NOVEL SYNTHESIS, RING TRANSFORMATION AND ANTICANCER ACTIVITY OF 1,3-THIAZINE, PYRIMIDINE AND TRIAZOLO[1,5-a]PYRIMIDINE DERIVATIVES

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**ABSTRACT.** Synthesis, heterocyclization and anticancer activity of a new series of heterocyclic compounds are described. Aminothiazine 1 was obtained from the base induced condensation of thiourea, benzaldehyde and ethyl cyanoacetate. The synthesis of N-phenyl amino pyrimidine derivative 2 was obtained as a result of reaction of aniline with compound 1. Compound 2 underwent ring opening and recyclization upon reaction with HCl or H\(_2\)O\(_2\)/NaOH to afford the acid derivative 3 or oxazine 4, respectively. Thiazine 1 undergoes ring transformation upon the effect of NH\(_4\)OH.HCl to produce pyrimidine derivative 5. Heterocyclization of compound 1 with thioureasarcobazide followed by oxidation with i/acetone afforded triazolopyrimidine 6 and 7, respectively. Alkylation of compound 1 was promoted by reaction of 1 with ethyl iodide to give alkylated thiazine 8 which in turn undergo ring transformation when subjected to reaction with hydrazine hydrate to give pyrazole derivative 9. Refluxing of amino-1,3-thiazine derivative 1 with ethyl bromoacetate in the presence of Et\(_3\)N produce the alkylated pyrimidine product 10. Hydrazonolysis of 1,3-thiazine 1 with hydrazine or phenyldiazene gave pyrimidine derivatives 11a,b, respectively. Compound 11b was cyclized with carbon disulfide or formaldehyde to produce triazolopyrimidines 12 and 13, respectively. Some of the new compounds were screened for anticancer activity and significant results were found for some compounds.

**KEY WORDS:** 1,3-Thiazine, Pyrimidine, Triazole, Pyrazole, Anticancer activity

**INTRODUCTION**

1,3-Thiazine derivatives are class of compounds with potential biological activity, such as growth promoting activities [1], anti-fungal activity [2], antiproliferative [3], anti-tumor activity [4], anticancer [5], analgesic activity [6,7], calming activity [8], anticonvulsant activity [9], antibiotic activity [10, 11], anti-inflammatory [11, 12], antimicrobial [13], antimycobacterial [14], antibacterial [15] and antihypertensive [7, 16]. On the other hand, pyrimidine derivatives are known to be biologically active compounds and have shown wide range of biological activities like antitubercular [17], antimicrobial, antioxidant and anti-inflammatory [18-20], anticancer [21], analgesic, anti-fungal activity, anti-leishmanial, antiviral activity [22, 23]. Recently, our research field focused to design and synthesis of biologically active heterocyclic compounds from readily available reagents [24-26]. Herein, we hope to use a simple and facile approach to synthesize a novel series of heterocyclic systems utilizing 2-amino-4-oxo-4-phenyl-4H-1,3-thiazine-5-carbonitrile as a synthetic precursor.

**EXPERIMENTAL**

All melting points are uncorrected and were measured using an Electro thermal Al 9100 apparatus. TLC was performed on Merck silica gel 60F\(_{254}\) with detection by UV light. The IR spectra (KBr disc) were recorded on a Pye Unicam Sp-3-300 or a Shimadzu FTIR 8101 PC.

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2-Amino-4-oxo-4-phenyl-4H-1,3-thiazine-5-carbonitrile (I)

A mixture of thiourea (0.01 mol), ethyl cyanoacetate (0.01 mol), benzaldehyde (0.01 mol), and anhydrous potassium carbonate (0.01 mol) in n-butanol (20 mL) was refluxed for 8 hours, after cooling, the solid obtained was dried and washed with petroleum ether (60-80 °C) to give yellow crystals from 2, yield 52%, m.p. > 300 °C. IR (KBr cm⁻¹): 3472 (OH, NH), 3111 (m, 10H, Ar-H), 10.0 (s, 1H, OH). Anal. calcd for C₇H₅N₂O (282.32): C, 70.75; H, 4.26; N, 19.0%. Found: C, 70.68; H, 4.24; N, 19.0.

