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Synthesis and antiproliferative activity *in vitro* of new propargyl thioquinolines*

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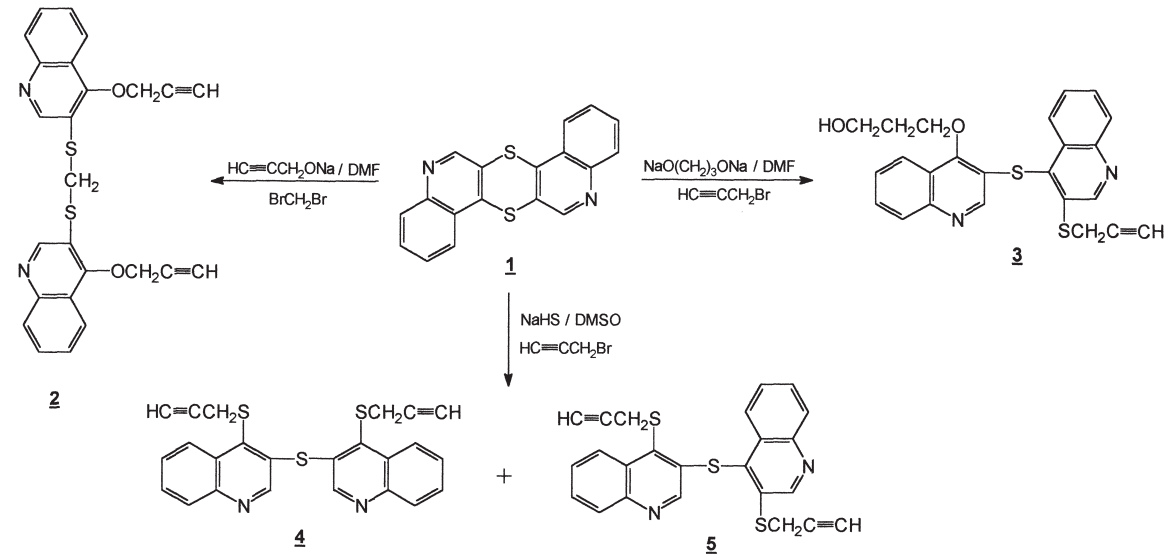
The series of new 3,4-disubstituted thioquinolines which possess one or two O, S, Se-propargyl groups has been synthesized on the basis of the reaction of thiquinanthrene with alkoxides. All the compounds obtained were tested for their antiproliferative activity *in vitro* against the cells of three human cancer cell lines: SW707 (colon cancer), T47D (breast cancer), and HCV29T (bladder cancer). Two compounds, 4-(3-hydroxypropoxy)-3′-propargylthio-3,4′-diquinolinyl sulfide (**3**) and 3-methylthio-4-propargylselenoquinoline (**13**) exhibited significant cytostatic activity (ID_{50} < 4 μg/ml) against the cells of all the human cancer lines used and are good candidates for further anticancer activity studies *in vitro* using a broad panel of human and murine cell lines and for *in vivo* preclinical screening in different mouse transplantable tumor models.

