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Synthesis and anticancer properties of 3-furan-2-yl-2-(4-furan/thiophen-2-ylthiazol-2-yl)acrylonitrile derivatives

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C H R O N I C L E

Article history:
Received February 2, 2022
Received in revised form
March 8, 2022
Accepted April 11, 2022
Available online
April 11, 2022

Keywords:
Arylation
Thiazol
Furan
Thiophen
Anticancer activity

A B S T R A C T

By the reaction of (4-furan-2-yl-thiazol-2-yl)- **3a** and (4-thiophen-2-yl-thiazol-2-yl)- **3b** acetonitriles with furfural **4** and 5-arylfurfyrals **5a-g** 3-furan-2-yl-2-(4-furan/thiophen-2-ylthiazol-2-yl)acrylonitrile derivatives **6a-i** were obtained. Anticancer activity screening was carried out within the framework of Developmental Therapeutic Program of the National Cancer Institute's (DTP, NCI, Bethesda, Maryland, USA). It was found out that (2*E*)-3-(2-furyl)-2-[4-(2-furyl)-1,3-thiazol-2-yl]acrylonitrile (**6a**) and 2-(4-thiophen-2-yl-thiazol-2-yl)-acrylonitriles **6h,i** possessed low activity and 2-(4-furan-2-yl-thiazol-2-yl)acrylonitrile derivatives **6b-g** showed moderate action. Compounds **6b-g** were sensitive to cell lines of MDA-MB-468 and T-47D Breast Cancer. In this case cytotoxic effect was observed with a range of GP = -38.24 – 1.28%.

1. Introduction

The thiazole nucleus is a very important heterocycle in many biologically active compounds that makes it one of the extensively studied heterocycles.[1-3] Thiazoles plays vital roles in many drug structures. Some examples of thiazole bearing products are tiazofurin and dasatinib (antineoplastic agents), ritonavir (anti-HIV drug), ravuconazole (antifungal agent), nitazoxanide (antiparasitic agent), fanetizole, meloxicam and fentiazac (anti-inflammatory agents), nizatidine (antiulcer agent), and thiamethoxam (insecticide).[4] On the other hand, furans are also an important scaffolds found in medicinal products and biological active molecules.[5,6] Some prominent drugs containing furan rings are rofecoxib, dantrolene, prazosin, ranitidine, nitrofurantoin, and furosemide.[4] It is expected that combination of these heterocyclic moieties in a single molecule is anticipated to give rise in the enhanced pharmacological properties. Thus, synthesis of novel compounds containing both thiazole and furane fragments and their further screening for biological activity attract a lot of interest from both scientific and practical viewpoints.

2. Results and Discussion

2.1 Chemistry

Synthesis of 3-furan-2-yl-2-(4-furan/thiophen-2-ylthiazol-2-yl)acrylonitrile derivatives. In view continuation of our research on bioactive compounds,[8-19] we synthesized and biologically evaluated of 3-furan-2-yl-2-(4-furan-2-yl-thiazol-2-yl)acrylonitrile **6a**, 3-(5-arylfuran-2-yl)-2-(4-furan-2-yl-thiazol-2-yl)- **6b-g** and 3-(5-arylfuran-2-yl)-2-(4-thiophen-2-yl-thiazol-2-yl)- **6h,i** acrylonitriles. As starting reagents were used 2-bromoacetylfuran **1a** and bromoacetylthiophen **1b**. They

