Synthesis of some new thienopyridine and pyridothienopyrimidine derivatives with expected antitumor activity

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Abstract:
The thioxopyridine derivative (2) on treatment with ethyl chloroacetate gave the corresponding ethyl 3-aminothieno [2,3-b]pyridin-2-carboxylate (3). Condensation of 3 with Ac2O gave the corresponding 4-H-pyrido[3',2':4,5]thieno[3,2-d] [1,3]oxazine derivative (4). Reaction of 4 with bifunctional groups gave 3,4-dihydropyrido[3',2':4,5]thieno[3,2-d]pyrimidines (5a, b) and 2-carbamoyl-3-acetamidothieno[2,3-b]pyridine derivative (6). Intramolecular cyclization of 6 by Ac2O/AcOH gave (7). Reaction of 5b with different electrophilic reagents were studied. Also, 5a upon treatment with ethyl chloroacetate and/or methyl iodide (K2CO3) furnished the corresponding N-ethylacetate (13) and N-methyl derivative (16) respectively. Hydrazinolysis of 13 gave the corresponding acetohydrazide (14) which on treatment with benzaldehyde furnished the corresponding 1H-pyrazol-4-yl derivative (15). The IR, 1H NMR and MS spectra of newly derivatives were discussed. The antitumor activity against the liver tumor cell line HepG2 of the prepared compounds were tested. Compounds 8a, 14 were more potent (IC50 = 2.75 and 2.12 μg/ml) than the standard drug (IC50 = 4.60 μg/ml).

Keywords — Cyanothioxypyridine, Thienopyridine, Pyridothienopyrimidine and anti-tumor, HepG2.

I. INTRODUCTION
In the last several decades, pyridothienopyrimidine derivatives have received considerable attention due to their wide-range of applications. Pyridothienopyrimidines are reported to exhibit anticanter [1-3], anti-inflammatory[4,5] antimalarial[6], anti-allergy [7], anti-microbial[8-9], antifilarial [10]. Insecticidal activities [11], also as V.E. GFR-2-inhibitors[12]. Moreover, as inhibitor of CLK1 and Dy RKIA kinases[13]. Encouraged by these reports, it was considered of interest to of synthesizing a new series of pyridothienopyrimidine derivatives as potential antitumor agents.

II. EXPERIMENTAL
All melting points are uncorrected. IR spectra (KBr) were recorded with a Perkin Elmer Spectrum RXIFT-IR systems. 1H NMR were measured with a Varian Gemini 200 MHz instrument using TMS as internal standard and mass spectra were measured with a Shimadzu GC-MS-QP 100 EX mass spectrometer.

Synthesis of 3-(4-bromophenyl)-2-cyanoprop-2-enothioamide (1)
A mixture of 4-bromobenzaldehyde (0.01 mol), thiocyanatoacetamide (0.01 mol) and (0.002 mmol) of piperidine in ethanol (50 ml) was heated under reflux for 6hr., the solid separated after concentration and cooling was filtered off, and crystallized from benzene 98% yield. m.p. 155°C IR., cm−1: 3413, 2950, 2215 and 1239 for NH3, CH aliphatic, C≡N and C=S group, respectively. Analysis for C10H9BrN2S (267.14): calcd. C 45.12, H 2.64, Br 29.95, N 10.48, S 12.00%. Found C 44.96, H 2.64, Br 29.91, N 10.49, S 12.00%.

Synthesis of ethyl 4-(4-bromophenyl)-5-cyano-1,6-dihydro-2-methyl-6-thiopyridopyrimidine-3-carboxylate (2)
A mixture of 1(0.01 mol), ethyl acetocacetate (0.015 mol) and (0.002 mmol) of piperidine in dioxane (50 ml) was heated under reflux for 6 hr. The reaction mixture was concentrated and cooled, the separated solid was filtered off, and crystallized from benzene 90% yield, m.p. 100°C. IR, cm−1: 3340, 2962, 2214, 1753 and 1376 cm−1 for NH3, CH aliphatic, C≡N, CO ester and C=S group, respectively. 1H NMR (DMSO-d6) δ(ppm): spectrum exhibited signals at 7.85(2H, d, J = 8.3 Hz, Ar–H), 7.10 (2H, d, J = 8.2 Hz, Ar–H), 2.97 (3H, s, CH3), 4.1 (2H, q, J = 7.2 Hz, CH2CH3), 1.19 (3H, t, J = 7.0 Hz, CH2CH3) and 9.84 (1H, s, NH).Analysis for C10H9BrN2S (377.26): calcd. C 50.89, H 3.45, Br 29.21, N 7.42, S 8.48.; found C 50.94, H 3.47, Br 29.91, N 10.49, S 8.50%.