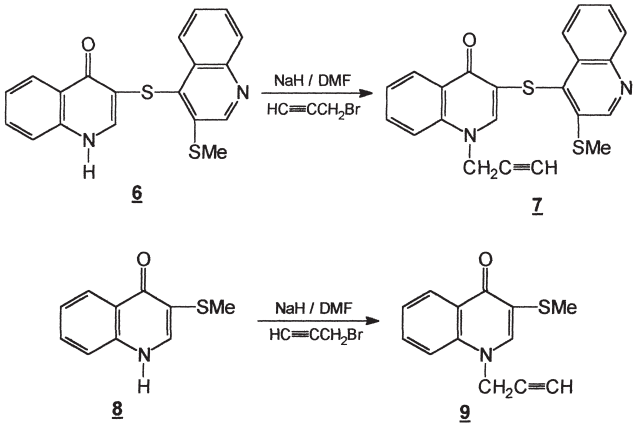
1. Introduction

Interest in the acetylenic compounds, especially terminal acetylenes, is continuously increasing because the introduction of the alkynyl group may significantly modify the chemical, physical and biological properties of such substances. Synthetic methods for preparation of this class of compounds are of interest especially with regard to the synthesis of biologically active enediyne and dienediyne antitumor antibiotics or similar molecular models [1–6]. Alkynylquinolines comprise an important class of compounds, which have been considered for utilisation as pesticides, analgesics, and insecticides and as intermediates for the preparation of pharmaceuticals and vinyl compounds [7, 8]. It has also been observed that the introduction of an alkynyl group may significantly modify the biological properties of antibacterial fluoroquinolone antibiotics [9, 10]. Several methods for the synthesis of alkynylquinolines have been reported in the literature [7, 8, 11]. A conventional method, currently widely used for introducing an acetylene group into a quinoline molecule, is palladium-catalyzed coupling of halogenated quinolines with terminal alkynes or with alkynylmetals [12–19]. On the other hand, no data about the synthesis and properties of acetylenic thioquinolines, in particular those containing a selenopropargylic substituent, are available. The above facts prompted us to prepare new terminal acetylenic derivatives of thioquinolines in order to investigate their biological properties and to use them for the synthesis of eneyne compounds. Previously, we have reported a simple and efficient method for the synthesis of propargyl thioquinolines [20]. This method is based on the reaction of thioquinanthrene (**1**) with alkoxides [21–25]. Apart from the synthetic chemical interest, these compounds are of relevance in the context of intermolecular interactions [26–28]. In the present paper, in which we continue our study of this class of compounds, we report the synthesis of new 3,4-disubstituted thioquinolines, which possess one or two O, S, Se-propargyl groups and the preliminary evaluation of their potential anticancer activities.

Scheme 1



Scheme 2



2. Investigations, results and discussion

The acetylenic derivatives of thioquinolines **2**–**5** were prepared according to previously reported methods [20, 21, 25], as illustrated in Scheme 1. The starting material used in these reactions was thioquinanthrene (**1**) which is easily available on a large scale [29]. Treatment of **1** with sodium propargyloxide in DMF solution at 70 °C followed by the addition, at room temperature, of dibromomethane as a bifunctional alkylating agent, according to a previously reported one-pot procedure [20], gave sulfide **2** in 77% yield. When **1** was treated with the disodium salt of propylene glycol in DMF solution, at 70 °C, followed by S-alkylation in aqueous solution using propargyl bromide, the sulfide **3** was obtained in 52% yield. The reaction of **1** with sodium hydrosulfide in DMSO solution followed by S-alkylation in aqueous solution with propargyl bromide gave a mixture of two compounds, which were successfully separated by a column chromatography and identified as sulfides **4** and **5** with a yield of 19% and 59%, respectively.

The *N*-propargyl 4-quinolones **7** and **9** were synthesized as shown in Scheme 2. The starting N-unsubstituted quinolones **6** and **8** were prepared by acid hydrolysis of 4-methoxy-3-methylthioquinoline and 4-methoxy-3′-methylthio-3,4′-diquinolinyl sulfide, according to published procedures [21]. Quinolone **6** and **8** were direct N-alkylated with propargyl bromide. The reactions were performed in the presence of NaH/DMF and the *N*-propargyl quinolones **7** and **9** were obtained in a yield of 67% and 81%, respectively.

The reactions leading to compounds **11** and **13** are illustrated in Scheme 3. The 4-chloro derivatives **10** and **12** were obtained following procedures described previously [30]. The bis-thiopropargyl compounds **11** was synthesized by nucleophilic substitution of 4-chloro substituents in **10** with thiourea in ethanol and subsequent S-alkylation of the bis-quinolinethiolate in aqueous sodium hydroxide with propargyl bromide. The selenium derivative **13** was similarly prepared from the reaction of **12** with selenourea [31]. ^{1}H NMR, MS and elemental analysis confirmed the structures of the resulting thioquinoline derivatives.

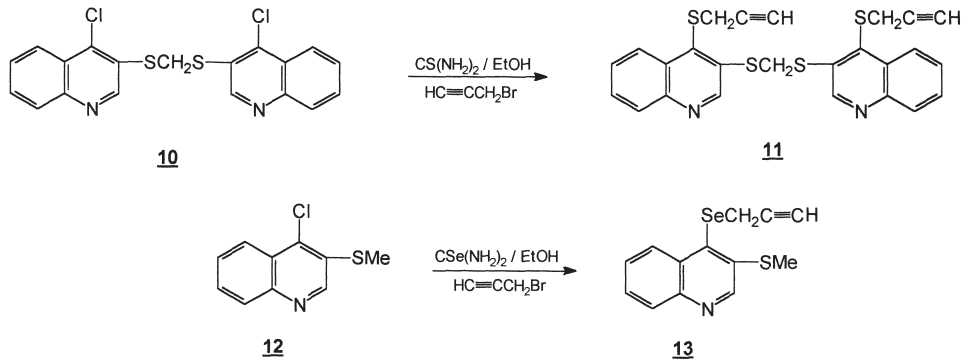
All the compounds obtained, which represent four groups, i.e. 4-quinolones (**7**, **9**), diquinolinyl sulfides (**3**–**5**), bis(4-substituted-3-quinolinylthio)methanes (**2**, **11**) and 3,4-disubstituted quinoline (**13**), were tested in an SRB assay for their antiproliferative activity *in vitro* against the cells of 3 human cancer cell lines: SW707 (colon cancer), T47D (breast cancer), HCV29T (bladder cancer). 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 of tumor cells by 50% as compared to the control untreated cells. Cisplatin was used as a reference 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 the Table.

