Synthesis and in vitro antiproliferative activity of novel 12(H)-quino[3,4-b][1,4]benzothiazine derivatives

Andrzej Zięba · Małgorzata Latocha · Aleksander Sochanik

Abstract Novel method of N-dealkylating quinobenzothiazinium salts 2, promoted by reaction with benzimidazole, led to a series of new azaphenothiazine derivatives having 12(H)-quino[3,4-b][1,4]benzothiazine 4 structure. Reaction of compounds 4 in an alkaline milieu with alkylating agents occur as N-alkylation of the thiazine nitrogen and yields quinobenzothiazine derivatives 7. In vitro antiproliferative activity of compounds 4 and 7 was tested using two cancer cell lines (SNB-19 and C-32) and cisplatin as a reference. Most of the studied azaphenothiazine derivatives showed activity against both cell lines investigated (5.6–12.4 μg/ml concentration range tested). Compounds 4(b–e) containing a halogen atom or methyl group at the 9-position of the quinobenzothiazine ring show activity in the tested concentration range only against C-32 cell line. Compound 4f with methyl group in 11-position of quinobenzothiazine ring lacked activity against either cell line. The presence of additional aminoalkyl substituents at the thiazine nitrogen atom in compounds 7 increases their activity against both examined cell lines, when compared to compounds 4.

Keywords Phenothiazine · Azaphenothiazine · Quinobenzothiazine · Antiproliferative activity · Cisplatin

Introduction Phenothiazines are an important class of three-ring heterocyclic compounds widely used in medicinal chemistry. Phenothiazines and their structural analogs (azaphenothiazines, benzophenothiazines) have been reported to possess antimicrobial (Bansode et al., 2009; Klitgaard et al., 2008), antitumor (Motohashi et al., 2000, 2006; Pluta et al., 2010), antioxidant (Kumar et al., 2010; Morak-Młodawska et al., 2010), antitubercular (Viveiros and Amaral, 2001; Amaral and Kristiansen, 2000), antimalarial (Domínguez et al., 1997), antipsychotropic (Lin et al., 1991; Isaacson, 1998), and anti-inflammatory (Sharma et al., 2005) activities. Modification of basic structural fragments of drugs, by altering molecular conformation, introducing additional substituents into aromatic or heterocyclic rings can affect drug-receptor interactions, as well as drug body distribution and metabolism (Patrick, 2005). In our previous papers, we reported a novel method of synthesizing quinoline fragment-containing phenothiazine derivatives that possess the structure of 5-alkyl-12(H)-quino[3,4-b][1,4]benzothiazinium salts 2. These compounds contain a totally planar tetracyclic fragment and have interesting antimicrobial and antiproliferative properties (Zięba et al., 2010, 2012). In this study, we present details of synthesis of novel quinobenzothiazine derivatives as free quinoline bases, and their derivatives containing aminoalkyl substituents at the thiazine nitrogen atom. We also demonstrate their antiproliferative activity.
Results and discussion

Chemistry

5-Alkyl-12(H)-quin[3,4-b][1,4]benzothiazinium salts 2 were obtained by cyclization of 1-alkyl-4-(arylamino)quinolinium-3-thiolates 1 in the presence of HCl donor (aniline hydrochloride) and atmospheric oxygen (Scheme 1) (Zięba et al., 2000; Zięba and Suwińska, 2006). 3-Thiolates 1 were obtained by reacting thioquinanthrenediinium salts with aromatic amines (Maślankiewicz and Zięba, 1992).

Phenothiazine derivatives with aminoalkyl substituents at the thiazine nitrogen atom cannot be obtained directly from salts 2 using this method, like 3-azaphenothiazine salts (Clarke et al., 1961), they do not form sodium salts in the presence of bases. Instead, they split off hydrogen chloride and form respective 5-alkyl-5(H)-quin[3,4-b][1,4]benzothiazinium 3 derivatives (Scheme 2) (Zięba et al., 2000; Zięba and Suwińska, 2006).

