Synthesis, Characterization and Anticancer Evaluation of Nitrogen Substituted 1-(3-Aminoprop-1-ynyl)-4-Hydroxyanthraquinone Derivatives

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Research Article

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Abstract

Anthraquinones are of significant interest due to their biological activity, coloring properties and synthetic applications. Here, we describe a mild and convenient method for modification of 1-ethynyl-4-hydroxyanthraquinone that was obtained from the Sonogashira reaction of 1-hydroxy-4-iodoanthraquinone with alkynes. The copper(I) catalyzed one-pot three component reaction (A^3 -coupling) of the new 1-ethynyl-4-hydroxyanthraquinone with secondary amines and formaldehyde was the main approach for the synthesis of nitrogen substituted 1-[3-(amino)prop-1-ynyl]-4-hydroxyanthraquinones. The influence of different substituent in the amine on reaction rate and yield has been evaluated. The cytotoxicity of 1-ethynyl-4-hydroxyanthraquinones was evaluated using the conventional MTT assay. Among all the compounds synthesized, anthraquinone-propargylamine derivatives **28**, **29**, **30** and **34** possess most promising cytotoxic potential towards glioblastoma cancer cells; compounds **14** and **19** shown selectivity towards the prostate cancer cells DU-145, and **18**, and **24** – towards breast cancer cells MCF-7. The grown inhibition on these cancer cells of **18** and **24** was comparable to those of standard drug Doxorubicin. Molecular modeling of new compounds in DNA G-quadruplex binding site was performed to help understand the observed SAR trends.

1. Introduction

The derivatives of anthracene-9,10-dione (anthraquinone) were of interest in many applications, in particular, are well known for their diverse and profound biological activities [1]. They are effective to treat tumors and cancers [2–4], and also used as antibacterial [5, 6], antifungal, insecticidal [7], antimicrobial [8, 9], and as antidiabetic [10] agents. Anthraquinones were widely studied for their structural evaluation and biological significance. Anthracenedione drugs are known to exert their biological effects through interaction with DNA resulting in modification of its structure hence inhibition of its replication. Anthraquinones mitoxantrone and ametantrone (1,4-bis[(aminoalkyl)amino]anthracene-9,10-diones) are potent synthetic anticancer drugs which blocks DNA synthesis by inhibiting the function of DNA topoisomerases [11, 12]. Several anthraquinone pharmacophores can realize their anticancer activity by affecting other molecular targets. For example, a new rhein-derived compound can target MDM2 for protein degradation by binding to MDM2 and blocking the interaction between MDM2 and MDM4 which leads to MDM2 self-ubiquitination and degradation; this in turn causes p53 activation and cancer cell apoptosis, particularly in cancer cells expressing high levels of MDM2 [13]. Purpurin (1,2,4-trihydroxy-9,10-anthraquinone) is a non-competitive inhibitor of adipocyte-derived leucine aminopeptidase (A-LAP) which play a crucial role in angiogenesis [14]. Emodin (1,3,8-trihydroxy-6-methylantraquinone) was characterized as an significant inhibitor of cell proliferation, presumably *via* down regulation of ERCC1 (excision repair cross-complementary 1) and DNA recombinase protein Rad51 [15], but its 2,4-dibromo derivatives exert their anti-proliferative activity at least in part, by inhibition of ATP citrate lyase (ACL), plays a critical role in generating cytosolic acetyl CoA [16]. Emodin and 2-chloroemodin were also considered as potential targets of dioxygenases (ALKBH 2, 3 proteins, and FTO) overexpression blockers [17]. Purpurin [18] and emodin [19] were also characterized as monoamine oxidase isoforms inhibitors.

A series of studies have been focused on optimization of efficacy and safety profile of anthraquinone-based compounds [20]. Of particular interest in the search of antitumor agents is the development of studies on the preparation of anthraquinone derivatives containing nitrogen substituents, including piperidine [21] and pyrimidine [22] fragments.

For synthesis of nitrogen substituted anthraquinones, besides to the routes for the construction of anthraquinone core (for example, of Friedel–Crafts condensations of benzene derivatives with functionalized phthalic anhydrides or phthaloyl dichlorides [23]), attention has been drawn to the development of C-N coupling processes, for example, the copper(0)-catalyzed Ullmann-type reaction of bromo/chloro anthraquinones with a variety of amines [24–27] or the Pd-catalyzed Buchwald-Hartwig cross-coupling reaction of halogen substituted anthraquinones [28, 29].

In the framework of our studies dealing with the development of convenient routes to functionalization of 1-hydroxyanthraquinone [30], we were interested in the preparation of anthraquinone derivatives, containing an aminopropargyl substituent in the anthraquinone core. Propargylamines are a versatile class of compounds whose application in medicinal and pharmaceutical chemistry has really soared [31]. The copper(I) catalyzed one-pot three component (A^3 -coupling) reaction among aldehyde, amine and terminal alkyne has become a popular approach to synthesize propargylamines [32, 33]. Therefore, the sequence of the Sonogashira cross-coupling reaction of 4-iodo-1-hydroxyanthraquinone with alkynes and the copper catalyzed Mannich reaction of 1-ethynyl-4-hydroxyanthraquinone with secondary amines and formaldehyde (37% Eq. solution or paraform) (A^3 -coupling) was used as the main synthetic approach in this studies. Taken into account the interest to substituted anthraquinones as anticancer agents we evaluated the cytotoxicity of the synthesized compounds toward cancer cell lines *in vitro*. The molecular docking of new compounds to G-quadruplex DNA motifs was carried out.

2. Results And Discussion

2.1. Chemical Synthesis

The cross-coupling reaction of 1-hydroxy-4-iodo-9,10-anthraquinone **1** [34] with phenylacetylene **2** was used as the model reaction to optimize the conditions (Scheme 1). The reaction of **1** and **4** in standard Sonogashira reaction conditions [35] in the presence of dichlorobis(triphenylphosphine)palladium, copper(I) iodide, and triethylamine as a base in benzene or toluene under reflux was unsuccessful. Carrying out the reaction in DMF at 100-120°C and using of an excess of triethylamine was found to be ineffective. An efficient way to improve the yield of the cross-coupling reaction products was the addition of tetraalkylammonium salts to the reaction mixture as proposed by Jeffery [36]. The ability to generate a stable form of the catalyst without the addition of stabilizing ligands as one of the role of tetraalkylammonium salts was reported by Reetz [37]. The cross-coupling reaction of 1-hydroxy-4-iodo-9,10-anthraquinone **1** with phenylacetylene **4** in the presence of dichlorobis(triphenylphosphine)palladium, copper(I) iodide, triethylamine (3 equiv.) and ammonium salts

(Bu₄NBr) (1 equiv.) in DMF by heating at 65°C for 1 h (TLC) afforded the 4-phenyl-1-hydroxyanthraquinone **3** in 78% yield. We got a similar result when using 0.2 equiv. of Bu₄NBr; the isolated yield of compound **3** composed to 82%. In this condition, the reaction of 1-hydroxy-4-iodo-9,10-anthraquinone **1** with 4-methoxyphenylacetylene **4**, 4-fluorophenylacetylene **5**, or 4-acetylamino-3-ethoxycarbonylphenylacetylene **6** led to the corresponding 4-aryl-1-hydroxyanthraquinones **7–9** in the isolated yield 52, 46, 41% respectively.

The reaction of iodoanthraquinone **1** with trimethylsilylacetylene **10** in the found condition proceeded more smoothly afforded the coupling compound **11** in the yield 83%. Desilylation by the action of tetrabutylammonium fluoride in methylene chloride afforded the corresponding terminal acetylene **12**. Thus, we proposed a simple and convenient three step procedure for the synthesis of 1-ethynyl-4-hydroxyanthracene-9,10-dione **12** with the yield about 49% from 1-hydroxyanthraquinone.

For the synthesis of *N*-substituted 1-(3-aminopropargyl)-4-hydroxyanthraquinones we studied the the Cu(I) iodide-catalyzed A³ coupling reaction between 1-ethynyl-4-hydroxyanthracene-9,10-dione **12**, formaldehyde and different secondary amines. We found that the reaction of compound **12**, formaldehyde (generated in situ from paraformaldehyde) and diethylamine **13** in dioxane in the presence of 0.02 equiv of copper(I) iodide at 65°C proceeds smoothly, and after 30 min the alkyne was almost consumed and the desired *N*-(dimethyl)- substituted 1-(3-aminopropargyl)-4-hydroxyanthraquinone **14** was isolated in the yield 50% (Scheme 2). Copper(I) chloride was less effective with increasing the reaction time to 1.5 h and yield decreasing to 39%. Performing the reaction in the presence of copper (II) acetate monohydrate in dioxane led to a slightly improved the yield to 57%. By using of Cu(OAc)₂×H₂O as the catalyst and aqueous formaldehyde as the reagent the yield of compound **14** increased to 73%. In this conditions 1-hydroxy-4-ethynylantraquinone **1** was reacted with acyclic secondary amines **15–17** (65°C, 1–2 h) to give desired compounds **18–20** with high yield (Scheme 2). Reaction of cyclic secondary amines pyrrolidines **21,22**, piperidines **25–27**, morpholine **31**, *N*-methylpiperazine **32**, and azocane **35** with aqueous formaldehyde and alkynylantraquinone **1** in the presence of Cu(OAc)₂×H₂O required longer time and afforded aminopropargyl substituted anthraquinones **23, 24, 28–30, 33, 34** and **36** in high yield. All the derivatives were purified by column chromatography (chloroform:ethylacetate, solvent mixture). After the purity controls of the synthesized compounds (TLC studies) and their melting points were determined, spectral analyzes were performed to prove the structures. ¹H-NMR, ¹³C NMR, and mass spectral analysis were found to prove the expected structures.