The compounds tested, with two exceptions (**7**, **9**), exhibited a potent antiproliferative activity. Compounds **7** and **9** bearing a propargyl group connected directly to the nitrogen atom showed only weak or no antiproliferative activity. It suggests that the group of 4-quinolones possesses

Table: Antiproliferative activity *in vitro* of acetylenic thioquinolines and referential cisplatin against the cells of human cancer cell lines

Compd.	Cell line/ID_{50} (μg/ml)		
	HCV29T	T47D	SW707
2	6.8 ± 3.6	3.7 ± 1.1	34.2 ± 3.7
3	2.9 ± 1.3	3.6 ± 1.5	4.5 ± 1.4
4	8.0 ± 2.9	4.8 ± 1.4	Neg
5	13.8 ± 1.9	4.2 ± 1.3	10.7 ± 3.0
7	Neg	Neg	Neg
9	55.3 ± 2.0	55.0 ± 1.1	Neg
11	Neg	8.8 ± 1.3	Neg
13	0.6 ± 1.6	1.8 ± 1.4	2.5 ± 1.6
Cisplatin	0.7 ± 1.0	2.1 ± 1.8	2.3 ± 1.1

Scheme 3



rather low cytotoxic potential. Among the diquinolinyl sulfides **3**–**5**, which possess one or two propargyl groups, the 4-hydroxypropoxy derivative **3** is the most active compound ($ID_{50} < 4$ μg/ml). These results indicate that the hydrophilic substituent 3-hydroxypropoxy may play an important role in the enhancement of cytostatic activity. It seems likely that only one propargyl group is required for antiproliferative activity in these compounds. In the series of bis-quinolinylthiomethanes (**2** and **11**), having propargyloxy and propargylthio groups at position 4 and 4′, both compounds revealed a moderate cytostatic activity. The replacement of the oxygen atoms of **2** by sulfur in compound **11** resulted in a slight decrease of activity. Especially noteworthy is compound **13**, which exhibits significant antiproliferative activity, ($ID_{50} < 3$ μg/ml) against the cells of human cancer lines used. It seems that the activity of compound **13** can be attributed to the presence of a propargylseleno group in the context of its very short intermolecular interactions [32].

In conclusion, compounds **3** and **13** seem to be good candidates for further anticancer activity studies *in vitro* using a broad panel of human and murine cell lines, with the aim of selecting the compounds for preclinical studies *in vivo*.

3. Experimental

3.1. Synthesis of the compounds

Melting points were determined in open capillary tubes on a Boetius apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Brucker MSL 300 spectrometer at 300 MHz in deuteriochloroform solvents with tetramethylsilane as the internal standard and chemical shifts are reported in ppm (δ) and *J* values in Hz. EI MS spectra were run on a LKB GC 2091 spectrometer at 15 eV. Elemental C, H, N, S analyses were obtained on a Carlo Erba Model 1108 analyzer. All the results 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. Visualization was by UV light and iodine. 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 [29].

3.1.1. Bis(4-propargyloxy-3-quinolinylthio)methane (**2**)

A suspension of thioquinanthrene (**1**) (0.80 g, 2.5 mmol) and the sodium propargyloxide (0.81 g, 15 mmol) and dry DMF (12 ml) was stirred at 70 °C for 30 min. The clear solution was then cooled to RT and dibromomethane (0.47 g, 2.7 mmol) was added dropwise for 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 0.85 g (77%) of pure product **2** with m.p. 113–114 °C (ethanol), lit. [20] m.p. 113–114 °C.

