Research Article

CYTOTOXIC SYMMETRICAL THIAZOLEDISELENIDES WITH INCREASED SELECTIVITY AGAINST MCF-7 BREAST CANCER CELLS

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ABSTRACT

A novel series of symmetrical thiazolediselenides were synthesized in good to moderate yields and there in vitro cytotoxic activity was evaluated against breast adenocarcinom (MCF-7) and compared with their cytotoxicity in normal fibroblast cells (WI-38) employing standard MTT assay. Additionally, there in vitro antimicrobial activities were also evaluated against gram-negative (Escherichia coli), gram-positive (Staphylococcus aureus) bacteria and a pathogenic yeast (Candida albicans). A significant difference in toxicity zones between breast solid tumor cells and normal WI-38 cells was observed indicating that it is not general selenium toxicity. Within this context, compounds 4b, 5, 7, 18 and 23 exhibited therapeutic indices (TI) up to eleven fold and in most cases were higher than TI of 5-fu suggesting their effectiveness as anti-cancer agents. On the other hand, compounds 4a, 5, 7, 18 and 22 exhibited good antibacterial activity against E. coli and S. aureus bacteria compared to the known drug, ampicillin. Moreover, compounds 4a, 7, 11, 13, 19, 22 and 23 exhibited good antifungal activity against C. albicans compared to colitrimazole. These initial promising results point to a reasonable activity of some of these compounds, which needs to be further investigated by using a considerably wider arsenal of human cancer and normal cells as well as humanopathogenic bacteria and fungi.

Keywords: Breast cancer/ Diselenides/Organoselenium/ selectivity/ Thiazole.

INTRODUCTION

Breast cancer has arisen as a global health problem being the second most prevalent solid tumor in the world and, by far the most frequent invasive malignancy in females. It accounts for approximately 1.7 million new cases and half million deaths per year, mostly in Europe [1, 2]. Given such high morbidity and mortality, there continues to be an unmet need for more effective and less cytotoxic therapies. Despite the significant advances in the understanding and diagnosis of breast cancer solid tumors, the available treatment options are far from satisfactory and till today there is no clear, proven and effective single agent that constitutes a systemic regimen recommended for treatment. This is mainly due to limited therapeutic selectivity and drug resistance which constitute major challenges in solid tumors drug discovery [3, 4]. Consequently, this necessitates the developing of more effective and less toxic therapies to overcome drug resistance and to expand the available drug arsenal to battle the disease.

A growing body of evidences from epidemiologic studies suggests that selenium disorder is implicated with increased risk of many diseases, including cancers [5-7]. In this context, many organoselenium compounds have demonstrated significant chemopreventive activity in vitro as well as in human tumor xenografts [8, 9]. Beside the chemopreventive activities shown by organoselenium compounds, recent studies also showed the potential of organoselenium compounds as chemotherapeutic anticancer agents (Figure 1) [10]. These
observations were supported by large numbers of preclinical 
and clinical studies intervention trials [e.g., SELECT trial in the 
USA and PRECISE trial in Europe] [11, 12]; however, these 
findings are still in need for further investigations and merit 
further research.

On the other hand, thiazole-containing compounds exhibit 
wide range of pharmacological activities and constitute a 
crucial part of many potent anticancer drugs such as 
epothilone (A and B) and tiazofurin (Figure 1). Some 
thiazoles were found to selectively inhibit the growth of 
various breast cancer cells in vitro and in xenograft human 
models at low micromolar concentrations. These compounds 
are able to inhibit the forkhead transcription factor (FoxM1) 
which is upregulated in breast cancer while not expressed in 
normal cells [13].

In 2009, we have developed selenium-containing 
multi-functional redox agents, of which some showed 
considerable cytotoxicity, yet also selectively, against certain 
type of cancer cells and range of pathogenic microorganisms 
[14][15, 16]. Since then, we are involved in the development 
of novel cancer therapy based on organoselenium redox 
modulators and the exploration of their corresponding 
intracellular diagnostics.[17-20] In this regard, we have 
further developed selenium pseudopeptides with significant 
cytotoxicity at sub-micromolar concentrations against 
different cancer cell lines and lower cytotoxicity in normal 
cells. It is worth mentioning that the selectivity was more 
pronounced in case of breast cancer (MCF-7) cells compared 
to the other investigated cancer cell lines. In depth analysis 
of the underlying cytotoxic mechanism(s) revealed to be 
mainly due to apoptosis induction. These findings were 
confirmed via estimation of various cellular alterations (e.g., 
cell morphology and cell cycle arrest) and biochemical 
changes (e.g., ROS and GSH levels, caspase activity) in 
addition to hits obtained from chemogenomic assay [21, 22]. 
Although one can only speculate about the exact mode(s) of 
action of organoselenium compounds, their cytotoxic 
mechanisms depend on modulation of the intracellular redox 
environment.

Promoted by the above mentioned findings, it’s likely that a 
combination of bioactive pharmacophores such as thiazoles 
with selenium will synergistically not only potentiate the 
overall cytotoxicity and redox activity but also enhance their 
corresponding chemotherapeutic properties. Furthermore,
such novel combination is expected to have better physico-chemical properties and pharmacological properties. Thus our aim is to synthesize a new series of organoselenium compounds based on the thiazole chromophore. Their corresponding selective cytotoxicity will be evaluated using human breast cancer cells (MCF-7) and compared with their cytotoxicity in normal fibroblast cells (WI-38) employing standard MTT assay.

RESULTS & DISCUSSIONS

Chemistry

The key starting 5-(2-(2-amino-4-phenylthiazol-5-yl)diselanyl)-4-phenylthiazol-2-amine (2) used in this study was synthesized by modification of the literature method [23]. Alkaline hydrolysis using K₂CO₃ in DMF offers good yield and superior purity rather than reduction by sodium borohydride (NaBH₄).

Owing to the fact that 2-aminothiazoles usually exists in nature in two forms i.e. amino and imino tautomeric forms, it is also expected that 2-aminothiazoleselenide 2 would be acting as as an amine and/or amidine (Figure 2).