We attempted, therefore, to perform N-dealkylation of salts 2 to obtain quinobenzothiazine derivatives 4 as free quinoline bases. There are no data available concerning N-dealkylation of azaphenothiazine salts. In an earlier publication, we described N-dealkylation of 1-alkylquinolinium salts achieved by heating their pyridine or DMF solutions (Maślankiewicz and Zięba, 1994). However, under such conditions salts 2 do not undergo the N-dealkylation reaction. On the other hand, by carrying the reaction of 5-alkyl-12(H)-quin[3,4-b][1,4]benzothiazinium salts 2 with benzimidazole at 200°C, the expected 12(H)-quin[3,4-b][1,4]benzothiazines 4 were obtained (Scheme 3) with good yield. This reaction is a novel, so far unreported, method of N-dealkylating azaphenothiazine salts. The best results were obtained using a fivefold molar excess of benzimidazole with respect to quinobenzothiazinium salts 2. It may be assumed that the other reaction product are benzimidazolium salts 5, the structure of which can be stabilized via delocalization of positive charge among the benzimidazole nitrogen atoms.

Benzimidazolium salts 5 were neither isolated from the reaction mixture nor identified in the course of this study, as the primary objective here was to obtain quinobenzothiazine 4 derivatives as free quinoline bases. Excess benzimidazole and benzimidazolium salts 5 that form during the reaction were separated from quinobenzothiazines 4 by pouring post-reaction mixtures into water. Both benzimidazole and salts 5 are well-soluble in water, whereas compounds 4 fall out of solution as solids.

In order to obtain quinobenzothiazine derivatives 7 containing aminoalkyl substituents at the thiazine nitrogen atom, compounds 4 were transformed, in the presence of sodium hydroxide, into salts 6, which were then alkylated using aminoalkyl chlorides (Scheme 4). The reaction occurred as N-alkylation at the thiazine nitrogen atom and led to compounds 7. The structure of compounds 7 was confirmed with 1H NMR spectroscopy by performing NOE 1H–1H homonuclear experiment. By irradiating methylene group protons at the thiazine nitrogen atom an enhancement of H1 and H11 proton signals from compounds 7 was obtained (Scheme 5).

Antiproliferative activity

The activity of the obtained compounds 4 and 7 was investigated in vitro using cultured SNB-19 and C-32 cell lines and cisplatin as a reference. The examined quinobenzothiazines 4 had various substituents (CH3, F, Cl, Br) introduced into 9- and 11-positions of the quinobenzothiazine ring.

In addition, they also contain a nitrogen atom in the 8-position of the quinobenzothiazine ring.

Compounds 7 contains aminoalkyl substituents: 2-(N-piperidyl)ethyl (compounds 7(a–d)) and 3-(N,N-dimethyl-amino)propyl (compound 7e) at the thiazine nitrogen atom.

One of the mechanisms involved in antiproliferative effects of chemotherapeutics is DNA intercalation. This
mode of action is typical for antiproliferative anthracycline antibiotics (e.g., doxorubicin) that feature planar tetracyclic (aromatic or heteroaromatic) fused rings. This mode of action, affecting cancer cells’ DNA, has been indeed suggested in reports concerning antiproliferative properties of phenothiazine and benzo[a]phenothiazine derivatives (Motohashi et al., 2000; Hossain et al., 2008; Hossain and Kumar, 2009). Structurally, compounds 4 and 7 studied herein are their analogs. The experiments demonstrated that the majority of the investigated compounds 4 and 7 showed antiproliferative activity toward examined cell lines within the 5.6–12.4 μg/ml concentration range (Table 1). In the case of compounds 4 (in the range of concentrations examined), the activity against both cell lines tested was displayed by compound 4a which contains no additional substituents in the benzene ring, and compound 4g which has an additional nitrogen atom at the 8-position of the quinobenzothiazine ring. Either compound showed similar activity against both cell lines. Such results may suggest that this structural fragment is not a decisive factor in antiproliferative activity of quinobenzothiazines 4 against SNB-19 and C-32 cell lines in vitro.