It is well known, that the reported reaction is thought to proceed through the alkyne activation forming a copper acetylide. After a nucleophilic addition on the intermediate formed by the reaction of formaldehyde and a secondary amine, the propargylamine derivative is obtained [32]. We performed also a 'one-pot' deprotection–A³-coupling tandem procedure for obtaining compound. Successful versions of the copper(I)-catalyzed reaction of azides with trimethylsilylalkynes in the presence of an organic base we reported [38, 39]. We found, that a simple mixing of **12**, formalin, and amine **13** in the presence of catalytic quantities (0.05 equiv.) of Cu(OAc)₂ × H₂O and Bu₄NF (2 equiv.) in THF under argon flow gave the

desired product **14** isolated in the yield 23%. No products of alkyne deprotection reaction (compound **12** or dimeric butadiyne) was observed in this conditions.

All the new compounds exhibited satisfactory spectral data correlating with their structures, IR spectrum of all final compounds **6–9, 11, 12, 14, 18–20, 23, 24, 28–30, 33, 34, 36** showed $C \equiv C$ stretching vibration around $2100–2205\text{ cm}^{-1}$. The structure of the synthesized 1-(3-aminopropargyl)-4-hydroxyanthraquinones was clearly confirmed by the results of the NMR study. In particular, the ^1H NMR spectra of **14, 18–20, 23, 28, 29, 33, 34, 36** contain the resonance signals of the CH_2 group represented as a singlet of two protons at the range of 3.63–3.81 ppm. For these protons in the spectra for compounds **24** and **30**, having substituent at the α -position of the heterocyclic ring, the doublet AB system centered at 3.72 and 3.92 ppm ($J = 17.6\text{ Hz}$) or 3.41 and 3.52 ppm ($J = 17.6\text{ Hz}$) was observed. The ESI mass spectrometric data of all the synthesized compounds showed peaks at relevant $[\text{M} + \text{H}]^+ m/z$ which complemented the IR and NMR spectra for the confirmation of expected structures of all the compounds

Cytotoxicity Studies

Four cancer cell lines, MCF-7 (breast cancer cells), DU-145 (prostate cancer cells), SNB-19, and U-87 MG (glioblastoma cells), and also a normal cell line of immortalized human fibroblasts were chosen for cytotoxicity evaluations. MTT assays were performed for quantitative evaluation of in vitro cytotoxicity [40]. Doxorubicin (DOX) is clinically used to treat cancer as drug in world and have a very wide antitumor spectrum. That we use them as positive control compounds. The cytotoxicity was determined by measuring the concentration inhibiting human tumor cell viability by 50% (GI_{50}). The results are presented in Table 1. The SAR revealed that the substituent at C-1 position of 4-hydroxyanthraquinones have a great influence on the cytotoxicity. Compounds **6, 7, 8, 9** with arylethynyl substituent exhibited low or insignificant cytotoxicity with high GI_{50} values on the cancer cell lines. Previously, we have reported that 4-hydroxyanthraquinones with 1-arylsubstituent have great anticancer potency [30]. Spacing the aromatic ring away from anthraquinone by an ethynyl group led to greatly decrease of the anticancer potency. In comparison, all the 1-(3-(*N*-substituted)aminoprop-1-ynyl)-4-hydroxyanthraquinones **14, 18–20, 23, 24, 28–30, 33, 34**, and **36** shown much more potent cytotoxicity with significantly lower GI_{50} values on most of the tumor cells. Thus, we demonstrate that 1-position 3-aminopropynyl modification of 4-hydroxyanthraquinone can significantly potentiate the anticancer activity. A remarkable increase in activity towards breast cancer cell line MCF-7 was observed for compounds **18, 24, 29, 36**; the effect in this cell line was comparable to that of Doxorubicin. Among these derivatives compounds **18** (with a dipropylamino- substituent at C-3) and **36** (with a cyclic azocane substituent at C-3) shown the higher cytotoxicity also towards normal cell lines. Among all analogues, compounds **14** and **19** with diethylaminopropynyl or di-*i*-propylaminopropynyl substituent showed high potency against prostate cancer cell line DU-145 (Table 1). The GI_{50} value for those derivatives approaches that of the positive control, doxorubicin. Compound **28**, contain the cyclic 3-(piperidino), **29** with 3-(4-methyl)piperidino-, and **30** with 3-(2-anabasynyl)piperidino substituent in the propin-1-yl side chain possess selective cytotoxicity towards glioblastoma cancer cells SNB-19 and U-87MG. Relative to doxorubicin, these derivatives

showed by at least 4–10 fold less toxicity against normal cell line. The synthesized 3-(pyrrolidino)propynyl- **23** was less active than 3-(piperidino)propynyl- **28** anthraquinone towards cancer cell lines. The N-methyl-piperidinopropynyl-1-hydroxyanthraquinone **34** demonstrated higher cytotoxicity than the morpholinopropynyl-1-hydroxyanthraquinone **33** on cancer cells. All the obtained results suggested that the substituent at the nitrogen of 4-(aminopropargyl)-1-hydroxyanthraquinones increased the cytotoxicity. There have been previous studies on the anticancer properties of aminoanthraquinones with the aminoalkylamino side chains at the 1–1,4 – 1,5- or 1,8-positions [41–45]. These reports suggest that the substitution by 1-(N,N-dimethylamino)ethylamine side chain led to optimal activity: compounds with 1-(N,N-dimethylamino)propylamine substituent shown two fold decrease of cytotoxicity on cancer cell lines [44]. The modification in the chain second amine function also changed the cytotoxicity; compounds with morpholino(propylenamino)- substituted anthraquinones were less potent than compounds with piperidino- or pyrrolidino(propylenamino)- substituted anthraquinones against leukemia P388 cells [42] and compound with piperidino- moiety were more active than the pyrrolidino- substituted one in the ovarian cancer cell lines [45]. Herein we demonstrate that 3-position amine modification of 1-(3-aminopropargyl)-substituent can also significantly potentiate the anticancer activity of hydroxyanthraquinone.

Table 1
Cytotoxicity of compounds 6–9, 14, 18–20, 23, 24, 28–30, 33, 34, 36

Compound	Growth inhibition of cells (GI ₅₀ , μ M) ^[a,b]				
	MCF-7	DU-145	SNB-19	U-87 MG	hTERT lung fibroblasts
6	> 100	> 100	78.09 $\pm$ 9.14	> 100	> 100
7	74.16 $\pm$ 9.14	> 100	62.03 $\pm$ 5.11	54.55 $\pm$ 6.08	68.25 $\pm$ 4.22
8	> 100	> 100	> 100	> 100	> 100
9	> 100	> 100	> 100	> 100	> 100
14	15.66 $\pm$ 2.14	6.55 $\pm$ 0.77	21.45 $\pm$ 1.33	17.74 $\pm$ 0.84	18.24 $\pm$ 0.88
18	5.45 $\pm$ 0.87	8.06 $\pm$ 0.45	4.23 $\pm$ 0.85	9.24 $\pm$ 0.64	8.23 $\pm$ 0.54
19	12.33 $\pm$ 2.74	6.16 $\pm$ 0.67	8.64 $\pm$ 1.07	9.66 $\pm$ 1.02	15.22 $\pm$ 2.34
20	8.46 $\pm$ 0.92	12.98 $\pm$ 1.41	10.29 $\pm$ 1.37	22.39 $\pm$ 1.17	12.45 $\pm$ 1.22
23	14.72 $\pm$ 2.15	13.64 $\pm$ 1.09	7.58 $\pm$ 0.44	17.06 $\pm$ 1.44	54.29 $\pm$ 3.07
24	6.02 $\pm$ 1.11	9.48 $\pm$ 1.55	7.08 $\pm$ 1.31	8.15 $\pm$ 0.72	15.46 $\pm$ 2.07
28	9.44 $\pm$ 1.03	8.33 $\pm$ 0.71	5.66 $\pm$ 1.08	6.05 $\pm$ 0.76	22.68 $\pm$ 2.08
29	7.07 $\pm$ 1.15	10.44 $\pm$ 1.03	5.02 $\pm$ 0.88	8.29 $\pm$ 1.42	21.26 $\pm$ 0.84
30	13.28 $\pm$ 2.04	47.19 $\pm$ 9.08	7.09 $\pm$ 1.13	6.33 $\pm$ 0.96	31.56 $\pm$ 2.48
33	34.62 $\pm$ 1.28	50.29 $\pm$ 2.15	30.15 $\pm$ 2.15	43.85 $\pm$ 2.45	54.09 $\pm$ 7.11
34	7.56 $\pm$ 1.11	14.16 $\pm$ 1.41	6.67 $\pm$ 0.62	15.77 $\pm$ 1.38	38.22 $\pm$ 2.41
36	7.48 $\pm$ 1.03	7.48 $\pm$ 1.44	5.13 $\pm$ 0.56	12.63 $\pm$ 1.37	6.25 $\pm$ 1.02
DOX ^c	5.11 $\pm$ 0.54	6.61 $\pm$ 0.34	7.62 $\pm$ 0.69	6.11 $\pm$ 0.15	3.18 $\pm$ 0.21
^[a] GI ₅₀ : concentration at which 50% growth inhibition of tumor cells is observed after 72 h incubation;					
^[b] The experimental results are given as the data average values obtained from three independently conducted experiments; ^[c] Doxorubicin.					