Synthesis of diethyl 3-aminio-4-(4-bromophenyl)-6-methylthieno[2,3-b]pyridin-2,5-dicarboxylate (3).
By stirring at room temperature 4.5hr. compound 2(0.01 mol), ethyl chloroacetate (0.01 mol), sodium methoxide (0.01 mol) and methanol (30 ml), the solid that separated was filtered off, washed with methanol and crystallized from ethanol, 60% yield, m.p. 190°C. IR, cm−1: 3393, 2915, 1730 and 1590 cm−1 for NH3, CH aliphatic, CO ester and C≡N group, respectively. 1H NMR (DMSO-d6) δ(ppm): spectrum exhibited signals at 7.69(2H, d, J = 8.2 Hz, Ar–H), 7.12 (2H, d, J = 8.4 Hz, Ar–H), 2.17 (3H, s, CH3), 4.10 (4H, q, J = 7.2 Hz, CH2CH2), 1.81 (6H, t, J = 6.9 Hz, 2 x CH2CH3) and 7.51 (2H, s, NH3); MS (m/z, %) 463 (1.18%): Analysis for C20H16BrN2S2

A mixture of compound 4 (0.01 mol) and hydrazine hydrate (0.02 mol) in ethanol (30 ml) was refluxed for (3hr). The solid which was separated out after concentration and cooling was dried and crystallized from ethanol, 90% yield, m.p. 260°C. IR, cm⁻¹ NH at 3315, CH aliphatic at 2860, CO(ester) at 1735 and CO (amidic) at 1698. ¹H NMR (DMSO-d₆) δ (ppm): spectrum exhibited signals at 7.62 (2H, t, J = 8.2 Hz, Ar-H), 7.35 (2H, d, J = 8.2 Hz, 21.7 (3H, s, CH₃), 3.57 (2H, s, NH₂); MS (m/z %) 473 (0.96%). Analysis for C₂₉H₂₂BrN₂O₂S (473.43): calcd. C 50.70, H 3.59, Br 16.90, N 11.83; S, 6.76; found C 50.69; H, 3.60; Br 16.82, N 11.80, S, 6.80%.

Synthesis of ethyl 2-(2-amino phenyl carbamoyl)-3-acetamido-4-(4-bromophenyl)-6-methylthieno [2,3-b] pyridin-5-carboxylate (6).

A mixture of compound 4 (0.01 mol) and o-phenylenediamine (0.01 mol) was stirred in chloroform (20 ml) for (16 hr) at room temp., leave aside over night to give compound 6 which was dried and crystallized from chloroform. 70% yield, m.p. 220°C. IR cm⁻¹ NH, NH₂ at 3460, 3420, CH aliphatic at 2912, CO(ester) at 1733 and CO (amidic) at 1652, 1660. ¹H NMR (DMSO-d₆) δ (ppm): spectrum exhibited signals at 7.96-7.41 (8H, m, Ar-H), 1.92 (3H, s, CH₃), 1.92 (3H, s, COCH₃); 4.03 (2H, q, J = 7.4 Hz, CH₂-CH₃); 1.08 (3H, t, J = 7.0 Hz, CH₃CH₂); 3.38 (2H, s, NH₂); 9.64 (1H, s, NH) and 9.18 (1H, s, CO NH); MS (m/z %) 567 (1.48%); Analysis for C₂₉H₂₂BrN₂O₂S (567.45): calcd. C 54.98, H 4.05, Br 14.10, N 9.87, S 5.64; found C 55.03, H 4.09, Br 14.11, N, 9.87, S 5.65%.

Synthesis of ethyl 3-(2-aminophenyl)-9-(4-bromophenyl)-2,7-dimethyl-4-oxo-3,4-dihydropyrido [3′,2′:4,5]thieno [3,2-d] pyrimidin-8-carboxylate(7).