This in turn provides an excellent entry point for the construction of bridgehead-nitrogen heterocycles which constitute an important subclass of compounds because of their wide use in medicinal chemistry. Within this context, thiazolo[3,2-a]pyrimidines (3a, 3b, 4a and 4b) were synthesized via one pot cyclocondensation of 2-aminothiazoleselenide 2 either with aromatic aldehydes and malononitrile/ethyl cyanoacetate or with the benzylidene derivatives of malononitrile/ethyl cyanoacetate (Scheme 1). The reaction is assumed to begin through the condensation of aminothiazoles and aldehyde to afford intermediate A. Subsequent Michael addition of malononitrile to A affords intermediate B which in turn undergoes intramolecular addition of the NH group to the CN group followed by isomerization to afford 4 in good yields (74-88 %). The structures of 3a, 3b, 4a and 4b were confirmed on the basis of their spectral data. The IR spectra of thiazolo[3,2-a]pyrimidines 4a shows characteristic absorption bands of a conjugated CN group at 2228 cm⁻¹, and broad absorption bands in the 3300-3400 cm⁻¹ region due to the presence of the hydroxyl group.

Figure 2. The amino and imino tautomeric forms of 2-aminothiazoles 2. Reagents and conditions (a) K₂CO₃, DMF, 75 °C, 3 hr.

Scheme 1. The synthesis of bridgehead-nitrogen heterocycles, thiazolo[3,2-a]pyrimidines (3a, 3b, 4a and 4b). Reagents and conditions (a) ethanol, conc. HCl, reflux 6 hr.
bands of NH2 at 3375 cm\(^{-1}\). In the 1H-NMR spectra, the NH2 signal was found at 2.5 ppm as singlet signal, and the aromatic protons was found downfield at 7.66 ppm as multiplets. The spectra for product 4a are given in the experimental section.

On the other hand, the reaction of 2-aminothiazolediselenide 2 with ethyl acetoacetate afforded 3-acetoacetyl derivative 5 instead of the anticipated thiazolo[3,2-a]pyrimidine 6. Reagents and conditions (a) ethyl acetoacetate, reflux, 1 hr; (b) ethanol, reflux, 2 hr.

The structure of 5 was confirmed on the basis of their spectral data. The IR spectra of 5 showed characteristic absorption bands of two carbonyl group at 1796 and 1683 cm\(^{-1}\). In the 1H-NMR spectra, the NH signal was found at 2.12 ppm as a singlet, and the aromatic protons was found downfield at 7.10 ppm as multiplets. A singlet signal found at 4.10 ppm corresponding to a CH2 proton. On the other hand, the structure of 7 was confirmed on the basis of their spectral data. The IR spectra of 7 showed characteristic absorption band of C=C at 1421 cm\(^{-1}\) in addition to the two carbonyl group at 1796 and 1683 cm\(^{-1}\). In the 1H-NMR spectra, the benzylidene signal was found at 7.88 ppm as a singlet, and the aromatic protons was found downfield at 7.22 ppm as multiplets. The spectra for product 5 and 7 are given in the Experimental section.

Our efforts were then directed to the synthesis of cyclic imides which have recently received much attention in drug discovery. These compounds constitute an integral part of various therapeutically and biologically relevant compounds (e.g., the natural alkaloid rebeccamycin, thalidomide, chlorophthallim, isoigranulatimide) and many of them are used as antioxidants, neuroprotectives, nootropics, anxiolytics, antinociceptives and antidepressants (Figure 1) [24][25].
In order to have structurally diversity, two amine-containing selenium were used namely; 2-Aminothiazolediselenide 2 and 4- (2- (4-amino-3-methylphenyl) diselanyl) – 2 - methylbenzenamine (17). The reaction of maleic, succinic and glutaric anhydrides with 2 and 17 in refluxing acetone afforded the corresponding N-substituted maleanilic (8 and 18), succinanilic (9 and 19) and glutaranilic (10 and 20) acids in quantitative yields. The ethyl esters 11, 12, 13, 21, 22 and 23 were obtained via acid-catalyzed esterification of the corresponding monoamidic acids. On the other hand, cyclic imides 14, 15, 16, 24, 25 and 26 were obtained by dehydration and subsequent ring-closure of the corresponding monoamidic acids up on gentle heating with acetic anhydride and sodium acetate (Scheme 3 and 4). The reaction was accomplished in 30 minutes and the product was easily isolated by ice-water precipitation.

**BIOLOGICAL ACTIVITY**

**Cytotoxic activity of compounds in breast cancer cells (MCF-7) and normal cells (WI-38)**

Recently, chemotherapy is suffering from a slim therapeutic index, with significant cytotoxicity from effective drug doses or tumor recurrence. Consequently, searching for new anticancer agents with lower toxicity to normal cells is of particular interest. New organoselenium compounds were therefore developed in an attempt to obtain compounds with superior chemotherapeutic index in terms of increased selectivity, higher cytotoxicity and lower side effects than the currently known chemotherapeutic agent. Within this context, the cytotoxic potency of the synthesized compounds was evaluated in breast adenocarcinoma (MCF-7) and compared with their cytotoxicity in normal lung fibroblast cells (WI-38) employing standard MTT assay using 5-fluorouracil (5-Fu) drug which is extensively used in adjuvant and palliative

![Scheme 3. Synthesis of diseleno N-amido-acids, N-amido-ethyl ester and cyclic imides using 2-aminothiazolediselenide 2 as the amine. Reagents and conditions (a) acetone, reflux, 3 hr; (b) ethanol, conc. H$_2$SO$_4$, r.t., 6 hr; (c) acetic anhydride, sodium acetate, 50 °C, 2 hr.]
chemotherapy for cancer. The IC50 values were estimated from the respective dose response curves (Table 1).

The therapeutic index (TI) is defined as the ratio of the drug concentration that inhibits 50% viability of the normal cells to the concentration that inhibits 50% viability of tumor cells (IC50 of WI-38 normal cell line/IC50 of MCF-7 cancer cell line). TI provides a simple index for evaluating the safety and efficacy of drugs. Agents with higher TI are more selective and often preferred, as they will be more effective in killing cancer cells at a lower concentration than those with lower TI.

The compounds under investigation could be divided into two classes: 1) cytotoxic compounds (4b, 5, 7, 18 and 23) which are able to reduce the viability of MCF-7 tumor cells and 2) compounds with mid-low cytotoxicity*. The difference in the diselenides cytotoxicity indicates that it is not general.

