Anticancer Activities of Some New Synthesized Thiazolo[3,2-a]Pyrido[4,3-d]Pyrimidine Derivatives

1,2 Ashraf M. Mohamed, 2,3 Abdel-Galil E. Amr, 1 Musaed A. Alsharari, 1 Husam R.M. Al-Qalawi, 4 Mosa O. Germoush and 3 Mohamed A. Al-Omar

1 Department of Chemistry, College of Science, Al-Jouf University, Sakaka, Al-Jouf, Saudi Arabia
2 Department of Applied Organic, National Research Centre, Dokki, Cairo, Egypt
3 Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Saudi Arabia
4 Department of Biology, College of Science, Al-Jouf University, Sakaka, Al-Jouf, Saudi Arabia

Abstract: Problem statement: This study describes the synthesis and anticancer activities of a new series of thiazolo[3,2-a]pyrimidines derivatives (2-7) using 3,5-bisarylmethylene-1-methyl-4-piperidone and 4-aryl-8-arylmethelene-6-methylpyrido[4,3-d]pyrimidine-2(1H)thiones as a starting materials. Approach: The antitumor activities of the newly synthesized compounds 4-7 were evaluated utilizing 60 different human tumor cell lines, representing leukemia, melanoma, lung, colon, brain, ovary, breast and prostate as well as kidney. Results: Some of the tested compounds exhibited better in vitro antitumor activities at low concentration (log10 GI_{50} = -4.7) against the used human tumor cell lines. Conclusion: From the obtained results, we can conclude that pyrimidine moieties fused to N-methylpiperdine ring are essential for antitumor activities. In the present work, we can suggest that the anticancer activity is due to the presence of nitrogen heterocyclic rings and the presence of sulfur atom generally enhancing the activity.

Key words: Synthesis, reactions, pyrimidinethione, thiazolopyrimidine, anticancer activity, starting materials, nitrogen heterocyclic, pyrimidines derivatives, biological activity

INTRODUCTION

Cancer poses a serious human health problem despite much progress in understanding its biology and pharmacology. Consequently, the design of new lead structures employed as antitumor agents is one of the most urgent research areas in contemporary medicinal chemistry. During our ongoing studies aimed at the discovery of new heterocycles endowed with antitumour activity, we have reported on the synthesis and antitumor activities of a series of heterocyclic compounds (Hammam et al., 2003; 2005; Amr et al., 2006; Velusamy and Palaniappan, 2011; Abd El-Salam et al., 2010). Pyrimidine has gained considerable attention because of its diversity in biological activity and widespread applications in pharmaceuticals fields (Katritzky and Rees, 1996; Francis et al., 2011). For instance, as Tie-2 kinase inhibitors (Matlooobi and Kappe, 2007; Chengguo et al., 2009), HIV-1 inhibitor (Gadhachanda et al., 2007; Naeem et al., 2009), antimalarial (Ngoy et al., 2011; Khan et al., 2009), adenosine A1 receptor antagonist (Chang et al., 2004), antitumor (Capdeville et al., 2002), analgesic (Rezvani and Shariati, 2010), cardiovascular (Atwal, 1988 and Hasanuzzaman et al., 2010) and antiallergic (Ozeki et al., 1989; Dahmardeh, 2011) activities. On the other hand, the importance of the pyridine ring in the chemistry of biological system has been greatly realized because of their presence as substructure in many natural products of therapeutic importance, involved in oxidation-reduction process. The potent biological activity of various vitamins and drugs (Joule and Mills, 2000; Henry, 2004; Li et al., 1999; Vacher et al., 1999; Nasratun et al., 2009) is primarily contributed by the presence of pyridine ring in their molecular make-up. Furthermore, the pyridine ring is found in the skeleton of many compounds with potent antibacterial, antifungal and antitumor properties (Millet et al., 2003; Mallea et al., 2003; Abou-Ghalia and Amr, 2004; Amr et al., 2009; Jill et al., 2011). In view of these reports and in continuation of our previous work in heterocyclic chemistry, we herein synthesized some new derivatives containing heterocyclic ring fused with N-methylpiperdine and/or pyrido [4,3-d] pyrimidine
structure for the evaluation of their anticancer activities. In view of a beforementioned biological activities and as a part of our interest in the sereach for novel anticancer agents, we report herein the synthesis of several thiazolo [3, 2-a] pyrido [4, 3-d] pyrimidine derivatives and evaluate of their anticancer activities.

**MATERIALS AND METHODS**

**Chemistry:** All melting points were determined on open glass capillaries using an Electrothermal IA 9000 digital melting point apparatus and are uncorrected. Elemental analyses were performed on Elementar, Vario El, Microanalytical Unit, National Research Centre, Cairo, Egypt and were found win ± 0.4% of the theoretical values. Infrared (IR) spectra were recorded on CarlZeise Spectrophotometer model ‘UR 10’ spectrophotometer using the KBr disc technique. ¹H NMR spectra were recorded on Varian Gemini 270 MHz spectrometer (DMSO-d₆ or CDCl₃) and the chemical shift are given in δ (parts per million) downfield from Tetramethylsilane (TMS) as an internal standard. The Mass Spectra (MS) were measured using a Finnegan SSQ 7000 mass spectrometer. The anticancer screening occurred in United States National Institute of Health (NIH)/National Cancer Institute (NCI). The starting material, 3,5-bisarylmethylene-1-methyl-4-piperidon (1) was synthesized according to the reported procedures (Lyle et al., 1973; Mcelvain and Rorig, 1948; Abdel-Latif and Lamiaa, 2010).