A solution of compound 6 (0.01 mol) in acetic anhydride and acetic acid (5 ml) was heated under reflux for (5hr). The solid that separated on cooling was filtered off and crystallized from butanol 60% yield, m.p. 350°C. IR, cm⁻¹ NH at 3418, CH aliphatic at 2911, 2960, CO(ester) at 1743 and CO (amidic) at 1652. ¹H NMR (DMSO-d₆) δ (ppm): spectrum exhibited signals at 7.89-7.42 (8H, m, Ar-H), 2.51(6H, s, 2 x CH₃), 4.10 (2H,q, J = 7.2 Hz, CH₂CH₃), 1.31 (3H, t, J = 7.0 Hz, CH₂CH₃) and 5.10 (2H, s, NH₂). Analysis for C₂₉H₂₂BrN₂O₂S (549.44): calcd. C 56.79, H 3.82, Br 14.56, N 10.19, S 5.82; found C 56.84, H, 3.85, Br 14.54, N 10.20, S, 5.84.

Synthesis of thienopyrimidine derivatives (8ₐₙ).

A mixture of compound 5b (0.01 mol), (maleic and/or phthalic anhydride) was heated in an oil bath for (1hr). The reaction mixture was diluted with water and the obtained solid was filtered off, dried and crystallized from ethanol to give compounds (8ₐₙ), respectively.

Ethyl-9-(4-bromophenyl)-3-(2,5-dioxo-2,5-dihydro-1H-pyrrolo-1-yl)-2,7-dimethyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-8-carboxylate (8a), yield 65%; m.p. 290°C. IR, cm⁻¹ CH aliphatic at 2986, CO(ester) at 1767 and CO (amidic) at 1675, 1650. MS (m/z %) 554 [M⁺, 1.92%]. Analysis for C₂₉H₂₂BrN₂O₂S (553.58): calcd. C 52.04, H 3.07, Br 14.46, N 10.12 S 5.78; found C 52.09, H 3.10, Br 14.44, N 10.12, S 5.79%.

Ethyl 9-(4-bromophenyl)-3-(1,3-dioxoisoindolin-2-yl)-2,7-dimethyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-8-carboxylate (8b). yield 70%; m.p. 270°C. IR, cm⁻¹ CH aliphatic at 2986, CO(ester) at 1755 and CO (amidic) at 1643, 1655. ¹H NMR (DMSO-d₆) δ(ppm): spectrum exhibited signals at 7.42-6.96 (8H, m, Ar-H), 2.73(3H, s, CH₃), 2.67 (3H, s, CH₃), 3.76 (2H, q, J = 7.2 Hz, CH₂CH₃) and 1.13 (3H, t, J = 7.0 Hz, CH₂CH₃). Analysis for C₃₀H₂₂BrN₂O₂S (603.44): calcd. C 55.68, H, 3.15, Br 13.26, N 9.28, S 5.30 ; found C 55.73, H 3.17 , Br 13.24, N 9.28, S 5.31%.
Synthesis of ethyl 9-(4-bromophenyl)-3-((4-chlorobenzene)diamino)-2,7-dimethyl-4-oxo-3,4-dihydropyrido[3',2':4,5]thieno[3,2-d]pyrimidin-8-carboxylate (9).

A mixture of compound S5 (0.01 mol), p-chlorobenzaldehyde (0.01 mol), few drops of piperidine was heated in an oil bath for (1 hr), the reaction mixture was diluted with water. The solid that separated out, dried and crystallized from ethanol 60% yield, m.p. 295°C. IR, cm\(^{-1}\): CO(ester) at 1743 and 1740, CO(amidic) at 1658. aliphatic at 2930, 2965, CO(ester) at 1739, CO(amidic) at 1630 and C=N at 1614. MS (m/z, %) 595 (0.97%). CH analysis for C49.82, H 3.80, Br 17.47, N 9.19, S 7.01%. Found: C 49.77, H 3.77, Br 17.45, N 9.18, S 7.00.

Synthesis of ethyl 9-(4-bromophenyl)-3-(cyclohexylideneamino)-2,7-dimethyl-4-oxo-3,4-dihydropyrido[3',2':4,5]thieno[3,2-d]pyrimidin-8-carboxylate (10).

A mixture of compound S5 with cyclohexanone (0.02 mol), few drops of piperidine was heated in an oil bath for (1 hr), the reaction mixture was diluted with water. The solid that separated out, dried and crystallized from ethanol to give Schiff's base 70% yield, m.p. 125°C. IR, cm\(^{-1}\): CO(amidic) at 1638. CO(amidic) at 1610. MS (m/z, %), 595 (0.97%). CH analysis for C56.42, H 3.32, Br 14.45, Cl 5.90, N 9.43. S 5.30%.