Modeling the possible interaction of new anthraquinones with the G-quadruplex of DNA

G-quadruplexes are widely represented in telomeric sequences, some promoter regions, as well as in the 5'-untranslated regions of mRNA. Stabilization of G-quadruplexes of telomeric sequences by small molecules promotes inhibition of telomerase, which exhibits increased activity in tumor cells. Binding of G-quadruplexes of oncogenic promoters leads to suppression of their expression. Thus, the interaction of molecules with the G-quadruplexes of DNA in tumor cells can trigger their apoptosis and develop a

cytotoxic effect. G-quadruplex is currently investigated as a target for contrasting unregulated cell proliferation, neurodegeneration and viral replication [46]. Small molecules with a anthraquinone core [47] and hetaryl fused anthracene-9,10-diones [48] were able to interact with G-quadruplexes and capable of forming four-strand structures. Recently, the anthracene-9-propargylamine scaffold was characterized as a new G-quadruplex ligand [49].

G-quadruplex is a structure consisting of four nitrogenous guanine bases linked by eight hydrogen bonds. The π -systems of guanines are located in one plane, which creates the possibility of stacking interactions with planar condensed aromatic systems of small molecules. Naphthalene diimide compound **MM41** stabilizes the G-quadruplex due to the interactions of its planar aromatic nucleus with the π -systems of the purine rings of all four guanines. The nitrogen atoms of the methylpiperazine and morpholine rings of branched substituents can be protonated, which makes it possible for the dynamic formation of hydrogen bonds with the oxygen atoms of phosphoric acid residues of neighboring nucleotides, depending on the position of the aromatic nucleus of the molecule above the plane of four guanines.

The results of docking studies of compounds **6, 7, 8, 9, 12, 14, 18, 19, 20, 23, 24, 28, 29, 30, 33, 34, 36**, and **MM41** in G-quadruplex binding site are listed in Table 2 and Fig. 1. Superposition of molecules over the plane of the G-quadruplex is given in Suppl. Part (Fig. 1S). The presence of a rigid acetylene bond causes the only possible position of the linear part of the substituent in the plane of the anthraquinone nucleus in all new compounds. The lowest estimated binding energy was observed for compound **14** (Table 2) with compact branched aliphatic substituent. The nitrogen atom of the substituent is capable of shifting the electron density from the terminal carbon atoms, creating the possibility of a π -sigma interaction.

Table 2. Results of molecular docking of the new 1-hydroxyanthraquinone derivatives

1	MM41	-0.212	-12.698
2	14	-0.326	-8.153
3	34	-0.284	-7.657
4	18	-0.243	-7.528
5	19	-0.275	-7.438
6	30	-0.218	-6.969
7	33	-0.254	-6.607
8	9	-0.191	-6.492
9	24	-0.249	-6.485
10	29	-0.239	-6.466
11	28	-0.230	-5.75
12	23	-0.228	-5.707
13	20	-0.176	-5.101
14	36	-0.178	-4.989
15	6	-0.171	-4.440
16	7	-0.151	-4.067
17	12	-0.180	-3.416
18	8	-0.126	-3.274
[a] Value is not genuine binding energy but estimated docking score.			

The anthraquinone nucleus of **14** can be more evenly located, interacting with all π -systems of guanines (Fig. 1, B). The methylpiperazine ring of compound **34**, apparently, causes more significant conformational difficulties, causing a displacement of the anthraquinone nucleus, which in this case is able to interact only with two nitrogenous bases of the G-quadruplex (Fig. 1, C). The binding energies for G-quadruplex complexes of compound **9** (-6.492 kcal/mol) was slightly higher than for other Sonogashira cross-coupling reaction products (**6**, **7**, **8**, **12**). In the case of compound **9**, a more large and polar ethyl-2-acetamidobenzoate substituent causes a pronounced displacement of the entire molecule away from the central symmetry axis of the G-quadruplex due to the formation of hydrogen bonds and electrostatic interactions with the phosphate group of the neighboring nucleotide. It becomes possible to form a hydrogen bond between the proton of the hydroxyl group of the anthraquinone nucleus and the keto-group of the purine ring of one of the guanines (Fig. 1, D). Finally, the docking of compounds **14**, **34**, and **9** as well as for **MM41** revealed a K⁺ binding of the core.

Conclusion

In summary, we developed a convenient method for modification of anthraquinone derivatives that can be used for modification of polyfunctionalized anthraquinones. Using this scheme, a series of 1-ethynyl-4-hydroxyanthraquinones and 1-(3-aminopropynyl)-4-hydroxy-anthraquinones were prepared for the first time. Their cytotoxicity was determined by MTT assays against the MCF-7, DU-145, SNB-19, U-87MG, and hTERT lung fibroblasts cell lines. Among all the compounds synthesized, *N*-substituted 1-(3-(amino)prop-1-ynyl)-4-hydroxyanthraquinones **14**, **19**, **24**, **28–30**, **34** stood out for their high selective cytotoxicity on the cancer cell lines than the others. The cytotoxicity of compounds **14** and **18** with alkyl substituent in aminopropargyl side chain on MCF-7 line was comparable to those of standard drug Doxorubicin. The GI₅₀ value for compounds **28–30** was similar to that of doxorubicin against glioblastoma cancer cells. Compounds **34** and **36** shown selectivity towards SNB-19 cell lines and compounds **14** and **19** demonstrated selectivity to DU-145 cells. The results reported herein pave the way for the further access of new targeted intercalating agents. In addition, due to their simplicity and effectiveness, it is likely that the new transformation of anthraquinone core will find use in the development of compounds with the 1-((*N*-substituted)aminopropyn-1-yl)anthraquinones, that could be used as scaffolds toward accessing other libraries of bioactive compounds.

Experimental

General chemistry

NMR spectra were acquired on Bruker AV-300 (¹H: 300.13 MHz, ¹³C: 75.47 MHz) or Bruker AV-400 (¹H: 400.13 MHz, ¹³C: 100.78 MHz) (Bruker BioSpin GmbH, Rheinstetten, Germany) spectrometer. Deuteriochloroform (CDCl₃) was used as a solvent, with residual CHCl₃ (δ_H = 7.24 ppm) or CDCl₃ (δ_C = 76.9 ppm) being employed as internal standards. NMR assignments were supported by using COSY, HMBC, and HSQC spectra if appropriate. In the description of the ¹H and ¹³C-NMR spectra for all compounds the anthraquinone skeleton and substituent atoms numeration system given in structure 14 and 36 was used (Scheme 2). IR absorption spectra were obtained for neat thin films by using a Bruker Vector-22 spectrometer. UV spectra were obtained on an HP 8453 UV-Vis spectrometer (Hewlette-Packard, Waldbronn, Germany) in EtOH solutions (10^{−4} mol/L). The specific rotation values [α]_D were determined on a PolAAr 3005 polarimeter. High-resolution mass spectrometry (HRMS) data were recorded on a Thermo Scientific DFS mass spectrometer (evaporator temperature 180–220°C, EI ionization at 70 eV. Melting points were determined using termosystem Mettler Toledo FP900 (USA).

The reaction progress and the purity of the obtained compounds were monitored by TLC on Sorbfil UV-254 plates (CHCl₃, CH₂Cl₂, CCl₄, CHCl₃:EtOAc – 1:1; detection under UV light). Column chromatography was performed by using silica gel 60 (0.063-0.200 mm, Merck KGaA, Darmstadt, Germany). Formalin (30% formaldehyde in aq. solution), CuI, CuCl, copper(II) acetate monohydrate, tetra-*n*-butylammonium fluoride trihydrate (TBAF), tetra-*n*-butylammonium bromide (Bu₄NBr, TBAB), phenylacetylene **2**, 4-(methoxyphenyl)acetylene **4**, 4-(fluorophenyl)acetylene **5**, (trimethylsilyl)acetylene **11**, diethylamine **13**, dipropylamine **15**, diisopropylamine **16**, dibutylamine **17**, pyrrolidine **21**, 2-methylpyrrolidine **22**, piperidine

25, 4-methylpiperidine **26**, morpholine **31**, *N*-methylpiperazine **32**, and azocane **35** were purchased from Alfa Aesar.

