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# New propargyl thioquinolines — synthesis, antiproliferative activity *in vitro* and structure-activity relationships*

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The series of the propargyl thioquinolines has been prepared on the basis of the reaction of thioquinanthrene (**1**) (1,4-dithiino[2,3-c:5,6-c′]-diquinoline) with sodium alkoxides. Some of these compounds have revealed good antiproliferative activity *in vitro* against the cells of human and murine cancer lines. $^{13}C$ NMR spectra were measured for the studied compounds to examine the electronic properties-activity relationships. A regression study on 10 compounds showed a linear correlation of antiproliferative activity with electronic properties, expressed as the $^{13}C$ NMR chemical shift for C-4 carbon atom ($R^2 = 0.97$). It was found that compounds with chemical shift for C-4 value falling in the range of 135–140 ppm exhibited significant antiproliferative activity, while compounds which possess moderate or low activity are located in the range 140–165 ppm. This finding leads to the expectation that the antiproliferative activity of propargyl thioquinolines can be predicted using the $^{13}C$ NMR chemical shift value of their C-4 carbon atom.

## 1. Introduction

An interest in acetylenic compounds, especially terminal acetylenes, is continuously increasing because the introduction of an alkynyl group may significantly modify the chemical, physical and biological properties of such substances. Synthetic methods for the preparation of this class of compounds are of interest especially with regard to the synthesis of biologically active ene-yne or ene-diyne antitumor antibiotics or similar molecules models [1–6]. The difficult availability of the natural ene-diyne systems, as well as problems with their total synthesis, have prompted several research groups to design, prepare, and test new simplified, fully synthetic analogues, characterized by a similar mode of action. Several cyclic and acyclic models have recently been developed, some of them including pyridine and quinoline units [5, 7–10]. Among the acetylenes also the alkynylquinolines comprise a large and important class of biologically active compounds [11, 12]. It is well known that the introduction of an alkynyl group may significantly modify biological properties of antibacterial fluoroquinolone antibiotics [13–15]. Several methods for the synthesis of alkynylquinolines have been reported [11, 12, 16]. A conventional method, widely used for introducing an acetylene group into a quinoline molecule, is a cross-coupling reaction of terminal alkynes with haloquinolines in the presence of a base with a Cu(I)Pd(0) catalyst [17–24]. It is noteworthy that much attention has been focused on the preparation of quinoline derivatives containing a internal acetylene group. On the other hand much less information is available concerning the synthesis of terminal acetylenes with exception of ethynylated derivatives of quinoline.

We have reported a simple and efficient method for the synthesis of thioquinolines, which possess one or two O, S, Se-propargyl groups [25]. This method is based on the reaction of thioquinanthrene (**1**) with alkoxides and employs readily available reagents and an operationally simple experimental procedure [26–30]. The new propargyl thioquinolines obtained exhibit antiproliferative activity *in vitro* against 3 human cancer cell lines: SW707 (rectal adenocarcinoma), T47D (breast cancer) and HCV29T (bladder cancer) [31]. The most active members of these series, 4-(3-hydroxypropoxy)-3′-propargylthio-3,4′-diquinoline sulfide (**2a**), bis(4-propargylthio-3-quinolinylthio) methane (**3**) and 3-methylthio-4-propargylselenoquinoline (**4a**) have an *in vitro* $ID_{50}$ value ranging from 8.8 to 0.6 μg/ml against the cells of all human cancer lines applied [31].

Here we report on the synthetic modification of propargyl thioquinolines with the aim to investigate structure-activity relationships.

## 2. Investigations, results and discussion

### 2.1. Chemistry and antiproliferative activity

In a previous paper we described the first example of the preparation and preliminary evaluation of the propargyl thioquinolines as new antiproliferative agents [31]. Compounds **2a**, **3** and **4a** evolved as promising candidates for further studies on their antiproliferative activity *in vitro* using a broad panel of human and murine cell lines, aiming to select those compounds with clear structure-activity relationships, which could be good candidates for studies *in vivo*. Thus, compounds **2a**, **3** and **4a** were tested in SRB or MTT (in the case of leukemia cells) assay for their antiproliferative activity *in vitro* against 3 human cancer cell lines: LoVo (colon cancer), MCF-7 (breast cancer), MES-SA (uterine cancer) and against 4 murine cancer cell lines: $LL_2$ (Lewis lung carcinoma), B16 (melanoma), P388 and WEHI-3 (leukemia). The results of cytotoxic activity *in vitro* were expressed as an $ID_{50}$ (μg/ml), i.e. the concentration of compound, which inhibits the proliferation in 50% of tumor cells as compared to the

HO(CH2)3O — S — SCH2C≡CH
**2a**

SCH2C≡CH — SCH2S — SCH2C≡CH
**3**

SeCH2C≡CH — SMe
**4a**

**Table 1: Antiproliferative activity *in vitro* of propargyl thioquinolines 2a, 3, 4a and referential cisplatin against the cells of human and murine cancer cell lines**

| Compd. | Cell line/$ID_{50}$ (μg/ml) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Human | | | Murine | | | |
| | LoVo | MCF-7 | MES-SA | $LL_2$ | B16 | P388 | WEHI-3 |
| **2a** | 3.5 ± 1.0 | 3.6 ± 1.1 | 3.4 ± 1.0 | 4.8 ± 1.1 | 3.3 ± 1.0 | 3.2 ± 1.0 | 3.3 ± 1.1 |
| **3** | 10.8 ± 1.2 | 21.2 ± 1.2 | 17.0 ± 1.8 | Neg | Neg | 40.3 ± 1.6 | 5.2 ± 4.1 |
| **4a** | 1.1 ± 1.1 | 2.2 ± 1.3 | 3.1 ± 1.2 | 2.2 ± 1.5 | 3.2 ± 1.0 | 1.4 ± 2.2 | 0.4 ± 1.2 |
| Cisplatin | 4.9 ± 1.5 | 3.2 ± 1.2 | 1.4 ± 1.0 | NT | NT | NT | 0.3 ± 1.7 |

NT – not tested

control of untreated cells. Cisplatin was applied as a referential cytotoxic agent (positive test control). A value of less than 4 μg/ml is considered as an antiproliferative activity criterion for synthetic compounds. The results of the cytotoxicity studies are summarized in Table 1. The data show that compounds **2a** and **4a** exhibit significant cytotoxicity against the cells of all human and murine cancer lines applied, with $ID_{50}$ values comparable to those of cisplatin. Compound **3** revealed relatively moderate antiproliferative activity against LoVo, MCF-7, MES-SA, P388 and WEHI-3 cells but was inactive against $LL_2$, and B16 cells in the concentration range applied. High antiproliferative activity of the compounds **2a** and **4a** has prompted an attempt at further synthetic modification of these type of compounds in order to better understand structural requirements for their cytotoxic activity.