A mixture of compound S5 (0.01 mol), ethyl chloroacetate (0.04 mol) and anhydrous potassium carbonate (0.04 mol) in dry acetone (30 ml) was refluxed for (24 hr), the excess acetone was evaporated and the reaction mixture was diluted with water, the solid that separated was crystallized from acetone, 80% yield, m.p. 200°C. IR, cm\(^{-1}\): CH aliphatic at 2930, 2965, CO(ester) at 1743 and CO(amidic) at 1658. \(^1\)H NMR (DMSO-d\(_6\)) \(\delta\) (ppm): spectrum exhibited signals at 7.39 (2H, d, J = 8.0 Hz, Ar-H), 7.11 (2H, d, J = 7.9 Hz, Ar-H), 2.20 (3H, s, CH\(_3\)), 2.09 (3H, s, CH\(_3\)), 2.51-1.30 (10H, m, 5 x CH\(_2\)), 3.46 (2H, q, \(J = 7.2\) Hz, CH-CH\(_3\)) and 1.05 (3H, t, \(J = 7.1\) Hz, CH-CH\(_3\)). Analysis for C\(_{26}\)H\(_{32}\)BrN\(_4\)O\(_5\): calcd: C 53.01, H 3.22, Br 17.49, N 9.18, S 6.99; found. C 53.00, H 3.21, Br 17.48, N 9.17, S 6.98.

Synthesis of diethyl 9,9'-bis-(4-bromophenyl)-2,2',7',7'-tetramethyl-4,4'-dioxo-4H,4'H-[3,3'-bipyrido[3',2':4,5]thieno[3,2-d]pyrimidin]-8,8'-dicarboxylate (12).

A mixture of compounds 4 (0.01 mol), and S5 (0.01 mol) was fused in an oil bath for (1 hr), the obtained solid was washed with ethanol, dried and recrystallized from ethanol 70% yield, m.p. 210°C. IR, cm\(^{-1}\): CH aliphatic at 2930, 2989, CO(ester) at 1764 and CO(amidic) at 1646. MS(m/z%) 914 (0.72%). Analysis for C\(_{40}\)H\(_{38}\)Br\(_2\)N\(_6\)O\(_8\)S\(_2\) (914.64); calcd. C 52.48, H 3.28, Br 17.49, N 9.18, S 6.99; found. C 52.53, H 3.31, Br 17.47, N 9.19, S 7.01%.

Synthesis of ethyl 9-(4-bromophenyl)-3-(2-ethoxy-2-oxoethyl)-2,7-dimethyl-4-oxo-3,4-dihydropyrido [3',2':4,5]thieno[3,2-d]pyrimidin-8-carboxylate (13).

A mixture of compound S5 (0.01 mol), ethyl chloroacetate (0.04 mol) and anhydrous potassium carbonate (0.04 mol) in dry acetone (30 ml) was refluxed for (24 hr), the excess acetone was removed by distillation and the residue poured with stirring into water, the obtained solid was filtered off, dried and recrystallized from ethanol 70% yield, m.p. 210°C. IR, cm\(^{-1}\): CH aliphatic at 2930, 2989, CO(ester) at 1745, 1759 and CO(amidic) at 1638. \(^1\)H NMR (DMSO-d\(_6\)) \(\delta\) (ppm): spectrum exhibited signals at 7.99 (2H, d, J = 5.1 Hz, Ar-H), 7.56 (2H, d, J = 5.1 Hz, Ar-H), 5.30 (2H, s, NCH\(_2\)), 3.94 (4H, q, \(J = 7.2\)Hz, 2 x CH\(_2\)-CH\(_3\)) and 1.24 (6H, t, \(J = 7.1\)Hz, 2 x CH\(_3\)). Analysis for C\(_{26}\)H\(_{32}\)BrN\(_2\)O\(_4\)S\(_2\): calcd. C 52.90, H 4.04, Br 14.69, N 7.71, S 5.88; found. C 52.91, H 4.07, Br 14.68, N 7.72, S 5.89%.