**Synthesis of thioypiridimine derivatives (2a-e):** To a solution of 1a-e (0.01 mole) in 25 ml absolute ethanol, 0.5 g potassium hydroxide and thiourea (0.76 g, 0.01 moles) were added. The reaction mixture was refluxed for 3 hrs. Left to cooland poured gradually onto cold water. The solid formed was filtered off, washed with water and crystallized from the proper solvent to give pyrimidin-2-(1H) thiones 2a-e, respectively.

**8-Benzylidene-3,4,5,6,7,8-hexahydro-6-methyl-4-phenylpyrido[4,3-d]pyrimidine-2(1H)-thione (2a):** Yield 89%, mp 190-193°C; IR (KBr) cm⁻¹: 3194, 3502; ¹H NMR (DMSO-d₆): 2.20 (s, 3H, CH₃), 2.85 (m, 2H, H-5), 3.0-3.19 (dd, 2H, J = 7.0 Hz, J = 5.0 Hz, H-7), 4.95 (s, 1H, H-4), 7.15-7.40 (m, 11H, Ar-H + C=CH), 9.18, 9.48 (2s, 2H, 2NH, exchangeable with D₂O); ¹³C NMR: 44.48 (CH₃), 53.91 (CH, pyrimidine), 125.63 (CH, methylene), 54.35, 54.39 (2CH₂-pyridine), 137.92 (C-pyridine), 138.26, 143.30, 180.6 (3C-pyrimidine), 126.65, 126.92, 128.13, 128.74, 129.49, 136.19, 143.29 (12C, Ar-C); MS (EI): m/z 347 [M⁺] (80), 346 (M⁺-H⁺) (100), 214 (346- C₆H₅CH=NH) (52), 254 (M⁺-C₆H₅ -H⁺) (19). Anal. Calcd. for C₂₁H₂₁N₃S: C, 72.58; H, 6.1; N, 12.1; S, 9.22. Found: C, 72.56; H, 6.12; N, 12.07; S, 9.25.

**8-(4-Flourobenzylidene)-3,4,5,6,7,8-hexahydro-6-methyl-4-(4-flourophenyl)pyrido[4,3-d]pyrimidine-2(1H)-thione (2b):** Yield 91%; mp 155-157°C; IR (KBr) cm⁻¹: 3204, 3344 (NH); ¹H NMR (DMSO-d₆): 2.20 (s, 3H, CH₃), 2.41-2.60 (m, 2H, H-5), 3.10-3.20 (dd, 2H, J = 7.0 Hz, J = 5.0 Hz, H-7), 4.96 (s, 1H, H-4), 7.11-7.50 (m, 9H, Ar-H+C = CH), 9.21, 9.51 (2s, 2H, 2NH, exchangeable with D₂O); ¹³C NMR: 44.47 (CH₃), 53.91 (CH, pyrimidine), 50.93, 52.71 (2CH₂-pyridine), 124.19 (CH, methylene), 136.81 (C-pyridine), 126.29, 126.47, 128.14, 128.61, 128.75, 128.89, 135.43, 143.33 (12C, Ar-C), 137.28, 140.41, 180.56 (3C-pyrimidine); MS (EI): m/z 383 [M⁺] (100), 339 (M⁺-C=Si) (11), 259 (383-F-C₆H₅CH=NH) (71); Anal. Calcd. For C₂₀H₁₆N₃S₂: C, 65.77; H, 4.99; N, 10.96; S, 8.36. Found: C, 65.75; H, 5.01; N, 10.94; S, 8.38.

**8-(2-Chlorobenzylidene)-3,4,5,6,7,8-hexahydro-6-methyl-4-(2-chlorophenyl)pyrido[4,3-d]pyrimidine-2(1H)-thione (2c):** Yield 82%; mp 200-202°C; IR (KBr) cm⁻¹: 3351, 3304 (NH); ¹H NMR (DMSO-d₆): 2.20 (s, 3H, CH₃), 2.50-2.71 (m, 2H, H-5), 3.21-3.30 (dd, 2H, J = 7.0 Hz, J = 5.0 Hz, H-7), 5.41 (s, 1H, H-4), 7.15-7.55 (m, 9H, Ar-H + C = CH), 9.10, 9.71 (2s, 2H, 2NH, exchangeable with D₂O); ¹³C NMR: 44.48 (CH₃), 50.98, 52.73 (2CH₂-pyridine), 53.91 (CH, pyrimidine), 125.63 (CH, methylene), 126.31, 126.52, 128.19, 128.62, 128.74, 128.89, 135.43, 143.33 (12C, Ar-C), 134.22 (C-pyridine), 137.32, 140.42, 180.59 (3C-pyrimidine); MS (EI): m/z 416 [M⁺] (50), 417 [M⁺+2] (35), 419 [M⁺+4] (8), 275 (M⁺-Cl-C₆H₅CH=NH-H₂) (100); Anal. Calcd. for C₂₁H₁₉ClN₃S₂Cl: C, 60.57; H, 4.6; N, 10.1; S, 7.7. Found: C, 60.6; H, 4.57; N, 10.07; S, 7.71.