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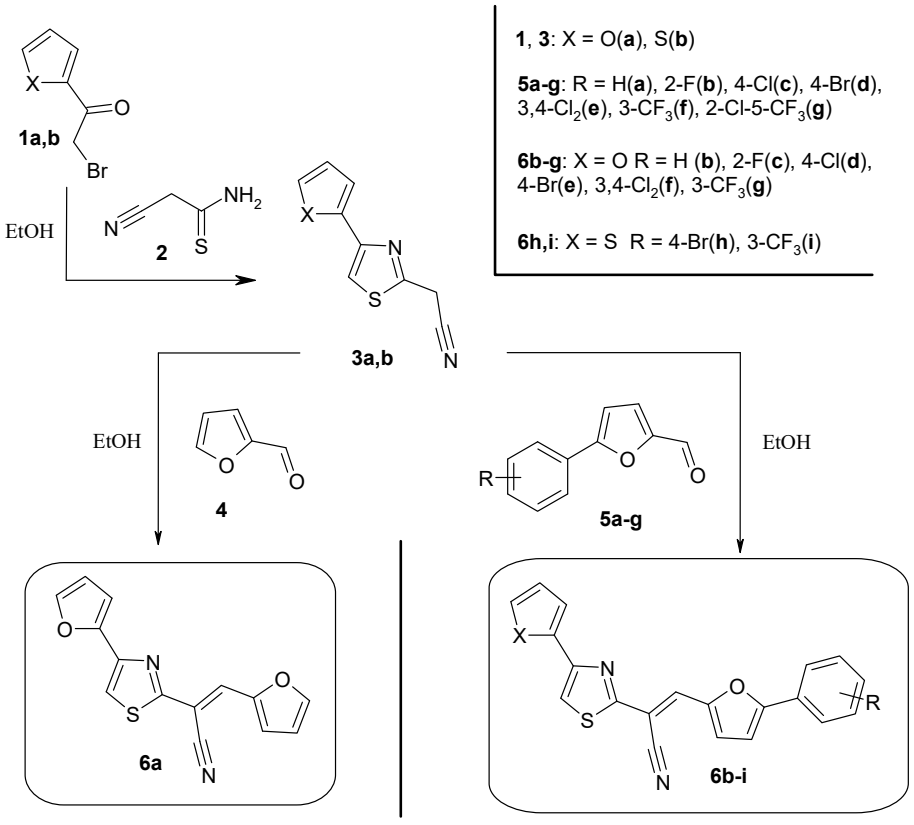
doi: 10.5267/j.ccl.2022.4.002

react with 2-cyanothioacetamide **2** to form (4-furan-2-yl-thiazol-2-yl)- **3a** and (4-thiophen-2-yl-thiazol-2-yl)- **3b** acetonitriles (**Scheme**).

The next step involves Knoevenagel condensation of synthesized **3a,b** with furfyral and 5-arylfurfyrals. In this step nucleophilic addition of active hydrogen from acetonitrile part with carbonyl group of substituted aldehydes followed by water elimination with the formation 3-furan-2-yl-2-(4-furan-2-yl-thiazol-2-yl)-acrylonitrile **6a**, 3-(5-arylfuran-2-yl)-2-(4-furan-2-yl-thiazol-2-yl)- **6b-g** and 3-(5-arylfuran-2-yl)-2-(4-thiophen-2-yl-thiazol-2-yl)- **6h,i** acrylonitriles as final compounds. In this step weak base piperidine used in catalytic amount. 5-Arylfurfurals **5a-g** were obtained by the reaction of arendiazonium salts with furfural in Meerwein reaction conditions[20] according to the procedure described us earlier[21] (**Scheme**).



Scheme.

2.2 Anticancer activity

The synthesized compounds were selected by the National Cancer Institute (NCI) Developmental Therapeutic Program (www.dtp.nci.nih.gov) for the *in vitro* cell line screening to investigate their anticancer activity. Primary anticancer assay was performed at approximately sixty human tumor cell lines panels derived from nine neoplastic diseases, in accordance with the protocol of the Drug Evaluation Branch, National Cancer Institute, Bethesda.[22-25] The screening results are shown in Table 1.

The synthesized compounds displayed different levels of anticancer activity. (2*E*)-3-(2-furyl)-2-[4-(2-furyl)-1,3-thiazol-2-yl]acrylonitrile **6a** showed low anticancer effect. 2-(4-Furan-2-yl-thiazol-2-yl)acrylonitrile derivatives **6b-g** possessed moderate activity. Bioisosteric replacement of the furan cycle with thiophen led to a significant loss of activity. 3-Furan-2-yl-2-(4-furan-2-yl-thiazol-2-yl)-acrylonitrile **6a** and 2-(4-thiophen-2-yl-thiazol-2-yl)-acrylonitriles **6h,i** demonstrated a low level of activity. Compounds **6b-g** were sensitive to MDA-MB-468 and T-47D Breast Cancer cell lines. In this case cytotoxic effect was observed with a range of GP = -38.24 – -1.28%. It should be noticed that compounds **6h,i** stimulated the growth of TK-10 Renal Cancer cell line with GP = 185.06 and 202.55%.