In order to determine whether a substituent at C-4 has any significant influence on the antiproliferative activity, new 4-hydroxyalkoxy-substituted analogues of compound **2a**, bearing 2-hydroxyethoxy, 4-hydroxybutoxy, and 4-[2-(2-hydroxyethoxy)-ethoxy] groups were prepared.

The new homologoues of **2** were synthesized according to our reported methods [30, 31] (Scheme 1). Treatment of thioquinanthrene (**1**) with the disodium salt of the corresponding glycol in DMF at 70 °C and subsequent S-alkylation using propargyl bromide gave sulfides **2** in 52–63% yields. These compounds were tested for their antiproliferative activity *in vitro* against 4 human cancer cell lines: A549 (lung cancer), SW707 (colorectal cancer), HCV29T (bladder cancer), T47D (breast cancer). The results are summarized in Table 2; previously reported [31] data for compound **2a** are included for comparison.

These results show that compounds **2b–d** have significant cytotoxic activity with $ID_{50}$ values ranging from 2.8 to 22.8 μg/ml. Among these, compound **2c** is more active than compound **2a**. Structure-activity correlation studies revealed that shortening or lengthening of the ω-hydroxyalkoxy chain to the hydroxypropoxy and hydroxybutoxy groups slightly decreased the antiproliferative activity, indicating that the lenght of the ω-hydroxyalkoxy group plays an unimportant role in determining cytotoxic activity. A polar terminus capable of hydrogen bonding, however, is necessary for good activity.

In order to get further insight into structure-activity relationships, compound **4a** was modified. These studies involved: substitution of selenium for sulfur and oxygen, formal shift of the propargyl group from C-4 into C-3, and introduction of a second acetylenic group at C-3. The resulting structure-activity relationship should then provide

**Table 2: Antiproliferative activity *in vitro* of propargyl thioquinolines 2 against the cells of human cancer cell lines**

| Compd. | Cell line/$ID_{50}$ (μg/ml) | | | |
|---|---|---|---|---|
| | A549 | SW707 | HCV29T | T47D |
| **2a** | – | 4.5 ± 1.4 | 2.9 ± 1.3 | 3.6 ± 1.5 |
| **2b** | 5.4 ± 1.4 | 10.5 ± 2.6 | 3.8 ± 1.2 | 4.1 ± 1.7 |
| **2c** | 4.7 ± 1.2 | 4.8 ± 1.4 | 2.8 ± 1.4 | 2.9 ± 1.7 |
| **2d** | 8.1 ± 2.0 | 22.8 ± 1.4 | 4.1 ± 1.1 | 5.1 ± 1.2 |

**Scheme 1**

1. NaO—R—ONa / DMF
2. HC≡CCH$_2$Br / NaOH aq

**2b** R = $(CH_2)_2$
**2c** R = $(CH_2)_4$
**2d** R = $(CH_2CH_2)_2O$

**Scheme 2**

RONa, DMF, 70 °C; R'Br, DMF, 20 °C

**4c** R = CH$_2$C≡CH, R' = Me
**4d** R = Me, R' = CH$_2$C≡CH
**4g** R = R' = Me

**Scheme 3**

CX(NH$_2$)$_2$, EtOH / rt; NaOH aq; HC≡CCH$_2$Br, NaOH aq

**4a** X = Se, R = Me
**4b** X = S, R = Me
**4f** X = Se, R = Et

**Scheme 4**

**Table 3: Antiproliferative activity *in vitro* of propargyl thioquinolines 4 against the cells of human cancer cell lines**

| Compd. | Cell line/$ID_{50}$ (µg/ml) | | | |
|---|---|---|---|---|
| | A549 | SW707 | HCV29T | T47D |
| **4a** | – | 2.5 ± 1.6 | 0.6 ± 1.6 | 1.8 ± 1.4 |
| **4b** | 6.8 ± 1.7 | 18.4 ± 2.2 | 17.6 ± 1.6 | 5.7 ± 1.1 |
| **4c** | 36.7 ± 1.2 | 38.5 ± 1.0 | 38.5 ± 1.1 | 21.0 ± 1.0 |
| **4d** | 33.9 ± 1.1 | 36.0 ± 1.1 | 39.1 ± 1.2 | 23.5 ± 1.0 |
| **4e** | 14.2 ± 1.5 | 18.5 ± 2.8 | 48.1 ± 1.2 | 4.1 ± 1.1 |
| **4f** | 3.5 ± 1.1 | 3.3 ± 1.1 | 2.3 ± 1.5 | 2.7 ± 1.1 |
| **4g** | Neg | Neg | 68.3 ± 1.4 | 49.3 ± 1.2 |

information about the influence of substituents on antiproliferative activity in these compounds.

Compound **4c** was synthesized as shown in Scheme 2 by reaction of **1** with sodium propargyloxide and subsequent S-alkylation with methyl bromide as reported [25, 31]. Compound **4d** was similarly prepared from **1** with sodium methoxide and propargyl bromide. 4-Methoxy-3-methylthioquinoline **4g** was prepared as described [27].

