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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, molecular docking study, and evaluation of the antiproliferative action of a new group of propargylthio- and propargylselenoquinolines

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Abstract This study describes the synthesis of a new group of halogenopropargylthio-, dipropargylthio-, and halogenopropargylseleno-quinoline derivatives. The ability of all of the synthesized compounds to inhibit the proliferation of the T-47D, MCF-7, MDA-MB-231, and SNB-19 cell lines was determined with the WST-1 assay. The normal fibroblast cell line (HFF-1) was used as a control. The cytotoxic properties of these new, modified propargylquinoline derivatives were comparable to those of cisplatin. The most active compounds, 4,7-dipropargylthiquinoline (**8b**) and 7-chloro-4-propargylselenoquinoline (**5b**), were docked into the binding site of human CYP1A1 and CYP1B1. Our data indicate that these derivatives may present promising chemotherapeutic agents, possibly targeting CYP1s pathway.

Keywords Propargylthioquinolines · Propargylselenoquinolines · Dipropargylthioquinolines · Anticancer activity · Molecular docking

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Introduction

Interest in cancer has grown during the past century as infectious diseases have increasingly been controlled as the result of improved sanitation, vaccination, and antibiotics. Moreover, the incidence of cancer is still rising, and in many cases, the applied treatment is ineffective (Clegg *et al.*, 2002; Silva, 1999). Thus, many research studies are performed with the goal of identifying new medicines and treatment options.

Acetylenic derivatives are an important class of compounds, since many of them have anticancer properties. This class of compounds includes both naturally occurring antitumor drugs, such as gummiferol (Fullas *et al.*, 1995), repandiol (Takahashi *et al.*, 1992), and enediyne, as well as synthetic ones, such as erlotinib (Sos *et al.*, 2009). Natural enediynes, such as calicheamicin, esperamicin, dynemicin, and namenamicin (Gredicak and Jeric, 2007; Grissom *et al.*, 1996; Nicolaou and Dai, 1991), are the most potent anticancer agents discovered to date. Some members of this class are three orders of magnitude more potent than other anticancer drugs, but their clinical use has been limited due to their toxicity and modest selectivity for cancer cells. This has prompted several research groups to design, synthesize, and test new simplified acetylenic analogs, characterized by a similar mode of action. Several cyclic and acyclic derivatives, some including pyridine or quinoline units, have recently been developed (Boryczka *et al.*, 2002, 2011; Lo *et al.*, 2007; Mól *et al.*, 2008; Rawat *et al.*, 2001; Wu *et al.*, 1996).

The arylhydrocarbon receptor (AhR) is a ligand-activated transcription factor that mediates cellular responses to numerous environmental contaminants (Pohjanvirta and Tuomisto, 1994). Molecular mechanism and biological consequences of AhR-mediated regulation of mammalian

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cytochrome P450 enzymes by foreign chemicals [e.g., polycyclic aromatic hydrocarbons (PAHs), aza-polycyclic aromatic hydrocarbons (aza-PAHs), and aryl acetylenes] have been studied extensively (Shimada *et al.*, 2008; Saeki *et al.*, 2003). Several forms of Cytochrome P450 are considered to have an important role in tumor development, because they can metabolize many potential carcinogens and mutagens (Gonzalez and Gelboin, 1994; Kawajiri and Fujii-Kuriyama, 1991). Moreover, cytochrome P450 activity may influence the response of established tumors to anticancer drugs (Guengerich, 1988; Kivistö *et al.*, 1995). High expression levels of some forms of Cytochrome P450 have been found in peri-tumor or tumor tissues in estrogen-associated cancers, such as breast and endometrial cancers (Gajjar *et al.*, 2012; Hevir *et al.*, 2011), although the presence of individual forms of Cytochrome P450 has previously been investigated in different types of cancer, including brain, lung, and colon cancer (Murray *et al.*, 1997).

Cytochrome P450 (CYP) enzymes are superfamily of hemoprotein monoxygenase. In humans, 18 CYP gene families, comprising over 50 enzymes, have been identified. The human CYP1 family is containing three members, CYP1A1, CYP1A2, and CYP1B1. CYP1A1 is well known as an aryl hydrocarbon hydroxylase and is capable of catalyzing a number of oxidations of PAHs. CYP1A1 is expressed, only in trace amounts, in the human liver, and mainly in extrahepatic tissues and is controlled by the AhR receptor. Human CYP1A2 is constitutively expressed in human liver but not in extrahepatic tissues. CYP1A2 gene expression is also regulated by the AhR-mediated signal pathway. CYP1B1, as well as CYP1A1, is primarily localized in the extrahepatic tissues and is characterized by its ability to metabolically activate PAHs (Chun and Kim, 2003).

P450s 1A1 and 1B1 have been shown, as mentioned above, to be induced in vivo by chemicals inducers, (e.g., PAHs, dioxins), and inhibited in vitro by many types of chemicals [e.g., synthetic organoselenum compounds such as 1,2-, 1,3-, and 1,4-phenylenebis(methylene)selenocyanate, and synthetic acetylenic PAHs such as 4-etynylbiphenyl] (Shimada *et al.*, 2008). Moreover, the aza-PAHs (quinoline, benzo[*f*]quinoline, benzo[*h*]quinoline, 1,7-phenantroline) showed similar or more potent AhR ligand activities than the corresponding parent PAHs. Significant enhancement of ligand activity was observed in chlorinated quinolines (3- to 783-fold). When the enhancing effect of the halogen substituent of quinoline on the AhR ligand activity was compared, chlorine and bromine atoms were more effective than the fluorine atom (Saeki *et al.*, 2003).

Aromatic compounds containing acetylene functional group have long been recognized as mechanism-based inhibitors of CYPs. Various acetylenic aromatic compounds have been prepared, and their inhibitory activities evaluated on human CYP1A1 and 1B1 (Fig. 1) (Shimada *et al.*, 2008).

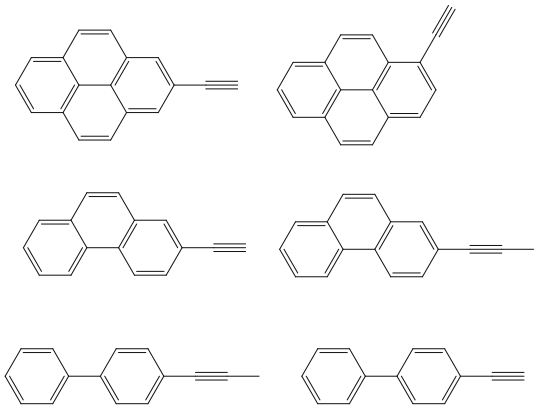


Fig. 1 Structures of representative synthetic aryl acetylenic CYP1 inhibitors

The generally accepted mechanism of inhibition by the acetylenes involves two possible pathways. First pathway involves the oxidation of the internal carbon of the triple bond which leads to heme destruction and enzyme deactivation through the formation of an Fe–O–CR=C(•/+)–Heme complex where a radical or positive charge is localized on the terminal carbon. Second pathway involves the oxidation of the terminal carbon of the triple bond which results in the formation of a reactive ketene intermediate. This ketene intermediate can covalently bind to a nucleophilic amino acid residue in the enzyme's active site leading to irreversible inhibition without destruction of the heme (Shimada *et al.*, 1998).