1-Hydroxy-4-iodo-9,10-anthraquinone **1** [34] and ethyl-5-ethynyl-anthranilate **6** [50] were obtained according to published procedures. (–)-Anabasine [**27**, (2*S*)-3-(piperidin-2-yl)pyridine] was isolated by extraction from the aerial part of the plant *Anabasis aphylla* L., $[\alpha]_D = -61.22$ ($c = 4.5$, EtOH) [51]. The solvents (DMF, PhCH₃, CHCl₃, CH₂Cl₂, 1,4-dioxane), as well as Et₃N were purified according to standard methods. Purity of all compounds was checked by TLC.

General procedures for substitution of the halogen atom in 1-hydroxy-4-iodoanthraquinone **1** with the residue of alkynes

To a stirred solution of 1-hydroxy-4-iodoanthraquinone **1** (100.0 mg, 0.285 mmol) in DMF (4.00 mL) under argon flow was added arylacetylene (**2–5**) or (trimethylsilyl)acetylene (**10**) (0.43 mmol), Pd(PPh₃)₂Cl₂ (20.1 mg, 0.028 mmol), TBAB (180 mg, 0.057 mmol), CuI (3.0 mg, 0.014 mmol), and Et₃N (0.12 mL, 0.86 mmol). The reaction mixture was heated to 65 °C under stirring for 1–3.5 h. The solvent was removed in vacuo and the residue was purified by column chromatography using chloroform (for **6**, **7**) or dichloromethane (for **8**, **9**, **11**) as eluting solvent. **Synthesis of 1-ethynyl-4-hydroxyanthraquinone (12)**

Conditions A. A stirred solution of (trimethylsilyl)alkynyl substituted anthraquinone (**11**) (100 mg, 0.31 mmol) in dichloromethane (5 mL), was treated with a solution of tetrabutyl ammonium fluoride (0.163 mg, 0.62 mmol) in dichloromethane (5 mL) and the mixture was stirred at 20 °C for 30 min. After completion based on TLC, the solvent was removed in vacuo. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (CCl₄) to give 57 mg (yield 74 %) of compound (**12**) as an orange powder.

General procedure for the synthesis of *N*-substituted 1-(3-aminoprop-1-ynyl)-4-hydroxyanthraquinones (**14**, **18–20**, **23**, **24**, **28–30**, **33**, **34**, **36**)

Conditions a. Synthesis of compound (**14**). A stirred mixture of 1-ethynyl-4-hydroxyanthraquinone (**12**) (100 mg, 0.4 mmol), paraformaldehyde (36 mg, 1.2 mmol), diethylamine (**13**) (88 mg, 1.2 mmol), copper chloride (1 mg, 0.008 mmol) in dioxane (10 mL) was heated to 65 °C for 1.5 h under argon. After the consumption of the starting materials, the solvent was removed under reduced pressure, and the crude material was purified via flash column chromatography (chloroform) to isolate 50 mg (yield 39%) of compound (**14**).

Conditions b. Synthesis of compound (**14**). A stirred mixture of 1-ethynyl-4-hydroxyanthraquinone (**12**) (100 mg, 0.4 mmol), paraformaldehyde (36 mg, 1.2 mmol), diethylamine (**13**) (88 mg, 1.2 mmol), copper iodide (1.5 mg, 0.008 mmol) in dioxane (10 mL) was heated to 65 °C for 30 min under argon. The solvent was removed under reduced pressure, and the crude material was purified via flash column chromatography (chloroform) to isolate 64 mg (yield 50%) of compound (**14**).

Conditions c. Synthesis of compound (**14**). A stirred mixture of 1-ethynyl-4-hydroxyanthraquinone (**12**) (100 mg, 0.4 mmol), paraformaldehyde (36 mg, 1.2 mmol), diethylamine (**13**) (88 mg, 1.2 mmol), Cu(OAc)₂×H₂O (4 mg, 0.02 mmol) in dioxane (10 mL) was heated to 65 °C for 30 min under argon. The solvent was removed under reduced pressure, and the crude material was purified via flash column chromatography (chloroform) to isolate 74 mg (57%) of compound (**14**).

Conditions d. Secondary amine (**13**, **15–17**, **21**, **22**, **25–27**, **31**, **32**, **35**) (2 mmol), formalin (60 mg, 2 mmol), and Cu(OAc)₂×H₂O (4 mg, 0.02 mmol) were successive added in argon to the solution of 1-ethynyl-4-hydroxyanthraquinone (**12**) (100 mg, 0.4 mmol) in dioxane (10 mL) and the reaction mixture was stirred at 65-70°C for a period from 30 min to 5 h (TLC-control). After the consumption of the starting materials, the reaction mixture was cold, evaporated and subjected to column chromatography (eluted with chloroform-ethylacetate).

Synthesis of compound (14) from 1-hydroxy-4-(trimethylsilyl)ethynylantraquinone (11). A stirred solution of compound (**11**) (130 mg, 0.4 mmol) in dioxane (10 mL) was successive treated with tetra-*n*-butyl ammonium fluoride (0.209 mg, 0.8 mmol), formalin (60 mg, 2 mmol), diethylamine **13** (146 mg, 2 mmol), and Cu(OAc)₂×H₂O (4 mg, 0.02 mmol) in an argon flow. The reaction mixture was stirred 30 min at room temperature and then heated to 65 °C for 2 h and evaporated. Compound **14** was isolated in the yield 23 % (eluted with chloroform).

1-Hydroxy-4-(phenylethynyl)anthracene-9,10-dione (6). Orange powder. Yield 72%; m.p.: 304.7 °C (decomp.); IR (KBr) ν : 3420, 3400 (OH), 2197 (C≡C), 1664 (C=O), 1637 (C=O), 1592, 1490, 1460, 871, 798, 745, 727, 686 (C=C, CH-Ar) cm⁻¹; UV (EtOH) $\lambda_{\max}$ (lg ϵ): 258 (4.25), 325 (3.79), 460 (3.49) nm; ¹H NMR (CDCl₃, 400 MHz): δ = 7.27 (d, 1H, *J* = 8.9 Hz, H-2), 7.32–7.42 (m, 3H, H-3,4,5), 7.68 (m, 2H, H-2,6), 7.62–7.87 (m, 3H, H-3,6,7), 8.29 (br d, 1H, *J* = 8.2 Hz, H-5), 8.34 (br d, 1H, *J* = 8.2 Hz, H-8), 13.33 (s, 1H, OH) ppm; ¹³C NMR (CDCl₃, 75 MHz): δ = 89.1 (C-12), 94.0 (C-11), 115.4 (C-1), 115.8 (C-9a), 122.9 (C-4), 123.6 (C-2), 126.2 (C-8), 127.3 (C-5), 128.0 (C-3,5), 128.2 (C-4), 131.6 (C-2,6), 131.9 (C-10a), 132.7 (C-8a), 133.4 (C-6), 133.7 (C-4a), 134.5 (C-7), 142.5 (C-3), 162.7 (C-1), 180.7 (C-10), 188.1 (C-9) ppm; HRMS (ESI) *m/z* calcd. for C₂₂H₁₂O₃, 324.0781, found 324.0778 [M]⁺.

1-Hydroxy-4-((4-methoxyphenyl)ethynyl)anthracene-9,10-dione (7). Vinous powder. Yield 52%; m.p.: 147.9 °C (decomp.); IR (KBr) ν : 3442 (OH), 2195 (C≡C), 1670 (C=O), 1631 (C=O), 1589, 1510, 1462, 1440, 827, 796, 727 (C=C, CH-Ar) cm⁻¹; UV (EtOH) $\lambda_{\max}$ (lg ϵ): 255 (4.48), 269 (4.43), 339 (4.05), 483 (3.72) nm; ¹H NMR (CDCl₃, 400 MHz): δ = 3.83 (s, 3H, 4-OCH₃), 6.90 (d, 2H, *J* = 8.5 Hz, H-3,5), 7.25 (d, 1H, *J* = 9.3 Hz, H-2), 7.63 (d, 2H, *J* = 8.5 Hz, H-2,6), 7.73–7.86 (m, 3H, H-3,6,7), 8.28 (br d, 1H, *J* = 8.3 Hz, H-5), 8.34 (br d, 1H, *J* = 8.3 Hz, H-8), 13.34 (s, 1H, OH) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ = 55.2 (OCH₃), 88.5 (C-12), 94.8 (C-11), 114.0 (C-3,5), 115.3 (C-1), 116.0 (C-9a), 116.2 (C-4), 124.0 (C-2), 126.5 (C-8), 127.6 (C-5), 132.3 (C-10a), 132.5 (C-8a), 133.5 (C-2,6), 133.7 (C-6), 134.1 (C-4a), 134.8 (C-7), 142.7 (C-3), 159.9 (C-4), 162.8 (C-1), 181.0 (C-10), 188.5 (C-9) ppm; HRMS (ESI) *m/z* calcd. for C₂₃H₁₄O₄, 354.0887, found