Compounds **4a**, **4f** and **4b** were obtained by nucleophilic displacement of chloride in the corresponding 4-chloro-3-alkylthioquinolines **5** by selenourea or thiourea in ethanol and subsequent S-alkylation of sodium salt **4-A** with propargyl bromide (Scheme 3) according to the reported method [31, 32]. The 4-chloro derivatives **5** were obtained as described [33].

For the purpose to obtain derivative **6** which possesses O-propargyl and S-propargyl groups, **1** was reacted with sodium propargyloxide and propargyl bromide (Scheme 4). Unexpectedly, 4-propargyloxy-3-(1-propynylthio)quinoline **4e** was isolated. The formation of **4e** can be explained in terms n+1-alkyne → n-alkyne isomerization which is the first step of the prototropic acetylene-allene rearrangement [34]. This process involves a 1,3-protons shifts and results in the migration of the triple bond between C-2 and C-1 in an acetylene group. Our results indicate that the above mentioned reaction proceeds through the stage of 4-propargyloxy-3-propargylthioquinoline **6**. It is worth noting that among two propargyl groups only the S-propargyl is isomerized. This observation is consistent with the fact that this type of base-promoted isomerisation occurs more readily with thioethers than with ethers [34].

The *in vitro* antiproliferative activity of compounds **4b–g** was tested against four human cancer cell lines: A549 (lung cancer), SW707 (colon cancer), HCV29T (bladder cancer), T47D (breast cancer) (Table 3). The data for **4a** are included for comparison [31].

The new compounds **4b–f** inhibit proliferation of the cells of all cancer lines applied, and the highest activity was displayed by **4f**. Considering the overall activities of **4a–c**, it can be postulated that substitution of selenium with sulfur or oxygen reduces the cytotoxic activity. $ID_{50}$ values for **4c** and **4d** indicate that formal shift of the propargyl group of compound **4c** from C-4 to C-3 (compound **4d**) does not influence the activity. Data of the compound **4e** indicate that the introduction of the second acetylenic group at C-3 increases activity, especially against the cells of T47D breast cancer cell line.

The compound with a 3-thioethyl group **4f** shows activity similar to the methyl derivative **4a**. It seems interesting that compound **4g** is much less cytotoxic than a compound with a propargyl substituent. It indicates that a propargyl group may be essential for antiproliferative activity of these compounds. Another noteworthy feature of the obtained results is the observation that T47D cells appear to be more sensitive to the cytotoxic effects of compounds **4a–g** than the 3 other human cancer cells lines applied.

Taking into consideration the overall *in vitro* activities of the compounds **4a–g** against A549, SW707, HCV29T and T47D cells, the average activity values indicate that cytotoxicity is in the order of **4a** > **4f** > **4b** > **4e** > **4d** = **4c** ≫ **4g**. The most cytotoxic compounds in these series, namely **4a** and **4f**, approached the activity of cisplatin. It seems most likely that electronic effects of the substituents at positions 3 and 4 play an important role in the determination of cytotoxic activity in this class of compounds.

### 2.2. $^{13}$C-NMR quantitative spectroscopic data-activity relationships

It is generally accepted that the overall molecular properties, electronic, steric, lipophilic and hydrogen bonding are essential in determining biological activity [35]. For the structure-activity relationship study, it was of interest to examine the correlation between the antiproliferative activity of propargyl thioquinolines and their electronic properties. We were particularly interested in the attempts to develop an experimental index to predict whether the molecule in question has cytotoxic activity. We decided to examine the $^{13}$C NMR chemical shifts as a measure of electronic properties and thus the electronic effects on cytotoxic activity. $^{13}$C chemical shifts reflect steric and electronic environments of an atom [36]. We assumed that these chemical shifts values would be good parameters of changes in the electronic properties of compounds. Therefore, $^{1}$H and $^{13}$C NMR spectroscopic studies were performed. The assignments of the NMR signals were performed by means of $^{1}$H-$^{1}$H COSY, $^{1}$H-$^{13}$C HMQC and HMBC experiments. An electronic properties-activity relationship was conducted for compounds **4a–f**, prepared in this study, and for compounds **2a**, **3**, **7** and **8** obtained previously. The selected $^{13}$C chemical shifts and antiproliferative activities against the cells of T47D breast cancer cell line are presented in Table 4. The data show that the antiproliferative activity *in vitro* of the studied compounds is strongly dependent on the structure of both the substituents at C-3 and C-4 of the quinoline moiety. For the compounds with the same methylthio group at C-3 and with propargylseleno or propargylthio or propargyloxy group at C-4 (compounds **4a**, **4b** and **4c**, respectively) their activities parallel the electron densities expressed as the $^{13}$C NMR chemical shifts in the quinoline ring system and in the propargyl substituent. It is known that chemical shifts of

**Table 4: Selected $^{13}$C NMR chemical shifts δ (ppm) and antiproliferative activity values against T47D cells ($ID_{50}$, μg/ml) of investigated compounds 2a, 3, 4, 7 and 8**

| Compd. | R | R′ | C-2 | C-3 | C-4 | $CH_2$ | C≡ | CH | $ID_{50}$ |
|---|---|---|---|---|---|---|---|---|---|
| **2a** | $OCH_2CH_2CH_2OH$ (3-S-quinolin-4-yl) | $CH_2C{\equiv}CH$ | 148.35 | 136.45 | 136.60 | 21.41 | 78.40 | 72.87 | 3.6 |
| **3** | $SCH_2C{\equiv}CH$ | 4-$SCH_2C{\equiv}CH$-3-$CH_2S$-quinoline | 149.85 | 135.09 | 141.64 | 23.57 | 78.51 | 72.76 | 8.8 |
| **4a** | $SeCH_2C{\equiv}CH$ | Me | 145.98 | 139.52 | 135.26 | 12.53 | 79.69 | 72.48 | 1.8 |
| **4b** | $SCH_2C{\equiv}CH$ | Me | 146.21 | 139.01 | 136.31 | 22.33 | 78.79 | 72.29 | 5.7 |
| **4c** | $OCH_2C{\equiv}CH$ | Me | 152.48 | 121.88 | 159.67 | 60.40 | 78.12 | 76.52 | 21.0 |
| **4d** | OMe | $CH_2C{\equiv}CH$ | 155.08 | 117.61 | 163.93 | 22.76 | 79.08 | 72.35 | 23.5 |
| **4e** | $OCH_2C{\equiv}CH$ | $C{\equiv}C{-}CH_3$ | 150.30 | 118.58 | 157.19 | 61.15 | 77.72 | 77.05 | 4.1 |
| **4f** | $SeCH_2C{\equiv}CH$ | Et | 147.53 | 138.40 | 137.04 | 12.82 | 79.73 | 72.50 | 2.7 |
| **7** | $SCH_2C{\equiv}CH$ | 4-$SCH_2C{\equiv}CH$-quinolin-3-yl | 150.94 | 135.73 | 141.93 | 23.69 | 78.53 | 72.94 | 4.8 |
| **8** | $OCH_2C{\equiv}CH$ | 4-$OCH_2C{\equiv}CH$-3-$CH_2S$-quinoline | 155.08 | 117.79 | 162.14 | 61.26 | 77.81 | 76.85 | 3.7 |