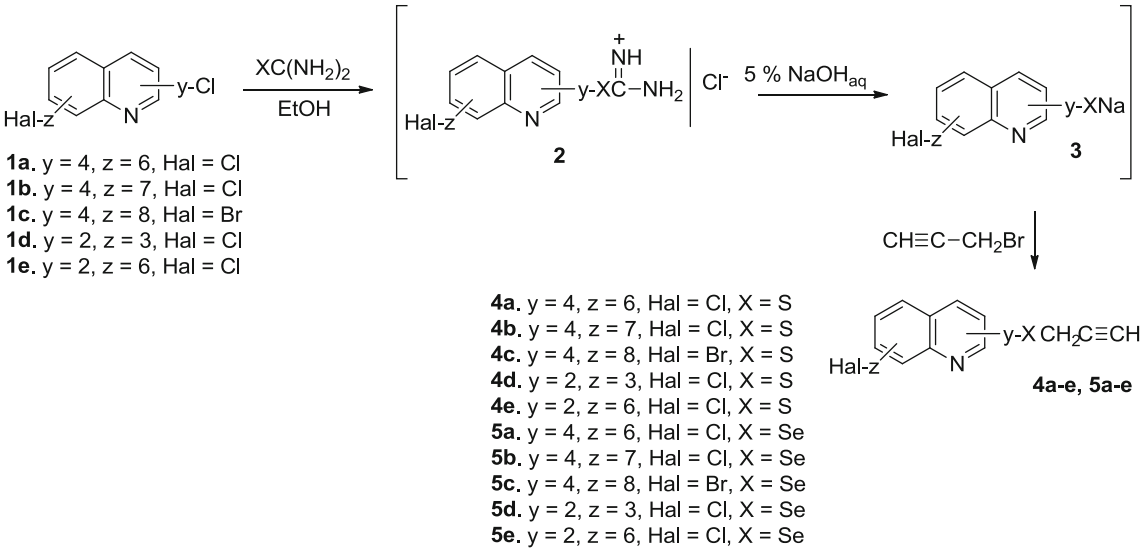
The expression of CYP1 family in different types of malignant tumors has important consequences for treatment of cancer. The expression of CYP1, especially extrahepatic CYPs 1A1 and 1B1 in tumor cells provides a molecular target for development of new anticancer drugs.

Keeping the above facts in mind, we have now synthesized halogenopropargylthio-quinolines **4**, halogenopropargylseleno-quinolines **5,** and dipropargylthio-quinolines **8** and evaluated their antiproliferative activity against different cancer cell lines with the WST-1 assay.

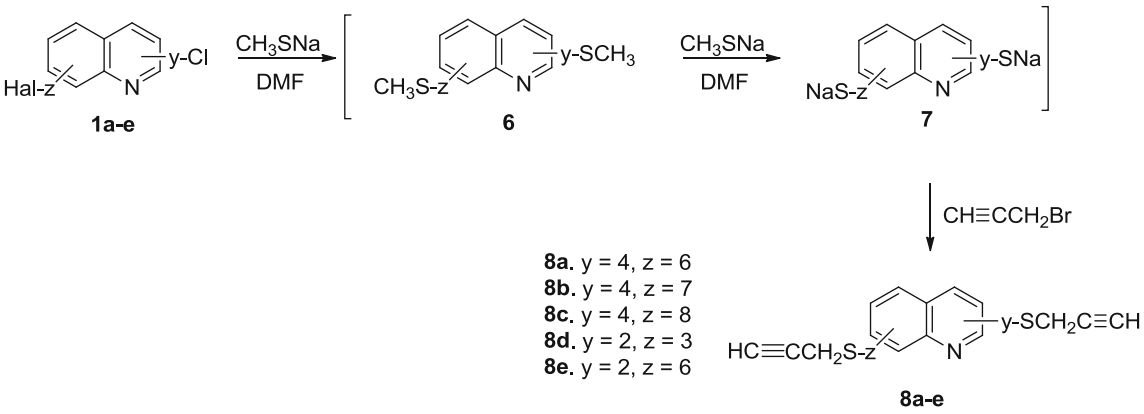
Results and discussion

Chemistry

Propargylthio- and propargylselenoquinolines **4a–e** and **5a–e** were synthesized using dihalogenoquinolines **1a–e** as the starting compounds, as shown in Scheme 1. Dihalogenoquinolines **1** were converted into uronium salts **2** by nucleophilic displacement of the chlorine atom by thiourea or selenourea in ethanol according to our previously reported methods (Mól *et al.*, 2008, Marciniec and Maslankiewicz, 2010). Hydrolysis of the salts **2** and subsequent



Scheme 1 Synthesis of propargylthioquinolines **4a–e** and propargylselenoquinolines **5a–e**



Scheme 2 Synthesis of dipropargylthioquinolines **8a–e**

S- or Se-alkylation of sodium thiolates **3** with propargyl bromide resulted in the synthesis of compounds **4** and **5**. The crude products were isolated from aqueous sodium hydroxide by filtration.

A high yield of dipropragylthioquinolines **8a–e** were produced from respective dihalogenoquinolines **1a–e** in a one-pot process performed with an excess of sodium methanethiolate (Maslankiewicz and Marciniec, 2009; Marciniec and Maslankiewicz, 2010). This process proceeds stepwise by halogen *ipso*-substitution resulting in dimethylthioquinolines **6**, which are then *S*-dealkylated to respective azinedithiolates **7**. They can be trapped by alkylation with propargyl bromide to produce dipropargylthioquinolines **8a–e** (Scheme 2).

All final compounds were pure and stable. The compounds were characterized by ^{1}H- and ^{13}C-nuclear magnetic resonance, IR, and CHN analysis. ^{1}H NMR spectra of propargylquinolines **4**, **5**, and **8** show a typical proton signals for the propargyl group at 2.21–2.32 ppm (triplet) and 3.68–4.16 (doublet) with a coupling constant of $^{4}J = \sim 2.7$ Hz. In ^{13}C NMR spectra of compounds **4**, **5**, and **8,** the signals at 10–20, 71–73, and 77–81 ppm also are attributed to the propargyl group.

In disubstituted quinolines **4**, **5**, and **8**, protons of the pyridine ring of the quinoline moiety formed an AX spin system, and protons of the benzene ring formed an AMX spin system. The assignments of both the ^{1}H and ^{13}C NMR spectra of the quinoline were based on the analysis of coupling patterns and 2D NMR experiments (COSY, HMQC, and HMBC).

Biological study

The antiproliferative activity of all fifteen compounds was tested in T-47D (human ductal carcinoma), MCF-7 (human adenocarcinoma), MDA-MB-231 (human adenocarcinoma), and SNB-19 (human glioblastoma) cells using the

WST-1 assay. Normal human fibroblasts (HFF-1) were used as a control when examining the cytotoxic properties of the new propargylquinoline derivatives. The in vitro cytotoxic activity results were expressed as the concentration of compound (nM/mL), which inhibits the proliferation of 50 % of tumor cells, as compared to the control untreated cells (IC_{50}). Cisplatin was used as a reference for cytotoxicity (positive control). The results of the cytotoxicity studies are summarized in Table 1. Among the tested compounds, only compounds **4b**, **5b** and **8b** exhibited promising activity against the different cell lines used.