(Amino (phenylamino) methylene) amino)-2-cyano-3-phenylacrylic acid (3)

2-Amino pyrimidine 2 (0.01 mol) in ethanol (20 mL) and concentrated hydrochloric acid (1 mL) was added, then refluxed for 3 hours, the resulting mixture was neutralized with sodium hydroxide solution, then concentrated and left to cool, the solid obtained was dried and washed with petroleum ether 60-80 °C to give yellow crystals from 3, yield 52%, m.p. > 300 °C. IR (KBr cm⁻¹): 3410, 3172 (OH, NH), 2208 (C=O), 1651 (C=O). ¹H NMR (DMSO-d₆, δ ppm): 7.41-7.73 (m, 10H, Ar-H), 10.0 (s, 1H, NH). Anal. calcd for C₇H₅N₂O₂ (206.32): C, 66.66; H, 4.61; N, 18.29. Found: C, 66.61; H, 4.68; N, 18.35.

2-Amino-4-oxo-3,4-diphenyl-3,4-dihydropyrimidine-2-carbonitrile (4)

A mixture of 2-amino pyrimidine 2 (0.01 mol) and sodium hydroxide solution (20 mL) [prepared from NaOH (0.02 mol) in ethanol (20 mL)], hydrogen peroxide (1 mL) was added drop wise with stirring at room temperature for 2 hours, the reaction mixture was triturated with water and neutralized with concentrated hydrochloric acid and stirred, the resulting solid was dried and crystallized from methanol to give white crystals from 4, yield 40%, m.p. > 300 °C. IR (KBr cm⁻¹): 3149 (NH), 2206 (C=N), 1649 (C=O). ¹H NMR (DMSO-d₆, δ ppm): 7.41-7.68 (m, 10H, Ar-H), 10.10 (NH). Anal. calcd for C₇H₅N₂O₂ (282.29): C, 70.58; H, 3.83; N, 14.33. Found: C, 70.56; H, 3.77; N, 14.29.

2-Amino-1-hydroxy-4-oxo-6-phenyl-1,4-dihydropyrimidine-5-carbonitrile (5)

A mixture of 2-aminothiazine 1 (0.01 mol), hydroxylamine hydrochloride (0.02 mol), and (3 drops) of triethyl amine. in n-butanol (20 mL) was refluxed for 8 hours, after cooling, the
formed precipitate was filtered off, dried and crystallized by acetic acid to give brown crystals from 5, yield 77%, m.p. > 310 °C. IR (KBr cm⁻¹): 3427 (OH, NH₂), 2210 (C=O), 1715 (Ar = C and C=O). Anal. calcd for C₁₃H₁₃N₅O₂ (285.28): C, 63.13; H, 5.30; N, 14.73. Found: C, 63.08; H, 5.36; N, 17.69.

5-Oxo-3-phenyl-4,5-dihydro-1H-pyrazole-4-carbonitrile (9)

A mixture of 2-amino thiadiazine 8 (0.01 mol), hydrazine hydrate (0.01 mol) in n-butanol (20 mL) was refluxed for 10 hours, after cooling, the formed precipitate was filtered off, dried and crystallized from ethanol/acetone to give yellow crystals from 9 yield 77 %, m.p.267-270 °C. IR (KBr cm⁻¹): 3436 (NH), 2221 (C=O), 1646 (C=O).¹H NMR (DMSO-d₆, δ ppm): 7.47-7.78 (m, 5H, Ar-H). Anal. calcd for C₁₃H₁₃N₅O₂ (285.28): C, 64.86; H, 3.81; N, 22.69. Found: C, 64.91; H, 3.75; N, 22.75.

Diethyl-2,2′-((5-cyano-4-oxo-6-phenyl-4H-1,3-thiazin-2-yl)azanediyl) diacetate (10)

A mixture of 2-amino thiadiazine 1 (0.01 mol), ethyl bromoacetate (0.01 mol), and (3 drops) of triethylamine in ethanol (25 mL) was refluxed for 6 hours, the resulting precipitate was filtered off, washed with water, dried and crystallized from ethanol to give yellow crystals of 10, yield 80%, m.p. 224-230 °C. IR (KBr cm⁻¹): 2223 (C=O, ester), 1661 (C=O, amide).¹H NMR (DMSO-d₆, δ ppm): 1.11 (t, 3H, J = 5.7 Hz, CH₂CH₃), 2.50 (s, 2H, CH₂), 4.08 (q, 2H, J = 7.29 (C, Ar-H), 12.25 (s, 1H, NH). Anal. calcd for C₁₃H₁₃N₅O₂ (228.21): C, 57.89; H, 3.53; N, 24.55. Found: C, 57.81; H, 3.58; N, 24.49.