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**Scheme 4.** Synthesis of diseleno N-amido-acids, N-amido-ethyl ester and cyclic imides using 4-({2-(4-amino-3-methylphenyl)diselanyl)-2-methylbenzenamine (17) as the amine. Reagents and conditions (a) acetone, reflux, 3 hr; (b) ethanol, conc. H2SO4, r.t., 6 hr; (c) acetic anhydride, sodium acetate, 50 °C, 2 hr.
Table 1. Influence of the compounds on the viability of MCF-7 and WI-38 cells and their corresponding therapeutic windows.\textsuperscript{a)}

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>In vitro Cytotoxicity IC\textsubscript{50} (µM)</th>
<th>TI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MCF-7</td>
<td>WI-38</td>
</tr>
<tr>
<td>5-FU</td>
<td>8±0.13</td>
<td>4±0.63</td>
</tr>
<tr>
<td>3a</td>
<td>44±1.38</td>
<td>b</td>
</tr>
<tr>
<td>3b</td>
<td></td>
<td>b</td>
</tr>
<tr>
<td>4a</td>
<td>48±1.79</td>
<td>87±3.92</td>
</tr>
<tr>
<td>4b</td>
<td>26±0.54</td>
<td>b</td>
</tr>
<tr>
<td>5</td>
<td>21±0.61</td>
<td>b</td>
</tr>
<tr>
<td>7</td>
<td>34±1.06</td>
<td>b</td>
</tr>
<tr>
<td>9</td>
<td>76±2.91</td>
<td>61±3.06</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>b</td>
</tr>
<tr>
<td>11</td>
<td>65±2.41</td>
<td>74±3.22</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>b</td>
</tr>
<tr>
<td>13</td>
<td>53±2.11</td>
<td>85±3.14</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>b</td>
</tr>
<tr>
<td>16</td>
<td>61±1.84</td>
<td>70±2.88</td>
</tr>
<tr>
<td>18</td>
<td>9±0.20</td>
<td>b</td>
</tr>
<tr>
<td>19</td>
<td></td>
<td>b</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td>b</td>
</tr>
<tr>
<td>21</td>
<td></td>
<td>b</td>
</tr>
<tr>
<td>22</td>
<td>55±3.33</td>
<td>77±2.75</td>
</tr>
<tr>
<td>23</td>
<td>18±0.96</td>
<td>b</td>
</tr>
</tbody>
</table>

\textsuperscript{a)} The metabolic activity of the cells was measured after 48h of incubation with different concentrations of the investigated compounds by means of an MTT assay. The IC\textsubscript{50} was determined from the dose-response curves as the mean of three parallel experiments; therapeutic index (TI) is the ratio of the IC\textsubscript{50} normal cells (WI-38) to the IC\textsubscript{50} breast cancer cells (MCF-7); 5-fluorouracil (5-Fu) was used as a positive control; \textsuperscript{b)} no growth inhibition was recorded.

Table 2. Diameters (in mm) of inhibition zones of agar diffusion assays against a variety of fungi and bacteria (growth was quantified after 1 and 2 days).\textsuperscript{a)}

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Diameter inhibition zone in mm (% activity index)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E. coli / S. aureus / C. albicans</td>
</tr>
<tr>
<td>3a</td>
<td>7(29) / 7(32) / b</td>
</tr>
<tr>
<td>3b</td>
<td>b / b / b</td>
</tr>
<tr>
<td>4a</td>
<td>9(38) / 7(32) / 11(39)</td>
</tr>
<tr>
<td>4b</td>
<td>b / b / b</td>
</tr>
<tr>
<td>5</td>
<td>10(42) / 14(64) / 7(25)</td>
</tr>
<tr>
<td>7</td>
<td>8(33) / 9(41) / 9(32)</td>
</tr>
<tr>
<td>9</td>
<td>b / 8(36) / 7(25)</td>
</tr>
<tr>
<td>10</td>
<td>b / b / -</td>
</tr>
<tr>
<td>11</td>
<td>8(33) / b / 9(32)</td>
</tr>
<tr>
<td>12</td>
<td>b / b / b</td>
</tr>
<tr>
<td>13</td>
<td>8(33) / b / 12(43)</td>
</tr>
<tr>
<td>16</td>
<td>b / b / b</td>
</tr>
<tr>
<td>18</td>
<td>11(46) / 12(55) / b</td>
</tr>
<tr>
<td>19</td>
<td>7(29) / b / 8(29)</td>
</tr>
<tr>
<td>20</td>
<td>b / b / b</td>
</tr>
<tr>
<td>21</td>
<td>b / b / b</td>
</tr>
<tr>
<td>22</td>
<td>10(42) / 9(41) / 13(46)</td>
</tr>
<tr>
<td>23</td>
<td>15(63) / 19(86) / 21(75)</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>24 (100) / 22 (100) / -</td>
</tr>
<tr>
<td>Colitrimazole</td>
<td>- / - / 28 (100)</td>
</tr>
</tbody>
</table>

\textsuperscript{a)} Diameters (mm) of zones of inhibition (agar diffusion assay) are provided. In each case, 6 mm disks with 20 µg of the test compounds were incubated. Ampicillin and colitrimazole were used as the positive control. \textsuperscript{b)} Values below 6 mm (25%) are of limited value as they refer either to inactive or non-diffusing compounds.
selenium cytotoxicity and it further refers to the substitution pattern of the diselenides.

*(The cytotoxicity threshold is at IC\textsubscript{50} ≤ 34 μM)*

Notably, treatment with test compounds was accompanied with morphological changes in culture. In culture, cells became rounded, cell layer partially condensed forming cell-free areas, and cells were detached from the culture plate. Furthermore, a significant difference in toxicity zones between breast solid tumor cells and normal WI-38 cells was noticed. The Ti values of cytotoxic compounds 4b, 5, 7, 18 and 23 were ranging from eleven to three fold therapeutic indices in killing MCF-7 cells relative to WI-38 normal cells. These values were higher than that of 5-fu suggesting their effectiveness as anti-cancer agents. Whilst this may be true, the selectivity is not solely limited to these cell lines used and these initial results need further investigations using a wider arsenal of cancer and normal cells.

**Antimicrobial evaluation**

To study the cytotoxicity beyond human cell lines, we also studied the effect on lower organisms i.e. fungi and bacteria. Thus the antimicrobial activity of the compounds was evaluated against gram-negative Escherichia coli (E. coli) and gram-positive Staphylococcus aureus (S. aureus) as well as against the pathogenic fungus Candida albicans (C. albicans). A standard agar diffusion assay was used and the diameters [mm] of inhibition zones are summarized in Table 2.