the methylthioquinoline and quinoline carbon atoms are sensitive to electron density in the quinoline system, and they shift upfield in an electron-rich environment [37, 38]. In the studied compounds, signals for C-2 and C-4 of the quinoline for the more active derivatives are shifted upfield in comparison with the chemical shifts of the corresponding less active compounds. Also the chemical shifts for the $CH_2$ and CH carbon atoms of the propargyl groups are located upfield in the spectra of the more active compounds. On the contrary, the signals for C-3 are shifted to low field. These results suggest that the electron-density distribution in the thioquinoline system and in the propargyl substituent strongly affects the cytotoxic activity. The relationships between electronic properties, expressed as the $^{13}$C NMR chemical shifts, and antiproliferative activities were investigated by simple linear regression using the program Microsoft Excel for Windows. To describe the structural variation of these 10 compounds, three individual $^{13}$C NMR chemical shifts for C-2, C-3, C-4, and two averaged $^{13}$C NMR chemical shifts for C-2 + C-4 and C-2 + C-4 + CH carbon atoms were used as independent variables in the regression analysis. For these selected descriptors the complete regression equations are presented in Table 5. Examination of these models showed that two compounds, **4e** and **8**, were outliers having a large residual, the difference between the actual $ID_{50}$ values and the

**Table 5: Linear regression equations**

| Entry | y = ax + b | | | | | | Compounds |
|---|---|---|---|---|---|---|---|
| | y | x | a | b | $R^2$ | n | |
| 1 | $ID_{50}$ | C-2 | 1.43 | −206.67 | 0.37 | 10 | **2a**, **3**, **4a–f**, **7**, **8** |
| 2 | $ID_{50}$ | C-3 | −0.44 | 64.66 | 0.29 | 10 | **2a**, **3**, **4a–f**, **7**, **8** |
| 3 | $ID_{50}$ | C-4 | 0.41 | −52.34 | 0.40 | 10 | **2a**, **3**, **4a–f**, **7**, **8** |
| 4 | $ID_{50}$ | C-2 + C-4 | 0.66 | −89.59 | 0.40 | 10 | **2a**, **3**, **4a–f**, **7**, **8** |
| 5 | $ID_{50}$ | C-2 + C-4 + CH | 0.83 | −95.04 | 0.35 | 10 | **2a**, **3**, **4a–f**, **7**, **8** |
| 6* | $ID_{50}$ | C-2 | 2.34 | −341.29 | 0.76 | 8 | **2a**, **3**, **4a–d**, **4f**, **7** |
| 7* | $ID_{50}$ | C-3 | −0.99 | 141.01 | 0.96 | 8 | **2a**, **3**, **4a–d**, **4f**, **7** |
| 8* | $ID_{50}$ | C-4 | 0.74 | −97.46 | 0.97 | 8 | **2a**, **3**, **4a–d**, **4f**, **7** |
| 9* | $ID_{50}$ | C-2 + C-4 | 1.15 | −160.11 | 0.94 | 8 | **2a**, **3**, **4a–d**, **4f**, **7** |
| 10* | $ID_{50}$ | C-2 + C-4 + CH | 1.37 | −191.31 | 0.95 | 8 | **2a**, **3**, **4a–d**, **4f**, **7** |

Abbreviation used: a, slope; b, intercept; y, $ID_{50}$ (μg/ml) for T47D cells; x, $^{13}$C NMR chemical shift value (ppm) of selected carbon atom or average $^{13}$C NMR chemical shift value (ppm) of selected carbon atoms; $R^2$, correlation coefficient; n, number of compounds used in linear regression analysis; * without compounds **4e** and **8**

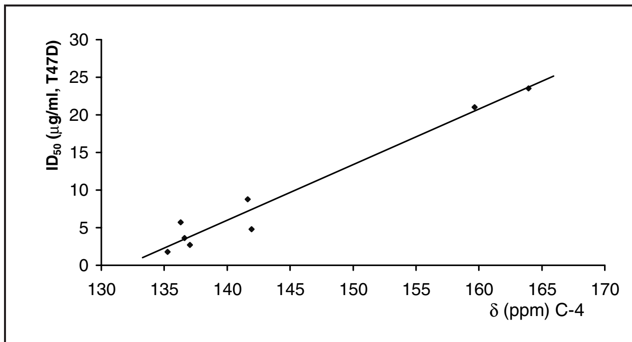


Fig.: Relationship between antiproliferative activity against T43D ($ID_{50}$, µg/ml) and $^{13}C$ NMR chemical shift ($\delta_C$, ppm) of C-4 for compounds **2a**, **3**, **4a–d**, **4f**, **7**

values predicted by the regression equation. For this reason compounds **4e** and **8** were eliminated from further considerations. The remaining 8 compounds were then examined and the best correlation found is for variable C-4 (Table 5, entry 8). This model indicates that chemical shift of C-4 can be used as a descriptor to explain 97% of the total variance of the biological activity. Other three parameters, chemical shifts for C-3 and averaged chemical shifts for C-2 + C-4 and C-2 + C-4 + CH explain 94–96% of the $ID_{50}$ data spread. The Figure shows the relationship between the antiproliferative activity against T47D cells of the compounds **2a, 3, 4a–d**, **4f, 7** and $^{13}C$ NMR chemical shift for C-4. This demonstrates a significant correlation between the electronic properties expressed as the chemical shifts of C-4, and the cytotoxic activity. It can be seen that compounds with chemical shift for C-4 values falling in the range of 135–140 ppm exhibit significant antiproliferative activity. Compounds which exhibit moderate or low activity are located in the range 140–165 ppm. The obtained results provide strong support for our proposition that the activity of propargyl thioquinolines can be predicted by using their C-4 chemical shifts values as a parameter which discerns the activity.