Table 1. Cytotoxic activity of the tested compounds in the concentration 10^{-5} M against 60 cancer cell lines

Test compounds	Average growth, %	Range of growth, %	Most sensitive cell line (cancer line/type) GP, %
6a	96.73	20.36 – 174.95	MDA-MB-468 (Breast Cancer) 20.36 T-47D (Breast Cancer) 44.26 MCF7 (Breast Cancer) 31.53
6b	80.61	-32.42 - 125.36	**MDA-MB-468 (Breast Cancer) -32.42** **T-47D (Breast Cancer) -26.02** OVCAR-4 (Ovarian Cancer) 11.03 MCF7 (Breast Cancer) 17.60 HCC-2998 (Colon Cancer) 32.12
6c	82.90	-11.02 - 108.98	**MDA-MB-468 (Breast Cancer) -11.02** T-47D (Breast Cancer) 14.48 OVCAR-4 (Ovarian Cancer) 19.57
6d	84.50	-27.06 -108.52	**T-47D (Breast Cance r) -27.06** **MDA-MB-468 (Breast Cancer) -26.75** OVCAR-4 (Ovarian Cancer) 4.22 MCF7 (Breast Cancer) 14.52
6e	81.42	**-26.38** - 106.46	**T-47D (Breast Cancer) -26.38** **MDA-MB-468 (Breast Cancer) -26.82** **OVCAR-4** (Ovarian Cancer) **-6.53** MCF7 (Breast Cancer) 15.36
6f	80.61	-38.24 - 121.28	**MDA-MB-468 (Breast Cancer) -38.24** **T-47D (Breast Cancer) -21.33** **TK-10 Renal Cancer -7.19** MCF7 (Breast Cancer) 12.52 HCC-2998 Colon Cancer 0.93 OVCAR-4(Breast Cancer) 37.58
6g	82.87	-37.00 - 118.37	**MDA-MB-468 (Breast Cancer) -37.00** **T-47D (Breast Cancer) -17.61** OVCAR-4 (Ovarian Cancer) 16.82 MCF7 (Breast Cancer) 22.44 HCC-2998 (Colon Cancer) 29.48
6h	96.04	6.37 – 185.06	MDA-MB-468 (Breast Cancer) 6.37 MCF7 (Breast Cancer) 28.92 T-47D (Breast Cancer) 40.02
6i	97.18	59.99 – 202.55	MCF7 (Breast Cancer) 59.99

3. Conclusions

In summary, we presented efficient synthetic approaches to a number of 3-furan-2-yl-2-(4-furan/thiophen-2-ylthiazol-2-yl)acrylonitrile derivatives for their further anticancer activity evaluation. We have shown that the proposed synthetic protocols provided the possibility to design 3-furan-2-yl-2-(4-furan/thiophen-2-ylthiazol-2-yl)acrylonitrile diversity with a considerable chemical novelty. Their structures were confirmed by ^{1}H NMR spectroscopy and microanalyses. The obtained results of the performed biological activity evaluation suggested the synthesized compounds as promising structures in anticancer drugs development. Further optimization of the structure to improve biological activity is currently in progress.

4. Experimental

4.1 Chemistry

All chemicals were of analytical grade and commercially available. When performing the synthetic part of the work, the reagents of the company Merck (Germany) and Sigma-Aldrich (USA) were used. All reagents and solvents were used without further purification and drying. All the melting points were determined in an open capillary and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian Mercury 400 (Agilent Technologies, San Francisco, USA) instrument with TMS or deuterated solvent as an internal reference. Mass spectra were run using Agilent 1100 series LC/MSD (Agilent Technologies, San Francisco, USA) with an API–ES/APCI ionization mode. Elemental analysis was performed on an Elementar Vario L cube instrument (Elementar Analysensysteme GmbH, Hanau, Germany). Satisfactory elemental analyses were obtained for new compounds (C±0.17, H±0.21, N±0.19).

