked flask (25 mL) fitted with a condenser. The mixture was

stirred at 120 ^{0}C for 24 h and concentrated in vacuo (see Supplementary Information). The residue was purified by flash column chromatography on silica gel (toluene → toluene: MeOH, 9:1).

IR spectra

The IR spectra were recorded at ambient temperature on a Perkin Elmer System 2000, using the technique of Attenuated Total Reflectance (ATR) for compounds (**15**) and (**16**). Other compounds (**17-21**) were recorded on a FTIR Nicolet 6700 using ATR (see Supplementary Information).

Computational aspects

The optimum ground-state geometry for compounds (**8-21**) were calculated using density functional theory (DFT). [77] The B3LYP functional and 6-311G 6-311++g (2d,p) basis set and the continuum model (PCM; Gaussian 03W) [78] was used in order to simulate the effects of the solvent -DMSO. All the calculations were performed on a server equipped with a 16 quad-core XEON (R) CPU E7310 processor operating at 1.60 GHz. The operating system was Open SUSE 10.3. (see Supplementary Information). Molecular docking of compound **13** into the 3D X-ray structure of tubulin (PDB code: 1SA0)[72] was carried out using the Auto-Dock Vina software (the Broyden-Fletcher-Goldfarb-Shanno (BFGS) method)[73] Configurations of protein/ dimethoxydibenzo[*b, f*]oxepine complex was created using UCSF Chimerasoftware.[74] The graphical user interface ADT was employed to set up the enzyme: all hydrogens were added. For macromolecules, generated pdbqt files were saved. The 3D structures of ligand molecules were built, optimized (B3LYP functional and 6-311G 6-311++g (2d,p) basis set) level, and saved in Mol2 format. The graphical user interface ADT was employed to set up also the ligand and pdbqt file was saved. Auto-Dock Vina software was employed for all docking calculations. The AutoDockTools program was used to generate the docking input files. In docking a grid box size of 44x46x44 points in x, y, and z directions was built, the maps were center located (115.574, 89.495, 7.664) in the catalytic site of the protein. A grid

spacing of 0.375 Å (approximately one forth of the length of carbon-carbon covalent bond) was used for the calculation of the energetic map.

Analysis of compounds (15-21):

3-nitrodibenzo[*b,f*]oxepine- (**15**): stirred at 120 ^{0}C for 24 h, yield 92% (373 mg; 1.56 mmol), dark yellow powder, mp 150.0-150.2 ^{0}C; ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C): δ= 2,54 (quintet, 6H, $(Me_3)_2$): 8.15 (d, $^3J_{H,H}$ =2.5 Hz, 1H, 4-H), 8.09 (dd, $^3J_{H,H}$ =8.5 Hz, $^3J_{H,H}$ =2.5 Hz, 1H, 2-H); 7.62 (d, $^3J_{H,H}$ =8.5, 1H, 1-H), 7.48 (ddd, $^3J_{H,H}$ =7.5, $^3J_{H,H}$ = 7.5 Hz, $^3J_{H,H}$ = 1.5 Hz, 1H,7-H), 7.45(dd, $^3J_{H,H}$ =7.5, $^3J_{H,H}$ = 1.5 Hz, 1H, 6-H), 7.41(dd, $^3J_{H,H}$ = 7.5, $^3J_{H,H}$ =1.5 Hz, 1H, 9-H), 7.28 (ddd, $^3J_{H,H}$ =7.5, $^3J_{H,H}$ = 7.5 Hz, $^3J_{H,H}$ = 1.5 Hz, 1H, 8-H), 7.08 (d (spin system AB), $^3J_{H,H}$=11.5 Hz, 1H,10-H), 6.98 (d (spin system AB), $^3J_{H,H}$=11.5 Hz, 1H, 11-H). ^{13}C NMR (125 MHz, DMSO-d_6, 25°C): δ= 156.93 (C-13), 156.86 (C-14), 149.05(C-3), 138.01 (C-12), 134.36(C-10), 132.06 (C-7), 131.12 (C-1), 130.80 (C-9), 130.43 (C-15), 129.10 (C-11), 126.73(C-8), 122.35 (C-6), 121.26 (C-2), 117.46 (C-4), 40.45 (C-DMSO-d_6) ppm. HRMS (EI+ 3.19e3): *m/z* calculated for $C_{14}H_9NO_3$ 239.0582; found 239.0583.