**8-(4-Chlorobenzylidene)-3,4,5,6,7,8-hexahydro-6-methyl-4-(4-chlorophenyl)pyrido[4,3-d]pyrimidine-2(1H)-thione (2d):** Yield 88%; mp 202-205°C; IR (KBr) cm⁻¹: 3176, 3248 (NH); ¹H NMR (DMSO-d₆): 2.32 (s, 3H, CH₃), 2.42-2.63 (m, 2H, H-5), 3.31-3.43 (2d, 2H, J = 7.0 Hz, J = 5.0 Hz, H-7), 5.02 (s, 1H, H-4), 7.10-7.60 (m, 9H, Ar-H + C=CH), 9.10, 9.60 (2s, 2H, 2NH, exchangeable with D₂O); ¹³C NMR: 44.48 (CH₃), 50.96, 54.74 (2CH₂-pyridine), 53.91 (CH, pyrimidine), 124.28 (CH, methylene), 126.42, 126.50, 128.15, 128.61, 128.79, 128.89, 135.43, 143.37 (12C, Ar-C), 137.36, 140.46, 180.82 (3C-pyrimidine), 136.88 (C-pyridine); MS (EI): m/z 416 [M⁺] (87), 417 [M⁺+2] (59), 419 [M⁺+4] (13), 414 [M⁺-H₂] (100), 275 (M⁺-Cl-C₆H₅CH=NH-H₂) (72); Anal. Calcd. for
Calcd. For C, 60.55; H, 4.62; N, 10.13; S, 7.68.

8-(3-Bromobenzylidine)-3,4,5,6,7,8-hexahydropyrimidine 2H-thione (2e): Yield 85%; mp 180-182°C; IR (KBr) cm⁻¹: 3346, 3275 (NH); ¹H NMR (DMSO-d₆): 2.23 (s, 3H, CH₃), 2.32-2.53 (m, 2H, H-5), 3.32-3.41 (dd, 2H, J = 7.0 Hz, J = 5.0 Hz, H-7), 5.31 (s, 1H, H-4), 7.30-7.60 (m, 9H, Ar-H + CH=CH), 9.01, 9.42 (2s, 2H, 2NH, exchangeable with D₂O); ¹³C NMR: 44.49 (CH₃), 50.95, 52.74 (2CH₃-pyrimidine), 53.74 (CH, pyrimidine), 124.23 (CH, methylene), 126.31, 126.48, 128.21, 128.71, 128.68, 128.87, 135.45, 143.37 (12Ar-C), 136.84 (C-pyrimidine), 137.29, 140.40, 140.57 (3C-pyrimidine). MS (EI): m/z 505 [M⁺] (47), 507 (M⁺+2) (95), 509 (M⁺+4) (45), 349 (M⁺-Br-C₆H₅) (100); Anal. Calcd. For C₂₃H₂₃N₅SCl, 62.45; 4.76; 9.58; 7.22. Found: C, 62.41; H, 4.80; N, 9.58; S, 7.21.

9-(2-Chlorobenzylidine)-2,3,6,7,8,9-hexahydropyrimidine 5H-5-(2-chlorophenyl)-thiazolo[3,2-alpyridin-4,3-d]pyrimidine (3e): Yield 79%; mp 143-145°C; IR (KBr) cm⁻¹: 1636 (C≡N); ¹H NMR (DMSO-d₆): 2.14 (s, 2H-C₆H), 2.73 (s, 3H, CH₃), 2.98-3.09 (m, 2H-C₆H₂), 3.18-3.21 (m, 2H-C₆H₂), 3.59-3.66 (m, 2H-C₆H₃), 5.54 (s, 1H-C₆H), 6.85-7.32 (m, 9H, Ar-H + CH=CH); ¹³C NMR: 44.39 (CH₃), 51.69, 53.40 (2CH₂-pyrimidine), 58.33 (CH, pyrimidine), 124.28 (CH, methylene), 115.21, 115.32, 129.81, 130.52, 134.32, 162.20 (12C, Ar-C), 136.91 (C-pyrimidine), 129.21, 134.80, 183.64 (3C-pyrimidine); MS (EI): m/z 442 [M⁺] (64), 444 (M⁺+2) (40), 446 (M⁺+4) (6), 406 (M⁺-Cl) (17), 362 (M⁺-CH₃-NCH₃-H) (18), 44 (100); Anal. Calcd. for C₂₃H₂¹N₅SCl, 62.43; H, 4.78; N, 9.50; S, 7.24. Found: C, 62.41; H, 4.80; N, 9.58; S, 7.21.
5.56 (s, 1H-C5), 6.66-7.28 (m, 9H, Ar-H + CH=C); 13C NMR: 24.64, 50.32 (2CH3, thiazole), 44.25 (CH2), 51.70, 53.40 (2CH3-pyridine), 58.33 (CH, pyrimidine), 115.14, 115.34, 128.11, 129.76, 130.45, 134.34, 162.27 (12C, Ar-C), 124.25 (CH, methylene), 136.86 (C-pyridine), 129.20, 134.80, 183.55 (3C-pyrimidine); MS (EI): m/z 531 [M]+ (45), 533 (M+2) (91), 535 (M+4) (44), 451 (M+Br) (100); Anal. Calcd. for C23H23N4SBr2: C, 51.99; H, 3.98; N, 7.91; S, 6.03. Found: C, 51.97; H, 4.01; N, 7.89; S, 6.05.