In this study, the obtained data indicated that the most active compounds against T-47D cell line were in the following order: **8b** > **8c** > **8d** > **5a** > **5b** > **4c**. As shown in Table 1, dipropargylthioquinoline **8b** had the highest antiproliferative activity that could be due to the presence of thiopropargyl groups in the 4- and 7-quinoline position. On the other hand, compounds **4a**, **4b**, **4e**, and **5a** proved to be effective against SNB-19 cell line. As shown in Table 1, 6-chloro-4-propargylthioquinoline **4a**, 6-chloro-2-propargylthioquinoline **4e**, and 7-chloro-4-propargylthioquinoline **4b** had higher antiproliferative activity that could be due to the presence of chlorine atom in the 6- or 7-quinoline position of the quinoline units. It is also noteworthy that compounds **4a**, **4e**, and **4b** showed higher cytotoxic activity than cisplatin in tested cancer cell line, while their toxicity in normal human fibroblasts was low. Moreover, MCF-7 cell line was found to be sensitive toward 4,6- or 4,7-disubstituted quinolines **8b**, **5b,** and **5a**. It is important to note that 4,7-dipropargylthioquinoline **8b** and 7-chloro-4-propargylselenoquinoline **5b** were more cytotoxic than cisplatin in MCF-7 cells. Moreover, compound **5b** was also more active than cisplatin in MDA-MB-231. Considering the overall activities of synthesized compounds, 6-chloro-4-propargylthioquinoline **4a** and 7-chloro-4-propargylthioquinoline **4b** exhibited a potent antiproliferative activity in SNB-19 cells. The substitution of chlorine atom in the 6- or 7-quinoline position with another thiopropargyl group in compounds **8a** and **8b** increased their anticancer activity in the T-47 and MCF-7 cell lines. In all types of cell lines, antiproliferative activity seems to be inherent to compounds **8b**, **5b**, and **4b**. These compounds seem to be good candidates for further in vitro anticancer activity studies using a broad panel cell lines with the aim of selecting compounds for in vivo studies.

Molecular docking

All synthesized compounds were docked to the active site of CYP1A1 and CYP1B1 and showed binding mode consistent with other docking studies (Mikstacka *et al.*, 2012; Sheng-Nan *et al.*, 2013). As exemplified in Figs. 2 and 3 (compounds **5b** and **8b**), quinoline ring formed π–π stacking interaction with Phe231 in CYP1B1 and Phe224 in CYP1A1. Additionally, edge-to-face interaction with Phe134 and Phe123 in CYP1B1 and CYP1A1, respectively, was observed. The propargyl moiety in compounds **5b** and **8b** was located in hydrophobic cavity formed by

Table 1 IC_{50} values (nM/mL) for the antiproliferative activity of compounds **4a–e**, **5a–e** and **8a–e**

Compound	IC_{50} (nM/ml)				
	T-47D	MCF-7	MDA-MB-231	SNB-19	HFF-1
4a	Neg	Neg	299.6 ± 13.5	2.52 ± 0.64	Neg
4b	107.0 ± 6.07	192.17 ± 9.75	84.74 ± 2.69	3.0 ± 0.90	206.30 ± 9.45
4c	64.8 ± 3.49	Neg	75.6 ± 2.16	113.04 ± 11.4	80.64 ± 1.62
4d	132.68 ± 5.35	248.24 ± 10.6	Neg	303.78 ± 9.24	366.79 ± 11.28
4e	Neg	214.0 ± 11.3	197.73 ± 2.43	2.52 ± 0.59	Neg
5a	32.39 ± 6.4	29.37 ± 4.70	284.97 ± 6.50	3.24 ± 0.60	35.6 ± 3.20
5b	36.31 ± 4.16	24.20 ± 1.63	26.17 ± 2.06	20.29 ± 1.07	58.03 ± 4.27
5c	123.66 ± 10.1	123.75 ± 8.8	192.50 ± 6.37	89.93 ± 4.21	Neg
5d	Neg	178.0 ± 17.7	Neg	44.86 ± 4.27	Neg
5e	Neg	Neg	Neg	57.32 ± 5.3	Neg
8a	192.92 ± 2.70	63.80 ± 5.19	106.11 ± 2.15	Neg	304.6 ± 2.59
8b	2.96 ± 0.33	14.84 ± 1.3	172.51 ± 8.73	185.50 ± 9.3	84.59 ± 1.7
8c	9.83 ± 0.59	167.32 ± 8.93	204.05 ± 5.50	322.77 ± 12.2	293.83 ± 8.60
8d	24.86 ± 0.66	95.71 ± 2.33	126.14 ± 3.59	Neg	167.32 ± 7.80
8e	222.60 ± 10.45	Neg	185.50 ± 9.84	Neg	Neg
Cisplatin	108.22 ± 7.65	26.14 ± 0.73	28.47 ± 3.53	2.83 ± 0.26	–

Neg negative in the concentration used

Phe258/Phe224/Leu264 in CYP1A1 and Phe268/Phe231/Phe256 for CYP1B1. No significant difference between studied CYP1 members in forming hydrophobic interactions with propargyloquinoline analogs was observed.

The docking results stay in line with cytotoxicity binding assay findings. The most potent compound **8b** (Fig. 2) was highly ranked by Glide scoring function in both CYPs. It is worth noting that Glide scoring function correctly predicted that **8b** is more potent than this sulfur analog **5b** (Fig. 3).

Although the WST-1 screening protocol did not conclude of any possible mechanism for the observed antiproliferative activity of the tested compounds, activity of **8b** and **5b** may be attributed due to the inhibition of CYPs route that requires to the further studies.

Materials and methods

General

Organic solvents (from Sigma-Aldrich and Chempur) were of reagent grade and were used without purification.

2,6- and 4,6-dichloroquinolines (**1e** and **1a**) were prepared from 6-chloroquinoline N-oxide and phosphoryl chloride as reported previously (Bachman and Cooper, 1944). The same experimental protocol was applied for the preparation of 2,3-dichloroquinoline (**1d**) from 3-chloroquinoline N-oxide and 8-bromo-4-chloroquinoline (**1c**) from 8-bromoquinoline N-oxide. All other reagents were from Sigma Aldrich and Alfa Aesar.

Purity of the synthesized compounds was confirmed by TLC performed on Merck silica gel 60 F254 aluminum sheets and an ethyl acetate as an eluent. Spots were detected by their absorption under UV light ($\lambda = 254$ nm).

Melting points (mp) were determined with a KSP–1N KRÜSS apparatus and are uncorrected.

IR spectra in KBr disks were recorded on Shimadzu IRAffinity-1 FTIR spectrophotometer.

All NMR spectra were recorded on a Bruker AVANS 300 spectrometer operating at 300.18 MHz and 75.48 MHz for ^{1}H and ^{13}C nuclei, respectively, in deuterochloroform ($CDCl_3$) solution. Coupling constant (J) values are presented in hertz (Hz), and spin multiples are given as s (singlet), d (double), t (triple), and m (multiple).

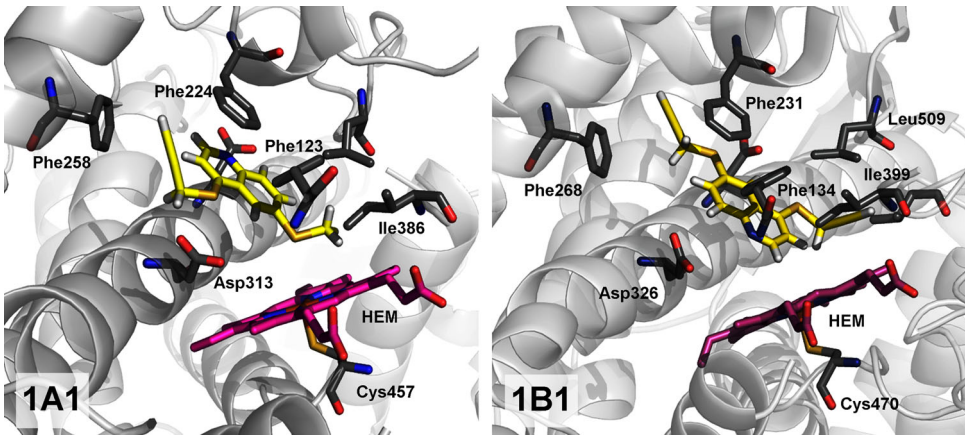


Fig. 2 Orientation of 4,7-dipropargylthioquinoline (**8b**) in the active site of CYP1A1 and 1B1