1-Hydroxy-4-((4-fluorophenyl)ethynyl)anthracene-9,10-dione (8). Red powder. Yield 46%; m.p.: 190.1 °C (decomp.); IR (KBr) ν : 3425 (OH), 2200 (C $\equiv$ C), 1666 (C=O), 1635 (C=O), 1593, 1508, 1462, 833, 794, 721, 710 (C=C, CH-Ar) cm^{-1} ; UV (EtOH) λ_{max} (lg ϵ): 257 (4.22), 325 (3.74), 458 (3.45) nm; ^1H NMR (CDCl_3 , 400 MHz): δ = 7.07 (t, 2H, J = 8.6 Hz, H-3,5), 7.26 (d, 1H, J = 8.9 Hz, H-2), 7.62–7.70 (m, 2H, H-2,6), 7.74–7.85 (m, 3H, H-3,6,7), 8.28 (d, 1H, J = 7.3 Hz, H-5), 8.33 (d, 1H, J = 7.3 Hz, H-8), 13.32 (s, 1H, OH) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ = 89.1 (C-12), 93.2 (C-11), 115.5 (C-4), 115.6 (C-3,5), $J_{\text{C-F}}$ = 21.9 Hz), 116.1 (C-9a), 119.4 (C-1, $J_{\text{C-F}}$ = 3.4 Hz), 124.0 (C-2), 126.6 (C-8), 127.6 (C-5), 132.2 (C-10a), 133.0 (C-8a), 133.8 (C-6), 133.9 (C-2,6), $J_{\text{C-F}}$ = 8.4 Hz), 134.0 (C-4a), 134.9 (C-7), 142.6 (C-3), 162.7 (C-4, $J_{\text{C-F}}$ = 250.0 Hz), 163.0 (C-1), 181.1 (C-10), 188.4 (C-9) ppm; HRMS (ESI) m/z calcd. for $\text{C}_{22}\text{H}_{11}\text{FO}_3$, 342.0687, found 342.0693[M] $^+$.

Ethyl 2-acetylamino-5-((4-hydroxy-9,10-dioxo-9,10-dihydroanthracen-1-yl)ethynyl)benzoate { 4-(4-acetylamino-3-ethoxycarbonylphenyl)ethynyl)-1-hydroxy-anthracene-9,10-dione} (9). Orange powder. Yield 41%; m.p.: 322.4 °C (decomp.); IR (KBr) ν : 3282, 3309 (NH, OH), 2198 (C $\equiv$ C), 1707 (C=O), 1682 (C=O), 1662 (C=O), 1591, 1516, 1480, 1454, 850, 791, 775, 725 (C=C, CH-Ar) cm^{-1} ; UV (EtOH) λ_{max} (lg ϵ): 250 (4.57), 278 (4.47), 332 (4.29), 361 (3.80) nm; ^1H NMR (CDCl_3 , 400 MHz): δ = 1.44 (t, 3H, J = 7.2 Hz, H-17), 2.25 (s, 3H, H-14), 4.41 (q, 2H, J = 7.2 Hz, H-16), 7.28 (d, 1H, J = 8.8 Hz, H-2), 7.76–7.88 (m, 4H, H-3,2,5,6), 8.26–8.39 (m, 3H, H-5,6,7), 8.76 (br d, 1H, J = 8.8 Hz, H-8), 11.21 (s, 1H, NH), 13.33 (s, 1H, OH) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ = 14.1 (C-17), 25.5 (C-14), 61.6 (C-16), 89.4 (C-12), 93.3 (C-11), 114.9 (C-3), 115.5 (C-4), 116.1 (C-9a), 117.3 (C-1), 120.2 (C-5), 124.0 (C-2), 126.6 (C-8), 127.6 (C-5), 132.3 (C-10a), 133.0 (C-8a), 133.8 (C-6), 134.0 (C-4a), 134.3 (C-6), 134.9 (C-7), 137.8 (C-2), 141.6 (C-4), 142.8 (C-3), 163.1 (C-1), 167.7 (C-15), 169.0 (C-13), 181.1 (C-10), 188.4 (C-9) ppm; HRMS (ESI) m/z calcd. for $\text{C}_{27}\text{H}_{19}\text{NO}_6$, 453.1207, found 453.1210 [M] $^+$.

1-Hydroxy-4-((trimethylsilyl)ethynyl)anthracene-9,10-dione (11). Brown powder. Yield 83%; m.p.: 152.8–152.9 °C; IR (KBr) ν : 3425 (OH), 2150 (C $\equiv$ C), 1670 (C=O), 1639 (C=O), 1593, 1480, 1461, 844, 793, 760, 725, 704 (C=C, CH-Ar) cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ = 0.33 (s, 9H, CH_3), 7.22 (d, 1H, J = 8.9 Hz, H-2), 7.73–7.84 (m, 3H, H-3,6,7), 8.26 (dd, 1H, J = 8.7, 1.8 Hz, H-5), 8.33 (dd, 1H, J = 8.7, 1.8 Hz, H-8), 13.29 (s, 1H, OH) ppm; ^{13}C NMR (CDCl_3 , 150 MHz): δ = -0.2 (3 CH_3), 100.5 (C-12), 104.2 (C-11), 115.4 (C-4), 115.9 (C-9a), 123.7 (C-2), 126.5 (C-8), 127.7 (C-5), 132.2 (C-10a), 133.7 (C-6), 133.9 (C-8a), 134.8 (C-7), 143.6 (C-3), 163.1 (C-1), 180.8 (C-10), 188.5 (C-9) ppm; HRMS (ESI) m/z calcd. for $\text{C}_{19}\text{H}_{16}\text{O}_3\text{Si}$, 320.0863, found 320.0863[M] $^+$.

1-Ethynyl-4-hydroxyanthracene-9,10-dione (12). Orange powder. Yield 74%; m.p.: 170.1 °C (decomp.); IR (KBr) ν : 3450 (OH), 3246 ($\equiv\text{C-H}$), 2045, 2100 (C $\equiv$ C), 1668, (C=O), 1637 (C=O), 1593, 1450, 812, 790, 725, 688 (C=C, CH-Ar) cm^{-1} ; UV (EtOH) λ_{max} (lg ϵ): 255 (4.48), 327 (3.33), 423 (3.77) nm; ^1H NMR (CDCl_3 , 400 MHz): δ = 3.49 (s, 1H, $\equiv\text{CH}$), 7.23–7.27 (m, 1H, H-2), 7.76–7.85 (m, 3H, H-3,6,7), 8.28 (dd, 1H, J = 8.6, 1.8 Hz, H-5), 8.30 (dd, J = 8.6, 2.2 Hz, 1H, H-8), 13.24 (s, 1H, OH) ppm; ^{13}C NMR (CDCl_3 , 75 MHz): δ = 81.8 (C-12), 81.9 (C-11), 104.2 (C-1), 104.3 (C-5), 104.4 (C-4), 104.5 (C-9a), 104.6 (C-2), 104.7 (C-8), 104.8 (C-10a), 104.9 (C-6), 105.0 (C-8a), 105.1 (C-7), 105.2 (C-3), 105.3 (C-1), 105.4 (C-10), 105.5 (C-9) ppm; HRMS (ESI) m/z calcd. for $\text{C}_{19}\text{H}_{10}\text{O}_3$, 278.0631, found 278.0631[M] $^+$.

8a), 133.6 (C-6), 133.8 (C-4a), 134.6 (C-7), 143.2 (C-3), 162.9 (C-1), 180.8 (C-10), 188.0 (C-9) ppm; HRMS (ESI) m/z calcd. for $C_{16}H_8O_3$, 248.0468, found 248.0471 $[M]^+$.

1-(3-(Diethylamino)prop-1-ynyl)-4-hydroxyanthracene-9,10-dione (14). Vinous powder. Yield 73%; m.p.: 110.8 °C (decomp.); IR (KBr) ν : 3435 (OH), 2924 (C-H), 2195, 2200 ($C\equiv C$), 1670 (C=O), 1639 (C=O), 1591, 1510, 1480, 1466, 840, 795, 691 (C=C, CH-Ar) cm^{-1} ; UV (EtOH) λ_{max} (lg ϵ): 254 (4.44), 442 (3.73) nm; 1H NMR ($CDCl_3$, 400 MHz): δ = 1.16 (t, 6H, J = 7.2 Hz, $2\times CH_3$), 2.74 (q, 4H, J = 7.2 Hz, $2\times CH_2$), 3.79 (s, 2H, H-13), 7.22 (d, 1H, J = 8.8 Hz, H-2), 7.73 (d, 1H, J = 8.8 Hz, H-3), 7.74–7.83 (m, 2H, H-6,7), 8.27 (dd, 1H, J = 8.6, 2.0 Hz, H-5), 8.31 (dd, J = 8.6, 2.1 Hz, 1H, H-8), 13.25 (br s, 1H, OH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.6 (C-16,16 α), 41.9 (C-13), 47.4 (C-15,15 α), 84.6 (C-11), 90.6 (C-12), 115.8 (C-4), 115.9 (C-9a), 123.9 (C-2), 126.5 (C-8), 127.6 (C-5), 132.2 (C-10a), 133.1 (C-8a), 133.7 (C-6), 134.0 (C-4a), 134.8 (C-7), 143.3 (C-3), 162.8 (C-1), 181.0 (C-10), 188.4 (C-9) ppm; HRMS (ESI) m/z calcd. for $C_{21}H_{19}NO_3$, 333.1360, found 333.1357 $[M]^+$.