In the light of the obtained data it is tempting to speculate that the quinoline N atom and the heteroatoms (O, S and Se) of the substituents in the most active propargyl thioquinoline are favorably positioned to form a specific hydrogen-bonded complex with a biological receptor. A specific interaction can also be suggested for terminal triple bond of the propargyl substituents and hydroxyl group of the hydroxyalkoxyl substituents. It is consistent with our previous observation that compounds **4a** and **4b** are able to form very short intermolecular hydrogen bonds of type C–H...N [39–42].

The correlation between the electronic properties expressed as $^{13}C$ NMR chemical shift and the cytotoxic activity of the propargyl thioquinolines provides an interesting basis for further studies in the field of new quinoline anticancer agents.

## 3. Experimental

### *3.1. Synthesis*

Melting points were determined in open capillary tubes on a Boetius apparatus and are uncorrected. $^1H$ NMR (300 MHz) spectra were recorded on a Bruker MSL 300 spectrometer in $CDCl_3$ solvents with tetramethylsilane as internal standard; chemical shifts are reported in ppm (δ) and *J* values in Hz. The 1 H- (500 MHz) and $^{13}C$-(125 MHz) NMR spectra were recorded on Bruker AMX-500 spectrometer, chemical shifts are referenced to the residual solvent signal ($CDCl_3$, $\delta_H = 7.26$, $\delta_C = 77.0$). Homonuclear $^1H$ connectivities were determined by performing COSY experiments. One-bond heteronuclear $^1H$-$^{13}C$ connectivities were determined by HMQC experiments. Two- and three-bond $^1H$-$^{13}C$ connectivities were determined by HMBC experiments optimized for a $^{2,3}J$ of 10 Hz. EI MS spectra were run on a LKB GC 2091 spectrometer at 15 eV. FAB MS spectra were recorded on a Finnigan MAT 95 spectrometer in FAB mode ($Cs^+$, 13 keV, nba). Elemental C, H, N, S analyses were obtained on a Carlo Erba Model 1108 analyzer. All the results were in an acceptable range. TLC was performed on silica gel 60 254F plates (Merck) using a mixture of chloroform and ethanol (15 : 1, v/v) as an eluent. UV light and iodine accomplished visualization. CC was performed on silica gel 60, < 63 µm (Merck) using a mixture of chloroform and ethanol (30 : 1, v/v) as an eluent. Solvents were dried and purified according to literature procedures. Thioquinanthrene **1** was obtained by exhaustive sulfurization of quinoline with elemental sulfur and recrystallized from DMF, m.p. 314–315 °C [43].

#### *3.1.1. General procedure for the synthesis of 4-(ω-hydroxyalkoxy)-3′-propargylthio-3,4′-diquinolinyl sulfide* (**2**)

A suspension of thioquinanthrene **1** (0.64 g, 2.0 mmol) and disodium salt of ethylene, 1,4-butylene or diethylene glycol (6.0 mmol) and dry DMF (12 ml) was stirred at 70 °C for 30 min under $N_2$. The solution was then cooled to RT and poured into 35 ml of 10% aqueous sodium hydroxide. Propargyl bromide (0.25 g, 2.1 mmol) was added dropwise to the aqueous layer, and the mixture was stirred for 15 min. The mixture was extracted with 3 × 10 ml of chloroform. The combined organic layer was washed with water, dried with anhydrous magnesium sulfate and evaporated in vacuo to give an oily residue. The crude product was purified by cc and crystallized from ethanol to give pure product **2**.

##### 3.1.1.1. 4-(Hydroxyethoxy)-3′-propargylthio-3,4′-diquinolinyl sulfide (**2b**)

Yield 52%, m.p. 133–134 °C. $^1H$ NMR (300 MHz) δ: 2.21 (t, J = 2.5 Hz, 1 H, CH), 3.72 (d, J = 2.5 Hz, 2 H, $CH_2S$), 4.06 (t, J = 4.2 Hz, 2 H, $CH_2O$), 4.56 (t, J = 4.2 Hz, 2 H, $CH_2O$), 7.52–8.34 (m, 8 H, Ar-H), 8.06 (s, 1 H, 2-H), 9.06 (s, 1 H, 2′-H). EI MS (15 eV) m/z (rel. intensity) 418 ($M^+$, 100), 373 (14), 357 (25), 335 (57).
$C_{23}H_{18}N_2O_2S_2$

##### 3.1.1.2. 4-(Hydroxybutoxy)-3′-propargylthio-3,4′-diquinolinyl sulfide (**2c**)

Yield 63%, m.p. 105–106 °C. $^1H$ NMR (300 MHz) δ: 1.90 (m, 2 H, $CH_2$), 2.06 (m, 2 H, $CH_2$), 2.26 (t, J = 2.5 Hz, 1 H, CH), 3.77 (d, J = 2.5 Hz, 2 H, $CH_2S$), 3.80 (t, J = 6.7 Hz, 2 H, $CH_2O$), 4.40 (t, J = 6.7 Hz, 2 H, $CH_2O$), 7.53–8.35 (m, 8 H, Ar-H), 8.08 (s, 1 H, 2-H), 9.05 (s, 1 H, 2′-H). EI MS (15 eV) m/z (rel. intensity) 446 ($M^+$, 45), 373 (20), 303 (100).
$C_{25}H_{22}N_2O_2S_2$