4.1.1 (4-Furan/thiophen-2-yl-thiazol-2-yl)acetonitriles **(3a,b)**. A mixture 0.1 mol of 2-bromoacetylfurane **1a** or 2-bromoacetylthiophene **1b** and 10 g (0.1 mol) cyanothioacetamide **2** in ethanol (25 ml) was refluxed for 2 h. The reaction mixture was poured onto ice-cold water (50 ml) and neutralized of conc. ammonium hydroxide. The resulting solid was collected, washed with water, and recrystallized from ethanol**.**

4.1.2 [4-(2-furyl)-1,3-thiazol-2-yl]acetonitrile (**3a**). Yield 69%, m.p. 43-44 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.82 (s, 1H, thiazol), 7.77 – 7.75 (m, 1H, furan), 6.82 (d, *J* = 3.4 Hz, 1H, furan), 6.61 (ddd, *J* = 3.1, 1.8, 0.8 Hz, 1H, furan), 4.62 (s, 2H, CH_2). ESI-MS: m/z 191 $[M+H]^+$. Anal. Calcd. for $C_9H_6N_2OS$ (%): C, 56.83; H, 3.18; N, 14.73. Found (%): C, 56.97; H, 3.11; N, 14.85.

4.1.3 [4-(2-thienyl)-1,3-thiazol-2-yl]acetonitrile (**3b**). Yield 73%, m.p. 50-51 °C, m.p. 49-51°C.[7]

4.1.4 General procedure for synthesis of 3-furan-2-yl-2-(4-furan/thiofen-2-yl-thiazol-2-yl)acrylonitrile derivatives (**6a-i).** The 0.01 mol of furfural **4** or 5-arylfurfural **5a-g** and 0.01 mol of thiazol-2-ylacetonitrile **3a,b** was dissolved in 20 ml of ethanol in the presence of 2 drops of piperidine. The flask was refluxed for 1 h. The precipitate formed were filtered off, washed with alcohol, and the product was purified by recrystallization from a mixture of ethanol–DMF**.**

4.1.5 (2E)-3-(2-furyl)-2-[4-(2-furyl)-1,3-thiazol-2-yl]acrylonitrile (**6a**). Yield 65%, m.p. 113-114 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.14 (d, *J* = 1.7 Hz, 1H, furan), 8.13 (s, 1H, CH=), 7.93 (s, 1H, thiazol), 7.79 (dd, *J* = 1.8, 0.7 Hz, 1H, furan), 7.38 (d, *J* = 3.6 Hz, 1H, furan), 6.90 (dd, *J* = 3.3, 0.5 Hz, 1H, furan), 6.84 (dd, *J* = 3.6, 1.8 Hz, 1H, furan), 6.67 – 6.60 (m, 1H, furan). ESI-MS: m/z 269 $[M+H]^+$. Anal. Calcd. for $C_{14}H_8N_2O_2S$ (%): C, 62.68; H, 3.01; N, 10.44. Found (%): C, 62.59; H, 2.96; N, 10.34.

4.1.6 ((2E)-2-[4-(2-furyl)-1,3-thiazol-2-yl]-3-(5-phenyl-2-furyl)acrylonitrile (**6b**). Yield 84%, m.p. 142-143 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.14 (s, 1H, CH=), 7.98 – 7.90 (m, 3H, C_6H_5), 7.81 – 7.79 (m, 1H, furan), 7.54 (t, *J* = 7.7 Hz, 2H, C_6H_5), 7.47 – 7.41 (m, 2H, furan), 7.37 (d, *J* = 3.7 Hz, 1H), 6.91 (d, *J* = 3.3 Hz, 1H, furan), 6.64 (dd, *J* = 3.2, 1.8 Hz, 1H, furan). ESI-MS: m/z 345 $[M+H]^+$. Anal. Calcd. for $C_{20}H_{12}N_2O_2S$ (%): C, 69.75; H, 3.51; N, 8.13. Found (%): C, 69.84; H, 3.45; N, 8.21.

4.1.7 ((2E)-3-[5-(2-fluorophenyl)-2-furyl]-2-[4-(2-furyl)-1,3-thiazol-2-yl]acrylonitrile (**6c**). Yield 83%, m.p. 137-138 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.16 (s, 1H, CH=), 8.01 (t, *J* = 7.8 Hz, 1H, C_6H_4), 7.93 (s, 1H, thiazol), 7.79 (d, *J* = 1.1 Hz, 1H, furan), 7.54 – 7.43 (m, 2H, C_6H_4), 7.44 – 7.36 (m, 2H, C_6H_4 + furan), 7.16 (t, *J* = 3.7 Hz, 1H, furan), 6.90 (d, *J* = 3.3 Hz, 1H, furan), 6.63 (dd, *J* = 3.3, 1.8 Hz, 1H, furan). ESI-MS: m/z 363 $[M+H]^+$. Anal. Calcd. for $C_{20}H_{11}FN_2O_2S$ (%): C, 66.29; H, 3.06; N, 7.73. Found (%): C, 66.35; H, 3.14; N, 7.61.