1-(3-(Dipropylamino)prop-1-ynyl)-4-hydroxyanthracene-9,10-dione (18). Brown powder. Yield 70%; m.p.: 98.4 °C (decomp.); IR (KBr) ν : 3415 (OH), 2958 (C-H), 2197 ($C\equiv C$), 1672 (C=O), 1633 (C=O), 1591, 1567, 1464, 829, 808, 792, 721 (C=C, CH-Ar) cm^{-1} ; UV (EtOH) λ_{max} (lg ϵ): 255 (4.28), 434 (3.78) nm; 1H NMR ($CDCl_3$, 400 MHz): δ = 0.94 (t, 6H, J = 7.4 Hz, H-17,17 α), 1.58 (m, 4H, H-16,16 α), 2.63 (t, 4H, J = 7.3 Hz, H-15,15 α), 3.78 (s, 2H, H-13), 7.21–7.25 (m, 1H, H-2), 7.73 (d, 1H, J = 8.9 Hz, H-3), 7.76–7.85 (m, 2H, H-6,7), 8.27 (dd, 1H, J = 8.5, 2.0 Hz, H-5), 8.29 (dd, J = 8.5, 2.0 Hz, 1H, H-8), 13.27 (br s, 1H, OH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 11.9 (C-17,17 α), 20.6 (C-16,16 α), 43.1 (C-13), 55.9 (C-15,15 α), 84.7 (C-11), 90.8 (C-12), 115.8 (C-4), 116.0 (C-9a), 123.9 (C-2), 126.5 (C-8), 127.5 (C-5), 132.3 (C-10a), 133.1 (C-8a), 133.7 (C-6), 134.0 (C-4a), 134.8 (C-7), 143.3 (C-3), 162.8 (C-1), 181.0 (C-10), 188.4 (C-9) ppm; HRMS (ESI) m/z calcd. for $C_{23}H_{23}NO_3$, 361.1673, found 361.1671 $[M]^+$.

1-(3-(Diisopropylamino)prop-1-ynyl)-4-hydroxyanthracene-9,10-dione (19). Brown powder. Yield 77%; m.p.: 95 °C (decomp.); IR (KBr) ν : 3421 (OH), 2966 (C-H), 2195, 2202 ($C\equiv C$), 1670 (C=O), 1637 (C=O), 1595, 1512, 1462, 838, 802, 793, 725 (C=C) cm^{-1} ; UV (EtOH) λ_{max} (lg ϵ): 256 (4.05), 301 (3.94), 401 (3.83), 448 (3.72) nm; 1H NMR ($CDCl_3$, 300 MHz): δ = 1.19 (d, 12H, J = 6.6 Hz, H-16,16 α ,17,17 α), 3.34 (quintet, 2H, J = 6.6 Hz, H-15,15 α), 3.81 (s, 2H, H-13), 7.21 (d, 1H, J = 8.9 Hz, H-2), 7.70 (d, 1H, J = 8.9 Hz, H-3), 7.75–7.85 (m, 2H, H-6,7), 8.27 (dd, 1H, J = 8.6, 2.0 Hz, H-5), 8.31 (dd, J = 8.6, 2.1 Hz, 1H, H-8), 8.26 (dd, 1H, J = 8.6, 1.8 Hz, H-5), 8.30 (dd, J = 8.6, 2.0 Hz, 1H, H-8), 13.20 (br s, 1H, OH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 20.5 (C-16,17,16 α ,17 α), 35.2 (C-15,15 α), 48.5 (C-13), 83.0 (C-11), 95.1 (C-12), 115.9 (C-4), 116.2 (C-9a), 123.7 (C-2), 126.4 (C-8), 127.4 (C-5), 132.2 (C-10a), 132.8 (C-8a), 133.5 (C-6), 134.0 (C-4a), 134.6 (C-7a), 142.9 (C-3), 162.6 (C-1), 180.9 (C-10), 188.4 (C-9) ppm; HRMS (ESI) m/z calcd. for $C_{23}H_{23}NO_3$, 361.1673, found 361.1671 $[M]^+$.

1-(3-(Dibutylamino)prop-1-ynyl)-4-hydroxyanthracene-9,10-dione (20). Brown powder. Yield 77%; m.p.: 85.7 °C (decomp.); IR (KBr) ν : 3423 (OH), 2955 (C-H), 2199, 2205 ($C\equiv C$), 1672 (C=O), 1641 (C=O), 1595,

1525, 1466, 805, 787, 725 (C=C, CH-Ar) cm^{-1} ; UV (EtOH) λ_{max} (lg ϵ): 254 (4.08), 440 (3.81) nm; ^1H NMR (CDCl_3 , 400 MHz): δ = 0.93 (t, 6H, J = 7.2 Hz, H-18,18), 1.31–1.42 (m, 4H, H-17,17), 1.47–1.58 (m, 4H, H-16,16), 2.63 (t, 4H, J = 7.5 Hz, H-15,15), 3.76 (s, 2H, H-13), 7.25 (d, 1H, J = 8.9 Hz, H-2), 7.73 (d, 1H, J = 8.9 Hz, H-3), 7.76–7.84 (m, 2H, H-6,7), 8.27 (dd, 1H, J = 8.7, 2.0 Hz, H-5), 8.29 (dd, J = 8.7, 2.0 Hz, 1H, H-8), 13.25 (br s, 1H, OH) ppm; ^{13}C NMR (CDCl_3 , 125 MHz): δ = 14.0 (C-18,18), 20.6 (C-17,17), 29.7 (C-16,16), 43.2 (C-13), 53.7 (C-15,15), 84.5 (C-11), 91.3 (C-12), 116.0 (C-4), 116.0 (C-9a), 123.8 (C-2), 126.5 (C-8), 127.5 (C-5), 132.3 (C-10a), 133.1 (C-8a), 133.6 (C-6), 134.1 (C-4a), 134.7 (C-7), 143.3 (C-3), 162.7 (C-1), 180.9 (C-10), 188.4 (C-9) ppm; HRMS (ESI) m/z calcd. for $\text{C}_{25}\text{H}_{27}\text{NO}_3$, 389.1986, found 389.1981[M] $^+$.

1-Hydroxy-4-(3-(pyrrolidin-1-yl)prop-1-ynyl)anthracene-9,10-dione (23). Brown powder. Yield 51%; m.p.: 129.2 °C (decomp.); IR (KBr) ν : 3427 (OH), 2926 (C-H), 2200 ($\text{C}\equiv\text{C}$), 1668 (C=O), 1637 (C=O), 1594, 1558, 1462, 837, 790, 745, 729 (C=C, CH-Ar) cm^{-1} ; UV (EtOH) λ_{max} (lg ϵ): 251 (4.27), 402 (3.58), 433 (3.55) nm; ^1H NMR (CDCl_3 , 400 MHz): δ = 1.97 (m, 4H, H-16,17), 2.95 (m, 4H, H-15,18), 3.86 (s, 2H, H-13), 7.23 (d, 1H, J = 8.8 Hz, H-2), 7.74 (d, 1H, J = 8.8 Hz, H-3), 7.77–7.84 (m, 2H, H-6,7), 8.26 (dd, 1H, J = 8.7, 2.0 Hz, H-5), 8.30 (dd, J = 8.7, 2.0 Hz, 1H, H-8), 13.26 (br s, 1H, OH) ppm; ^{13}C NMR (CDCl_3 , 125 MHz): δ = 23.9 (C-16,17), 44.0 (C-13), 52.4 (C-15,18), 84.8 (C-11), 89.5 (C-12), 115.4 (C-4), 116.0 (C-9a), 123.9 (C-2), 126.6 (C-8), 127.6 (C-5), 132.3 (C-10a), 133.3 (C-8a), 133.8 (C-6), 134.0 (C-4a), 134.8 (C-7), 143.1 (C-3), 163.0 (C-1), 181.0 (C-10), 188.4 (C-9) ppm; HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{17}\text{NO}_3$, 331.1203, found 331.1198 [M] $^+$.