Compounds 4(b–e) containing a halogen atom or methyl group at the 9-position of the quinobenzothiazine ring show activity in the tested concentration range only against C-32 cell line. Compound 4f with methyl group at the 11-position of the quinobenzothiazine ring did not display any activity against either cell line tested. The presence of additional aminoalkyl substituents at the thiazine nitrogen atom in compounds 7 increases their activity against both examined cell lines, when compared to compounds 4.

The results obtained herein demonstrate that replacement of aminoalkyl substituent, which contains a piperidyl
Table 1 Antiproliferative activity in vitro of 12(H)-quino[3,4-b][1,4]benzothiazines 4, 7 and cisplatin (reference) against two cancer cell lines studied

| Compound | Antiproliferative activity IC₅₀ (µg/ml) |
|----------|---------------------------------------|
|          | SNB-19 | C-32 |
| 4a       | 9.6 ± 0.9 | 8.9 ± 0.5 |
| 4b       | Neg | 9.4 ± 0.9 |
| 4c       | Neg | 7.8 ± 0.3 |
| 4d       | Neg | 8.6 ± 0.6 |
| 4e       | Neg | 8.7 ± 0.8 |
| 4f       | Neg | Neg |
| 4g       | 10.2 ± 0.6 | 8.7 ± 0.3 |
| 7a       | 6.7 ± 0.5 | 5.6 ± 0.4 |
| 7b       | 12.4 ± 1.2 | 7.0 ± 0.5 |
| 7c       | 6.6 ± 0.4 | 6.9 ± 0.8 |
| 7d       | 7.3 ± 0.7 | 7.9 ± 0.7 |
| 7e       | 8.2 ± 0.8 | 6.5 ± 0.5 |
| Cisplatin | 2.7 ± 0.3 | 5.8 ± 0.4 |

Neg negative at the concentration used

ring, with a substituent containing N,N-dimethylamine group does not affect substantially antiproliferative activity. Compounds 7d and 7e which feature the same quinobenzothiazine ring but different aminoalkyl substituents at the nitrogen atom (12-position) show similar activity.

Experimental

Melting points were determined in open capillary tubes and are uncorrected. NMR spectra were recorded using a Bruker DRX 500 spectrometer. Standard experimental conditions and standard Bruker program were used. The ¹H NMR spectral data are given relative to the TMS signal at 0.0 ppm. EI MS spectra were recorded using an LKB GC MS 20091 spectrometer at 70 eV.

Synthesis of 12(H)-quino[3,4-b][1,4]benzothiazines 4

Mixture of 1 mmol quinobenzothiazinium salt 2 and 5 mmol (0.595 g) benzimidazole was heated for 2 h at 200 °C. The resulting reaction mix was dissolved in 10 ml ethanol and poured into 200 ml of water. The precipitate which formed was filtered off, washed with water, and air-dried. The raw product was purified by liquid chromatography using a silica gel-filled column and chloroform/ethanol (10:1 v/v) as eluent.

12(H)-Quino[3,4-b][1,4]benzothiazine (4a)

Yield 79 %; m.p.: 204–205 °C; ¹H-NMR (CD3OD, 500 MHz) δ (ppm): 6.85–6.91 (m, 2H, H arom), 6.93–6.97 (m, 1H, H arom), 6.99–7.04 (m, 1H, H arom), 7.44–7.49 (m, 1H, H-2), 7.56–7.61 (m, 1H, H-3), 7.73–7.76 (m, 1H, H-4), 8.01 (s, 1H, H-6), 8.05–8.09 (m, 1H, H-1); EI-MS m/z: 264 (M⁺, 100 %); Anal. calcd. for C15H12N2S: C, 72.67; H, 4.58; N, 10.60; S, 12.15. Found: C, 72.57; H, 4.43; N, 10.53; S, 12.09.