A mixture of compound 13 (0.01 mol), and hydrazine hydrate (0.02 mol) in ethanol (20 ml) was refluxed for (6 hr), the reaction mixture was concentrated cooled and the obtained was filtered off and recrystallized from ethanol 80% yield, m.p. 320°C. IR, cm\(^{-1}\): NH, NH\(_2\) at 3412, 3430, CH aliphatic at 2895, 2920, CO(ester) at 1742 and CO(amidic) at 1640. \(^1\)H NMR (DMSO-d\(_6\)) \(\delta\) (ppm): spectrum exhibited signals at 7.37 (2H, d, J = 5.1Hz, Ar-H), 7.33 (2H, d, J = 5.1 Hz, Ar-H), 2.82 (3H, s, CH\(_3\)), 2.72(3H, s, CH\(_3\)), 4.07 (2H, q, \(J = 7.0\) Hz, CH\(_2\)-CH\(_3\)), 1.26 (3H, t, \(J = 6.0\)Hz, CH\(_3\)), 5.51 (2H, s, NH\(_2\)) and 13.56 (1H, s, NH): Analysis for C\(_{26}\)H\(_{32}\)BrN\(_2\)O\(_4\)S\(_2\): calcd. C 49.77, H 3.77, Br 15.08, N 13.20, S 6.03; found. C 49.82, H 3.80, Br 15.07 N 13.20, S 6.05%.
Synthesis of ethyl 9-(4-bromophenyl)-3-(3-hydroxy-5-phenyl-1H-pyrazol-4-yl)-2,7-dimethyl-4-oxo-3,4-dihydropyrido[3',2':4,5]thieno[3,2-d]pyrimidin-8-carboxylate (15).

A mixture of compound 14 (0.01 mol) and benzaldehyde (0.01 mol) in butanol (50 ml) was refluxed (8 hr), the reaction mixture was concentrated cooled and the obtained solid was filtered off and recrystallized from butanol 80% yield, m.p. 285°C. IR, cm⁻¹ NH at 3350, CH aliphatic at 2917, CO(ester) at 1757 and CO(amidic) at 1639. 1H NMR (DMSO-d₆) δ (ppm): spectrum exhibited signals at 7.98-6.02 (9H, m, Ar-H), 2.78 (3H, s, CH₃), 2.51 (3H, s, CH₃), 4.40 (2H, q, J = 7.2 Hz, CH₂CH₃), 1.81 (3H, t, J = 7.0Hz, CH₂CH₃), 5.55 (1H, s, NH) and 11.52 (1H, s, OH): MS (m/z%) 617 [M⁺, 1.32%]. Analysis for C₆H₅BrN₂O₅S (616.49): calcd. C56.45, H 3.57, Br 12.98, N 8.91; found C 56.43, H 3.60, Br 12.95, N 11.35, S 5.19.

Synthesis of ethyl 9-(4-bromophenyl)-2,3,7-trimethyl-4-oxo-3,4-dihydropyrido[3',2':4,5]thieno[3,2-d]pyrimidin-8-carboxylate (16).

A mixture of compound 5₆ (0.01 mol), methyl iodide (0.02 mol) and anhydrous potassium carbonate (0.04 mol) in dry acetone (40 ml) was refluxed on water bath for (24 hr), the excess acetone water removed by distillation and the residue was poured with stirring into water, the obtained solid was filtered off, dried and recrystallized from acetone 60% yield, m.p. 155°C. IR, cm⁻¹. CH aliphatic at 2971, CO(ester) at 1757 and CO(amidic) at 1639. 1H NMR (DMSO-d₆) δ (ppm): spectrum exhibited signals at 7.52 (2H, d, J = 8.4 Hz, Ar-H), 7.39 (2H, d, J = 8.3Hz, Ar-H), 3.56(3H s, NCH₃), 2.56 (6H, s, 2x CH₃), 4.27 (2H, q, J = 7.3Hz, CH₂CH₃) and 1.11 (3H, t, J = 6.9Hz, CH₂CH₃): MS (m/z%) 471[M⁺–1, 6.35%]: Analysis for C₂₁H₁₇BrN₂O₅S (472.35): calcd. C 53.35, H 3.81, Br 16.94, N 8.89, S 6.77; found. C 53.40, H 3.84, Br 16.92, N 8.90, S 6.79%.

Cytotoxicity assays

The cytotoxicity Was measured using the MTT (3-[4,5-dimethylthiazole-2-yl]-2,5-diphenyltetrazolium bromide) cell viability assay [15,16]. In brief, cells were seeded in 96-well plates and treated with graded concentrations of tested compounds. Then the medium was replaced with fresh medium and cells were incubated with MTT. Four hours later, cells were lysed by addition of dimethylsulphoxide (DMSO). The solubilized formazan products were quantified for absorbance at a wavelength of 570 nm.

Cytotoxicity against the liver tumor cell line (HepG2) in vitro.

Compounds 2,3,4,5₆,6,7,8,₇,8₈, 9,10,11,12,13, 14, 15 and 16 were evaluated for their human tumor cell growth inhibitory activity against HepG₂ (hepatocarcinoma). The measurement of cell growth and viability were determined as described previously [15,16].