6-methoxy-3-nitrodibenzo[*b,f*]oxepine (**16**): stirred at 120 ^{0}C for 24 h, yield 88% (404 mg; 1.50 mmol), yellow powder, mp 180.0-180.3 ^{0}C; ^{1}H NMR (500 MHz, DMSO-d_6, 25°C):δ= 2,54 (quintet, 6H, $(Me_3)_2$), 8.09 (d, $^3J_{H,H}$ = 8.5 Hz, 1H, 2-H), 7.94 (d, $^3J_{H,H}$ = 2.5 Hz, 1H, 4-H), 7.64 (d, $^3J_{H,H}$ = 8.5, 1H, 1-H), 7.22 (d, $^3J_{H,H}$ =3 Hz, 1H,7-H), 7.21 (d, $^3J_{H,H}$ =6 Hz, 1H, 9-H), 7.09 (d (spin system AB), $^3J_{H,H}$= 11.5 Hz, 1H, 10-H), 7.01 (d, $^3J_{H,H}$ =11.5 Hz, 1H, 11-H), 6.96 (dd, $^3J_{H,H}$ =6 Hz, $^3J_{H,H}$ =3Hz, 1H, 8-H), 3.95 (3H, OCH_3) ppm. ^{13}C NMR (125 MHz, DMSO-d_6, 25°C): δ= 156.73 (C-13), 152.26 (C-6), 148.86(C-3), 144.46(C-14), 138.31(C-12), 134.39(C10), 131.54(C-15), 131.07(C-1), 129.19 (C-11), 126.81(C-9), 121.75(C-8), 121.28 (C-2), 117.19 (C-4), 114.98 (C-7), 57.12 (OCH_3) 40.45(C-DMSO-d_6) ppm. HRMS (ESI TOF, MeOH): *m/z* calculated for $C_{15}H_{11}NO_4Na$ (M++Na) 292.0586; found 292.0576.

3-methoxy-7-nitrodibenzo[*b,f*]oxepine (**17**): stirred at 120 ^{0}C for 24 h, yield 95% (436 mg; 1.62 mmol), dark brown powder, mp 174.9-175.3 ^{0}C; ^{1}H NMR (500 MHz, DMSO-d_6, 25°C): δ= 2,54 (quintet, 6H, $(Me_3)_2$), 8.17 (d, $^3J_{H,H}$ = 2.0 Hz, 1H, 6-H), 8.08 (dd, $^3J_{H,H}$ = 9.0 Hz, $^3J_{H,H}$ =2.0 Hz, 1H, 8-H), 7.57 (d, $^3J_{H,H}$ = 9.0 Hz, 1H, 9-H), 7.31 (d, $^3J_{H,H}$ = 8.5 Hz, 1H, 1-H), 7.11 (d, $^3J_{H,H}$ = 2.5 Hz, 1H, 4-H), 6.99 (d (spin system AB), $^3J_{H,H}$= 11.5 Hz, 1H, 11-H), 6.86 (dd, $^3J_{H,H}$ =8.5, Hz , $^3J_{H,H}$ =2.5 Hz, 1H, 2-H), 6.81(d (spin system AB), $^3J_{H,H}$= 11.5 Hz, 1H, 10-H), 3.84 (s, 3H,OCH_3) ppm. ^{13}C (125 MHz, DMSO-d_6, 25°C): δ=163.03 (C-3), 157.95 (C-13), 156.27(C-14), 148.76(C-7), 138.55(C-15),134.28(C-11), 131,62 (C-1), 130.85(C-9), 126.61(C-10), 123.09(C-12), 121.33(C-8), 117.69 (C-6), 112.80(C-2), 108.01 (C-4), 56.60 (OCH_3), 40.45(C-DMSO-d_6) ppm. HRMS (EI+ 5.98e3): *m/z* calculated for $C_{15}H_{11}NO_4$ 269.0688; found 269.0687.