4.1.8 ((2E)-3-[5-(4-chlorophenyl)-2-furyl]-2-[4-(2-furyl)-1,3-thiazol-2-yl]acrylonitrile **(6d).** Yield 84%, m.p. 139-140 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.11 (s, 1H, CH=), 7.94 – 7.87 (m, 3H, C_6H_4 + thiazol), 7.79 (d, *J* = 1.0 Hz, 1H, furan), 7.58 (d, *J* = 8.6 Hz, 2H, C_6H_4), 7.44 (d, *J* = 3.8 Hz, 1H, furan), 7.39 (d, *J* = 3.7 Hz, 1H, furan), 6.89 (d, *J* = 3.3 Hz, 1H, furan), 6.63 (dd, *J* = 3.3, 1.8 Hz, 1H, furan). ESI-MS: m/z 378 $[M+H]^+$. Anal. Calcd. for $C_{20}H_{11}ClN_2O_2S$ (%): C, 63.41; H, 2.93; N, 7.39. Found (%): C, 63.41; H, 2.93; N, 7.39.

4.1.9 ((2E)-3-[5-(4-bromophenyl)-2-furyl]-2-[4-(2-furyl)-1,3-thiazol-2-yl]acrylonitrile (**6e**). Yield 86%, m.p. 173-174 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.11 (s, 1H, CH=), 7.92 (s, 1H, thiazol), 7.83 (d, *J* = 8.6 Hz, 2H, C_6H_4), 7.80 – 7.78 (m, 1H, furan), 7.72 (d, *J* = 8.6 Hz, 2H, C_6H_4), 7.44 (d, *J* = 3.8 Hz, 1H, furan), 7.40 (d, *J* = 3.7 Hz, 1H, furan), 6.90 (d, *J* = 3.3 Hz, 1H, furan), 6.63 (dd, *J* = 3.3, 1.8 Hz, 1H, furan). ESI-MS: m/z 424 $[M+H]^+$. Anal. Calcd. for $C_{20}H_{11}BrN_2O_2S$ (%): C, 56.75; H, 2.62; N, 6.62. Found (%): C, 56.86; H, 2.54; N, 6.71.

4.1.10 (2E)-3-[5-(3,4-dichlorophenyl)-2-furyl]-2-[4-(2-furyl)-1,3-thiazol-2-yl]acrylonitrile (**6f**). Yield 78%, m.p. 151-152 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.08 (s, 2H, C_6H_5 + CH=), 7.90 (s, 1H, thiazol), 7.85 – 7.67 (m, 3H, C_6H_5 + furan), 7.45 (s, 1H, furan), 7.41 (s, 1H, furan), 6.87 (s, 1H, furan), 6.62 (s, 1H, furan). ESI-MS: m/z 413 $[M+H]^+$. Anal. Calcd. for $C_{20}H_{10}Cl_2N_2O_2S$ (%): C, 58.13; H, 2.44; N, 6.78. Found (%): C, 58.04; H, 2.59; N, 6.73.

4.1.11 (2E)-3-{5-[2-chloro-5-(trifluoromethyl)phenyl]-2-furyl}-2-[4-(2-furyl)-1,3-thiazol-2-yl]acrylonitrile (**6g**). Yield 75%, m.p. 141-142 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.26 (s, 1H, CH=), 8.22 – 8.13 (m, 2H, C_6H_4), 7.93 (s, 1H, thiazol), 7.82 – 7.71 (m, 3H, C_6H_4 + furan), 7.55 (d, *J* = 3.5 Hz, 1H, furan), 7.47 (d, *J* = 3.6 Hz, 1H, furan), 6.90 (d, *J* = 3.3 Hz, 1H, furan), 6.64 (dd, *J* = 3.2, 1.5 Hz, 1H, furan). ESI-MS: m/z 446 $[M+H]^+$. Anal. Calcd. for $C_{21}H_{11}F_3N_2O_2S$ (%): C, 61.16; H, 2.69; N, 6.79. Found (%): C, 61.26; H, 2.59; N, 6.68.