9-Fluoro-12(H)-quino[3,4-b][1,4]benzothiazine (4b)

Yield 68 %; m.p.: 168–169 °C; ¹H NMR (CD3OD, 500 MHz) δ (ppm): 6.64–6.68 (m, 1H, H arom), 6.70–6.75 (m, 1H, H arom), 6.87–6.91 (m, 1H, H arom), 7.44–7.49 (m, 1H, H-2), 7.56–7.61 (m, 1H, H-3), 7.73–7.76 (m, 1H, H-4), 8.01 (s, 1H, H-6), 8.05–8.09 (m, 1H, H-1); EI-MS m/z: 285 (M⁺, 100 %); Anal. calcd. for C15H21N2S: C, 71.97; H, 3.86; N, 11.95. Found: C, 71.85; H, 3.97; N, 11.10; S, 12.77.

9-Chloro-12(H)-quino[3,4-b][1,4]benzothiazine (4c)

Yield 64 %; m.p.: 173–174 °C; ¹H NMR (CD3OD, 500 MHz) δ (ppm): 6.93–6.97 (m, 1H, H arom), 6.99–7.01 (m, 1H, H arom), 7.07–7.10 (m, 1H, H-2), 7.68–7.73 (m, 1H, H-3), 7.78–7.82 (m, 1H, H-4), 8.12 (s, 1H, H-6), 8.17–8.20 (m, 1H, H-1); EI-MS m/z: 306 (M⁺, 100 %); Anal. calcd. for C15H19ClN2S: C, 67.09; H, 3.31; N, 11.26. Found: C, 65.32; H, 3.15; N, 9.77; S, 11.23.

9-Bromo-12(H)-quino[3,4-b][1,4]benzothiazine (4d)

Yield 54 %; m.p.: 96–98 °C; ¹H NMR (CD3OD, 500 MHz) δ (ppm): 7.41–7.48 (m, 1H, H arom), 7.50–7.56 (m, 1H, H arom), 7.78–7.82 (m, 1H, H-1), 8.03 (s, 1H, H-6), 8.00–8.04 (m, 1H, H-4), 8.06–8.10 (m, 1H, H-6), 8.17–8.20 (m, 1H, H-1); EI-MS m/z: 329 (M⁺, 100 %); Anal. calcd. for C15H17BrN2S: C, 54.73; H, 2.76; N, 8.51; S, 9.74. Found: C, 54.68; H, 2.73; N, 8.44; S, 9.71.

11-Methyl-12(H)-quino[3,4-b][1,4]benzothiazine (4f)

Yield 65 %; m.p.: 81–83 °C; ¹H NMR (CD3OD, 500 MHz) δ (ppm): 2.36 (s, 3H, CH3), 6.77–6.84 (m, 2H, H arom).
12(H)-Pyrido[2,3-e]quino[3,4-b][1,4]thiazine (4g)

Yield 65%; m.p.: 210–211 °C; 1H NMR (CD2OD, 500 MHz) δ (ppm): 6.97–7.01 (d.d, 3J = 8 Hz, 3J = 4.6 Hz, 1H, H arom), 7.67–7.90 (d.d, 3J = 8 Hz, 4J = 1.5 Hz, 1H, H arom), 7.51–7.55 (m, 1H, H-2), 7.62–7.67 (m, 1H, H-2), 7.77–7.81 (m, 1H, H-4), 8.24–7.86 (d.d, 3J = 4.6 Hz, 4J = 1.5 Hz, 1H, H arom), 8.07–8.11 (m, 2H, H-1, H-6); EI-MS m/z: 251 (M+, 100%); Anal. calcd. for C14H12N2S: C, 68.61; H, 3.62; N, 16.72; S, 12.67. Found: C, 68.66; H, 3.55; N, 16.69; S, 12.71.

Synthesis of 12(H)-quino[3,4-b][1,4]benzothiazines 7

A mixture of 15 ml water-free 1,4-dioxane, 1 mmol quinobenzothiazine 4 and 5 mmol (0.2 g) sodium hydroxide was refluxed for 2 h. Next, 10 ml of anhydrous benzene was added and the benzene-water azeotrope was distilled off. The resulting reaction mix was refluxed for 2 h while adding portionwise a 1.3 mmol aliquot of the alkylating factor (N-(3-chloropropyl)-N,N-dimethylamino hydrochloride or N-(2-chloroethyl)-piperidine hydrochloride). After cooling down to rt, the reaction mix was poured into 50 ml of water and extracted with 15 ml chloroform. The resulting solution was dried over anhydrous calcium chloride and evaporated under vacuum. The dry residue was purified by chromatography using a silica gel-filled column and chloroform-ethanol (10:1 v/v) as eluent. Quinobenzothiazines 7 were obtained as yellow oils.