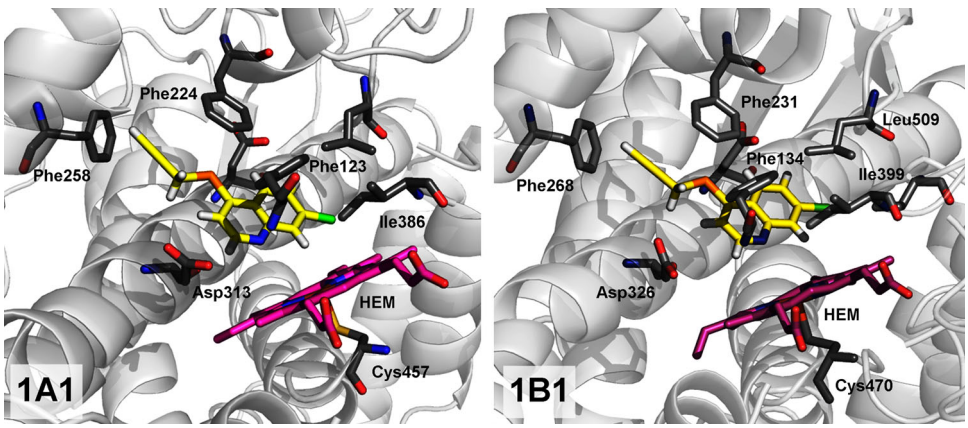


Fig. 3 Orientation of 7-chloro-4-propargylselenoquinoline (**5b**) in the active site of CYP1A1 and 1B1

Mass spectrometry analyses: samples were prepared in acetonitrile/water (10/90 v/v) mixture. The LC/MS system consisted of a Waters Acquity UPLC, coupled to Waters TQD mass spectrometer. All the analyses were carried out using an Acquity UPLC BEH C_{18},50 × 2.1 mm reversed-phase column. A flow rate of 0.3 mL/min and a gradient of (5–95) % B over 5 min was used. Eluent A: water/0.1 % HCO_2H; eluent B: acetonitrile/0.1 % HCO_2H.

Elemental analysis (C, H, and N) was obtained on a EuroVector model 3018 analyzer, and the data were within ±0.4 % of the theoretical values.

Column chromatography separations were carried out on column with Merck Kieselgel 60 using ethyl acetate as an eluent.

Chemistry

*General procedure for synthesis of propargylthio- and propargylselenoquinolines **4a–e** and **5a–e***

A mixture of the dihalogenoquinoline (**1a–e**) with 1.1 molar eqvs. of thiourea or selenourea in ethanol (1 mL/1 mmol of **1a–e**) was stirred at 50 °C for 45 min under argon atmosphere. The mixture was then transferred to cold 5 % aqueous NaOH (10 mL/1 mmol of **1a–e**), and propargyl bromide (1.1 mmol/1 mmol of **1a–e**) was added dropwise to the aqueous layer. The mixture was stirred for 30 min, and resultant solid was filtered off, washed with water, and air-dried to give crude products **4a–e** and **5a–e**. Obtained crude products were crystallized from ethanol to give pure propargylthio- and propargylselenoquinolines **4a–e** and **5a–e**.

*6-Chloro-4-(3-propynylthio)quinoline (**4a**)* White solid (EtOH); yield 82 %; mp 144–145 °C; IR (KBr) ν_{max} 3268 (≡C–H), 2107 (–C≡C–), 1559, 1490, 1347, 1286, 861, 832 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.32$ (1H, t, $J = 2.7$ Hz, SCH_2CCH), 3.85 (2H, d, $J = 2.7$ Hz, SCH_2CCH), 7.41 (1H, d, $J = 4.8$ Hz, H-3), 7.68 (1H, dd, $J = 9.0$ Hz, $J = 2.1$ Hz, H-7), 8.04 (1H, d, $J = 9.0$ Hz, H-8), 8.08 (1H, d, $J = 2.1$ Hz, H-5), 8.78 (1H, d, $J = 4.8$ Hz, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 19.9$ (CH_2, SCH_2CCH), 72.6 (C, SCH_2CCH), 77.8 (CH, SCH_2CCH), 117.6 (CH, C-3), 122.6 (CH, C-5), 127.1 (C, C-4a), 130.8 (CH, C-7), 131.7 (CH, C-8), 132.6 (C, C-6), 144.7 (C, C-4), 145.9 (C, C-8a), 149.5 (CH, C-2); tR = 5.47 min, monoisotopic mass 233.0, $[M+H]^+$ 234.0; Anal. Calc. for $C_{12}H_8ClNS$: C 61.67; H 3.45; N 5.99. Found: 61.82; H 3.65; N 5.90.

*7-Chloro-4-(3-propynylthio)quinoline (**4b**)* White solid (EtOH); yield 71 %; mp 110–111 °C. IR (KBr) ν_{max} 3295 (≡C–H), 1603, 1560, 1488, 1289, 1077, 884, 812 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.32$ (1H, t, $J = 2.7$ Hz, SCH_2CCH), 3.85 (2H, d, $J = 2.7$ Hz, SCH_2CCH), 7.38 (1H, d, $J = 4.8$ Hz, H-3), 7.52 (1H, dd, $J = 9.0$ Hz, $J = 1.8$ Hz, H-6), 8.02 (1H, d, $J = 9.0$ Hz, H-5), 8.09 (1H, d, $J = 1.8$ Hz, H-8), 8.78 (1H, d, $J = 4.8$ Hz, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 19.8$ (CH_2, SCH_2CCH), 72.6 (C, SCH_2CCH), 77.8 (CH, SCH_2CCH), 116.8 (CH, C-3), 124.8 (CH, C-5), 127.5 (CH, C-6), 128.9 (C, C-4a), 129.0 (CH, C-8), 135.8 (C, C-7), 145.8 (C, C-4), 148.0 (C, C-8a), 150.4 (CH, C-2); tR = 5.44 min, monoisotopic mass 233.0, $[M+H]^+$ 234.0; Anal. Calc. for $C_{12}H_8ClNS$: C 61.67; H 3.45; N 5.99. Found: 61.76; H 3.35; N 6.01.

*8-Bromo-4-(3-propynylthio)quinoline (**4c**)* White solid (EtOH); yield 90 %; mp 150–151 °C. IR (KBr) ν_{max} 3216 (≡C–H), 2102 (–C≡C–), 1567, 1484, 1373, 1280, 824, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.32$ (1H, t, $J = 2.7$ Hz, SCH_2CCH), 3.87 (2H, d, $J = 2.7$ Hz, SCH_2CCH), 7.40–7.46 (2H, m, H-3 and H-6), 8.07–8.10 (2H, m, H-5 and H-7), 8.92 (1H, d, $J = 4.8$ Hz, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 20.0$ (CH_2, SCH_2CCH), 72.6 (C, SCH_2CCH), 77.7 (CH, SCH_2CCH), 117.4 (CH, C-3), 123.3 (CH, C-5), 125.4 (C, C-4a), 126.9 (CH, C-6), 127.5 (C, C-8), 133.7 (CH, C-7), 144.7 (C, C-4), 146.4 (C, C-8a), 150.0 (CH, C-2); tR = 6.23 min, monoisotopic mass 276.95, $[M+H]^+$ 278.0; Anal. Calc. for $C_{12}H_8BrNS$: C 51.82; H 2.90; N 5.04. Found: C 51.80; H 2.99; N 5.14.