Cytotoxicity evaluation using viability assay were performed by a Regional Center for Mycology and Biotechnology (RCMP), Al-Azhar University. The inhibitory activity of the synthetic compounds against the liver carcinoma cell line (HepG2) is given in (Figs. 2, suplementry material). The IC₅₀ values were in the low concentration in microgram range.

III. RESULTS AND DISCUSSION

The new derivatives were prepared following the reaction sequences depicted in schemes 1-3. Reflux of p-bromobenzaldehyde and cyanothioacetamide in dioxane with a catalytic amount of piperidine afforded arylidine cyanothioacetamide 1 in good yield.

Compound 1 reacts with ethyl acetoacetate in the presence of a catalytic amount of piperidine in boiling dioxane to produce the corresponding thioxopyridine derivative 2. The reaction probably follows through mechanism followed in chart 1.

Treatment of 2 with ethyl chloroacetate, CH₃ONa gave thieno[2,3-b] pyridine 3 via the nonisolable intermediate A. Acetylation of amino ester 3 with acetic anhydride gave non-isolated N-acetylated intermediate B which cyclized under the reaction conditions to yield oxazinone derivative 4.

Condensation of oxazinone derivative 4 with formamide (Mahmoud, N., et al., 2008) afforded thieno[2,3-d] pyrimidine derivative 5a, while hydrazinolysis took place to give 3-amino-3H-thieno[2,3-d] pyrimidine-4-one 5b.

In addition the reaction of 4 with o-phenylenediamine leads to opening of the oxazinone ring and formation of ethyl 2-(2-aminothienyl)-3-acetamido-4-(4-bromophenyl)-6-methylthieno [2,3-b]pyridin-5-carboxylate 6. Cyclocondensation of 6 by Ac₂O/AcOH afforded the corresponding pyridothieno pyrimidine 7.
Also, compound 5b was used as precursor for the preparation of several new compounds. This reaction of 5b with maleic anhydride and phthalic anhydride gave thienopyrimidine derivatives 8 and 9. Condensation of 5b with p-chlorobenzaldehyde gave the corresponding arylidene derivative 9, similarly compound 5b condensed with cyclohexanone to give compound 10. Reaction of 5b with ethyl chloroacetate gave the diethyl dicarboxylate derivative 11. On the other hand, reaction of 5b with compound 4 gave the bispyrido thienopyrimidine derivative 12.

Treatment of 5b with methyl iodide in dry acetone/K2CO3 gave the corresponding 3-methylpyridothieno pyrimidine derivative 16. The structures newly synthesized derivatives were supported by correct analytical data, IR, 1H NMR and mass spectra studies (cf experimental part).

Cyclization of carbohydrazide 14 with benzaldehyde in boiling ethanol afforded 3-(1H-pyrazol-4-yl)-4-oxo-3,4-dihydropyrido[3,2':4,5]thieno| 2,3-d|pyrimidin-8-carboxylate 15. The reaction probably follows through the mechanism flowed in chart 2.

Cytotoxicity against the liver tumor cell line (HepG2) in vitro

The cytotoxic antitumour activity for Compounds 2,3,4,5a,6,7,8,8b, 9,10,11,12,13, 14, 15 and 16, were evaluated against HepG2 (hepatocarcinoma). The IC50 values were in the low concentration in microgram range. Compounds 8b, 9 and 14 had the most prominent activity against the HepG2 and (IC50= 2.75 µg/ml, 5.45 mg/ml and 2.12µg/ml respectively(Fig1). Surprisingly, compounds 8a and 14 were more potent than the standard drug (IC50 of standard drug = 4.60 µg/ml) in HepG2 cell line. Compounds 2,6 and 9 had moderate inhibitory activity against HepG2 with IC50 = 26.30µg/ml, 5.45 µg/ml and 11.10µg/ml respectively. While compounds 3,4b,7, 8b, 10,11,12,13,15 and 16 had weak activity.

![Scheme (2)](image)

![Scheme (3)](image)
IV. CONCLUSION

In conclusion, the pyridothienopyrimidine with 3-(1H-1-pyrazol-1-yl) 8a, 3-((4-chloro-benzeldimino)amino) 9 and 3-(2-hydrazone-oxo ethyl) 14 functions exhibited of some new heterocyclic compounds. Structure of the synthesized the most active compounds against HepG_2 as compared with the used standard drug. However, the remaining compounds exhibited moderate to lower antitumor activities.

REFERENCES