12-(2-(N-piperidyl)ethyl)-12(H)-quino[3,4-b][1,4]benzothiazine (7a)

Yield 45%; an oil; 1H NMR (CDCl3, 500 MHz) δ (ppm): 1.10–1.19 (m, 6H, H piperidyl), 2.05–2.18 (m, 4H, H piperidyl), 2.35–2.47 (t, J = 6.6 Hz, 2H, N piperidylCH2), 4.12–4.28 (t, J = 6.6 Hz, 2H, CH2), 7.04–7.09 (m, 1H, H arom), 7.16–7.20 (m, 1H, H arom), 7.26–7.29 (m, 1H, H arom), 7.35–7.38 (m, 1H, H arom), 7.58–7.60 (m, 1H, H arom), 7.66–7.68 (m, 1H, H arom), 7.94–7.96 (m, 1H, H arom), 8.08–8.11 (m, 1H, H-1), 8.49 (s, 1H, H-6); EI-MS m/z: 361 (M+, 100%); Anal. calcd. for C22H23N3S: C, 73.10; H, 6.41; N, 11.62; S, 8.87. Found: C, 73.11; H, 6.33; N, 11.56; S, 8.83.

9-Fluoro-12-(2-(N-piperidyl)ethyl)-12(H)-quino[3,4-b][1,4]benzothiazine (7b)

Yield 56%; an oil; 1H NMR (CDCl3, 500 MHz) δ (ppm): 1.22–1.42 (m, 6H, H piperidyl), 2.18–2.35 (m, 4H, H piperidyl), 2.48–2.67 (t, J = 7.1 Hz, 2H, N piperidylCH2), 4.12–4.24 (t, J = 7.1 Hz, 2H, CH2), 6.85–6.88 (m, 1H, H-8), 6.89–6.95 (m, 1H, H-10), 7.12–7.18 (m, 1H, H-11), 7.48–7.54 (m, 1H, H-2), 7.58–7.64 (m, 1H, H-3), 7.98–8.04 (m, 2H, H-1, H-4), 8.48 (s, 1H, H-6); EI-MS m/z: 379 (M+, 100%); Anal. calcd. for C23H22FN3S: C, 69.63; H, 5.84; N, 11.07; S, 8.45. Found: C, 69.51; H, 5.79; N, 11.00; S, 8.41.

9-Methyl-12-(2-(N-piperidyl)ethyl)-12(H)-quino[3,4-b][1,4]benzothiazine (7c)

Yield 52%; an oil; 1H NMR (CDCl3, 500 MHz) δ (ppm): 1.24–1.43 (m, 6H, H piperidyl), 2.20–2.34 (m, 7H, CH3, H piperidyl), 2.54–2.61 (t, J = 7.3 Hz, 2H, N piperidylCH2), 4.17–4.23 (t, J = 7.3 Hz, 2H, CH2), 6.92–6.97 (d, 4J = 1.1 Hz, 1H, H-8), 6.98–7.02 (d.d, 3J = 8.2 Hz, 4J = 1.1 Hz, 1H, H-10), 7.06–7.09 (d, 3J = 8.2 Hz, 1H, H-11), 7.46–7.51 (m, 1H, H-2), 7.57–7.62 (m, 1H, H-3), 7.98–8.00 (m, 2H, H-1, H-4), 8.48 (s, 1H, H-6); EI-MS m/z: 376 (M+, 100%); Anal. calcd. for C23H22N3S: C, 73.56; H, 6.71; N, 11.19; S, 8.54. Found: C, 73.50; H, 6.64; N, 11.12; S, 8.48.