Synthesis of 5-aryl-9-arylmethylene-6,7,8,9-tetrahydro-7-methyl-2H-thiazolo[3,2-alpyrido[4,3-d]pyrimidine-3(5H)-ones (4a-e): To a mixture of 2a-e (0.01 mol), chloroacetic acid (1 g, 0.01 mol), 6 g of fused sodium acetate in 30 ml of glacial acetic acid and 15 ml of acetic anhydride was refluxed for 3 hrs., poured gradually onto cold water. The solid formed was filtered off and crystallized from the proper solvent to give pyrido[4,3-d]pyrimidinones 4a-e, respectively.

Benzylidene-6,7,8,9-tetrahydro-7-methyl-5-phenyl-2H-thiazolo[3,2-alpyrido[4,3-d]pyrimidine-3(5H)-one (4a): Yield 69%; mp 214-216°C; IR (KBr) cm⁻¹: 1734 (C=O); 1H NMR (DMSO-d6): 2.21 (s, 3H, CH3), 2.62 (s, 2H-C5), 3.70-4.02 (m, 2H-C5), 4.12 (s, 2H-C5), 5.81 (s, 1H-C6), 7.33-7.52 (m, 10H, Ar-H), 7.72 (s, 1H, CH=C); 13C NMR: 30.61 (CH2 thiazole), 44.21 (CH), 45.31 (CH, pyrimidine), 51.41, 53.43 (2CH3-pyridine), 126.42, 126.82, 127.32, 128.11, 128.63, 128.73, 135.32, 143.22 (12C, Ar-C), 124.23 (CH, methylene), 136.91 (C-pyridine), 129.65, 134.84, 163.66 (3C-pyrimidine), 171.11 (C=O); MS (EI): m/z 287 [M]+, 344 (M+2) (100), 327 (386-SCH3-C=O) (7); Anal. Calcd. for C23H23N2SO3: C, 71.28; H, 5.46; N, 10.84; S, 8.27. Found: C, 71.30; H, 5.43; N, 10.82; S, 8.29.

(4a)-Flourobenzylidene-6,7,8,9-tetrahydro-7-methyl-5-(4-flourophenyl)-2H-thiazolo[3,2-]

(4b): Yield 79%; mp 232-234°C; IR (KBr) cm⁻¹: 1737 (C=O); 1H NMR (DMSO-d6): 2.28 (s, 3H, CH3), 2.61 (s, 2H-C5), 3.83-4.09 (m, 2H-C5), 4.18 (s, 2H-C5), 5.90 (s, 1H-C6), 7.31-7.54 (m, 8H, Ar-H), 7.72 (s, 1H, CH=C); 13C NMR: 30.62 (CH2 thiazole), 44.26 (CH), 45.33 (CH, pyrimidine), 51.41, 53.41 (2CH3-pyridine), 124.21 (CH, methylene), 126.43, 126.81, 127.42, 128.18, 128.53, 128.73, 135.28, 143.30 (12C, Ar-C), 129.31, 134.85, 163.33 (3C-pyrimidine), 136.83 (C-pyridine), 171.00 (C=O); MS (EI): m/z 456 [M]+ (62), 444 (M+2) (62), 458 (M+4) (27), 420 (M+Cl) (100); Anal. Calcd. for C23H23N2SOCl: C, 60.50; H, 4.19; N, 9.21; S, 7.02. Found: C, 60.50; H, 4.21; N, 9.19; S, 7.04.

(4c)-Bromobenzylidene-6,7,8,9-tetrahydro-7-methyl-5-(2-chlorophenyl)-2H-thiazolo[3,2-

(4d): Yield 71%; mp 201-212°C; IR (KBr) cm⁻¹: 1736 (C=O); 1H NMR (DMSO-d6): 2.26 (s, 3H, CH3), 2.62 (s, 2H-C5), 3.81-4.17 (m, 2H-C5), 4.21 (s, 2H-C5), 6.33 (s, 1H-C6), 7.33-7.52 (m, 8H, Ar-H), 7.72 (s, 1H, CH=C); 13C NMR: 30.64 (CH2, thiazole), 44.25 (CH5), 45.31 (CH, pyrimidine), 51.42, 53.43 (2CH3-pyridine), 124.25 (CH, methylene), 126.41, 126.80, 127.31, 128.21, 128.59, 128.71, 135.26, 143.32 (12C, Ar-C), 136.81 (C-pyridine), 129.26, 134.86, 163.53 (3C-pyrimidine), 171.22 (C=O); MS (EI): m/z 456 [M]+ (89), 444 (M+2) (62), 458 (M+4) (27), 420 (M+Cl) (100); Anal. Calcd. for C23H23N2SOCl: C, 60.50; H, 4.19; N, 9.21; S, 7.02. Found: C, 60.50; H, 4.21; N, 9.19; S, 7.04.

(4e)-Bromobenzylidene-6,7,8,9-tetrahydro-7-methyl-5-(4-bromophenyl)-2H-thiazolo[3,2-