##### 3.1.1.3. 4-[2-(2-Hydroxyethoxy)-ethoxy]-3′-propargylthio-3,4′-diquinolinyl sulfide (**2d**)

Yield 58%, m.p. 58–60 °C. $^1H$ NMR (300 MHz) δ: 2.62 (t, J = 2.5 Hz, 1 H, CH), 3.74 (d, J = 2.5 Hz, 2 H, $CH_2S$), 3.77–4.55 (m. 8 H, 4 × $CH_2O$), 7.54–8.36 (m, 8 H, Ar-H), 8.11 (s, 1 H, 2-H), 9.06 (s, 1 H, 2′-H). EI MS (15 eV) m/z (rel. intensity) 462 ($M^+$, 81), 373 (13), 303 (47).
$C_{25}H_{22}N_2O_3S_2$

#### *3.1.2. 3-Methylthio-4-propargyloxyquinoline* (**4c**)

A suspension of thioquinanthrene **1** (0.80 g, 2.5 mmol) and sodium propargyloxide (1.17 g, 15 mmol) in dry DMF (12 ml) was stirred at 70 °C for 30 min. The clear solution was cooled to RT and methyl bromide (0.74 g, 5.2 mmol) was added dropwise during 30 min. The reaction mixture was stirred for 1 h and then poured into 35 ml of 10% aqueous sodium hydroxide. The mixture was extracted with 3 × 10 ml of chloroform. The combined organic layer was washed with water and dried with anhydrous magnesium sulfate. After removal of the solvent the residue was purified by cc to give 0.68 g (59%) of pure product **4c**, m.p. 97–98 °C (ethanol). $^1H$ NMR (500 MHz) δ: 2.52 (t, J = 2.4 Hz, 1 H, CH), 2.56 (s, 3 H, $CH_3S$), 5.05 (d, J = 2.4 Hz, 2 H, $CH_2S$), 7.55 (m, $^3J_{(5,6)} = 8.3$ Hz, $^3J_{(6,7)} = 7.0$ Hz, $^4J_{(6,8)} = 1.1$ Hz, 1 H, 6-H), 7.68 (m., $^3J_{(7,8)} = 8.4$ Hz, $^3J_{(6,7)} = 7.0$ Hz, $^4J_{(5,7)} = 1.4$ Hz, 1 H, 7-H), 8.05 (dd, $^3J_{(7,8)} = 8.4$ Hz, $^4J_{(6,8)} = 1.1$ Hz, 1 H, 8-H), 8.20 (dd, $^3J_{(5,6)} = 8.3$ Hz, $^4J_{(5,7)} = 1.4$ Hz, 1 H, 5-H), 8.84 (s, 1 H, 2-H). $^{13}C$ NMR (125 MHz) δ: 152.48 (C-2), 121.88 (C-3), 159.67 (C-4), 124.15 (C-4a), 122.18 (C-5), 126.86 (C-6), 129.58 (C-7), 129.15 (C-8), 148.60 (C-8a), 60.40 ($CH_2$), 78.12 ($CH_2$-*C*), 76.52 (*C*H), 16.94 ($CH_3$). EI MS (15 eV) m/z (rel. intensity) 229 ($M^+$, 42), 216 (100), 214 (68), 190 (80).
$C_{13}H_{11}NOS$

#### *3.1.3. 4-Methoxy-3-propargylthioquinoline* (**4d**)

A suspension of thioquinanthrene **1** (0.80 g, 2.5 mmol) and sodium methoxide (0.81 g, 15 mmol) in dry DMF (12 ml) was stirred at 70 °C for 30 min. The clear solution was cooled to RT and propargyl bromide (0.61 g, 5.2 mmol) was added dropwise during 30 min. The reaction mixture was stirred for 1 h and then poured into 35 ml of 10% aqueous sodium hydroxide. The mixture was extracted with 3 × 10 ml of chloroform.

The combined organic layer was washed with water and dried with anhydrous magnesium sulfate. After removal of the solvent the residue was purified by cc to give 0.78 g (68%) of pure product **4d** with m.p. 73–75 °C (ethanol), lit.[25] m.p. 73–75 °C. $^1$H NMR (500 MHz) δ: 2.19 (t, J = 2.6 Hz, 1 H, CH), 3.67 (d, J = 2.6 Hz, 2 H, $CH_2S$), 4.16 (s, 3 H, $CH_3$), 7.56 (m, $^3J_{(5,6)}$ = 8.5 Hz, $^3J_{(6,7)}$ = 6.9 Hz, $^4J_{(6,8)}$ = 1.2 Hz, 1 H, 6-H), 7.71 (m, $^3J_{(7,8)}$ = 8.4 Hz, $^3J_{(6,7)}$ = 6.9 Hz, $^4J_{(5,7)}$ = 1.5 Hz, 1 H, 7-H), 8.07 (dd, $^3J_{(7,8)}$ = 8.4 Hz, $^4J_{(6,8)}$ = 1.2 Hz, 1 H, 8-H), 8.12 (dd, $^3J_{(5,6)}$ = 8.5 Hz, $^4J_{(5,7)}$ = 1.5 Hz, 1 H, 5-H), 8.94 (s, 1 H, 2-H). $^{13}$C NMR (125 MHz) δ: 155.08 (C-2), 117.61 (C-3), 163.93 (C-4), 123.69 (C-4a), 122.03 (C-5), 126.75 (C-6), 130.10 (C-7), 129.40 (C-8), 149.49 (C-8a), 22.76 (*C*H$_2$), 79.08 (CH$_2$-*C*), 72.35 (*C*H), 61.99 (*C*H$_3$).