12-(2-(N-piperidyl)ethyl)-12(2,4-e)quino[3,4-b][1,4]thiazine (7d)

Yield 49%; an oil; 1H NMR (CDCl3, 500 MHz) δ (ppm): 1.22–1.32 (m, 6H, H piperidyl), 2.01–2.28 (m, 4H, H piperidyl), 2.41–2.50 (t, J = 6.6 Hz, 2H, N piperidylCH2), 4.01–4.12 (t, J = 6.6 Hz, 2H, CH2), 7.02–7.08 (m, 1H, H-11), 7.28–7.34 (m, 1H, H arom), 7.41–7.47 (m, 1H, H arom), 7.52–7.59 (m, 1H, H arom), 7.92–7.99 (m, 2H, H arom), 8.06–8.11 (m, 1H, H-1), 8.44 (s, 1H, H-6); EI-MS m/z: 362 (M+, 100%); Anal. calcd. for C23H22N3S: C, 69.58; H, 6.12; N, 15.46; S, 8.84. Found: C, 69.54; H, 6.07; N, 15.40; S, 8.82.

12-(3-(N,N-dimethylamino)propyl)-12(H)-pyrido[2,4-e]quino[3,4-b][1,4]thiazine (7e)

Yield 58%; an oil; 1H NMR (CDCl3, 500 MHz) δ (ppm): 1.63–1.78 (m, 2H, CH2CH2CH2), 1.98 (s, 6H, N(CH3)2), 2.18–2.24 (t, J = 7.2 Hz, 2H, CH2N(CH3)2), 4.01–4.12 (t, J = 7.3 Hz, 2H, NCH2), 7.04–7.11 (m, 1H, H-11), 7.28–7.36 (m, 1H, H arom), 7.41–7.48 (m, 1H, H arom), 7.53–7.61 (m, 1H, H arom), 7.98–8.01 (m, 2H, H arom), 8.08–8.14 (m, 1H, H-1), 8.46 (s, 1H, H-6); EI-MS m/z: 336 (M+, 100%); Anal. calcd. for C19H20N4S: C, 67.83; H,
The synthesized compounds were evaluated for their anticancer activity using two cultured cell lines: SNB-19 (human glioblastoma, DSMZ - German Collection of Microorganisms and Cell Cultures, Braunschweig, Germany) and C 32 (human amelanotic melanoma, ATCC—American Type Culture Collection, Rockville, MD, USA). The cultured cells were kept at 37 °C and 5 % CO2. The cells were seeded (1 × 10⁴ cells/well/100 μl D-MEM supplemented with 12 % FCS and streptomycin and penicillin) using 96-well plates (Corning).

**WST-1 assay**

Antiproliferative effect of compounds 4 and 7 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 concentrations between 0 and 100 μg/ml) for 72 h, cells were incubated with WST-1 (10 μl) for 2 h, and the absorbance of the samples against a background control was read at 450 nm using a microplate reader. Results are expressed as means of at least two independent experiments performed in triplicate.

**Acknowledgments** The study is supported by the Medical University of Silesia (Grant KNW-1-073/P/1/0).

**Open Access** This article is distributed under the terms of the Creative Commons Attribution License which permits any use, distribution, and reproduction in any medium, provided the original author(s) and the source are credited.

**References**

Amaral L, Kristiansen JE (2000) Phenothiazines: an alternative to conventional therapy for the initial management of suspected multi-drug resistant tuberculosis. Int J Antimicrob Agents 14:173–176

Bansode TN, Shelke JV, Dongre VG (2009) Synthesis and antimicrobial activity of some new N-acyl substituted phenothiazines. Eur J Med Chem 44:5094–5098

Clarke FH, Silverman GB, Wotnick CM, Sperber N (1961) 3-Azaphenothiazine and dialkylaminoalkyl derivatives. J Org Chem 26:1126–1132

Dominguez JN, Lopez S, Charris SI, Irazo L, Lobo G, Semenov A, Olson JE, Rosenthal PJ (1997) Synthesis and antimarial effects of phenothiazine inhibitors of a plasmodium falciparum cysteine protease. J Med Chem 40:2726–2732