In general, most compounds exhibited good-moderate toxicity against gram-negative (E. coli) bacteria and the gram-positive (S. aureus) bacteria. In this context, compounds 4a, 5, 7, 18 and 22 were the most active compound against E. coli and S. aureus. On the other hand, compounds 4a, 7, 11, 13, 19, 22 and 23 were the most active against C. albicans. These initial promising results point toward a reasonably activity of some of these compounds, which needs to be further investigated by using a considerably wider arsenal humanopathogenic bacteria and fungi.

**Conclusions**

The synthesis of a novel series of symmetrical thiazolediselenides was described. Most of the compounds were easily prepared in one step and in good to moderate yields. The cytotoxicity of the compounds was evaluated against breast adenocarcinom (MCF-7) and compared with their cytotoxicity in normal fibroblast cells (WI-38) employing standard MTT assay.

The compounds under investigation were divided into cytotoxic and non-cytotoxic compounds showing that it is not general selenium cytotoxicity. Compounds 4b, 5, 7, 18 and 23 showed Ti values ranging from three to eleven fold therapeutic indices in killing MCF-7 cells compared to WI-38 normal cells. These values were even higher than that of 5-fu Ti suggesting their effectiveness as anti-cancer agents.

Additionally, the cytotoxicity beyond human cell lines were also studied using E. coli (gram-negative) and S. aureus (gram-positive) bacteria as well as C. albicans (pathogenic fungi) using the standard agar diffusion assay. Compounds 4a, 5, 7, 18 and 22 were the most toxic against C. albicans. On the other hand, compounds 4a, 7, 11, 13, 19, 22 and 23 were found to be the most active against E. coli and S. aureus bacteria.

We are fully aware that a clear QSAR will require diverse sets of compounds including sulfur and tellurium-containing analogues, to screen for further activities and selectivity. Therefore, in order to derive reliable structure–activity relationships and to obtain a better understanding of the mode(s) of action, this library should be expanded to include wider diselenides functionalities as well as structural variants. While it might appear that these compounds are not fantastic in their activity, there is enough evidence to suggest that further study is warranted and this justifies the realization of more in-depth studies and additional experiments to investigate the exact mode(s) of action responsible for the pronounced biological activity apparently exhibited by this compound and to identify possible intracellular targets (such as specific organelles, membranes or proteins).

Eventually, these findings raise wealth of more questions. For example, what are the possible applications and the corresponding pharmacological and pharmacokinetic properties of such compound?

**EXPERIMENTAL**

**Chemistry**

All chemical reagents for the synthesis of compounds were purchased from Sigma-Aldrich-Fluka or Merck (AMD) and used without further purification unless stated otherwise. TLC plates (silica gel 60 F254, 0.20 mm) were purchased from...
Merck. All melting points are in degree centigrade (uncorrected) and were determined on Gallenkamp electric melting point apparatus. Elemental analyses were carried out at Micro analytical Center, Faculty of Science, Cairo University. IR spectra were recorded (KBr), (υ cm-1) on a Mattson 5000 FTIR Spectrophotometer at Micro analytical Center Faculty of Science, Mansoura University. The 1H-NMR Spectra were measured on a Varian Spectrophotometer at 300 MHz, using TMS as an internal reference and DMSO-d6 or CDCl3 as solvent at Chemistry Department, Faculty of Science, Cairo University. The chemical shifts (δ) are reported in parts per million and where referenced to the residual solvent peak. 13C NMR (75 MHz) was recorded in DMSO-d6 using a Bruker AV 400 spectrometer at Chemistry Department, Faculty of Science, Assiut University. Mass spectra were recorded on (Kratos, 70 eV) MS equipment and/or a Varian MAT 311A Spectrometer, at Microanalytical Center, Faculty of Science, Cairo University. Reaction mixtures were monitored by thin layer chromatography (TLC) using EM science silica gel coated plates with visualization by irradiation with ultraviolet lamp.

Biological Testing was carried out by Mr. Ahmed Abbas at Drug Department, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt.

**Synthesis and characterization**

**Synthesis of 4-phenyl-5-selenocyanatothiazol-2-amine (1)**

To a well stirred solution of malononitrile (0.2 gm, 3 mmol) in DMSO (2 mL), SeO2 (0.67 gm, 6 mmol) was added. The mixture became reddish after 10 min and an exothermic reaction with vigorous gas evolution began during the next 5 min. When the gas evolution was ceased the reaction mixture was filtered to remove any solids present, then aminothiazole (0.8 gm, 4.5 mmol) was added with stirring. Stirring was continued for additional 1 h at room temperature. The homogenous solution was diluted with ice-cold water, the precipitate formed was filtered off, air dried and recrystallized from ethanol to give 1.

**Synthesis of 5-(2-(2-amino-4-phenylthiazol-5-yl)diselanyl)-4-phenylthiazol-2-amine (2)**

DMF (2 mL) was introduced into 2 mmol of 1 in 25-mL two-necked flask fitted with a magnetic stirrer, a septum and a condenser connected to an argon-filled balloon. The solution was heated to 75 oC and K2CO3 (2 mmol dissolved in 1 mL of water) was slowly introduced by a syringe. The resulting mixture was further heated at 75 oC for 3 h and then hydrolyzed with ice-cold water and the precipitate formed was filtered off and recrystallized from ethanol to give 2.

**Synthesis of 4,4'-diselanediybis(2-methylaniline)(17)[26, 27]**

DMF (2 mL) was introduced into 25-mL two-necked flask fitted with a magnetic stirrer, a septum and a condenser connected to an argon-filled balloon and containing 2 mmol of 2-toluidine-4-selenocyanate [27]. The solution was heated to 75 oC and K2CO3 (2 mmol dissolved in 1 mL of water) was slowly introduced by a syringe. The resulting mixture was further heated at 75 oC for 3 h and then hydrolyzed with ice-cold water and the precipitate formed was filtered off and recrystallized from ethanol.