1-Hydroxy-4-(3-(2-methylpyrrolidin-1-yl)prop-1-ynyl)anthracene-9,10-dione (24). Brown powder. Yield 85%; m.p. 94.2 °C (decomp.); IR (KBr) ν : 3420 (OH), 2924 (C-H), 2198 ($\text{C}\equiv\text{C}$), 1670 (C=O), 1637 (C=O), 1592, 1520, 1481, 1462, 839, 829, 790, 727 (C=C, CH-Ar) cm^{-1} ; UV (EtOH) λ_{max} (lg ϵ): 252 (4.12), 403 (3.73), 433 (3.71) nm; ^1H NMR (CDCl_3 , 400 MHz): δ = 1.17 (d, 3H, J = 6.5 Hz, H-19), 1.42–1.54 (m, 1H, H-17), 1.70–1.91 (m, 2H, H-16), 1.95–2.06 (m, 1H, H-17), 2.70–2.82 (m, 2H, H-15,18), 3.17–3.25 (m, 1H, H-18), 3.72 and 3.92 (AB, d, 2H, J = 17.6 Hz, H-13), 7.22 (d, 1H, J = 8.9 Hz, H-2), 7.73 (d, 1H, J = 8.9 Hz, H-3), 7.76–7.84 (m, 2H, H-6,7), 8.27 (dd, 1H, J = 8.8, 2.0 Hz, H-5), 8.29 (dd, J = 8.8, 1.8 Hz, 1H, H-8), 13.26 (br s, 1H, OH) ppm; ^{13}C NMR (CDCl_3 , 125 MHz): δ = 18.5 (C-19), 21.5 (C-17), 32.7 (C-16), 41.4 (C-13), 52.9 (C-18), 57.0 (C-15), 84.2 (C-11), 90.9 (C-12), 115.7 (C-4), 115.9 (C-9a), 123.7 (C-2), 126.4 (C-8), 127.5 (C-5), 132.2 (C-10a), 133.1 (C-8a), 133.6 (C-6), 134.0 (C-4a), 134.7 (C-7), 143.2 (C-3), 162.7 (C-1), 180.9 (C-10), 188.3 (C-9) ppm; HRMS (ESI) m/z calcd for $\text{C}_{22}\text{H}_{19}\text{NO}_3$, 345.1360, found 345.1356 [M] $^+$.

1-Hydroxy-4-(3-(piperidin-1-yl)prop-1-ynyl)anthracene-9,10-dione (28). Brown powder. Yield 49%; m.p. 148.6 °C (decomp.); IR (KBr) ν : 3425 (OH), 2931 (C-H), 2197 ($\text{C}\equiv\text{C}$), 1668 (C=O), 1643 (C=O), 1593, 1518, 1462, 829, 808, 794, 724 (C=C, CH-Ar) cm^{-1} ; UV (EtOH) λ_{max} (lg ϵ): 250 (4.08), 440 (3.75) nm; ^1H NMR (CDCl_3 , 300 MHz): δ = 1.42–1.53 (m, 2H, H-17), 1.62–1.72 (m, 4H, H-16,18), 2.69 (br s, 4H, H-15,19), 3.63 (s, 2H, H-13), 7.22 (d, 1H, J = 8.9 Hz, H-2), 7.73–7.84 (m, 3H, H-3,6,7), 8.27 (dd, 1H, J = 8.7, 2.2 Hz, H-5), 8.30 (dd, J = 8.7, 2.0 Hz, 1H, H-8), 13.27 (br s, 1H, OH) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ = 23.8 (C-17), 25.9 (C-16,18), 48.8 (C-13), 53.3 (C-15,19), 84.6 (C-11), 91.0 (C-12), 115.8 (C-4), 116.0 (C-9a), 122.9 (C-2), 133.1 (C-8a), 133.6 (C-6), 134.0 (C-4a), 134.8 (C-7), 143.2 (C-3),

162.8 (C-1), 181.1 (C-10), 188.4 (C-9) ppm; HRMS (ESI) m/z calcd. for $C_{22}H_{19}NO_3$, 345.1360, found, 345.1356 $[M]^+$.

1-Hydroxy-4-(3-(4-methylpiperidin-1-yl)prop-1-ynyl)anthracene-9,10-dione (29). Brown powder. Yield 41%; m.p. 144.8 °C (decomp.); IR (KBr) ν : 3420 (OH), 2900 (C-H), 2197 (C $\equiv$ C), 1668 (C=O), 1643 (C=O), 1594, 1580, 1492, 1466, 810, 793, 756, 723 (C=C, CH-Ar) cm^{-1} ; UV (EtOH) λ_{max} (lg ϵ): 250 (3.98), 438 (3.73) nm; 1H NMR ($CDCl_3$, 400 MHz): δ = 0.94 (d, 3H, J = 6.6 Hz, H-20), 1.29–1.38 (m, 2H, H-16,18), 1.38–1.46 (m, 1H, H-17), 1.67–1.74 (m, 2H, H-16,18), 2.32–2.41 (m, 2H, H-15,19), 3.00–3.07 (m, 2H, H-15,19), 3.64 (s, 2H, H-13), 7.22 (d, 1H, J = 8.8 Hz, H-2), 7.74 (d, 1H, J = 8.8 Hz, H-3), 7.76–7.83 (m, 2H, H-6,7), 8.27 (dd, 1H, J = 8.8, 2.0 Hz, H-5), 8.30 (dd, J = 8.8, 2.0 Hz, 1H, H-8), 13.27 (s, 1H, OH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.8 (C-20), 30.2 (C-17), 34.2 (C-16,18), 48.5 (C-13), 52.8 (C-15,19), 84.6 (C-11), 91.1 (C-12), 115.8 (C-4), 116.0 (C-9a), 123.9 (C-2), 126.5 (C-8), 127.6 (C-5), 132.3 (C-10a), 133.1 (C-8a), 133.7 (C-6), 134.0 (C-4a), 134.8 (C-7), 143.2 (C-3), 162.8 (C-1), 181.1 (C-10), 188.4 (C-9) ppm; HRMS (ESI) m/z calcd. for $C_{23}H_{21}NO_3$, 359.1516, found 359.1515 $[M]^+$.

1-Hydroxy-4-(3-(2-(pyridin-3-yl)piperidin-1-yl)prop-1-ynyl)anthracene-9,10-dione (30). Dark orange powder. Yield 84%; m.p. 160.4 °C (decomp.); $[\alpha]_D^{22}$ = 0.788 (c 0.5, $CHCl_3$); IR (KBr) ν : 3428 (OH), 2926 (C-H), 2202 (C $\equiv$ C), 1670 (C=O), 1639 (C=O), 1593, 1578, 1479, 1462, 804, 790, 780, 723, 720 (C=C, CH-Ar) cm^{-1} ; UV (EtOH) λ_{max} (lg ϵ): 250 (3.65), 442 (3.76) nm; 1H NMR ($CDCl_3$, 500 MHz): δ = 1.43–1.56 (m, 1H, H-16), 1.60–1.70 (m, 1H, H-16), 1.73–1.89 (m, 4H, H-17,18), 2.86–2.94 (m, 1H, H-19), 3.09–3.14 (m, 1H, H-19), 3.41 and 3.52 (AB, d 2H, J = 17.6 Hz, H-13), 3.70–3.78 (m, 1H, H-15), 7.23 (d, 1H, J = 8.8 Hz, H-2), 7.26–7.31 (m, 1H, H-24), 7.72 (d, 1H, J = 8.8 Hz, H-3), 7.75–7.88 (m, 3H, H-6,7,25), 8.28 (dd, 1H, J = 8.6, 1.8 Hz, H-5), 8.33 (dd, 1H, J = 8.6, 1.8 Hz, H-8), 8.51 (d, 1H, J = 5.6 Hz, H-23), 8.71 (d, 1H, J = 1.6 Hz, H-21), 13.29 (s, 1H, OH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 24.5 (C-17), 25.8 (C-18), 35.5 (C-16), 45.2 (C-13), 53.0 (C-19), 62.7 (C-15), 85.5 (C-11), 90.0 (C-12), 115.6 (C-4), 115.9 (C-9a), 123.5 (C-2), 123.8 (C-24), 126.5 (C-8), 127.5 (C-5), 132.2 (C-10a), 133.1 (C-8a), 133.7 (C-6), 133.9 (C-4a), 134.8 (C-7), 135.2 (C-25), 139.1 (C-20), 143.2 (C-3), 148.5 (C-23), 149.4 (C-21), 162.8 (C-1), 180.9 (C-10), 188.4 (C-9) ppm; HRMS (ESI) m/z calcd. for $C_{27}H_{22}N_2O_3$, 422.1625, found 422.1623 $[M]^+$.