4.1.12 (2E)-3-[5-(4-bromophenyl)-2-furyl]-2-[4-(2-thienyl)-1,3-thiazol-2-yl]acrylonitrile (**6h**). Yield 84%, m.p. 176-177 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.09 (s, 1H, CH=), 8.08 (s, 1H, thiazol), 7.84 (d, *J* = 8.6 Hz, 2H, C_6H_4), 7.73 (d, *J* = 8.6 Hz, 2H, C_6H_4), 7.68 – 7.63 (m, 1H, furan), 7.59 (dd, *J* = 5.0, 0.9 Hz, 1H, furan), 7.46 (d, *J* = 3.7 Hz, 1H, thiophen),

7.40 (d, *J* = 3.7 Hz, 1H, thiophen), 7.15 (dd, *J* = 5.0, 3.7 Hz, 1H, thiophen). ESI-MS: m/z 440 $[M+H]^+$. Anal. Calcd. for $C_{20}H_{11}BrN_2OS_2$ (%): C, 54.68; H, 2.52; N, 6.38. Found (%): C, 47.68; H, 2.28; N, 6.31.

4.1.13 (2E)-2-[4-(2-thienyl)-1,3-thiazol-2-yl]-3-{5-[3-(trifluoromethyl)phenyl]-2-furyl}acrylonitrile (**6i**). Yield 69%, m.p. 146-147 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.27 (s, 1H, CH), 8.22 – 8.17 (m, 1H, C_6H_4), 8.13 (s, 1H, C_6H_4), 8.08 (s, 1H, thiazol), 7.76 (t, *J* = 6.5 Hz, 2H, C_6H_4), 7.65 (d, *J* = 3.5 Hz, 1H, furan), 7.59 (d, *J* = 5.0 Hz, 1H, furan), 7.55 (d, *J* = 3.7 Hz, 1H, thiophen), 7.49 (d, *J* = 3.7 Hz, 1H, thiophen), 7.19 – 7.13 (m, 1H, thiophen). ESI-MS: m/z 429 $[M+H]^+$. Anal. Calcd. for $C_{21}H_{11}F_3N_2OS_2$ (%): C, 58.87; H, 2.59; N, 6.54. Found (%): C, 58.96; H, 2.52; N, 6.43.

4.2 Anticancer activity

The tested substances were added to the culture at an alone concentration (10^{-5} M), and the cultures were incubated for 48 h. Endpoint definition was carried out with a protein-binding dye, sulforhodamine B (SRB). Results for every tested compound were reported as the percent growth of the processed cells when compared to the untreated control cells (http://dtp.nci.nih.gov). The percent growth was evaluated spectrophotometrically versus not processed controls. The cytotoxic and/or growth inhibitory effects of the most active substancess were tested in vitro contrary the full panel of about 60 human cancer cell lines at 10-fold dilutions of five concentrations ranging from 10^{-4} to 10^{-8} M. The 48-h continuous drug exposure protocol was followed, and an SRB protein assay was used to estimate cell viability or growth. Using the seven absorbance measurements [time zero, (Tz), control growth in the lack of drug, (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth was calculated at each of the drug concentration levels. Percentage growth inhibition was calculated as:

$[(Ti - Tz)/(C - Tz)] \times 100$ for concentrations for which $Ti \geq Tz$;
$[(Ti - Tz)/Tz] \times 100$ for concentrations for which $Ti < Tz$.

Three dose-response parameters were calculated for every compound. Growth inhibition of 50% (GI_{50}) was calculated of $[(Ti - Tz)/(C - Tz)] \times 100 - 50$, which is the drug concentration resulting in a 50% below net protein magnification in the treated cells (measured by SRB staining) as compared to the net protein increase seen in the control cells. The drug concentration resulting in total growth inhibition (TGI) was calculated from Ti = Tz. The LC50 (concentration of drug resulting in a 50% contraction in the measured protein at the end of the drug treatment as compared to that at the starting) indicating a net loss of cells next treatment was calculated from $[(Ti - Tz)/Tz] \times 100 = -50$. Significances were calculated for each of these three parameters if the level of activity was reached; however, if the effect was not reached or was exceeded, the value for that parameter was pronounced as more or less than the maximum or minimum concentration was tested.

Acknowledgements

We are grateful to Dr. V.L. Narayanan from Drug Synthesis and Chemistry Branch, National Cancer Institute, Bethesda, MD, USA, for *in vitro* evaluation of anticancer activity. The study was conducted as part of the research work of Danylo Halytsky Lviv National Medical University, funded by the Ministry of Health of Ukraine № state registration 0121U109330.

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