**General procedure for the preparation of thiazolo[3,2-a]pyrimidines (3a, 3b, 4a and 4b)**

**Method A**

To a stirred solution of 2 (0.1 gm; 1.96 mmol), aromatic aldehyde (4 mmol), malononitrile/ethyl cyanoacetate (4 mmol) in ethanol (10 mL) and catalytic drops of conc. HCl were added. The reaction mixture was heated under reflux for 6 hr. The reaction mixture was cooled and poured into ice-water beaker, and the separated product was recrystallized from ethanol.

**Method B**

To a stirred solution of 2 (0.1 gm; 1.96 mmol) and appropriate chalcone (4 mmole) in ethanol (10 mL), catalytic drops of conc. HCl were added. The reaction mixture was heated under reflux for 6 hr. The reaction mixture was cooled and poured into ice-water beaker, and the separated product was recrystallized from ethanol.

**Diethyl 2,2'-diselanediybis(5-aminoo-7-(3-methoxyphenyl)-3-phenyl-7H-thiazolo[3,2-a]pyrimidine-6-carboxylate) (3a)**

Yellow powdery crystals; yield 90%; mp > 300 oC; Rf = 0.95 [Pet. ether (60-80 oC)/ethyl acetate (4:2)]; IR (KBr): Υmax. cm-1: 3302(NH2), 1717(C=O), 1560(C=C), 1088(C-O); 1H NMR (300 MHz, DMSO-d6) δ 8.27 (s, 3H, Ar-H), 8.19 – 7.95 (m, 5H, Ar-H), 7.85 – 7.24 (m, 5H, Ar-H), 7.12 (d, J = 8.9 Hz, 5H, Ar-H), 4.29 (q, J = 7.5, 6.8 Hz, 4H, 2CH2), 3.86 (s, 6H, 2OCH3), 3.50 (s, 2H, 2CH) 2.70 (s, 4H, 2NH2), 1.29 (t, J = 7.1, 0.7 Hz, 6H, 2CH3); 13C NMR (75
MH, DMSO) δ 170.57, 162.33, 162.25, 155.38, 153.15, 134.40, 132.30, 123.88, 116.21, 116.05, 115.91, 113.34, 113.78, 101.43, 98.52, 63.98, 61.98, 58.43, 56.69, 56.44, 54.70, 13.26; EIMS m/z (%) 972 [M+, (11.11)]; Anal. Calcd. for C44H40N6O6S2Se2 (972.08): C, 54.43; H, 4.15; N, 8.15.

**General procedure for the preparation of 5-(2-(2-amino-4-phenylthiazol-5-yl)diselanyldiyl)-4-phenylthiazol-2-oxobutanamide (5)**

A suspension of 2 (0.1 gm; 1.96 mmol) in ethyl acetate (10 ml) was heated under reflux for 1 hr. The reaction mixture was cooled and poured into ice-water container then filtered and dried. The separated product was recrystallized from ethanol to give compound 5.

(N,N',N',N'-tetakis(5,5'-Diselenidiylbis(4-phenylthiazole-5(3H)-yl)-2(3H)-ylidene))bis(3-oxobutanamide) (5)

Brown crystals; yield 60%; mp 261°C; RF = 5.5 [pet. ether (60-80)/ethyl acetate (4:1)]; IR (KBr): Umax. cm⁻¹: 1796(C=O), 1683(C=O), 1656 (C=C), 1160 (C=Cl); 1H NMR (300 MHz, DMSO-d6) δ 7.95-7.91 (m, 2H, Ar-H), 7.25 – 7.21 (m, 2H, Ar-H), 7.20-7.18 (m, 2H, Ar-H), 7.15-7.10 (m, 4H, Ar-H), 4.10 (s, 4H, 2CH2), 2.21 (s, 6H, 2CH3), 2.12 (s, 2H, 2NH); EIMS m/z (%) 678 (M+, (58.49))]; Anal. Calcd. for C26H22N4O4S2Se2 (767.94): C, 46.16; H, 3.28; N, 8.28.

**General procedure for the preparation of (2E,2'E,N,N',N'E,N,N'E')-5(5,5'-Diselenidiylbis(4-phenylthiazole-5(3H)-yl)-2(3H)-ylinde))bis(2-(4-chlorobenzylidene)-3-oxobutanamide) (7)**

A mixture of 5 (0.25 gm; 0.36 mmol) and 4-chlorobenzaldehyde (0.1 gm; 0.72 mmole) in absolute ethanol (10 ml) was refluxed for 1 hr. The resulting solid product was filtered off, washed several times with water, dried and recrystallized from ethanol.

(2E,2'E,N,N',N'E,N,N'E')-5(5,5'-Diselenidiylbis(4-phenylthiazole-5(3H)-yl)-2(3H)-ylindene))bis(2-(4-chlorobenzylidene)-3-oxobutanamide) (7)

Yellow powder crystals; yield 80%; mp < 300°C; RF = 1.5 [pet. ether (60-80)/ethyl acetate (4:1)]; IR (KBr): Umax. cm⁻¹: 1796(C=O), 1683(C=O), 1656 (C=C), 1160 (C=Cl); 1H NMR (300 MHz, DMSO-d6) δ 7.98 (s, 2H, Ar-H), 7.54 – 7.22 (m, 18H, Ar-H), 2.58 (s, 6H, 2CH3), 2.22 (s, 2H, 2NH); 13C NMR (75 MHz, DMSO) δ 198.77, 195.37, 175.86, 172.24, 165.35, 156.21, 148.80, 138.20, 134.21, 132.5 (C=N).
Shaaban S. et al., June-July, 2015, 4(4), 1654-1668

134.19, 132.70, 128.65, 128.24, 128.02, 126.4, 125.59, 120.85, 83.74, 80.78, 25.05; EIMS m/z (%) 922 [M+], 921 [M+–1]; Anal. Calcd. for C40H28Cl2N4O4S2Se2: C, 44.07; H, 2.58; N, 7.95.

General procedure for the preparation of maleanilic 8 and 18, succinanilic 9 and 19 and glutaranilic 10 and 20 acids

To a stirring solution of anhydride (2 mmol) in dry acetone (10 mL), the corresponding amine (1 mmol) was added dropwise at room temperature. The mixture was vigorously refluxed for 3 h. The reaction mixture was poured into ice water and the separated product was filtered, dried and recrystallized from ethanol.