*3.1.4. General procedure for the synthesis of 4-propargylseleno and 4-propargylthio-3-alkylthioquinolines*

A mixture of 4-chloro-3-alkylthioquinoline **5** (2.0 mmol), selenourea (0.26 g, 2.1 mmol) or thiourea (0.16 g, 2.1 mmol) in 99.8% ethanol (8 ml) was stirred at RT for 1 h. The reaction mixture was poured into 20 ml of 5% aqueous sodium hydroxide. Propargyl bromide (0.29 g, 2.4 mmol) was added dropwise to the aqueous layer, and the mixture was stirred for 15 min. The resultant solid was filtered off, washed with water and air-dried to give a crude product which was purified by cc and then crystallized from a mixture of benzene and hexane to give pure products.

3.1.4.1 3-Methylthio-4-propargylselenoquinoline (**4a**)

Yield 79%, m.p. 97–98 °C, lit. [31] m.p. 97–98 °C. $^1$H NMR (500 MHz) δ: 2.14 (t, J = 2.7 Hz, 1 H, CH), 2.65 (s, 3 H, $CH_3$), 3.56 (d, J = 2.7 Hz, 2 H, $CH_2$Se), 7.59 (m, $^3J_{(5,6)}$ = 8.3 Hz, $^3J_{(6,7)}$ = 6.9 Hz, $^4J_{(6,8)}$ = 1.4 Hz, 1 H, H-6), 7.65 (m, $^3J_{(7,8)}$ = 8.3 Hz, $^3J_{(6,7)}$ = 6.9 Hz, $^4J_{(5,7)}$ = 1.5 Hz, 1 H, 7-H), 8.04 (dd, $^3J_{(7,8)}$ = 8.3 Hz, $^4J_{(6,8)}$ = 1.4 Hz, 1 H, 8-H), 8.48 (dd, $^3J_{(5,6)}$ = 8.3 Hz, $^4J_{(5,7)}$ = 1.4 Hz, 1 H, 5-H), 8.74 (s, 1 H, 2-H). $^{13}$C NMR (125 MHz) δ: 145.98 (C-2), 139.52 (C-3), 135.26(C-4), 130.30 (C-4a), 127.64 (C-5), 128.00 (C-6), 128.64 (C-7), 129.88 (C-8), 145.64 (C-8a), 12.53 (*C*H$_2$), 79.69 (CH$_2$-*C*), 72.48 (*C*H), 16.56 (*C*H$_3$).

3.1.4.2. 3-Methylthio-4-propargylthioquinoline (**4b**)

Yield 77%, m.p. 97–98 °C, lit. [25] m.p. 97–98 °C. $^1$H NMR (500 MHz) δ: 2.06 (t, J = 2.6 Hz, 1 H, CH), 2.66 (s, 3 H, $CH_3$), 3.68 (d, J = 2.6 Hz, 2 H, $CH_2S$), 7.60 (m, $^3J_{(5,6)}$ = 8.3 Hz, $^3J_{(6,7)}$ = 6.9 Hz, $^4J_{(6,8)}$ = 1.4 Hz, 1 H, 6-H), 7.65 (m., $^3J_{(7,8)}$ = 8.3 Hz, $^3J_{(6,7)}$ = 6.9 Hz, $^4J_{(5,7)}$ = 1.5 Hz, 1 H, 7-H), 8.05 (dd, $^3J_{(7,8)}$ = 8.3 Hz, $^4J_{(6,8)}$ = 1.4 Hz, 1 H, 8-H), 8.54 (dd, $^3J_{(5,6)}$ = 8.3 Hz, $^4J_{(5,7)}$ = 1.4 Hz, 1 H, 5-H), 8.78 (s, 1 H, 2-H). $^{13}$C NMR (125 MHz) δ: 146.21 (C-2), 139.01 (C-3), 136.31 (C-4), 130.11 (C-4a), 125.35 (C-5), 127.94 (C-6), 128.64 (C-7), 129.83 (C-8), 145.96 (C-8a), 22.33 (*C*H$_2$), 78.76 (CH$_2$-*C*), 72.29 (*C*H), 15.77 (*C*H$_3$).

3.1.4.3. 3-Ethylthio-4-propargylselenoquinoline (**4f**)

Yield 68%, m.p. 82–83 °C. $^1$H NMR (500 MHz) δ: 1.42 (t, J = 7.4 Hz, 3 H, $CH_3$), 2.09 (t, J = 2.7 Hz, 1 H, CH), 3.16 (q, J = 7.4 Hz, 2 H, $CH_2S$), 3.59 (d, J = 2.7 Hz, 2 H, $CH_2$Se), 7.59 (m, $^3J_{(5,6)}$ = 8.3 Hz, $^3J_{(6,7)}$ = 6.9 Hz, $^4J_{(6,8)}$ = 1.4 Hz, 1 H, 6-H), 7.66 (m, $^3J_{(7,8)}$ = 8.3 Hz, $^3J_{(6,7)}$ = 6.9 Hz, $^4J_{(5,7)}$ = 1.5 Hz, 1 H, 7-H), 8.04 (dd, $^3J_{(7,8)}$ = 8.3 Hz, $^4J_{(6,8)}$ = 1.4 Hz, 1 H, 8-H), 8.50 (dd, $^3J_{(5,6)}$ = 8.3 Hz, $^4J_{(5,7)}$ = 1.4 Hz, 1 H, 5-H), 8.79 (s, 1 H, 2-H). $^{13}$C NMR (125 MHz) δ: 147.53 (C-2), 138.40 (C-3), 137.04 (C-4), 130.59 (C-4a), 127.92 (C-5), 127.95 (C-6), 128.84 (C-7), 129.90 (C-8), 145.85 (C-8a), 12.82 (*C*H$_2$Se), 79.73 (CH$_2$-*C*), 72.50 (*C*H), 14.14 (*C*H$_3$), 27.71 (CH$_2$S). EI MS (15 eV) m/z (rel. intensity) 307 (M$^+$, 29), 278 (100), 234 (21).