*3-Chloro-2-(3-propynylthio)quinoline (**4d**)* White solid (EtOH); yield 89 %; mp 95–96 °C; IR (KBr) ν_{max} 3305 (≡C–H), 2121 (–C≡C–), 1576, 1488, 1371, 1195, 1150, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.21$ (1H, t, $J = 2.7$ Hz, SCH_2CCH), 4.16 (2H, d, $J = 2.7$ Hz, SCH_2CCH), 7.49 (1H, ddd, $J = 9.0$ Hz, $J = 9.0$, Hz, $J = 0.9$ Hz, H-6), 7.72–7.66 (2H, m, H-5 and H-7), 7.99 (1H, dd, $J = 9.0$ Hz, $J = 0.9$ Hz, H-8), 8.03 (1H, s, H-4); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 18.9$ (CH_2, SCH_2CCH), 70.7 (C, SCH_2CCH), 79.7 (CH, SCH_2CCH), 126.3 (CH, C-6), 126.5 (C, C-3), 126.6 (C, C-4a), 126.8 (CH, C-5), 128.1 (CH, C-8), 129.9 (CH, C-7), 134.1 (CH, C-4), 146.2 (C, C-8a), 155.7 (C, C-2); tR = 7.17 min, monoisotopic mass 233.0, $[M+H]^+$ 234.0; Anal. Calc. for $C_{12}H_8ClNS$: C 61.67; H 3.45; N 5.99. Found: 61.59; H 3.33; N 6.12.

*6-Chloro-2-(3-propynylthio)quinoline (**4e**)* White solid (EtOH); yield 93 %; mp 87–88 °C; IR (KBr) ν_{max} 3289 (≡C–H), 1592, 1486, 1382, 1290, 1091, 893 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.22$ (1H, t, $J = 2.7$ Hz, SCH_2CCH), 4.16 (2H, d, $J = 2.7$ Hz, SCH_2CCH), 7.24 (1H, d, $J = 9.0$ Hz, H-3), 7.61 (1H, dd, $J = 9.0$ Hz, $J = 2.4$ Hz, H-7), 7.71 (1H, d, $J = 2.4$ Hz, H-5), 7.85, (1H, d, $J = 9.0$ Hz, H-4), 7.91 (1H, d, $J = 9.0$ Hz, H-8); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 18.0$ (CH_2, SCH_2CCH), 70.7

(C, SCH_2CCH), 79.8 (CH, SCH_2CCH), 121.3 (CH, C-3), 126.4 (CH, C-5), 126.7 (C, C-4a), 129.7 (CH, C-8), 130.6 (CH, C-7), 131.1 (C, C-6), 134.8 (CH, C-4), 146.6 (C, C-8a), 157.7 (C, C-2); tR = 8.03 min, monoisotopic mass 233.0, $[M+H]^+$ 234.0; Anal. Calc. for $C_{12}H_8ClNS$: C 61.67; H 3.45; N 5.99. Found: C 61.37; H 3.25; N 5.89.

*6-Chloro-4-(3-propynylseleno)quinoline (**5a**)* White solid (EtOH); yield 86 %; mp 127–128 °C; IR (KBr) ν_{max} 3283 (≡C–H), 1554, 1488, 1399, 1345, 1281, 1152, 1076, 862, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.32$ (1H, t, $J = 2.7$ Hz, $SeCH_2CCH$), 3.85 (2H, d, $J = 2.7$ Hz, $SeCH_2CCH$), 7.63 (1H, d, $J = 4.8$ Hz, H-3), 7.69 (1H, dd, $J = 9.0$ Hz, $J = 2.1$ Hz, H-7), 8.04-8.07 (2H, m, H-5 and H-8), 8.74 (1H, d, $J = 4.8$ Hz, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 11.5$ (CH_2, $SeCH_2CCH$), 72.8 (C, $SeCH_2CCH$), 79.2 (CH, $SeCH_2C\underline{C}H$), 123.4 (CH, C-3), 124.8 (CH, C-5), 129.3 (C, C-4a), 130.9 (CH, C-7), 131.8 (CH, C-8), 132.9 (C, C-6), 141.4 (C, C-4), 146.2 (C, C-8a), 149.6 (CH, C-2); tR = 5.98 min, monoisotopic mass 280.95, $[M+H]^+$ 282.0; Anal. Calc. for $C_{12}H_8ClNSe$: C 61.6; H 3.45; N 5.99. Found: C 61.57; H 3.34; N 5.79.

*7-Chloro-4-(3-propynylseleno)quinoline (**5b**)* White solid (EtOH); yield 70 %; mp 105–106 °C; IR (KBr) ν_{max} 3299 (≡C–H), 1554, 1486, 1288, 1185, 1079, 879, 825 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.32$ (1H, t, $J = 2.7$ Hz, $SeCH_2CCH$), 3.85 (2H, d, $J = 2.7$ Hz, $SeCH_2CCH$), 7.54 (1H, dd, $J = 9.0$ Hz, $J = 1.8$ Hz, H-6) 7.58 (1H, d, $J = 4.5$ Hz, H-3), 7.99 (1H, d, $J = 9.0$ Hz, H-5), 8.10 (1H, d, $J = 1.8$ Hz, H-8), 8.74 (1H, d, $J = 4.5$ Hz, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz); $\delta = 11.3$ (CH_2, $SeCH_2CCH$), 72.8 (C, $SeCH_2CCH$), 79.0 (CH, $SeCH_2CCH$), 122.2 (CH, C-3), 126.9 (C, C-4a), 127.0 (CH, C-5), 127.9 (CH, C-6), 128.8 (CH, C-8), 136.0 (C, C-7), 143.3 (C, C-4), 147.8 (C, C-8a), 150.0 (CH, C-2); tR = 6.04 min, monoisotopic mass 280.95, $[M+H]^+$ 282.0; Anal. Calc. for $C_{12}H_8ClNSe$: C 61.67; H 3.45; N 5.99. Found: C 61.76; H 3.55; N 5.80.

*8-Bromo-4-(3-propynylseleno)quinoline (**5c**)* White solid (EtOH); yield 94 %; mp 139–140 °C; IR (KBr) ν_{max} 3184 (≡C–H), 2137 (–C≡C–), 1565, 1479, 1376, 1279, 1183, 1091, 826, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.32$ (1H, t, $J = 2.7$ Hz, $SeCH_2CCH$), 3.73 (2H, d, $J = 2.7$ Hz, $SeCH_2CCH$), 7.45 (1H, dd, $J = 9.0$ Hz, $J = 9.0$ Hz, H-6), 7.65 (1H, d, $J = 4.5$ Hz, H-3), 8.02 (1H, dd, $J = 9.0$ Hz, $J = 1.8$ Hz, H-7), 8.10 (1H, d, $J = 9.0$ Hz, $J = 1.8$ Hz, H-5), 8.87 (1H, d, $J = 4.5$ Hz, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 11.5$ (CH_2, $SeCH_2CCH$), 72.8 (C, $SeCH_2\underline{C}CH$), 79.0 (CH, $SeCH_2CCH$), 122.7 (CH, C-3), 125.3 (C, C-8), 125.4 (CH, C-5), 127.2 (CH, C-6), 129.5 (C, C-4a), 133.8 (CH, C-7), 143.9 (C, C-4), 144.7 (C, C-8a), 149.9 (CH, C-2); tR = 6.51 min, monoisotopic mass 324.90, $[M+H]^+$ 326.0; Anal. Calc. for $C_{12}H_8BrNSe$: C 44.34; H 2.4; N 4.31. Found: C 44.45; H 2.51; N 4.41.