(5): Yields 65 1% mp 167-169°C; IR (KBr) cm⁻¹: 1735 (C=O); 1H NMR (DMSO-d6): 2.27 (s, 3H, CH3), 2.62 (s, 2H-C5), 3.85-4.10 (m, 2H-C5), 4.19 (s, 2H-C5), 6.06 (s, 1H-C6), 7.29-7.58 (m, 8H, Ar-H), 6.78 (s, 1H, CH=C); 13C NMR: 30.60 (CH2, thiazole), 44.28 (CH5), 45.30 (CH, pyrimidine), 51.39, 53.43 (2CH3-pyridine), 124.25 (CH, methylene), 126.41, 126.82, 127.43, 128.16, 128.51, 128.72, 135.26, 134.32 (12C, Ar-C), 136.80 (C-pyridine), 129.33, 134.82, 163.35 (3C-pyrimidine), 171.32 (C=O); MS (EI): m/z 545 [M]+ (31), 547 (M+2) (66), 549 (M+4) (28), 376 (M+BrC2H4Cl=CH) (100); Anal. Calcd. for C23H23N2SOBr2: C, 50.66; H, 3.51; N, 7.70; S, 5.88. Found: C, 50.68; H, 3.53; N, 7.68; S, 5.86.
Synthesis of 5-aryl-9-arylmethylene-6,7,8,9-tetrahydro-2,7-dimethyl-2H-thiazolo[3,2-a]pyrido[4,3-d]pyrimidin-3(5H)-ones (5a-e): A mixture of 2a-e (0.01 mole), 2-bromopropionic acid (0.01 mole), 6 g of fused sodium acetate in 30 ml of glacial acetic acid and 15 ml of acetic anhydride was refluxed for 2 hrs, poured onto cold water. The solid formed was filtered off and crystallized from the proper solvent to give pyrido[4,3-d]pyrimidin-3(5H)-ones 5a-e, respectively.

9-Benzylidene-6,7,8,9-tetrahydro-2,7-dimethyl-5-phenyl-2H-thiazolo[3,2-a]pyrido[4,3-d]pyrimidin-3(5H)-one (5a): Yield 69%; mp 216-218°C; IR (KBr) cm⁻¹: 1726 (C=O); ¹H NMR (DMSO-d₆): 2.12 (s, 2H-C₆), 2.71 (s, 3H, CH₃, pyridine ring), 3.65-4.22 (2d, 2H-C₈), 4.51 (q, 1H-C₂), 6.05 (s, 1H, CH-C₅), 1.41 (d, 3H, CH₃, thiazole ring), 7.30-7.50 (m, 11H, Ar-H+ CH=C); ¹³C NMR: 20.1 (CH₃, thiazole ring), 43.71 (CH, thiazole), 44.21 (CH₃, pyridine ring), 45.61 (CH, pyrimidine). Found: C, 65.88; H, 4.83; N, 7.58; S, 5.72.

9-(4-Flourobenzylidene)-2,7-dimethyl-6,7,8,9-tetrahydro-2,7-dimethyl-2H-thiazolo[3,2-a]pyrido[4,3-d]pyrimidin-3(5H)-one (5b): Yield 69%; mp 216-218°C; IR (KBr) cm⁻¹: 1726 (C=O); ¹H NMR (DMSO-d₆): 2.12 (s, 2H-C₆), 2.71 (s, 3H, CH₃, pyridine ring), 3.65-4.22 (2d, 2H-C₈), 4.51 (q, 1H-C₂), 6.05 (s, 1H, CH-C₅), 1.41 (d, 3H, CH₃, thiazole ring), 7.30-7.50 (m, 11H, Ar-H+ CH=C); ¹³C NMR: 20.1 (CH₃, thiazole ring), 43.71 (CH, thiazole), 44.21 (CH₃, pyridine ring), 45.60 (CH, pyrimidine). Found: C, 65.90; H, 4.81; N, 7.32; S, 5.72. Anal. Calcd. for C₂₃H₂₆N₂O: C, 71.79; H, 4.57; N, 10.46; S, 6.78. Found: C, 71.81; H, 5.75; N, 10.46; S, 7.98.

9-(4-Chlorobenzylidene)-2,7-dimethyl-6,7,8,9-tetrahydro-2,7-dimethyl-2H-thiazolo[3,2-a]pyrido[4,3-d]pyrimidin-3(5H)-one (5c): Yield 69%; mp 216-218°C; IR (KBr) cm⁻¹: 1726 (C=O); ¹H NMR (DMSO-d₆): 2.12 (s, 2H-C₆), 2.71 (s, 3H, CH₃, pyridine ring), 3.65-4.22 (2d, 2H-C₈), 4.51 (q, 1H-C₂), 6.05 (s, 1H, CH-C₅), 1.41 (d, 3H, CH₃, thiazole ring), 7.30-7.50 (m, 11H, Ar-H+ CH=C); ¹³C NMR: 20.1 (CH₃, thiazole ring), 43.71 (CH, thiazole), 44.21 (CH₃, pyridine ring), 45.60 (CH, pyrimidine). Found: C, 65.90; H, 4.81; N, 7.32; S, 5.72. Anal. Calcd. for C₂₃H₂₆N₂O: C, 71.79; H, 4.57; N, 10.46; S, 6.78. Found: C, 71.81; H, 5.75; N, 10.46; S, 7.98.

9-(4-Bromobenzylidene)-2,7-dimethyl-6,7,8,9-tetrahydro-2,7-dimethyl-2H-thiazolo[3,2-a]pyrido[4,3-d]pyrimidin-3(5H)-one (5d): Yield 69%; mp 216-218°C; IR (KBr) cm⁻¹: 1726 (C=O); ¹H NMR (DMSO-d₆): 2.12 (s, 2H-C₆), 2.71 (s, 3H, CH₃, pyridine ring), 3.65-4.22 (2d, 2H-C₈), 4.51 (q, 1H-C₂), 6.05 (s, 1H, CH-C₅), 1.41 (d, 3H, CH₃, thiazole ring), 7.30-7.50 (m, 11H, Ar-H+ CH=C); ¹³C NMR: 20.1 (CH₃, thiazole ring), 43.71 (CH, thiazole), 44.21 (CH₃, pyridine ring), 45.60 (CH, pyrimidine). Found: C, 65.90; H, 4.81; N, 7.32; S, 5.72. Anal. Calcd. for C₂₃H₂₆N₂O: C, 71.79; H, 4.57; N, 10.46; S, 6.78. Found: C, 71.81; H, 5.75; N, 10.46; S, 7.98.