3.1.2. 4-(3-Hydroxypropoxy)-3′-propargylthio-3,4′-diquinolinyl sulfide (**3**)

A suspension of thioquinanthrene (**1**) (0.64 g, 2.0 mmol) and the disodium salt of propylene glycol (0.72 g, 6.0 mmol) and dry DMF (12 ml) was stirred at 70 °C for 30 min under nitrogen. 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 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 0.45 g (52%) of pure product **3** with m.p. 122–123 °C (ethanol). ^{1}H NMR δ: 2.23 (m., 2 H, CH_2), 2.26 (t, J = 2.6 Hz, 1 H, CH), 3.77 (d, J = 2.6 Hz, 2 H, CH_2S), 4.06 (t, J = 6.0 Hz, 2 H, CH_2O), 4.51 (t, J = 6.0 Hz, 2 H, CH_2O), 7.54–8.35 (m, 8 H, Ar-H), 8.01 (s, 1 H, H-2), 9.06 (s, 1 H, H′-2). EI MS (15 eV) m/z (rel. intensity) 432 (M^+, 100), 373 (M-C_3H_7O, 12.7), 335 (M-$C_3H_6O-C_3H_3$, 61.2).
$C_{24}H_{20}N_2O_2S_2$

3.1.3. 4,4′-Dipropargylthio-3,3′-diquinolinyl sulfide (**4**) *and 3′-propargylthio-4-propargylthio-3,4′-diquinolinyl sulfide* (**5**)

A suspension of thioquinanthrene (**1**) (0.64 g, 2.0 mmol) and sodium hydrosulfide ($NaHS \times H_2O$, 0.3 g) and DMSO (12 ml) was stirred at 70 °C for 20 min. The solution was then cooled to RT and poured into 35 ml of 10% aqueous sodium hydroxide. Propargyl bromide (0.50 g, 4.2 mmol) was added dropwise to the aqueous layer and 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 concentrated *in vacuo*. The crude product was separated by CC to give two products: a faster eluting compound **4** (0.16 g, 19%,) with m.p. 132–134 °C (ethanol) and slower moving compound **5** (0.51 g, 59%) with m.p. 135–136 °C (ethanol).

(**4**): ^{1}H NMR δ: 2.13 (t, J = 2.6 Hz, 2 H, 2 × CH), 3.83 (d, J = 2.6 Hz, 4 H, 2 × CH_2S), 7.66–7.79 (m, 4 H, 2 × H-6 and 2 × H-7), 8.08–8.60 (m, 4 H, 2 × H-5 and 2 × H-8), 8.63 (s, 2 H, 2 × H-2). EI MS (15 eV) m/z (rel. intensity) 428 (M^+, 16.2), 389 (M-C_3H_3, 15.4), 357 (M-C_3H_3S, 18.6), 318 (M-$C_3H_3S-C_3H_3$, 100).
$C_{24}H_{16}N_2S_3$

(**5**): ^{1}H NMR δ: 2.20 (t, J = 2.6 Hz, 1 H, CH), 2.27 (t, J = 2.6 Hz, 1 H, CH), 3.79 (d, J = 2.6 Hz, 2 H, CH_2S), 3.90 (d, J = 2.6 Hz, 2 H, CH_2S), 7.52–8.61 (m, 8 H, Ar-H), 7.88 (s, 1 H, H-2), 9.10 (s, 1 H, H′-2). EI MS (15 eV) m/z (rel. intensity) 428 (M^+, 20.1), 389 (M-C_3H_3, 7.1), 357 (M-C_3H_3S, 31.4), 318 (M-$C_3H_3S-C_3H_3$, 100).
$C_{24}H_{16}N_2S_3$

3.1.4. 1-Propargyl-1,4-dihydro-4-oxo-3′-methylthio-3,4′-diquinolinyl sulfide (**7**)

To a suspension of oil-free sodium hydride (ca.20 mg) in 5 ml of dry DMF, 1,4-dihydro-4-oxo-3′-methylthio-3,4′-diquinolinyl sulfide (**6**) (0.35 g, 1 mmol) was added slowly under nitrogen. The mixture was stirred at RT for 30 min, and then propargyl bromide (0.13 g, 1.1 mmol) was added. After that, the reaction mixture was stirred at RT for 2 h and was then poured into 15 ml of 10% aqueous sodium hydroxide. The resultant solid was filtered off, washed with water and air-dried to give a crude product, which after crystallization from a DMF-ethanol mixture gave 0.26 g (67%) **7** with m.p. 260–262 °C. ^{1}H NMR δ: 2.42 (t, J = 2.5 Hz, 1 H, CH), 2.64 (s, 3 H, CH_3S), 4.70 (d, J = 2.5 Hz, 2 H, CH_2N), 7.39–8.70 (m, 8 H, Ar-H), 7.58 (s, 1 H, H-2), 8.80 (s, 1 H, H′-2). EI MS (15 eV). M/z (rel. intensity) 388 (M^+, 12.4), 349 (M-C_3H_3, 11.2), 341 (M-CH_3S, 100), 302 (M-$C_3H_3-CH_3S$, 60.2).
$C_{22}H_{16}N_2OS_2$