3.1.4.4. 4-Propargyloxy-3-(1-propynylthio)quinoline (**4e**)

A suspension of thioquinanthrene **1** (0.80 g, 2.5 mmol) and sodium propargyloxide (1.17 g, 15 mmol) in dry DMF (12 ml) was stirred at 70 °C for 30 min. The clear solution was cooled to RT and propargyl bromide (0.61 g, 5.2 mmol) was added dropwise during 30 min. The reaction mixture was stirred for 1 h and then poured into 35 ml of 10% aqueous sodium hydroxide. The mixture was extracted with 3 × 10 ml of chloroform. The combined organic layer was washed with water and dried with anhydrous magnesium sulfate. After removal of the solvent the residue was purified by column chromatography to give 0.58 g (46%) of pure product **4e**, m.p. 99–100 °C (ethanol). $^1$H NMR (500 MHz) δ: 2.09 (s, 3 H, $CH_3$), 2.57 (t, J = 2.5 Hz, 1 H, CH), 4.93 (d, J = 2.5 Hz, 2 H, $CH_2O$), 7.57 (m, $^3J_{(5,6)}$ = 8.3 Hz, $^3J_{(6,7)}$ = 7.0 Hz, $^4J_{(6,8)}$ = 1.1 Hz, 1 H, 6-H), 7.69 (m., $^3J_{(7,8)}$ = 8.4 Hz, $^3J_{(6,7)}$ = 7.0 Hz, $^4J_{(5,7)}$ = 1.4 Hz, 1 H, 7-H), 8.08 (dd, $^3J_{(7,8)}$ = 8.4 Hz, $^4J_{(6,8)}$ = 1.1 Hz, 1 H, 8-H), 8.13 (dd, $^3J_{(5,6)}$ = 8.3 Hz, $^4J_{(5,7)}$ = 1.4 Hz, 1 H, 5-H), 9.11 (s, 1 H, 2-H). $^{13}$C NMR (125 MHz) δ: 150.30 (C-2), 118.58 (C-3), 157.19 (C-4), 123.44 (C-4a), 121.77 (C-5), 127.15 (C-6), 129.54 (C-7), 129.63 (C-8), 148.80 (C-8a), 61.15 (*C*H$_2$), 77.72 (CH$_2$-*C*), 77.05 (*C*H), 95.02 (S-*C*), 62.00 (*C*-CH$_3$), 5.18 (*C*H$_3$). EI MS (15 eV) m/z (rel. intensity) 253 (M$^+$, 69), 214 (100), 182 (13). *Anal.* Calcd for $C_{15}H_{11}NOS$: C 71.12, H 4.38, N 5.53, S 12.66. Found: C 70.91, H 4.42, N 5.38, S 12.83.

***3.2. Antiproliferative assay in vitro***

*3.2.1. Cells*

The following established *in vitro* human cancer cell lines were applied: SW707 (rectal adenocarcinoma), T47D (breast carcinoma), and HCV29T (bladder cancer). The first 2 lines were obtained from the American Type Culture Collection (Rockville, Maryland, USA) and maintained at the Cell Culture Collection of the Institute of Immunology and Experimental Therapy, Wroclaw, Poland. The human uroepithelial cell line HCV29T, established in Fibiger Institute, Copenhagen, Denmark, was obtained from Dr. J. Kieler in 1982 and maintained at the Institute of Immunology and Experimental Therapy, Wroclaw, Poland.
Twenty-four hours before addition of the tested agents, the cells were plated in 96-well plates (Sarstedt, USA) at a density of $10^4$ cells per well in 100 µl of culture medium. The cells were cultured in the opti-MEM medium supplemented with 2 mM glutamine (Gibco, Warsaw, Poland), streptomycin (50 µg/ml), penicillin (50 U/ml) (both antibiotics from Polfa, Tarchomin, Poland) and 5% fetal calf serum (Gibco, Grand Island, USA). The cell cultures were maintained at 37 °C in humid atmosphere saturated with 5% $CO_2$.

*3.2.2. SRB assay*

The details of this technique were described by Skehan et al. [44]. The cytotoxicity assay was performed after 72 h exposure of the cultured cells to varying concentrations (from 0.1 to 100 µg/ml) of the tested agents. The cells attached to the plastic were fixed by gently layering cold 50% TCA (trichloroacetic acid, Aldrich-Chemie, Germany) on the top of the culture medium in each well. The plates were incubated at 4 °C for 1 h and then washed five times with tap water. The background optical density was measured in the wells filled with culture medium, without the cells. The cellular material fixed with TCA was stained with 0.4% sulforhodamine B (SRB, Sigma, Germany) dissolved in 1% acetic acid (POCh, Gliwice, Poland) for 30 min. Unbound dye was removed by rinsing (4 ×) with 1% acetic acid. The protein-bound dye was extracted with 10 mM unbuffered Tris base (POCh, Gliwice, Poland) for determination of optical density (at 540 nm) in a computer-interfaced, 96-well microtiter plate reader Multiskan RC photometer (Labsystems, Helsinki, Finland). Each compound in given concentration was tested in triplicates in each experiment, which was repeated 3–5 times.

*3.2.3. MTT assay*

This technique was applied for the cytotoxicity screening against mouse leukemia cells growing in suspension culture. An assay was performed after 72 h exposure to varying concentrations (from 0.1 to 100 µg/ml) of the tested agents. For the last 3–4 h of incubation 20 µl of MTT solution were added to each well (MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; stock solution: 5 mg/ml). The mitochondria of viable cells reduce the pale yellow MTT to a navy blue formazan: the more viable cells are present in well, the more MTT will be reduced to formazan. When incubation time was completed, 80 µl of the lysing mixture were added to each well (lysing mixture: 225 ml dimethylformamide, 67.5 g sodium dodecyl sulphate and 275 ml of distilled water). After 24 h, when formazan crystals had been dissolved, the optical densities of the samples were read on an Multiskan RC photometer at 570 nm wavelength.
Each compound in given concentration was tested in triplicates in each experiment, which was repeated 3–5 times.
The results of cytotoxic activity *in vitro* were expressed as an $ID_{50}$ – the dose of compound (in µg/ml) that inhibits proliferation rate of the tumor cells by 50% as compared to the control untreated cells.

* Part LXXII in the series of azinyl sulfides.

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