9-(4-Iodosobenzylidene)-2,7-dimethyl-6,7,8,9-tetrahydro-2,7-dimethyl-2H-thiazolo[3,2-a]pyrido[4,3-d]pyrimidin-3(5H)-one (5e): Yield 69%; mp 216-218°C; IR (KBr) cm⁻¹: 1726 (C=O); ¹H NMR (DMSO-d₆): 2.12 (s, 2H-C₆), 2.71 (s, 3H, CH₃, pyridine ring), 3.65-4.22 (2d, 2H-C₈), 4.51 (q, 1H-C₂), 6.05 (s, 1H, CH-C₅), 1.41 (d, 3H, CH₃, thiazole ring), 7.30-7.50 (m, 11H, Ar-H+ CH=C); ¹³C NMR: 20.1 (CH₃, thiazole ring), 43.71 (CH, thiazole), 44.21 (CH₃, pyridine ring), 45.60 (CH, pyrimidine). Found: C, 65.90; H, 4.81; N, 7.32; S, 5.72. Anal. Calcd. for C₂₃H₂₆N₂O: C, 71.79; H, 4.57; N, 10.46; S, 6.78. Found: C, 71.81; H, 5.75; N, 10.46; S, 7.98.
Synthesis of 5-aryl-2,9-diaryl-6,7,8,9-tetrahydro-7-methylthiazolo[3,2-α]pyrido[4,3-d]pyrimidin-3(5H)-one (6a-e): Method A. A mixture of compounds 2a, b, d (0.05 mole), chloroacetic acid (1.0g, 0.01 mole), 2g of fused sodium acetate in 20 mL of glacial acetic acid and 10 mL of acetic anhydride was refluxed for 12 min, then equimolecular amount of the appropriate aldehydes was added. The reaction mixture was refluxed for 2 h and then poured onto cold water. The solid formed was filtered off and crystallized from the proper solvent.

Method A. A mixture of 4a, b, d (0.01 mole), equimolecular amount of appropriate aldehyde and 30 mL of acetic anhydride was refluxed for 1 h, left to cool, poured onto cold water. The solid formed was filtered off and crystallized from the proper solvent to give 6a-e. The products were identified by their mp and Rf-values in comparison with authentic samples previously obtained by method A. Method A gave better yield than method B.

2-(4-Fluorobenzylidene)-9-(4-chlorobenzylidene)-5-(4-fluorophenyl)-6,7,8,9-tetrahydro-7-methylthiazolo[3,2-α]pyrido[4,3-d]pyrimidin-3(5H)-one (6d): Yield 85% [A], 75% [B]; mp 155-157°C; IR (KBr) cm⁻¹: 1711 (C=O); 1H NMR (CDCl₃): 2.44 (s, 3H, CH₃), 2.62-3.15 (d, 2H-C₆H₄), 3.21-3.84 (2d, 2H-C₆H₄), 5.62 (s, 1H-C₆H₄), 7.11-7.61 (m, 12H, Ar-H ), 7.70 (s, 1 H, CH=C₆H₄), 7.82 (s, 1H, CH=C₆H₄); 13C NMR: 44.20 (CH₃), 56.01 (CH₃), 56.17 (CH₃-C₆H₄) (60); Found: C, 64.05; H, 4.06; N, 7.69; S, 5.87. Found: C, 65.97; H, 4.04; N, 7.68; S, 5.89.

2-(4-Methoxybenzylidene)-9-(4-chlorobenzylidene)-5-(4-chlorophenyl)-6,7,8,9-tetrahydro-7-methylthiazolo[3,2-α]pyrido[4,3-d]pyrimidin-3(5H)-one (6e): Yield 72% [A], 65% [B]; mp 162-164°C; IR (KBr) cm⁻¹: 1711 (C=O); 1H NMR (CDCl₃): 2.25 (s, 3H, CH₃), 2.90 (s, 3H, OCH₃), 3.11-3.36 (d, 2H-C₆H₄), 3.51-3.81 (2d, 2H-C₆H₄), 5.91 (s, 1H-C₆H₄), 7.11-7.63 (m, 14H, Ar-H + 2 CH₂=CH₂); 13C NMR: 44.19 (CH₃), 45.58 (CH₂, pyrimidine), 51.37, 53.38 (2CH₂-pyridine), 56.01 (OCH₃), 118.20 (C, thiazole), 124.60, 124.23 (2CH₂-methylene), 126.45, 126.84, 127.33, 128.14, 128.66, 128.76, 135.35, 143.25 (18C, Ar-C), 134.70 (C, pyridine), 136.64, 139.70, 163.23 (3C-pyrimidine), 166.61 (C=O); MS (EI): m/z 545 [M⁺] (71), 547 (M⁺+2) (27), 544 (M⁺+H) (100), 433 (544-CH₂C₆H₄) (85); Found: C, 65.97; H, 4.04; N, 7.68; S, 5.89.
9-(4-Chlorobenzylidene)-6,7,8,9-tetrahydro-5-(4-chlorophenyl)-7-methyl-2-(4-tolyl-diazenyl)-2H-thiazolo[3,2-a]pyrido[4,3-d]pyrimidin-3(5H)-one (7c): Yield 77%; mp 202-205°C; IR (KBr) cm⁻¹: 1730 (C=O); ¹H NMR (CDCl₃): 2.28 (s, 3H, CH₃), 2.34 (s, 3H, CH₃-Ph), 2.82-3.15 (d, 2H-C₆H₅), 3.51-3.84 (m, 2H-CH₂), 30.40 (CH, pyrimidine), 39.60, 44.00, 45.40 (CH, pyrimidine), 51.40, 53.40 (2CH₂-phenyl), 54.50 (CH₃-Ph), 59.00 (CH₃-Ph), 115.40, 125.00, 126.22, 126.49, 128.00, 128.14, 128.50, 128.64, 134.60 (CH₃-Ph), 136.66 (C-pyridine), 136.80 (Ar-C), 142.10 (CH, methylene), 152.40 (CH, pyridine), 167.30 (C=O), 169.00 (C=O). MS: m/z 560 [M+H]⁺, 574 [M+2H]⁺ (22), 366 (M⁻C₆H₅CH₂N-CH₃), 135.40, 151.50, 189.00 (C=O), 196.00 (C=O). Anal. Calcd. for C₉H₈N₂O₂S: C, 62.71; H, 4.38; N, 12.19; S, 5.58. Found: C, 62.73; H, 4.40; N, 12.20; S, 5.65.