3.1.5. 1-Propargyl-1,4-dihydro-4-oxo-3-methylthioquinoline (**9**)

To a suspension of oil-free sodium hydride (50 mg, 2 mmol) in 5 ml of dry DMF, 1,4-dihydro-4-oxo-3-methylthioquinoline (**8**) (0.38 g, 2 mmol) was added slowly under nitrogen. The mixture was stirred at RT for 30 min and propargyl bromide (0.25 g, 2.1 mmol) was added. The reaction mixture was stirred at RT for 2 h and was then poured into 15 ml of 10% aqueous sodium hydroxide. The resultant solid was filtered off, washed with water and air-dried to give a crude product, which after crystallization from ethanol gave 0.37 g (81%) **9** with m.p. 211–212 °C. ^{1}H NMR δ: 2.43 (s, 3 H, CH_3S), 2.56 (t, J = 2.5 Hz, 1 H, CH), 4.85 (d, J = 2.5 Hz, 2 H, CH_2N), 7.40–8.50 (m., 4 H, Ar-H), 7.94 (s, 1 H, H-2). EI MS (15 eV) m/z (rel. intensity) 229 (M^+, 65.4), 196 (M-CH_4-OH, 100).
$C_{13}H_{11}NOS$

3.1.6. Bis(4-propargylthio-3-quinolinylthio)methane (**11**)

A mixture of bis(4-chloro-3-quinolinylthio)methane (**10**) (0.4 g, 1.0 mmol), thiourea (0.16 g, 1 mmol) and 99.8% ethanol (6 ml) was stirred at 40 °C for 30 min and then cooled down to RT. The reaction mixture containing the bis-isothiuronium salt was poured into 20 ml of 5% 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 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 ethanol to give 0.35 g (74%) of **11** with m.p. 144–145 °C. ^{1}H NMR δ: 2.04 (t, J = 2.5 Hz, 2 H, 2 × CH), 3.64 (d, J = 2.5 Hz, 4 H, 2 × CH_2S), 4.75 (s, 2 H, SCH_2S), 7.60–7.75 (m,, 4 H, 2 × H-6 and 2 × H-7), 8.08–8.55 (m, 4 H, 2 × H-5 and 2 × H-8), 9.02 (s, 2 H, 2 × H-2). EI MS (15 eV) m/z (rel. intensity) 474 (M^+, 11.3), 244 (M-$C_{12}H_8NS_2$, 56.7), 205 (M-$C_{15}H_{11}NS_2$, 100).
$C_{25}H_{18}N_2S_4$

3.1.7. 3-Methylthio-4-propargylselenoquinoline (**13**)

A mixture of 4-chloro-3-methylthioquinoline (**12**) (0.42 g, 2.0 mmol), selenourea (0.26 g, 2.1 mmol) and 99.8% ethanol (8 ml) was stirred at RT for 30 min. The reaction mixture was poured into 20 ml of 5% 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 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 0.46 g (79%) of **13** with m.p. 97–98 °C. ^{1}H NMR δ: 2.10 (t, J = 2.7 Hz, 1 H, CH), 2.67 (s, 3 H, CH_3S), 3.57 (d, J = 2.7 Hz, 2 H, CH_2S), 7.57–7.69 (m, 2 H, H-6 and H-7), 8.04–8.51 (m, 2 H, H-5 and H-8), 8.76 (s, 1 H, H-2). EI MS (15 eV) m/z (rel. intensity) 293 (M^+, 32.3), 278 (M-CH_3, 100), 254 (M-C_3H_3, 57.6).
$C_{13}H_{11}NSSe$

3.2. Antiproliferative assay in vitro

3.2.1. Cells

The following established *in vitro* human cancer cell lines were used: SW707 (rectal adenocarcinoma), T47D (breast carcinoma), and HCV29T (bladder cancer). The first two lines were obtained from the American Type Culture Collection (Rockville, Maryland, U.S.A.) and maintained at the Cell Culture Collection of the Institute of Immunology and Experimental Therapy, Wrocław, Poland. Human uroepithelial cell line HCV29T established in the 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 agents under test, the cells were plated in 96-well plates (Sarstedt, U.S.A.) 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, U.S.A.). The cell cultures were maintained at 37 °C in a humid atmosphere saturated with 5% CO_2.

3.2.2. SRB assay

The details of this technique were described by Skehan et al [33]. 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 agents under test. 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 (4x) 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 a given concentration was tested in triplicate 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 the proliferation rate of the tumor cells by 50% as compared to the control untreated cells.

* Part LXVIII in the series of azinyl sulfides

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