(2Z,2’Z)-4,4’-((5,5’-Diselanediylbis(4-phenylthiazole-5,2-diyli))bis(azanediyl))bis(4-oxobut-2-enoic acid) (8)

Yellow powdery crystals; yield 82%; mp 281°C; Rf = 0.11 [pet. ether (60–80)/ethyl acetate (4:1)]; IR (KBr): υmax cm−1: 3067(C=CH), 2926(C=CH), 1726(C=O), 1670(C=O), 1625(C=C), 1511(C=C), 1464(C=C), 1072(C=O), 967 (dd, J = 11.95 Hz, 4H, Ar=CH); EIMs m/z (%) 710 [M+, (16.92)]; Anal. Calcd. for C26H22N4O6S2Se2 (709.93): C, 44.02; H, 3.12; N, 6.11.

(2Z,2’Z)-4,4’-((5,5’-Diselanediylbis(2-methyl-4,1-phenylene))bis(azanediyl))bis(4-oxobut-2-enoic acid) (19)

Yellow powdery crystals; yield 63%; mp 158°C; Rf = 0.45 [pet. ether (60–80)/ethanol (4:1)]; IR (KBr): υmax cm−1: 3401(O-H), 1711(C=O), 1665(C=O), 1483(C=C), 1083(C=N); 1H NMR (300 MHz, DMSO-d6) δ 11.20 (s, 2H), 7.98–7.95 (m, 2H, Ar-H), 7.76–7.70 (m, 2H, Ar-H), 7.33–7.29 (m, 2H, Ar-H), 6.69 (dd, J = 11.12 Hz, 4H, 2CH=CH), 2.39 (s, 6H, 2CH3- Ar); EIMs m/z: 568 [M+, (33.08)]; Anal. Calcd. for C22H20N2O6Se2 (557.97): C, 46.66; H, 3.56; N, 4.95. Found: C, 46.72; H, 3.48; N, 5.03.

5,5’-((5,5’-Diselanediylbis(4-phenylthiazole-5,2-diyli))bis(azanediyl))bis(5-oxopentanoic acid) (10)

Orange powdery crystals; yield 92%; mp 281°C; Rf = 0.23 [pet. ether (60–80)/ethyl acetate (4:1)]; IR (KBr): υmax cm−1: 3066(C=CH), 2921(C=CH), 1726(C=O), 1670(C=O), 1625(C=C), 1509(C=C), 1072(C=O), 967 (dd, J = 11.95 Hz, 4H, Ar=CH); EIMs m/z (%) 710 [M+, (16.92)]; Anal. Calcd. for C26H22N4O6S2Se2 (709.93): C, 44.07; H, 3.12; N, 6.11.

(2Z,2’Z)-4,4’-((5,5’-Diselanediylbis(2-methyl-4,1-phenylene))bis(azanediyl))bis(5-oxopentanoic acid) (20)

Yellow powdery crystals; yield 88%; mp 160°C; Rf = 0.45 [pet. ether (60–80)/ethyl acetate (4:1)]; IR (KBr): υmax cm−1: 3272(O-H), 1725(C=O), 1652(C=O), 1419(C=C), 1124(C=N); 1H NMR (300 MHz, DMSO-d6) δ 12.11 (s, 2H, 2COOH), 9.31 (s, 2H, 2NH), 7.64–7.49 (m, 6H, Ar-H), 2.69–2.49 (m, 8H), 2.37 (s, 6H, 2CH3-Ar); 13C NMR (75 MHz, DMSO) δ 173.73, 173.53, 161.67, 129.64, 128.8, 125.61, 120.85, 30.57, 29.04, 14.33; EIMs m/z: 573 [M+–1, (0.05)]; Anal. Calcd. for C22H24N2O6Se2 (572): C, 46.33; H, 4.24; N, 4.91. Found: C, 46.40; H, 4.19; N, 4.88.

5,5’-((5,5’-Diselanediylbis(2-methyl-4,1-phenylene))bis(azanediyl))bis(5-oxopentanoic acid) (10)

Orange powdery crystals; yield 92%; mp 281°C; Rf = 0.23 [pet. ether (60–80)/ethyl acetate (4:1)]; IR (KBr): υmax cm−1: 3111(O-H), 1725(C=O), 1670 (C=O), 1616(C=C), 1067(C=N); 1H NMR (300 MHz, DMSO-d6) δ 11.24 (s, 2H), 7.80–7.75 (m, 2H), 7.73–7.50 (m, 3H), 7.45–7.30 (m, 5H), 2.28 (dt, J = 12.8, 8.4 Hz, 8H), 1.60 (m, 4H); EIMs m/z: 739 [M++, 14.79] 738 [M+, (21.25)]; Anal. Calcd. for C28H26N4O6S2Se2: C, 45.60; H, 3.56; N, 7.61. Found: C, 45.66; H, 3.49; N, 7.58.

General procedure for the preparation of ethyl ester derivatives 11, 12, 13, 21, 22 and 23

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To a solution of the corresponding acid (0.1 mmol) in ethanol (10 ml), conc. H2SO4 (200 µl) was added and the mixture was stirred at room temperature for 6 h. The mixture was poured into ice water and the separated solid was recrystallized from ethanol.

**Diethyl 4,4’-((5,5’-diselenanediylbis(4-phenylthiazole-5,2-diyl))bis(azanediyl))bis(4-oxobutanoate) (11)**

Yellow powder crystals; yield 66%; mp 298oC; Ref. = 4.8 [pet. ether (60-80)/ethyl acetate (4:1)]; IR (KBr): Umax. cm-1: 1724(C=O), 1624(C=O), 1643(C=O), 1094(C=N); 1H NMR (300 MHz, DMSO-d6) δ 8.07-7.89 (m, 5H, Ar-H), 7.46-7.03 (m, 5H, Ar-H), 6.76 (dd, J= 16.6 Hz, 4H, 2CH=CH2), 4.41 (q, J=7.11 Hz, 4H, 2CH2), 1.19 (t, J=7.18 Hz, 6H, 2CH3); EIMS m/z: 779 (M+, 17.52); Anal. Calcd. for C30H30N4O6S2Se2 (765.99): C, 47.12; H, 3.95; N, 7.37.