2-methoxy-7-nitrodibenzo[*b,f*]oxepine (**18**): stirred at 120 ^{0}C for 24 h, yield 95% (436 mg; 1.62 mmol), bright brown powder, mp 176.0-176.4 ^{0}C; ^{1}H NMR (500 MHz, DMSO-d_6, 25°C): δ= 2,54 (quintet, 6H, $(Me_3)_3$), 8.13 (d, $^3J_{H,H}$ =2.5 Hz, 1H, 6-H), 8.08 (dd, $^3J_{H,H}$ =8.5 Hz, $^3J_{H,H}$ =2.5, 1H, 8-H), 7.61 (d, $^3J_{H,H}$ =8.5 Hz, 1H, 9-H), 7.37 (d, $^3J_{H,H}$ =9.0 Hz, 1H, 4-H), 7.04 (d (spin system AB), $^3J_{H,H}$= 11.5Hz, 1H, 11-H), 7.02 (dd, $^3J_{H,H}$ =9.0 Hz, $^3J_{H,H}$ =3.0 Hz, 1H, 3-H), 6.98 (d (spin system AB), $^3J_{H,H}$= 11.5Hz, 1H, 10-H), 6.97 (d, $^3J_{H,H}$ =3.0 Hz, 1H, 1-H), 3.78(s, 3H, OCH_3) ppm. ^{13}C (125 MHz, DMSO-d_6, 25°C): δ= 157.57 (C-2), 157.28 (C-14), 150.52 (C-13), 149.06 (C-7), 137.98 (C-15),134.30 (C-11), 131,20 (C-9), 131.12(C-12), 129.42(C-10), 123.08(C-4), 121.13(C-8), 117.28 (C-6), 117.19(C-3), 114.96 (C-1), 56.50 (OCH_3), 40.45(C-DMSO-d_6) ppm. HRMS (EI+ 1.09e4): *m/z* calculated for $C_{15}H_{11}NO_4$ 269.0688; found 269.0691.

1-methoxy-7-nitrodibenzo[*b,f*]oxepine (**19**): stirred at 120 ^{0}C for 24 h, yield 95% (436 mg; 1.62 mmol), bright brown powder, mp 141.8-142.0 ^{0}C; ^{1}H NMR (500 MHz, DMSO-d_6, 25°C): δ= 2,54 (quintet, 6H, $(Me_3)_2$), 8.14 (d, $^3J_{H,H}$ =2.5 Hz, 1H, 6-H), 8.09 (dd, $^3J_{H,H}$ =8.5

Hz, $^{3}J_{H,H}$=2.5 Hz, 1H, 8-H), 7.60 (d, $^{3}J_{H,H}$=8.5, 1H, 9-H), 7.45 (dd, $^{3}J_{H,H}$ =8.5 Hz, $^{3}J_{H,H}$ =8.0 Hz, 1H, 3-H), 7.19 (d (spin system AB), $^{3}J_{H,H}$= 11.5Hz, 1H, 11-H), 7.06 (d, $^{3}J_{H,H}$ =8.0 Hz, 1H, 4-H), 6.98 (d (spin system AB), $^{3}J_{H,H}$= 11.5Hz, 1H, 10-H), 6.96 (d, $^{3}J_{H,H}$ =8.5 Hz, 1H, 2-H), 3.87 (s, 3H, OCH_3) ppm. ^{13}C (125 MHz, DMSO-d_6, 25°C): δ= 158.58 (C-13), 157.98 (C-1), 156.97(C-14), 149.00(C-7), 138.59(C-15), 132.57(C-3), 130,87 (C-9) 128.95(C-11), 128.37(C-10), 121.38(C-8), 119.17(C-12), 117.49 (C-6), 114.46 (C-4), 109.36 (C-2), 57.12 (OCH_3), 40.45 (C-DMSO-d_6) ppm. HRMS (EI+1.36e4): *m/z* calculated for $C_{15}H_{11}NO_4$ 269.0688; found 269.0690.