6-Cyano-5-oxo-7-phenyl-1,5-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-2-sulfonic acid (7)

A mixture of pyrimidine derivative 6 (0.01 mol) and iodine (0.01 mol) in glacial acetic acid (20 mL) was stirred for 2 hours, the formed precipitate was filtered off, washed with water, dried and crystallized by ethanol to give white crystals from 7, yield 69%, m.p. 310-312 °C. IR (KBr cm⁻¹): 3448 (OH, NH), 2230 (C=O), 1679 (C=O).¹H NMR (DMSO-d₆, δ ppm): 7.51-7.71 (m, 5H, Ar-H), 8.61 (s, 1H, NH), 12.25 (s, 1H, SH). Anal. calcd for C₁₃H₁₁N₅O₇ (317.28): C, 53.56; H, 2.62; N, 26.01. Found: C, 53.56; H, 2.59; N, 25.95.

2-Mercapto-5-oxa-7-phenyl-1,5-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carbonitrile (6)

A mixture of 2-aminothiazine 2 (0.01 mol), thiourea (0.01 mol), and (3 drops) of triethylamine in n-butanol (20 mL) was refluxed for 6 hours, the reaction mixture was kept at room temperature overnight, the precipitate obtained was filtered off, dried and crystallized from ethanol to yield yellow crystals from 6, yield 68%, m.p. 220-226 °C. IR (KBr cm⁻¹): 3376 (NH), 2213 (C=N), 1622 (C=O), 1233 (SH).¹H NMR (DMSO-d₆, δ ppm): 7.54-7.68 (m, 5H, Ar-H), 8.17 (s, 1H, NH), 13.17 (s, 1H, OH). Anal. calcd for C₁₃H₁₃N₅O₂ (269.28): C, 53.52; H, 2.62; N, 26.01. Found: C, 53.56; H, 2.59; N, 25.95.
5.7 Hz, CH₂CH₃), 7.54-7.92 (m, 5H, Ar-H). ¹³C NMR (DMSO-d₆, δ ppm): 13.8 (CH₃CH₂), 32.9 (NCH₂CO), 61.3 (OCOCH₃), 94.3, 115.6 (C=N), 127.1, 128.5, 128.6, 129.8, 131.8, 138.0, 165.7 and 167.9 (Ar-C and 2 C=O). Anal. calcd for C₁₉H₁₉N₅O₈S (401.44): C, 56.85; H, 4.77; N, 10.47. Found: C, 56.92; H, 4.81; N, 10.40.

1,2-Diamino-4-oxo-6-phenyl-1,4-dihydropyrimidine-5-carbonitrile (11a)

To a solution of 1,3-thiazine 1 (0.01 mol) in n-butanol (30 mL), hydrazine hydrate (0.02 mol) was added, the reaction mixture was refluxed for 12 hours, the reaction mixture left to cool and kept at room temperature overnight, the formed precipitate was filtered off, dried and crystallized from ethanol to give orange crystals from 11a, yield 87%, m.p. 236-243 °C. IR (KBr cm⁻¹): 3456, 3221 (2NH₃), 2218 (C≡N), 1652 (C=O). ¹H NMR (DMSO-d₆, δ ppm): 7.15 (s, 2H, NH), 7.45-7.78 (m, 5H, Ar-H). Anal. calcd for C₁₉H₁₉N₅O₂ (277.22): C, 58.14; H, 3.99; N, 30.82. Found: C, 58.07; H, 3.91; N, 30.87.

2-Amino-4-oxo-6-phenyl-1-(phenylamino)-1,4-dihydropyrimidine-5-carbonitrile (11b)

To a solution of 1,3-thiazine 1 (0.01 mol) in n-butanol (30 mL), phenyl hydrazine (0.01 mol) was added, the reaction mixture was refluxed for 12 hours, the reaction mixture left to cool and kept at room temperature overnight, the formed precipitate was filtered off, dried and crystallized from ethanol to give brown crystals from 11b, yield 80%, m.p. 246-252 °C. IR (KBr cm⁻¹): 3427, 3293, 3139 (NH, NH₂), 2206 (C≡N), 1634 (C=O). ¹H NMR (DMSO-d₆, δ ppm): 7.74-8.08 (m, 10H, Ar-H), 10.38 (s, 2H, NH₂), 11.76 (s, 1H, NH). ¹³C NMR (DMSO-d₆, δ ppm): 112.9, 117.2 (C=N), 118.1, 119.8, 122.7, 128.0, 128.2, 129.3, 129.5, 130.4, 131.0, 136.3, 161.8 and 181.7 (Ar-C and C=O). Anal. calcd for C₁₉H₁₄N₅O (303.32): C, 67.32; H, 4.32; N, 23.09. Found: C, 67.41; H, 4.25; N, 23.13.