9-(4-Chlorobenzylidene)-6,7,8,9-tetrahydro-5-(4-chlorophenyl)-7-methyl-2-(4-methoxyphenyl-diazenyl)-2H-thiazolo[3,2-a]pyrido[4,3-d]pyrimidin-3(5H)-one (7d): Yield 80%; mp 198-201°C; IR (KBr) cm⁻¹: 1710 (C=O); ¹H NMR (DMSO-d₆): 2.28 (s, 3H, CH₃), 2.83-3.15 (d, 2H-C₆H₅), 3.86 (s, 3H, OCH₃), 3.51-3.95 (m, 2H-CH₂), 4.10 (s, 1H, CH-C₆H₅), 5.72 (s, 1H, CH₂), 115.40, 125.00, 126.49, 128.00, 128.14, 128.50, 128.64, 134.60 (CH₃-Ph), 136.80 (Ar-C), 136.80 (C=O). MS: m/z 590 [M+H]⁺, 604 (M⁻-CH₃CH₂N), 135.40, 151.50, 189.00 (C=O), 196.00 (C=O). Anal. Calcd. for C₉H₈N₂O₂S: C, 64.78; H, 4.36; N, 7.34; S, 5.59. Found: C, 64.74; H, 4.30; N, 7.49; S, 5.62.

Anticancer activity: Some of the synthesized compounds were selected and screened for their anticancer activity. Each compound was tested at five different concentrations against 60 cell lines of nine types of human cancers, namely, leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast cancer. Results are expressed as log₁₀GI₅₀, which the drug concentration (M) is causing a 50% reduction in the net protein increase in control cells during the drug incubation (Negouei et al., 2009) Table 1. Some of the synthesized compounds showed good anticancer activity at low concentration compared with 5-fluorouracil.
Table 1: In vitro inhibition results of cancer cell lines of the tested derivatives (GI 50 (μM))*

<table>
<thead>
<tr>
<th>Panel/cell line</th>
<th>Compound</th>
<th>3b</th>
<th>3d</th>
<th>4a</th>
<th>4b</th>
<th>4d</th>
<th>5b</th>
<th>5c</th>
<th>5d</th>
<th>6b</th>
<th>7b</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-small cell lung cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A 549/ATCC</td>
<td></td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
</tr>
<tr>
<td>EKVX</td>
<td></td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
</tr>
<tr>
<td>HOP-62</td>
<td></td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
</tr>
<tr>
<td>HOP-92</td>
<td></td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
</tr>
<tr>
<td>NCI-H226</td>
<td></td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
</tr>
<tr>
<td>NCI-H23</td>
<td></td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
</tr>
<tr>
<td>NCI-H322M</td>
<td></td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
</tr>
<tr>
<td>NCI-H460</td>
<td></td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
</tr>
<tr>
<td>NCI-H522</td>
<td></td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
<td>-5.3</td>
</tr>
<tr>
<td><strong>Leukemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCRF-CE</td>
<td></td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
</tr>
<tr>
<td>CCRF-CEM</td>
<td></td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
</tr>
<tr>
<td>HL-60 (TB)</td>
<td></td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
</tr>
<tr>
<td>K-562</td>
<td></td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
</tr>
<tr>
<td>Molt-4</td>
<td></td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
</tr>
<tr>
<td>RPMI-8226</td>
<td></td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
</tr>
<tr>
<td>SR</td>
<td></td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
</tr>
<tr>
<td><strong>CNS cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-268</td>
<td></td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
</tr>
<tr>
<td>SF-295</td>
<td></td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
</tr>
<tr>
<td>HL-60 (TB)</td>
<td></td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
</tr>
<tr>
<td>K-562</td>
<td></td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
</tr>
<tr>
<td>Molt-4</td>
<td></td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
</tr>
<tr>
<td>RPMI-8226</td>
<td></td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
</tr>
<tr>
<td>SR</td>
<td></td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
</tr>
<tr>
<td><strong>CNS cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-268</td>
<td></td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
</tr>
<tr>
<td>SF-295</td>
<td></td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
</tr>
<tr>
<td>HL-60 (TB)</td>
<td></td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
</tr>
<tr>
<td>K-562</td>
<td></td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
</tr>
<tr>
<td>Molt-4</td>
<td></td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
</tr>
<tr>
<td>RPMI-8226</td>
<td></td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
</tr>
<tr>
<td>SR</td>
<td></td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.3</td>
</tr>
</tbody>
</table>