Hossain M, Kumar GS (2009) DNA intercalation of methylene blue and quinacrine: new insights into base and sequence specificity from structural and thermodynamic studies with polynucleotides. Mol BioSyst 5:1311–1322

Hossain M, Giri P, Kumar GS (2008) DNA intercalation by quinacrine and methylene blue: a comparative binding and thermodynamic characterization study. DNA Cell Biol 27:81–90

Isaacson EL (1998) Central nervous system depressants. In: Delgado JN, Remers WA (eds) Wilson and Gisvold’s textbook of organic medicinal and pharmaceutical chemistry, 10th edn. Lippincott-Raven Publishers, Philadelphia, pp 435–461

Klitaard JK, Skov MN, Kallipolitis BH, Kolmos HJ (2008) Reversal of methicillin resistance in Staphylococcus aureus by thioridazine. J Antimicrob Chemother 62:1215–1221

Kumar M, Sharma K, Samarth RM, Kumar A (2010) Synthesis and antioxidant activity of quinolinobenzothiazinones. Eur J Med Chem 45:4467–4472

Lin G, Midha KK, Hawes EM (1991) Synthesis of the piperidinone metabolites of piperidine type phenothiazine antipsychotic drugs via ruthenium tetroxide oxidation. J Heterocycl Chem 28:215–219

Maslankiewicz A, Zięba A (1992) 5,12-Di-(1-alkyl)thioquinanthrene-dinium bis-salts and 1-alkyl-3-alkylthio-1,4-dihydro-4-thioxoquinolines. Heterocycles 34:247–258

Maslankiewicz A, Zięba A (1994) 1-Alkyl-3,4-di(alkylthio)quinolinium salts. Polish J Chem 68:1957–1971

Morak-Młodawska B, Pluta K, Matralis AN, Kourounakis A (2010) Antioxidant activity of newly synthesized 2,7-diazaphenothiazines. Arch Pharm Chem Life Sci 343:268–273

Motohashi N, Kawase M, Saito S, Sakagami H (2000) Antitumor potential and possible targets of phenothiazine-related compounds. Curr Drug Targets 1:237–245

Motohashi N, Kawase M, Satoh K, Sakagami H (2006) Cytotoxic potential of phenothiazines. Curr Drug Targets 7:1055–1066

Patrick GL (2005) An introduction to medicinal chemistry, 3rd edn. Oxford University Press, Oxford, pp 271–298

Pluta K, Jeleni M, Morak-Młodawska B, Zimecki M, Artym J, Kocięba M (2010) Anticancer activity of newly synthesized azaphenothiazines from NCI’s anticancer screening bank. Pharmacol Rep 62:319–332

Sharma S, Srivastava VK, Kumar A (2005) Synthesis and anti-inflammatory activity of some heterocyclic derivatives of phenothiazine. Pharmazie 60:18–22

Viveiros M, Amaral L (2001) Enhancement of antibiotic activity against poly-drug resistant Mycobacterium tuberculosis by phenothiazines. Int J Antimicrob Agents 17:225–228

Zięba A, Suwińska K (2006) 1-Alkyl-4-(3-pyridinylamino)quinolinium-3-thiolates and their transformation into new diazaphenothiazine derivatives. Heterocycles 68:495–503

Zięba A, Masłankiewicz A, Suwińska K (2000) 1-Alkyl-4-arylaminquinolinium-3-thiolates and 7-alkyl-12H-quino[3,4-b][1,4]benzothiazinium salts. Eur J Org Chem 16:2947–2953

Zięba A, Sochanik A, Szurowka A, Rams M, Mrozek A, Cmoch P (2010) Synthesis and in vitro antiproliferative activity of 5-alkyl-12(H)-quino[3,4-b][1,4]benzothiazinium salts. Eur J Med Chem 45:4733–4739

Zięba A, Czuba ZP, Król W (2012) Antimicrobial activity of novel 5-alkyl-12(H)-quino[3,4-b][1,4]benzothiazinium salts. Acta Pol Pharm Drug Res 69:1149–1152