2-Mercapto-5-oxo-1,7-diphenyl-1,5-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carbonitrile (12)

To ethanolic potassium hydroxide solution (20 mL) [prepared from KOH (0.01 mol) in ethanol (20 mL)], was added pyrimidine derivative 11b (0.01 mol) and carbon disulfide (0.01 mol), the reaction mixture was refluxed for 6 hours, the formed precipitate was filtered off, dried and crystallized from ethanol to give white crystals from 12, yield 66%, m.p. > 300 °C. IR (KBr cm⁻¹): 3440 (NH), 2231 (C≡N), 1680 (C=O). ¹H NMR (DMSO-d₆, δ ppm): 7.54-7.67 (m, 10H, Ar-H), 13.17 (s, 1H, SH). Anal. calcd for C₁₉H₁₈N₅O₂S (345.38): C, 62.60; H, 3.21; N, 20.28. Found: C, 62.68; H, 3.16; N, 20.35.

5-Oxo-1,7-diphenyl-1,2,4,5-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carbonitrile (13)

To ethanolic sodium hydroxide solution (20 mL) [prepared from NaOH (0.01 mol) in ethanol (20 mL)], was added pyrimidine derivative 11b (0.01 mol) and formaldehyde (0.01 mol). The reaction mixture was refluxed for 6 hours, the formed precipitate was filtered off, dried and crystallized from ethanol to give brown crystals from 13 yield 48%, m.p. >300 °C. ¹H NMR (DMSO-d₆, δ ppm): 3.32 (s, 2H, CH₂), 7.56-8.30 (m, 10H, Ar-H), 11.85 (s, 1H, NH). Anal. calcd for C₁₉H₁₉N₅O₂S (185.18): C, 64.86; H, 3.81; N, 22.69. Found: C, 64.91; H, 3.77; N, 22.73.

Anticancer activity

Reagents. Fetal bovine serum (FBS) and L-glutamine were from Gibco Invitrogen Co. (Scotland, UK). RPMI-1640 medium was from Cambrex (New Jersey, USA). Doxorubicin, dimethyl sulfoxide (DMSO), penicillin, streptomycin and sulforhodamine B (SRB) were from Sigma Chemical Co. (Saint Louis, USA).

Cell cultures

Three human tumor cell lines, MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), and SF-268 (CNS cancer) were used. MCF-7 was obtained from the European Collection of Cell Cultures (ECACC, Salisbury, UK) and NCI-H460 and SF-268 were kindly provided by the National Cancer Institute (NCl, Cairo, Egypt). They grow as monolayer and routinely maintained in RPMI-1640 medium supplemented with 5% heat inactivated FBS, 2 mM glutamine and antibiotics (penicillin 100 U/mL, streptomycin 100 μg/mL) at 37 °C in a humidified atmosphere containing 5% CO₂. Exponentially growing cells were produced by plating 1.5 x 10⁵ cells/mL for MCF-7, SF-268 and 0.75 x 10⁵ cells mL⁻¹ for NCI-H460, followed by 24 h of incubation. The effect of the vehicle solvent (DMSO) on the growth of cell lines which it was evaluated in all experimental by exposing untreated control cells to the maximum concentration (0.5%) of DMSO used in each assay.

Tumor cell growth assay

The effects of the newly synthesized compounds 2, 5, 10 and 11b on the in vitro growth of human tumor cell lines were evaluated according to the procedure adopted by the National Cancer Institute (NCI, USA) in the ‘In vitro Anticancer Drug Discovery Screen’ that uses the protein-binding dye sulforhodamine B to assess cell growth [27, 28]. Briefly, exponentially cells growing in 96-well plates were then exposed for 48 h to five serial concentrations of each compound starting from a maximum concentration of 150 μM. Following this exposure period adherent cells were fixed, washed and stained. The bound stain was solubilized and the absorbance was measured at 492 nm in a plate reader (Bio-Tek Instruments Inc., Power wave XS, Wincoski, USA). For each test compound and cell line, a dose response curve was obtained and the growth inhibition of 50% (GI₅₀), corresponding to the concentration of the compounds that inhibited 50% of the net cell growth was calculated as described elsewhere. Doxorubicin was used as a positive control and tested in the same manner.