2,4-dimethoxy-7-nitrodibenzo[*b,f*]oxepine (**20**): stirred at 120 ^{0}C for 24 h, yield 95% (484 mg; 1.62 mmol), bright brown powder, mp 139.1-139.4 ^{0}C; ^{1}H NMR (500 MHz, DMSO-d_6, 25°C): δ= 2,54 (quintet, 6H, $(Me_3)_2$), 8.09 (dd, $^{3}J_{H,H}$ =8.5 Hz, $^{3}J_{H,H}$ =2.5 Hz, 1H, 8-H), 7.90 (d, $^{3}J_{H,H}$ =2.5Hz, 1H, 6-H), 7.64 (d, $^{3}J_{H,H}$ =8.5 Hz, 1H, 9-H), 7.05 (d (spin system AB), $^{3}J_{H,H}$= 11.5Hz, 1H, 11-H), 7.02(d (spin system AB), $^{3}J_{H,H}$= 11.5Hz, 1H, 10-H), 6.78 (d, $^{3}J_{H,H}$ =2.5 Hz, 1H, 3-H), 6.54 (d, $^{3}J_{H,H}$ = 2.5 Hz, 1H, 1-H), 3.93 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3) ppm. ^{13}C (125 MHz, DMSO-d_6, 25°C): δ= 157.73 (C-2), 157.06 (C-14), 152.77 (C-4), 148.84 (C-7), 138.55 (C-13), 138.27 (C-15), 134.51 (C-11), 131.55 (C-12), 131.11 (C-9), 129.46 (C-10), 121.12 (C-8), 116.97 (C-6), 104.85(C-1), 102.36 (C-3), 57.19 (OCH_3), 56.51 (OCH_3), 40.45 (C-DMSO-d_6) ppm. HRMS (EI+ 3.80e3): *m/z* calculated for $C_{16}H_{13}NO_5$ 299.0794; found 299.0792.

3,6-dinitrodibenzo[*b,f*]oxepine (**21**): stirred at 120 ^{0}C for 24 h, yield 90% (435 mg; 1.53 mmol), brown powder above 149.8-150.1 ^{0}C the decomposition. ^{1}H NMR (500 MHz, DMSO-d_6, 25°C): δ= 2,54 (quintet, 6H, $(Me_3)_2$), 8.20 (dd, $^{3}J_{H,H}$ =8.5 Hz, $^{3}J_{H,H}$ =2.5 Hz, 1H, 2-H), 8.06 (d, $^{3}J_{H,H}$= 2.5 Hz, 1H, 4-H), 8.05 (dd, $^{3}J_{H,H}$= 8.0 Hz, $^{3}J_{H,H}$= 1.5 Hz, 1H, 7-H), 7.77 (dd, $^{3}J_{H,H}$= 8.0 Hz, $^{3}J_{H,H}$= 1.5 Hz, 1H, 9-H), 7.72 (d, $^{3}J_{H,H}$=8.5 Hz, 1H, 1-H), 7.51 (t, $^{3}J_{H,H}$= 8.0 Hz, 1H, 8-H), 7.18 (d (spin system AB), $^{3}J_{H,H}$= 11.5Hz, 1H, 11-H), 7.14 (d (spin system AB),

$^{3}J_{H,H}$= 11.5Hz, 1H, 10-H) ppm. ^{13}C (125 MHz, DMSO-d6, 25°C): δ=155.99(C-13), 149.28 (C-3), 147.33 (C-6), 143.93 (C-14), 137.37 (C-12), 135.43 (C-9), 133.02(C-11), 131.83 (C-1), 131.06 (C-10), 127.39 (C-8), 126.43 (C-7), 122.31(C-2), 117.37(C-4), 115.41 (C-15), 40.45 (C-DMSO-d_6) ppm. HRMS (EI+ 1.87e4): *m/z* calculated for $C_{14}H_8N_2O_5$ 284.0433; found 284.0439.

The analysis DSC of (**9**) were carried out with DSC Q2000 TA Instruments.

Acknowledgements

This work was supported by the National Science Centre (NCN Poland, UMO-2012/07/B/ST5/03194).Supplementary Information

Experimental procedures, spectroscopic characterization of all new compounds with IR, the optimum ground-state geometry for compounds (**8-21**) and thermal analysis data for (**9**). This material is available free of charge via the Internet.

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