*3-Chloro-2-(3-propynylseleno)quinoline (**5d**)* White solid (EtOH); yield 90 %; mp 89–90 °C; IR (KBr) ν_{max} 3288 (≡C–H), 1576, 1487, 1365, 1327, 1290, 1133, 1110, 895, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.23$ (1H, t, $J = 2.7$ Hz, $SeCH_2CCH$), 4.06 (2H, d, $J = 2.7$ Hz, $SeCH_2CCH$), 7.49 (1H, ddd, $J = 9.0$ Hz, $J = 9.0$ Hz, $J = 0.9$ Hz, H-6), 7.72–7.68 (2H, m, H-5 and H-7), 7.99 (1H, dd, $J = 9.0$ Hz, $J = 0.9$ Hz, H-8), 8.17 (1H, s, H-4); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 12.7$ (CH_2, $SeCH_2CCH$), 70.8 (C, $SeCH_2CCH$), 80.9 (CH, $SeCH_2CCH$), 118.8 (C, C-3), 126.4 (CH, C-6), 126.8 (CH, C-5), 127.4 (C, C-4a), 128.3 (CH, C-8), 130.0 (CH, C-7), 137.3 (CH, C-4), 147.0 (C, C-8a), 155.9 (C, C-2); tR = 8.04 min, monoisotopic mass 280.95, $[M+H]^+$ 282.0; Anal. Calc. for $C_{12}H_8ClNSe$: C 61.67; H 3.45; N 5.99. Found: C 61.62; H 3.43; N 5.89.

*6-Chloro-2-(3-propynylseleno)quinoline (**5e**)* White solid (EtOH); yield 94 %; mp 72–73 °C; IR (KBr) ν_{max} 3287 (≡C–H), 1588, 1482, 1386, 1329, 1284, 1134, 1083, 879, 829 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.24$ (1H, t, $J = 2.7$ Hz, $SeCH_2CCH$), 4.07 (2H, d, $J = 2.7$ Hz, SCH_2CCH), 7.38 (1H, d, $J = 9.0$ Hz, H-3), 7.62 (1H, dd, $J = 9.0$ Hz, $J = 2.4$ Hz, H-7), 7.74 (1H, d, $J = 2.4$ Hz, H-5), 7.84 (1H, d, $J = 9.0$ Hz, H-8), 7.93 (1H, d, $J = 9.0$ Hz, H-4); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 10.3$ (CH_2, $SeCH_2CCH$), 71.0 (C, $SeCH_2CCH$), 81.0 (CH, $SeCH_2C\underline{C}H$), 123.6 (CH, C-3), 126.5 (CH, C-5), 127.0 (C, C-4a), 129.9 (CH, C-4), 130.6 (CH, C-7), 131.4 (C, C-6), 134.5 (CH, C-8), 147.2 (C, C-8a), 155.4 (C, C-2); tR = 8.01 min, monoisotopic mass 280.95, $[M+H]^+$ 282.0; Anal. Calc. for $C_{12}H_8ClNSe$: C 61.67; H 3.45; N 5.99. Found: C 61.58; H 3.38; N 5.71.

*General procedure for synthesis of dipropargylthioquinolines **8a–e***

A mixture of dihalogenoquinoline (**1a–e**) with 10 molar eqvs. of sodium methanethiolate and dry DMF (6 mL/1 mmol of **1a–e**) was boiled with stirring under argon atmosphere for 4 h (the reaction must be carried out in hood as it proceeds with strong evolution of dimethyl sulfide). This mixture was then cooled to 70 °C, and the volatile components were evaporated under vacuum from water bath. The residue was cooled down in an ice-water bath, (under argon atmosphere) carefully acidified with 20 % hydrochloric acid (1.5 mL/1 mmol of **1a–e**), and then kept at vacuum to remove methanethiol. This residue contains crude (non-isolated) dimercaptoquinolines **7** was added to a solution of 8 % aqueous sodium hydroxide (4 mL/1 mmol of **1a–e**), and then propargyl bromide (2.2 mmol/1 mmol of **1a–e**) was added dropwise on

stirring. The stirring was continued at rt for 1 h. The solid was filtered off, washed with water, and dried on air. Obtained crude compounds **8a–e** were separated by column chromatography and finely were crystallized from ethanol to give pure dipropargylthioquinolines **8a–e**.

*4,6-Di(3-propynylthio)quinoline (**8a**)* Yellow solid (EtOH); yield 89 %; mp 114–115 °C; IR (KBr) ν_{max} 3285 (≡C–H), 3185 (≡C–H), 2108 (–C≡C–), 1601, 1552, 1495, 1401, 1352, 1283, 1189, 829 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.30–2.33 (2H, m, 2× $SCH_2CC\underline{H}$), 3.76 (2H, d, J = 2.4 Hz, $SC\underline{H}_2CCH$), 3.86 (2H, d, J = 2.4 Hz, $SC\underline{H}_2CCH$), 7.42 (1H, d, J = 4.8 Hz, H-3), 7.45 (1H, dd, J = 9.0 Hz, J = 0.9 Hz, H-7), 8.06-8.11 (2H, m, H-5 and H-8), 8.74 (1H, d, J = 4.8 Hz, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.9 (CH_2, SCH_2CCH), 22.1 (CH_2, SCH_2CCH), 72.1 (C, SCH_2CCH), 72.7 (C, SCH_2CCH), 77.7 (CH, SCH_2CCH), 79.0 (CH, SCH_2CCH), 117.3 (CH, C-3), 122.6 (CH, C-5), 126.7 (C, C-4a), 129.9 (CH, C-8), 131.4 (CH, C-7), 134.7 (C, C-6), 145.3 (C, C-4), 145.8 (C, C-8a), 148.3 (CH, C-2;. tR = 4.76 min, monoisotopic mass 269.03, $[M+H]^+$ 270.0; Anal. Calc. for $C_{15}H_{11}NS_2$: C 66.88; H 4.1; N 5.20. Found: C 66.78; H 4.10; N 5.24.

*4,7-Di(3-propynylthio)quinoline (**8b**)* White solid (EtOH); yield 82 %; mp 107–108 °C; IR (KBr) ν_{max} 3278 (≡C–H), 3266 (≡C–H), 2016 (–C≡C–), 1602, 1559, 1485, 1415, 1339, 1293, 1072, 861, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.28 (1H, t, J = 2.7 Hz, SCH_2CCH), 2.32 (1H, t, J = 2.7 Hz, SCH_2CCH), 3.79 (2H, d, J = 2.7 Hz, SCH_2CCH), 3.85 (2H, d, J = 2.7 Hz, SCH_2CCH), 7.35 (1H, d, J = 4.8 Hz, H-3), 7.52 (1H, dd, J = 9.0 Hz, J = 1.8 Hz, H-6), 8.00 (1H, d, J = 9.0 Hz, H-5), 8.07 (1H, d, J = 1.8 Hz, H-8), 8.75 (1H, d, J = 4.8 Hz, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.8 (CH_2, SCH_2CCH), 21.2 (CH_2, SCH_2CCH), 72.1 (C, SCH_2CCH), 72.5 (C, SCH_2CCH), 78.0 (CH, SCH_2CCH), 78.9 (CH, SCH_2CCH), 116.4 (CH, C-3), 123.7 (CH, C-5), 124.6 (C, C-4a), 126.9 (CH, C-6), 127.1 (CH, C-8), 138.4 (C, C-7), 145.6 (C, C-4), 147.7 (C, C-8a), 149.9 (CH, C-2), tR = 4.68 min, monoisotopic mass 269.03, $[M+H]^+$ 270.0; Anal. Calc. for $C_{15}H_{11}NS_2$: C 66.88; H 4.12; N 5.20. Found: C 66.75; H 4.22; N 5.29.