* Data obtained from NCT's in vitro disease-oriented tumor cell screen; GI 50: drug molar concentration causing 50% cell growth inhibition, NA= No Activity
RESULTS

In continuation to our search for new heterocyclic chemistry based anticancer, the suggestion, synthesis, structure elucidation of some thiopyrimidine derivatives 2-7 were realized herein using 3,5-bisarylmethylene-1-methyl-4-piperidone and 4-aryl-8-arylmethylene-6-methylpyrido[4,3-d]pyrimidine-2(1H)thiones as a starting materials. Some of the synthesized compounds were selected and screened for their anticancer activity. Each compound was tested at five different concentrations against 60 cell lines of nine types of human cancers, namely, leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast cancer. Some of the tested compounds were better exhibited in vitro antitumor activities at low concentration (log\_10 GI\_50 = -4.7) against the used human tumor cell lines. From the in vitro observed data it has been noticed that, some of the synthesized compounds seem to be the most active prepared derivatives against all the tested cell lines.

DISCUSSION

Chemistry: The synthetic strategy to synthesize the target products 2-7 is depicted in Fig. 1 and 2. Preparation of 3, 5-bisarylmethylene-1-methyl-4-piperidone (1a-f) was established according to the reported procedure (Lyle et al., 1973; McElvain and Rorig, 1948; Pattaraporn and Tharapong, 2009). The corresponding pyrimidine thione derivatives (2a-e) were obtained from condensation of 1a-e with thiourea in ethanolic potassium hydroxide solution under reflux. When compounds 1a-d, f reacted with 2-amino-2-thiazoline in butanol/DMSO mixture afforded compounds 3a-e in good yields. Reaction of compounds 2a-e with chloroacetic acid or with 2-bromopropionic acid in the presence of sodium acetate in acetic acid/acetic anhydride mixture gave thiazolopyrimidene derivatives 4a-e and 5a-e, respectively (Fig. 1). Compounds 4a,b,d contain an active methylene group, then these compounds reacted with aromatic aldehydes in the presence of acetic acid/acetic anhydride mixture, the corresponding arylmethylene thiazolopyrimidines derivatives 6a-e were obtained (Fig. 2). The products 6a-e could be also obtained from reaction of 2a,b,d with chloroacetic acid, followed by treatment with aromatic aldehyde in the presence of sodium acetate in refluxing acetic acid/acetic anhydride mixture. Compounds 4a,b,d were coupled with aryl diazonium salts in the presence of pyridine to give arylazo-thiazolopyrimidines derivatives 7a-d (Fig. 2).
Antitumor screening: Antitumor activity screening for the synthesized compounds utilizing 59 different human tumor cell lines, representing leukemia, melanoma and cancers of the lung, colon, brain, ovary, breast, prostate as well as kidney, was carried out according to the previously reported standard procedure (Fylaktaki et al., 2004; Jung et al., 2005; Ngoy et al., 2011 and Shuangning et al., 2010). The obtained results (Table 1) represent concentrations of the used investigated compounds resulting in growth inhibition of 50% (GI_{50}) for the tested human tumor cell lines. From the in vitro observed data it has been noticed that, the selected compounds 3b, 3c, 3d, 4a, 4b, 4d, 5b, 5c, 5d, 6c, 6b, 6d, 7b and 7d seem to be the most active prepared derivatives against all the tested cell lines.

Structural-Activity Relationship (SAR): From the above-obtained results (Table 1), we can conclude that thiopyrimidine moieties fused to N-methylpiperidine ring are essential for antitumor activities. In the present work, we can suggest that the anticancer activity is due to:

- The presence of nitrogen heterocyclic rings
- The most active compounds being 3b, 3c, 3d, 4a, 4b, 4d, 5b, 5c, 5d, 6c, 6b, 6d, 7b and 7d against all the tested cell lines.
- The presence of the nitrogen and sulfur atoms generally enhancing the activity
- The difference in activity between the compounds which is due to the indicated subsistents in the phenyl group of the molecule

CONCLUSION

In our previous works, we reported that fused pyrimidine derivatives were proved to be active anticancer agents. In the present work, a series of thiopyrimidine derivatives were synthesized using 3,5-bisarylmethylene-1-methyl-4-piperidone and 4-aryl-8-arylmethene-6-methylpyrido[4,3-d]pyrimidine-2(1H)thiones as a starting materials.

The antitumor activities of the newly synthesized compounds were evaluated utilizing 60 different human tumor cell lines, representing leukemia, melanoma, lung, colon, brain, ovary, breast, prostate as well as kidney. Some of the tested compounds were better exhibited in vitro antitumor activities at low concentration (log_{10} GI_{50} = -4.7) against the used human tumor cell lines. In the present work, we can suggest that the anticancer activity is due to the presence of nitrogen heterocyclic rings and the presence of the sulfur atom.

ACKNOWLEDGEMENT

The researchers extend their appreciation to the Deanship of Scientific Research at King Saud University for funding the work through the research project No. RGP-VPP-099.

REFERENCES