**Diethyl 4,4’-((5,5’-diselenanediylbis(4-phenylthiazole-5,2-diyl))bis(azanediyl))bis(4-oxobutanoate) (12)**

Orange powder crystals; yield 90%; mp 265oC; Ref = 0.8 [pet. ether (60-80)/ethyl acetate (4:1)]; IR (KBr): Umax. cm-1: 1724(C=O), 1620(C=O), 1637(C=O), 1024(C-N); 1H NMR (300 MHz, DMSO-d6) δ 8.20 (m, 5H, Ar-H), 7.59 (m, 2H, Ar-H), 7.41 (m, 4H, 2CH3), 3.39 (q, J = 1.96 Hz, 4H, 4CH2), 2.23 (t, J = 7.20 Hz, 6H, 2CH3), 1.92 (t, J= 7.16 Hz, 4H, 2CH2), 1.19 (t, J=7.18 Hz, 6H, 2CH3); EIMS m/z (%): [M+ (2.48)]; Anal. Calcd. for C26H28N2O6Se2 (654.03): C, 50.17; H, 4.53; N, 4.50. Found: C, 50.22; H, 4.61; N, 4.62.

**Diethyl 4,4’-((diselenanediylbis(2-methyl-4,1-phenylene))bis(azanediyl))bis(4-oxobutanoate) (22)**

Yellow powder crystals; yield 80%; mp 158oC; Ref = 6.5 [pet. ether (60-80)/ethyl acetate (4:1)]; IR (KBr): Umax. cm-1: 1724(C=O), 1652(C=O), 1637(C=C), 1121(C-O), 1096(C-N); 1H NMR (300 MHz, DMSO-d6) δ 8.1 (s , 2H, 2NH), 7.76 – 7.49 (m, 5H, Ar-H), 7.21 – 7.10 (m, 5H, Ar-H), 4.10 (q, J = 7.18 Hz, 4H, 2CH2), 2.52-2.49 (m, 8H, 4CH2), 2.22 (s, 6H, 2CH3), 1.23 (t, J= 7.18 Hz, 6H, 2CH3); EIMS m/z (%): 628 [M+, (9.05)]; Anal. Calcd. for C26H32N3O6Se2 (628.06): C, 49.85; H, 5.15; N, 4.47. Found: C, 50.03; H, 5.00; N, 4.52.

**Diethyl 5,5’-((diselenanediylbis(2-methyl-4,1-phenylene))bis(azanediyl))bis(5-oxopentanoate) (23)**

Yellow powder crystals; yield 75%; mp 165oC; Ref = 6.5 [pet. ether (60-80)/ethyl acetate (4:1)]; IR (KBr): Umax. cm-1: 1728(C=O), 1652(C=O), 1149(C=C), 1078(C-N),1024(C-O); EIMS m/z: 658 ( M++2, 8.92), 657 ( M++1,4.46), 656 (M+, 18.70), 655 (5.81), 654 (5.59), 626 (0.59), 602 (0.59), 115 (100.0, base peak), 113 (1.31), 110 (1.17), 100 (2.57), 95 (3.38); Anal. Calcd. for C28H36N2O6Se2 (665.09): C, 51.38; H, 5.54; N, 4.28. Found: C, 51.29; H, 5.61; N, 4.21.

**General procedure for the preparation of cyclic imides 14, 15, 16, 24, 25 and 26**

A mixture of appropriate acid (0.1 mmol), freshly fused sodium acetate (100 mg) and acetic anhydride (5 ml) was heated for 2 h at 55 oC. The reaction was cooled and...
quenched with ice water and the separated solid was recrystallized from ethanol.

1,1′-(5,5′-Diselanediylbis(4-phenylthiazole-5,2-diyi))bis(1H-pyrole-2,5-dione) (14)

Yellow powder crystals; yield 75%; mp 265oC; Ref = 4.3 [pet. ether (60-80)/ethyl acetate (4:1)]; IR (KBr): Umax. cm-1: 3020(C-H), 1812(C=O), 1422(C=C), 1140(C-N); 1H NMR (300 MHz, DMSO-d6) δ 8.02-7.93 (m, 5H, Ar-H), 7.58-7.48 (m, 5H, Ar-H), 6.76 (dd, J = 7.5 Hz, 4H, 2CH=CH); EIMS m/z (%) 532 [M++, (0.26)]; Anal. Calcd. for C22H16N2O4Se2 (531.94): C, 49.79; H, 3.14; N, 5.15.

1,1′-(5,5′-Diselanediylbis(4-phenylthiazole-5,2-diyi))bis (pyrrolidine-2,5-dione) (15)

Orange powder crystals; yield 70%; mp 292oC; Ref = 6 [pet. ether (60-80)/ethyl acetate (4:1)]; IR (KBr): Umax. cm-1: 3020(C-H), 1812(C=O), 1653(C=C), 1095(C-N); 1H NMR (300 MHz, DMSO-d6) δ 7.82 – 7.75 (m, 2H, Ar-H), 7.70 – 7.52 (m, 2H, Ar-H), 7.32-7.28 (m, 4H, Ar-H), 7.03-6.69 (m, 2H, Ar-H), 2.50 (s, 8H, 4CH2); EIMS m/z (%) 674 [M++, (0.48)]; Anal. Calcd. for C26H14N4O4S2Se2 (673.91): C, 46.44; H, 2.70; N, 8.33. Found: C, 46.36; H, 2.62; N, 8.47.

1,1′-(5,5′-Diselanediylbis(4-phenylthiazole-5,2-diyi))bis (piperidine-2,6-dione) (16)

Orange powder crystals; yield 75%; mp < 300oC; Ref = 5.7 [pet. ether (60-80)/ethyl acetate (4:1)]; IR (KBr): Umax. cm-1: 3109(C-H), 1744(C=O), 1713(C=O), 1088(C-N); 1H NMR (300 MHz, DMSO-d6) δ 7.96 – 7.90 (m, 2H, Ar-H), 7.66 – 7.62 (m, 2H, Ar-H), 7.44-7.40 (m, 4H, Ar-H), 7.13-6.69 (m, 2H, Ar-H), 2.20-2.18 (m, 8H, 4CH2), 2.93-1.85 (m, 4H, 2CH2); EIMS m/z (%) [702 (16.55)]; Anal. Calcd. for C28H22N4O4S2Se2 (701.94): C, 48.01; H, 2.61; N, 8.00. Found: C, 48.09; H, 3.12; N, 8.07.