RESULTS AND DISCUSSION

In the present work, it is intended to investigate the synthetic possibilities of novel 2-amino-4-oxo-4-phenyl-4H,1,3-thiazine-5-carbonitrile and its transformation to pyrimidine and condensed systems. The anticancer properties of the prepared compounds were screened in an attempt to determine new heterocyclic agents which could be useful as a hint in a drug discovery program.

One pot multicomponent reaction of benzaldehyde, thiourea and ethyl cyanoacetate in ethanolic potassium carbonate resulted in 1,3-thiazine cyclization affording aminocyanothiazine derivative 1 as a kinetic controlled product (Scheme 1). The structure of aminothiazine 1 was supported by 1H NMR which revealed signal at δ 13.07 ppm for NH₂ and multiplet at δ 7.32-7.68 ppm for aromatic protons. The IR spectrum also showed the functional groups C=O at 1640 cm⁻¹ and C≡N at 2232 cm⁻¹ for NH₂ and aromatic protons. The IR spectrum also showed two bands at 3196 and 3153 cm⁻¹ for NH₂ group. The structure of aminothiazine 1 was also potentiated by ring transformation to pyrimidine derivatives by the effect of nitrogen nucleophile. The synthesis of the more stable product known as N-phenylaminopyrimidine derivative 2 was obtained as a result of the nucleophilic reaction of aniline with cyano-1,3-thiazine derivative 1 in n-butanol (Scheme 1).

IR spectrum of 2 showed bands at 3427 cm⁻¹, 2206 cm⁻¹ and 1675 cm⁻¹ for NH₂, C≡N and C=O groups, respectively. Its 1H NMR spectrum displayed signals at δ 12.56 ppm for NH₂ and 7.49-7.69 ppm for aromatic protons. Compound 2 suffered acid induced ring opening upon treatment with HCl to produce the acid derivative 3 (Scheme 1). Its IR spectrum showed absorption bands at 3410, 3172, 2208 and 1651 cm⁻¹ corresponding to OH, NH C≡N and C=O

groups, respectively. H NMR spectrum showed signals at δ 11.5 ppm for OH, 10.0 ppm for NH, and 7.41-7.73 ppm for aromatic protons. Also oxidative ring opening of cyanopyrimidine 2 was achieved by keeping compound 2 in H2O2 in the presence of NaOH in one pot flask to produce oxazine 4 (Scheme 1). Its IR spectrum showed bands at 3149 cm⁻¹ for NH and 2206, 1649 cm⁻¹ for C≡N and CO respectively. H NMR spectrum showed signal at δ 10.10 ppm for NH and 7.41-7.68 ppm for aromatic protons. Cyanothiazine derivative 1 undergo ring cleavage followed by heterocyclization producing N-hydroxypyrimidine derivative 5 in good yield (77%) upon reaction with hydroxyl amine hydrochloride (Scheme 2). The structure was agreement with the spectral data (see the experimental section).

Scheme 1. Synthesis and reaction of 1,3-thiazine derivative 1.

Triazolopyrimidine of type 6 was prepared upon the reaction of thiazine derivative 1 with thiourea in the presence of triethylamine (Scheme 2). IR spectra showed absorption bands at 3376 cm⁻¹ for NH, 2213 cm⁻¹ for C≡N, 1622 cm⁻¹ for CO, and 1233 cm⁻¹ for SH. H NMR spectrum showed signals at δ 12.25 ppm for SH, 8.61 ppm for NH, and 7.51-7.71 ppm for aromatic protons. Compound 6 was transformed to the sulphonic acid derivative 7 by the oxidation with I2/AcOH.