*4,8-Di(3-propynylthio)quinoline (**8c**)* Yellow solid (EtOH); yield 90 %; mp 177–178 °C; IR (KBr) ν_{max} 3271 (≡C–H), 3235 (≡C–H), 2018 (–C≡C–), 1568, 1484, 1378, 1262, 1168, 822, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.23 (1H, t, J = 2.7 Hz, SCH_2CCH), 2.31 (1H, t, J = 2.7 Hz, SCH_2CCH), 3.82 (2H, d, J = 2.7 Hz, SCH_2CCH), 3.85 (2H, d, J = 2.7 Hz, SCH_2CCH), 7.43 (1H, d, J = 4.8 Hz, H-3), 7.45, (1H, dd, J = 9.0 Hz, J = 9.0 Hz, H-6), 7.54 (1H, dd, J = 9.0 Hz, J = 0.9 Hz, H-7), 7.90 (1H, dd, J = 9.0 Hz, J = 0.9 Hz, H-5), 8.80 (1H, d, J = 4.8 Hz, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.8 (CH_2, SCH_2CCH), 19.9 (CH_2, SCH_2CCH), 71.3 (C, SCH_2CCH), 72.5 (C, SCH_2CCH), 77.9 (CH, SCH_2CCH), 79.5 (CH, SCH_2CCH), 117.3 (CH, C-3), 120.4 (CH, C-5), 125.8 (CH, C-7), 126.3 (C, C-4a), 126.5 (CH, C-6), 137.4 (C, C-8), 144.8 (C, C-4), 146.1 (C, C-8a), 148.2 (CH, C-2); tR = 6.31 min, monoisotopic mass 269.03, $[M+H]^+$ 270.0; Anal. Calc. for $C_{15}H_{11}NS_2$: C 66.88; H 4.12; N 5.20. Found: C 66.92; H 4.25; N 5.33.

*2,3-Di(3-propynylthio)quinoline (**8d**)* Yellow solid (EtOH); yield 89 %; mp 98–99 °C IR (KBr) ν_{max} 3288 (≡C–H), 3272 (≡C–H), 1570, 1546, 1380, 1360, 1136, 1114, 988, 776, 751 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.23–2.25 (2H, m, 2× $SCH_2CC\underline{H}$), 3.68 (2H, d, J = 2.4 Hz, $SC\underline{H}_2CCH$), 4.14 (2H, d, J = 2.4 Hz, $SC\underline{H}_2CCH$), 7.46 (1H, ddd, J = 7.8 Hz, J = 7.6 Hz, J = 1.2 Hz, H-6), 7.67 (1H, ddd, J = 8.4 Hz, J = 7.8 Hz, J = 0.8 Hz, H-7), 7.75 (1H, dd, J = 7.6 Hz, J = 0.8 Hz, H-5), 7.96 (1H, dd, J = 8.4 Hz, J = 1.2 Hz, H-8), 8.23 (1H, s, H-4); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.2 (CH_2, SCH_2CCH), 22.9 (CH_2, SCH_2CCH), 70.6 (C, SCH_2CCH), 72.6 (C, SCH_2CCH), 79.1 (CH, SCH_2CCH), 80.0 (CH, SCH_2CCH), 125.6 (C, C-3), 125.9 (CH, C-6), 126.2 (C, C-4a), 127.5 (CH, C-5), 128.0 (CH, C-8), 130.4 (CH, C-7), 141.1 (CH, C-4), 147.3 (C, C-8a), 159.9 (C, C-2); tR = 7.64 min, monoisotopic mass 269.03, $[M+H]^+$ 270.0; Anal. Calc. for $C_{15}H_{11}NS_2$: C 66.88; H 4.12; N 5.20. Found: C 66.92; H 4.35; N 5.16.

*2,6-Di(3-propynylthio)quinoline (**8e**)* Yellow solid (EtOH); yield 91 %; mp 109–110 °C; IR (KBr) ν_{max} 3253 (≡C–H), 2124 (–C≡C–), 1584, 1576, 1482, 1383, 1295, 1145, 1066, 899, 821 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.21 (1H, t, J = 2.7 Hz, SCH_2CCH), 2.25 (1H, t, J = 2.7 Hz, SCH_2CCH), 3.71 (2H, d, J = 2.7 Hz, SCH_2CCH), 4.17 (2H, d, J = 2.7 Hz, SCH_2CCH), 7.25 (1H, d, J = 9.0 Hz, H-3), 7.71 (1H, dd, J = 9.0 Hz, J = 2.1 Hz, H-7), 7.80 (1H, d, J = 2.1 Hz, H-5), 7.78–7.93 (2H, m, H-4 and H-8); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.0 (CH_2, SCH_2CCH), 22.6 (CH_2, SCH_2CCH), 70.6 (C, SCH_2CCH), 71.9 (C, SCH_2CCH), 79.6 (CH, SCH_2CCH), 80.0 (CH, SCH_2CCH), 121.0 (CH, C-3), 126.4 (C, C-4a), 128.1 (CH, C-5), 128.7 (CH, C-8), 131.7 (CH, C-7), 132.2 (C, C-6), 135.1 (CH, C-4), 147.2 (C, C-8a), 157.4 (C, C-2); tR = 8.46 min, monoisotopic mass 269.03, $[M+H]^+$ 270.0; Anal. Calc. for $C_{15}H_{11}NS_2$: C 66.88; H 4.12; N 5.20. Found: C 66.93; H 4.19; N 5.22.

Docking study

The structures of all the synthesized molecules were prepared using LigPrep v. 2.5 (Schrödinger, LLC, New York,

NY, USA), and the appropriate ionization states at pH = 7.4 were assigned using Epik v. 2.3 (Schrödinger, LLC, New York, USA). The crystal structure of human cytochrome P450 1B1 (PDB ID: 3PM0) (Wang *et al.*, 2011) and 1A1 (PDB ID: 4I8V) (Walsh *et al.*, 2013) in complex with α-naphthoflavone (ANF) was retrieved from Brookhaven Protein Data Bank (http://www.rcsb.org/pdb/home/home.do). The Protein Preparation Wizard was used to assign the bond orders, check the steric clashes, and assign appropriate amino acid ionization states. The receptor grids were generated (the OPLS_2005 force field) by set up the grid box on the center of co-crystalized ligand. Automated docking was performed by using Glide v. 5.8 (Schrödinger, LLC, New York, USA) at SP level with the flexible docking option turned on. The docking procedure was validated by re-docking of the ANF molecule to the active site of selected CYPs which resulted in predicted docking pose with RMSD lower than 1 Å, calculated for the best scored pose. The ligand-receptor complexes were visualized by the means of PyMOL Molecular Graphics System, v. 1.5.0.4 (Schrödinger, LLC, New York, USA).

Biological study

Cell culture

The synthesized compounds were tested against tumor cells SNB-19 (human glioblastoma, DSMZ—German Collection of Microorganisms and Cell Cultures, Braunschweig, Germany), MCF-7 (human adenocarcinoma, mammary gland, derived from metastatic site: pleural effusion, ATCC - American Type Culture Collection Rockville, MD, USA), T-47D (human ductal carcinoma, mammary gland, derived from metastatic site: pleural effusion, ATCC), MDA-MB-231(human adenocarcinoma, mammary gland; ATCC), and toward nontumor cells HFF-1 (normal human fibroblasts derived from foreskin, ATCC). The cultured cells were kept at 37 °C and 5 % CO_2. The cells were seeded (5×10^3 cells/well/100 µL DMEM supplemented with FBS (Fetal Bovine Serum, Lonza) to a final concentration of 10 % and streptomycin 10 mg/ml and penicillin 1,000 IU/ml (Sigma) using 96-well plates (Corning).

Biological activity of compounds

Antiproliferative effect of synthesized compounds was determined using the Cell Proliferation Reagent WST-1 assay (Roche Diagnostics, Mannheim, Germany). This colorimetric assay is based on the cleavage of the tetrazolium salt WST-1 by mitochondrial dehydrogenases in viable cells, leading to formazan formation. After exposure to tested compounds at various concentrations of each compound (0.4–400 nM/ml), cell viability was quantified by a cell proliferation assay. The amount of WST-1-formazan produced was measured at 450 nm, and appropriate calculations were performed as described previously. The cytotoxic activity of the test compound compared to cisplatin (positive control). The experiments were repeated in triplicate for each tested compound concentration. Test compounds were prepared initially at concentration of 1 mg/ml DMSO. Solvent control (DMSO) was included to check that the DMSO had no effect at the concentration used.