1-Hydroxy-4-(3-morpholinoprop-1-ynyl)anthracene-9,10-dione (33). Brown powder. Yield 48%; m.p. 172.8 °C (decomp.); IR (KBr) ν : 3415 (OH), 2918 (C-H), 2197 (C $\equiv$ C), 1670 (C=O), 1641 (C=O), 1591, 1512, 1466, 858, 796, 725 (C=C, CH-Ar) cm^{-1} ; UV (EtOH) λ_{max} (lg ϵ): 254 (4.25), 436 (3.55) nm; 1H NMR ($CDCl_3$, 400 MHz): δ = 2.71–2.82 (m, 4H, H-15,19), 3.65 (s, 2H, H-13), 3.80 (t, 4H, J = 4.5 Hz, H-16,18), 7.23 (d, 1H, J = 8.8 Hz, H-2), 7.73 (d, 1H, J = 8.8 Hz, H-3), 7.77–7.84 (m, 2H, H-6,7), 8.27 (dd, 1H, J = 8.6, 2.0 Hz, H-5), 8.30 (dd, 1H, J = 8.6, 1.8 Hz, H-8), 8.27 (dd, 1H, J = 8.7, 1.8 Hz, H-5), 8.30 (dd, 1H, J = 8.7, 2.0 Hz, H-8), 13.27 (s, 1H, OH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 48.4 (C-13), 52.4 (C-15,19), 66.9 (C-16,18), 85.0 (C-11), 89.9 (C-12), 115.4 (C-4), 116.0 (C-9a), 123.9 (C-2), 126.5 (C-8), 127.6 (C-5), 132.3 (C-10a), 133.2 (C-8a), 133.8 (C-6), 133.9 (C-4a), 134.8 (C-7), 143.1 (C-3), 162.9 (C-1), 181.1 (C-10), 188.4 (C-9) ppm; HRMS (ESI) m/z

1-Hydroxy-4-(3-(4-methylpiperazin-1-yl)prop-1-ynyl)anthracene-9,10-dione (34). Brown powder solid. Yield 58%; m.p. 133.8 °C (decomp.); IR (KBr) ν : 3432 (OH), 2931 (C-H), 2197 (C $\equiv$ C), 1673 (C=O), 1634 (C=O), 1593, 1510, 1464, 812, 796, 727 (C=C, CH-Ar) cm^{-1} ; UV (EtOH) λ_{max} (lg ϵ): 255 (4.07), 439 (3.74) nm; ^1H NMR (CDCl_3 , 400 MHz): δ = 2.30 (s, 3H, H-20), 2.41–2.63 (m, 4H, H-16,18), 2.70–2.87 (m, 4H, H-15,19), 3.67 (s, 2H, H-13), 7.21 (d, 1H, J = 8.8 Hz, H-2), 7.74 (d, 1H, J = 8.8 Hz, H-3), 7.76–7.83 (m, 2H, H-6,7), 8.26 (dd, 1H, J = 8.8, 2.0 Hz, H-5), 8.29 (dd, 1H, J = 8.8, 1.8 Hz, H-8), 13.26 (br s, 1H, OH) ppm; ^{13}C NMR (CDCl_3 , 75 MHz): δ = 45.6 (C-20), 47.7 (C-13), 51.7 (C-15,19), 54.7 (C-16,18), 84.5 (C-11), 90.1 (C-12), 115.3 (C-4), 115.6 (C-9a), 123.5 (C-2), 126.2 (C-8), 127.3 (C-5), 131.9 (C-10a), 132.8 (C-8a), 133.4 (C-6), 133.6 (C-4a), 134.4 (C-7), 142.9 (C-3), 162.5 (C-1), 180.7 (C-10), 188.1 (C-9) ppm; HRMS (ESI) m/z calcd. for $\text{C}_{22}\text{H}_{20}\text{O}_3\text{N}_2$, 360.1468, found 360.1474 $[\text{M}]^+$.

1-(3-(Azocan-1-yl)prop-1-ynyl)-4-hydroxyanthracene-9,10-dione (36). Brown powder. Yield 70%; m.p. 128.8 °C (decomp.); IR (KBr) ν : 3425 (OH), 2197 (C $\equiv$ C), 1670 (C=O), 1633 (C=O), 1591, 1572, 1511, 1480, 1462, 829, 809, 795, 725 (C=C, CH-Ar) cm^{-1} ; UV (EtOH) λ_{max} (lg ϵ): 255 (4.01), 442 (3.76) nm; ^1H NMR (CDCl_3 , 300 MHz): δ = 1.53–1.72 (m, 10H, H-16,17,18,19,20), 2.72–2.85 (m, 4H, H-15,21), 3.71 (s, 2H, H-13), 7.22 (d, 1H, J = 8.8 Hz, H-2), 7.73 (d, 1H, J = 8.8 Hz, H-3), 7.76–7.82 (m, 2H, H-6,7), 8.27 (dd, 1H, J = 8.8, 2.0 Hz, H-5), 8.31 (dd, 1H, J = 8.8, 1.8 Hz, H-8), 13.27 (br s, 1H, OH) ppm; ^{13}C NMR (CDCl_3 , 125 MHz): δ = 25.9 (C-17,18,19), 48.9 (C-13), 53.3 (C-15,16,20,21), 81.6 (C-11), 91.3 (C-12), 114.1 (C-4), 114.3 (C-9a), 122.0 (C-2), 124.6 (C-8), 125.7 (C-5), 130.4 (C-10a), 131.1 (C-8a), 131.9 (C-6), 132.2 (C-4a), 132.9 (C-7), 141.6 (C-3), 160.9 (C-1), 179.2 (C-10), 186.6 (C-9) ppm; HRMS (ESI) m/z calcd. for $\text{C}_{24}\text{H}_{23}\text{NO}_3$, 373.1673, found 373.1671 $[\text{M}]^+$.

MTT assay

DMEM with 10% fetal bovine serum (Gibco, USA) was used for culturing. Cytotoxic activity of synthesized compounds (**6–9, 14, 18–20, 23, 24, 28–30, 33, 34, 36**) was evaluated against four different tumor cells including breast carcinoma (MCF-7), human prostate cancer (DU-145), glioblastoma cancer (SNB19), and U-87 MG using MTT assay. The noncancer control was immortalized human fibroblasts (ATCC number CRL-4058). Cytotoxicity of the tested compounds was assessed using the MTT assay and the standard procedure [40]. Cells were inoculated into 96-well plates (3,000 cells per well) and incubated at 37°C in 5% CO₂ for attachment. Medium in wells was replaced after 24 h with fresh medium containing the tested compounds in DMSO (1 % v/v) and incubated for 72 h. The cell viability was assessed through an MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-phenyl-2H-tetrazolium bromide] conversion assay. 1% MTT was added to each well. Four hours later DMSO was added and mixed for 15 min. Optical density (D) of the samples was measured on a BioRad 680 multi-well spectrophotometer (USA) at the wavelength of 570 nm. All compounds were tested at concentrations of 10, 25, 50, and 100 μM using the required controls, i.e., negative, DMSO (solvent), and positive, doxorubicin (standard cytostatic). Each experiment was performed independently in triplicate with three tests in each. Results were reported as mean inhibitory concentration $\text{GI}_{50} \pm \text{SEM}$.

Molecular modeling

Molecular modeling was carried out in the *CCDC Hermes 1.10.5* visualization environment using applications from the *CSD Discovery 2020* package [52]. Three-dimensional structures of the derivatives were obtained empirically in the *Conformer Generator* [53] application. For the calculations, the XRD model of intramolecular human telomeric DNA G-quadruplex bound by the naphthalene diimide compound [54] with PDB ID 3UYH (resolution 1,95 Å) from Protein Data Bank was chosen. To model a possible mechanism of stabilization of G-quadruplex, molecular docking of new compounds was performed at the binding site of naphthalene diimide compound MM41 using *GOLD* [55]. The search area for docking was selected according to the size of MM41. Docking was performed in comparison with the MM41 molecule. The three-dimensional structure of MM41 were obtained in the PubChem database and prepared in the *Conformer Generator* application. Non-covalent interactions of compounds in the binding site were visualized using *Biovia Discovery Studio Visualizer* [56].

Declarations

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Conflicts of Interest: The authors declare that they have no conflict of interests.

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Figures

Figure 1

Docking of new compounds in G-quadruplex binding site. A – ligand MM41, B – compound 14, C – compound 34, D – compound 9. Noncovalent interactions of molecules are shown by dotted lines: green - hydrogen bonds, orange – electrostatic interactions, purple – stacking and π -sigma interactions.

Figure 2

Synthesis of 1-alkynyl-4-hydroxyanthraquinones. Reagent and conditions: (a): Pd(Ph₃)₂Cl₂, CuI, Et₃N, Bu₄NBr, DMF, 65°C, 1h; (b): Bu₄NF, CH₂Cl₂, rt, 30 min.

Figure 3

Synthesis of N-substituted 1-(3-(amino)prop-1-ynyl)-4-hydroxyanthracene-9,10-diones. Reagent and conditions: (a): CuI, dioxane, 65oC, 30 min; (b): CuCl, dioxane, 65oC, 90 min; (c): Cu(OAc)₂·H₂O, 65oC, dioxane, 2h; (d): Cu(OAc)₂·H₂O, 65oC, 30 min – 5h; (e) Bu₄NF (2 equiv.), Cu(OAc)₂·H₂O, 30 min, rt, then 65oC, 2h.

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