Compound 1 undergo N-alkylation upon the effect of ethyl iodide in presence of NaOH to give 8, which undergo ring opening followed by heterocyclization to give pyrazolone 9 upon treating with hydrazine hydrate (Scheme 2). The IR spectrum of 9 showed absorption bands at 3436 cm⁻¹ for NH, 2221 cm⁻¹ for C≡N, and 1646 cm⁻¹ for C=O. H NMR spectrum showed multiplet at 9.84 ppm for 2NH protons and multiplet at 7.47-7.78 ppm for aromatic protons. Upon refluxing of amino-1,3-thiazine derivative 1 and ethyl bromoacetate in the presence of triethyl amine resulted N-alkylation producing bis-N(ethoxy carbonyl methyl) thiazine derivative 10 (Scheme 2). IR spectrum showed absorption bands at 2223 cm⁻¹, 1735 cm⁻¹, and 1661cm⁻¹ for C≡N, C=O ester and C=O amide respectively. H NMR spectrum showed down field multiplet signal at δ 7.54-7.92 ppm for aromatic protons, quartet signal at 4.08 ppm for CH2=CH3 and triplet at 1.11 ppm for CH3CH3 protons, in addition to singlet at 2.5 ppm.
corresponding to NCH 2 CO protons. The refluxing of 1,3-thiazine derivative 1 and hydrazine hydrate or phenyl hydrazine resulted in ring transformation affording diaminopyrimidine derivatives 11a, b, respectively (Scheme 2). The IR spectrum of 11a showed absorption bands at 3456, 3221 cm⁻¹ for NH₂ groups, 2218 cm⁻¹ for C≡N group, and 1652 cm⁻¹ for C=O group. ¹H NMR spectrum showed signal at δ 7.15 and 9.85 ppm for 2NH₂ in addition to aromatic protons at 7.45-7.78 ppm. The IR spectrum of 11b showed bands at 3139 cm⁻¹ for NH, NH₂, 2206 cm⁻¹ for C≡N and 1634 cm⁻¹ for C=O, its ¹H NMR showed signal at δ 11.76 ppm, 10.38 ppm for NH and NH₂, and 6.74-8.08 ppm for aromatic protons. Compound 11b bearing of suitably located functionality for further cyclization, thus intramolecular cyclization of diaminopyrimidine derivative 11b with carbon disulphide afforded triazolopyrimidine derivative 12 (Scheme 2). IR spectrum of 12 showed bands at 3440, 2231, and 1680 cm⁻¹ for NH, C≡N, and C=O, respectively. Its ¹H NMR showed signal at δ 13.17 ppm for SH and 7.54-7.70 ppm for aromatic protons. Using formaldehyde as cyclizing agent a triazole derivative 13 was obtained (Scheme 2). Its structure was agreement with the spectral data (see the experimental section).

Scheme 2. Heterocyclization of 1,3-thiazine derivative 1.

Anticancer activity

The results of anticancer activity are given in concentrations that were able to cause 50% of cell growth inhibition (GI_{50}) after a continuous exposure of 48 hours and show means ± SEM of three independent experiments performed in duplicate (Table 1). Where diethyl-2,2’-((5-cyano-4-oxo-6-phenyl-4H-1,3-thiazin-2-yl)azanediyl) diacetate (10) showed the highest inhibitory effects against all three tumor cell lines. Such activity is not higher than the corresponding reference doxorubicin, while 2-amino-6-oxo-1,4-diphenyl-1,6-dihydropyrimidine-5-carbonitrile (2), 2-amino-1-hydroxy-4-oxo-6-phenyl-1,4-dihydropyrimidine-5-carbonitrile (5) and 2-amino-4-oxo-6-phenyl-1-(phenylamino)-1,4-dihydropyrimidine-5-carbonitrile (11b) showed lower inhibitory effect. It is obvious that by comparing the structures of the four compounds, we found that the presence of thiazine ring system substituted with bis-N-(ethoxy carbonyl methyl) is responsible for their reactivity over the compounds 2, 5 and 11b, on the other hand, we can observe the presence of NH_{2} in compounds 2, 5 and 11b decrease the anticancer activity.

Table 1. Effect of compounds 2, 5, 10 and 11b on the growth of three human tumor cell lines.

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<th>Compound</th>
<th>GI_{50}, μmol L^{-1}</th>
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<td></td>
<td>NCI-H460</td>
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<tr>
<td>2</td>
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<tr>
<td>5</td>
<td>28.2 ± 3.4</td>
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<tr>
<td>10</td>
<td>12.4 ± 2.3</td>
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<tr>
<td>11b</td>
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<tr>
<td>Doxorubicin</td>
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REFERENCES

Novel synthesis of 1,3-thiazine, pyrimidine and triazolo[1,5-a]pyrimidine derivatives