Calculations of the IC_{50} values were performed using GraphPad Prism 6 (GraphPad Software, San Diego, USA).

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References

Bachman GB, Cooper DE (1944) Quinoline derivatives from 2- and 4-chloroquinolines. J Org Chem 09(4):302–309

Boryczka S, Wietrzyk J, Nasulewicz A, Pełczyńska M, Opolski A (2002) New propargylthioquinolines: synthesis, antiproliferative activity in vitro and structure-activity relationships. Pharmazie 57(11):733–739

Boryczka S, Mól W, Milczarek M, Wietrzyk J, Bębenek E (2011) Synthesis and in vitro antiproliferative activity of novel (4-chloro- and 4-acyloxy-2-butynyl)thioquinolines. Med Chem Res 20(8):1402–1410

Chun YJ, Kim S (2003) Discovery of cytochrome P450 1B1 inhibitors as new promising anti-cancer agents. Med Res Rev 23(6): 657–668

Clegg LX, Feuer EJ, Midthune DN, Fay MP, Hankey BF (2002) Impact of reporting delay and reporting error on cancer incidence rates and trends. J Natl Cancer Inst 94(20):1537–1545

Fullas F, Brown DM, Wani MC, Wall ME, Chagwedera TE, Farnsworth NR, Pezzuto JM, Kinghorn AD (1995) Gummiferol, a cytotoxic polyacetylene from the leaves of Adeniagummifera. J Nat Prod 58(10):1625–1628

Gajjar K, Martin-Hirsch PL, Martin FL (2012) CYP1B1 and hormone-induced ancer. Cancer Lett 324:13–30

Gonzalez FJ, Gelboin HV (1994) Role of human cytochromes P450 in the metabolic activation of chemical carcinogens and toxins. Drug Metab Rev 26(1–2):165–183

Gredicak M, Jeric I (2007) Enediyne compounds: new promises in anticancer therapy. Acta Pharm 57:133–150

Grissom JW, Gunawardena GU, Klingberg D, Huang D (1996) The chemistry of enediynes, enyneallenes and related compounds. Tetrahedron 52:6453–6518

Guengerich FP (1988) Roles of cytochrome P-450 enzymes in chemical carcinogenesis and cancer chemotherapy. Cancer Res 48(11):2946–2954

Hevir N, Šinkovec J, Rižner TL (2011) Disturbed expression of phase I and phase II estrogen-metabolizing enzymes in endometrial cancer: lower levels of CYP1B1 and increased expression of S-COMT. Mol Cell Endocrinol 331:158–167

Kawajiri K, Fujii-Kuriyama Y (1991) P450 and human cancer. Jpn J Cancer Res 82(12):1325–1335

Kivistö KT, Kroemer HK, Eichelbaum M (1995) The role of human cytochrome P450 enzymes in the metabolism of anticancer

agents: implications for drug interactions. Br J Clin Pharmacol 40(6):523–530

Lo YH, LinIL LinCF, Hsu CC, Yang SH, Lin SR, Wu MJ (2007) Novel acyclic enediynes inhibit Cyclin A and Cdc25C expression and induce apoptosis phenomenon to show potent antitumor proliferation. Bioorg Med Chem 15:4528–5436

Marciniec K, Maślankiewicz A (2010) From 2,3-, 2,6-, 3,4- and 4,6-dichloroquinolines to isomeric chloroquinolinesulfonyl chlorides. Heterocycles 81:305–316

Maślankiewicz A, Marciniec K (2009) Synthesis of 4- and 7-quinolinesulfonamides from 4,7-dichloroquinoline. Heterocycles 78(1):93–101

Mikstacka R, Agnes M, Rimando AM, Dutkiewicz Z, Stefański T, Sobiak S (2012) Design, synthesis and evaluation of the inhibitory selectivity of novel trans-resveratrol analogues on human recombinant CYP1A1, CYP1A2 and CYP1B. Bioorg Med Chem 20:5117–5126

Mól W, Matyja M, Filip B, Wietrzyk J, Boryczka S (2008) Synthesis and antiproliferative activity in vitro of novel (2-butynyl)thioquinolines. Bioorg Med Chem 16:8136–8141

Murray GI, Taylor MC, McFadyen MC, McKay JA, Greenlee WF, Burke MD, Melvin WT (1997) Tumor-specific expression of cytochrome P450 CYP1B1. Cancer Res 57(14):3026–3031

Nicolaou K, Dai W-M (1991) Chemistry and biology of the enediyne anticancer antibiotics. Angew Chem Int Ed Engl 30:1387–1416

Pohjanvirta R, Tuomisto J (1994) Short-term toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in laboratory animals: effects, mechanisms, and animal models. Pharmacol Rev 46(4):483–549

Rawat DS, Benites PJ, Incarvito CD, Rheingold AL, Zaleski JM (2001) The contribution of ligand flexibility to metal center geometry modulated thermal cyclization of conjugated pyridine and quinolinemetalloenediynes of copper(I) and copper(II). Inorg Chem 40:1846–1857

Saeki K, Matsuda T, Kato TA, Yamada K, Mizutani T, Matsui S, Fukuhara K, Miyata N (2003) Activation of the human Ah receptor by aza-polycyclic aromatic hydrocarbons and their halogenated derivatives. Biol Pharm Bull 26(4):448–452

Sheng-Nan L, Yu-Ping C, Keng-Chang T, Chia-Yu C, Tian-Shung W, Yune-Fang U (2013) Inhibition of CYP1 by berberine, palmatine, and jatrorrhizine: selectivity, kinetic characterization, and molecular modeling. Toxicol Appl Pharm 272:671–680

Shimada T, Yamazaki H, Foroozesh M, Hopkins NE, Alworth WL, Guengerich FP (1998) Selectivity of polycyclic inhibitors for human cytochrome P450s 1A1, 1A2, and 1B1. Chem Res Toxicol 11(9):1048–1056

Shimada T, Tanaka NK, Takenaka S, Imai Y, Hopkins NE, Foroozesh MK, Alworth WL, Yamazaki H, Guengerich FP, Komori M (2008) Interaction of polycyclic aromatic hydrocarbons with human cytochrome P450 1B1 in inhibiting catalytic activity. Chem Res Toxicol 21(12):2313–2323

Silva IS (1999) Cancer epidemiology: principles and methods. International Agency for Research on Cancer (IARC), Lyon

Sos ML, Koker M, Weir BA, Heynck S, Rabinovsky R, Zander T, Seeger JM, Weiss J, Fischer F, Frommolt P, Michel K, Peifer M, Mermel C, Girard L, Peyton M, Gazdar AF, Minna JD, Garraway LA, Kashkar H, Pao W, Meyerson M, Thomas RK (2009) PTEN loss contributes to erlotinib resistance in EGFR-mutant lung cancer by activation of Akt and EGFR. Cancer Res 69(8):3256–3261

Takahashi A, Endo T, Nozoe S (1992) Repandiol, a new cytotoxic diepoxide from the mushrooms *Hydnum repandum* and *H. repandum* var. album. Chem Pharm Bull (Tokyo) 40(12):3181–3184

Walsh AA, Szklarz GD, Scott EE (2013) Human cytochrome P450 1A1 structure and utility in understanding drug and xenobiotic metabolism. J Biol Chem 288(18):12932–12943

Wang A, Savas U, Stout CD, Johnson EF (2011) Structural characterization of the complex between alpha-naphthoflavone and human cytochrome P450 1B1. J Biol Chem 286(7):5736–5743

Wu MJ, Lin CF, Chen HT, Duh TH, Wang SS, Hsu SC (1996) Molecular design, chemical synthesis and biological studies of novel enediynes related to dynemicin A. Bioorg Med Chem Lett 6:2183–2186