1,1′-(Diselanediylbis(2-methyl-4,1-phenylene))bis(1H-pyrole-2,5-dione) (24)

Yellow powder crystals; yield 70%; mp 255oC; Ref = 4.8 [pet. ether (60-80)/ethyl acetate (4:1)]; IR (KBr): Umax. cm-1: 3063(C-H), 1746(C=O), 1422(C=C), 1174(C-N); 1H NMR (300 MHz, DMSO-d6) δ 7.81-7.79 (m, 3H, Ar-H), 7.28-7.20 (m, 3H, Ar-H), 6.86 (dd, J = 7.46 Hz, 4H, 2CH=CH); EIMS m/z (%) 532 [M++1, (11.03)]; Anal. Calcd. for C22H16N2O4Se2 (531.94): C, 49.83; H, 3.04; N, 5.28. Found: C, 49.79; H, 3.14; N, 5.15.

1,1′-(Diselanediylbis(2-methyl-4,1-phenylene))bis (pyrroline-2,5-dione) (25)

Yellow powder crystals; yield 70%; mp 155oC; Ref = 4.8 [pet. ether (60-80)/ethyl acetate (4:1)]; IR (KBr): Umax. cm-1: 3063(C-H), 1746(C=O), 1422(C=C), 1174(C-N); 1H NMR (300 MHz, DMSO-d6) δ 8.38 – 8.30 (m, 2H, Ar-H), 6.80-6.77 (m, 4H, Ar-H), 2.81 (s, 8H, 4CH2), 2.37 (s, 6H, 2CH3)); 13C NMR (75 MHz, DMSO) δ 176.62, 138.20, 136.87, 133.60, 129.59, 128.39, 125.30, 120.74, 28.60, 17.06; EIMS m/z (%) 520 [M++, (0.03)]; Anal. Calcd. for C22H20N2O4Se2 (535.98): C, 49.45; H, 3.77; N, 5.24. Found: C, 49.38; H, 3.79; N, 5.30.

1,1′-(Diselanediylbis(2-methyl-4,1-phenylene))bis (piperidine-2,6-dione) (26)

Yellow powder crystals; yield 80%; mp 158oC; Ref = 4.4 [pet. ether (60-80)/ethyl acetate (4:1)]; IR (KBr): Umax. cm-1: 3063(C-H), 1796 (C=O), 1718(C=O), 1054(C-N); 1H NMR (300 MHz, DMSO-d6) δ 7.90 – 7.72 (m, 3H, Ar-H), 7.64-7.59 (m, 3H, Ar-H), 2.35 (s, 6H, 2CH3), 2.25-2.19 (m, 8H, 4CH2), 2.10-2.08 (m, 4H, 2CH2); EIMS m/z: 564 [M++, (0.14)]; Anal. Calcd. for C24H24N2O4Se2 (564.01): C, 51.26; H, 4.30; N, 4.98. Found: C, 51.33; H, 4.21; N, 5.11.

BIOLICAL STUDIES

Cytotoxicity assay

The mammary gland breast cell line (MCF-7) and human fibroblast cell line (WI-38) were obtained from ATCC via Holding company for biological products and vaccines (VACSERA), Cairo, Egypt. The reagents RPMI-1640 medium, MTI, DMSO and 5-Fluorouracil were purchased from sigma co., St. Louis, USA and Fetal Bovine serum was purchased from Gibco, UK. The cells were cultured in RPMI-1640 medium supplemented with 10% (v/v) calf serum (Hyclone Laboratories, Ogden, UT), 60 mg/ml penicillin G and 100 mg/ml streptomycin sulfate maintained at 37 °C in a humidified atmosphere containing about 15% (v/v) CO2 in air.

MTT [3-(4,5-dimethylthiazol-2-yl)2,5-diphenyltetrazolium bromide] (Sigma) was used to measure the metabolism activity of cells which are capable of reducing it by dehydrogenases to a violet colored formazan product. Briefly, 120 μL aliquots of a cell suspension (50,000 cells mL-1) in 96-well microplates were incubated at 37 °C and 10% CO2 and allowed to grow for two days. Then 60 μL of serial dilutions...
of the test compounds were added. After 48h of incubation at 37 °C and 10% CO2, 75 µL MTT in phosphate buffered saline (PBS) were added to a final concentration of 0.5 mg mL⁻¹. After 2 h the precipitate of formazan crystals was centrifuged and the supernatant discarded. The precipitate was washed with 100 µL PBS and dissolved in 100 µL DMSO. The resulting color was measured at 590 nm using an ELISA plate reader. All investigations were carried out in two parallel experiments. The IC50 values were determined as the concentrations of tested materials, which showed 50% of the absorbance of untreated control cells as estimated from the dose-response curves. 5-fluorouracil (5-Fu) was used as a positive control.

**Antimicrobial activity**

Chemical compounds were individually tested against gram positive (Staphylococcus aureus) and gram negative (Escherichia coli) bacterial pathogens as well as Candida albicans fungus (yeast) strain. Antimicrobial tests were carried out by the agar well diffusion method using 100 µL of suspension containing 1x10⁸ CFU/mL of pathological tested bacteria and 1x10⁴ spores/mL of fungi spread on nutrient agar (NA), and potato dextrose agar (PDA) medium respectively. After the media had cooled and solidified, paper discs of 6 mm diameter soaked with 20 µl of the test compounds (1mg/ml) were added to the agar plates and incubated at 30°C. After incubation time, antimicrobial activity was evaluated by measuring the zone of inhibition against the test organisms and compared with that of the standard. The antibacterial activity of a common standard antibiotic ampicillin and the antifungal coltrimazole were chosen as positive control using the same procedure as above at the same concentration. The relative (%) activity index was calculated as shown below:

\[
\% \text{ activity index} = \left( \frac{\text{inhibition zone of the test compounds}}{\text{inhibition zone of the standard drug}} \right) \times 100.
\]

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**Conflict of Interest**

The authors have declared no conflict of interest.

**SHORT SUMMARY**

A novel series of symmetrical thiazolediselenides were synthesized and their cytotoxic properties were evaluated on human breast adenocarcinom and compared with their cytotoxicity in normal fibroblast cells (WI-38) employing standard MTT assay. Of the tested compounds, 4b, 5, 7, 18 and 23 exhibited therapeutic indices (TI) up to eleven fold and were higher than that of 5-fu suggesting their effectiveness as anti-cancer agents.

![Chemical structure of thiazolediselenides](image-url)
REFERENCES