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Der Pharma Chemica, 2010, 2(5):507-521
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis and anticancer evaluation of novel tetrahydronaphthalen-6-ylthiazole heterocycles against human HePG2 and MCF7 cell lines

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ABSTRACT

A new *series of tetrahydronaphthalen-6-ylthiazole derivatives incorporated into/or fused to different five or six membered nitrogen and sulphur containing heterocycles including pyrazoles, triazolothiazoles, thiazolidinones, pyrimidinethione ,thiazolotriazine and/or sulphonamides was synthesized starting from the new 4-(1,2,3.4-tetrahydronaphthalen-6-yl)-2 – hydrazinothiazole (2) and/ or the 2-chlorothiazole derivative 18 as synthons. The anticancer activity of eleven of these compounds was evaluated against two human cell lines of liver cancer (HePG2) and breast cancer (MCF7). The compounds tested in most of cases were selective towards the both types of cancer where the most potent compounds showed* IC_{50} *= 0.40 – 0.45 ug/mL*

Keywords: Tetrahydronaphthyl-2- hydrazinothiazole, 2-chlorothiazole, pyrazoles, thiazolotriazole, thiazolotriazine, thiazolidinone, pyrimidinethione, Schiff bases, propenone, sulphonamides, HePG2, MCF7 cell lines, anticancer activity

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INTRODUCTION

The chemistry of 1,2,3,4-tetrahydronaphthalen-6-yl heterocycles especially those including thiazole moiety and/or nitrogen, oxygen or sulphur heterocycles such as pyrazoles ,isoxazoles, thiadiazoles, pyrroles, pyridines and/or pyrimidines, has been of increasing interest since many of these compounds have found useful applications as chemotherapeutic agents of promising anticancer [1-5], antimicrobial [6-8] or antiviral [9,10] activities.

During our drug discovery program [1, 2,11-14] and in continuation of our recent article [15] concerning the synthesis and anticancer activity of novel tetralin-6-yl heterocycles, it was of interest to introduce a new safer series of tetralin-6-yl-thiazoles incorporated into another nitrogen and/or sulphur heterocycles or side chains to be evaluated as anticancer agents.

MATERIALS AND METHODS

Chemistry

All melting points are uncorrected and were taken in open capillary tubes using silicon oil on Gallenkamp apparatus. Elemental microanalyses were performed on Elemetar, Vario EL, Microanalytical Unit, National Research Centre, Cairo-Egypt. Infrared spectra were recorded on Jasco FT/IR-330E, Fourier Transform Infrared Spectrophtometer at cm^{-1} scale using KBr discs. ^{1}H-NMR spectra were determined by using JEOL EX-270 or JEOL ACA500 NMR Spectrometers are measured in δ scale using TMS as an internal standard. Mass spectra were measured using mass spectrometer Finnigan MAT SSQ-7000 and GCMS-QP 1000EX Shimadzu Gas Chromatography MS Spectrometer All reactions were followed by TLC (aluminium sheets) using $CHCl_3$/CH_3OH (9:1, v/v) eluent and detected by UV lamp.The chemical names given to the prepared compounds are according to the IUPAC system.

2-Hydrazino-4-(1,2,3,4-tetrahydronaphthalen-6-yl)thiazole (2)

A mixture of 6-bromoacetyl-1,2,3,4-tetrahydronaphthalene(**1**)[16] (2.5 g, 0.01 mole) and thiosemicarbazide (0.91 g, 0.01 mole) in abs. ethanol (30 ml) was refluxed for 4 h. The reaction mixture was cooled and made alkaline using 10% soln. of NaOH (1 ml), then poured onto ice/cold water acidified with hydrochloric acid. The formed precipitate was filtered, washed with water and recrystallized from cyclohexane to give 90% yield of compound **2**, m.p. 160-161 ^oC Analysis, $C_{13}H_{15}N_3S$ (245.4) Calcd. C,63.63, H, 6.16, N, 17.12% . Found:, C, 63.97, H, 6.66, N, 17.45%. IR. (KBr, cm-1) showed absorbance bands at 3365, 3219, 3090 (NH, NH2), at 2929 (CH_2 tetralin) and at 1634 (C=N). MS. M+ at m/z 245(80%) and at m/z 157 (100%) of $C_{10}H_{11}$-CN

2-(4-Methoxybenzylidene)-1-[4-1,2,3,4-tetrahydronaphthalen-6-yl)-thiazol-2-yl]hydrazine (3a), and the 2-(4-methylbenzylidene)- derivative (3b), the 2-(thiophen-2-yl)- methylene-(3c) derivative and 2-(1H-indol-3-yl)-methylene-1-[4-(1,2,3,4-tetrahydronaphthalen-6-yl)-thiazol-2-yl]-hydrazine (3d)

A mixture of compound **2** (2.45 g, 0.01 mol) and the appropriate aldehyde, namely :p-anisaldehyde, p-tolualdehyde, thiophene-2-carboxaldehyde and/or 1H-indol-3-carboxaldehyde (0.01 mol) in abs. ethanol (30 ml) was refluxed for 6 h. The formed precipitate was filtered and recrystallized from ethanol to give compounds **3a-d** respectively.(Tables 1,2)

1-[4-(1,2,3,4-Tettrahydronaphthalen-6-yl)-thiazol-2-yl]-2-[(4-methoxyphenyl)-(4 -methylpiperazin-1-yl)methyl]-hydrazine (4a), 1-[4-(tetrahydronaphthalen-6-yl)thiazol-2-yl]-2-[(thiophen-2-yl)(4-methylpiperazin-1-yl)methyl]hydrazine (4b) and 1-[4-(tetrahydronaphthalen-6-yl)-thiazol-2-yl]-2-[(1H-indol-3-yl)(4-methylpiperazin-1-yl)methyl]hydrazine (4c)

A mixture of compound **2** (0.49 g, 0.002 mol) , the appropriate aldehyde, namely: p-anisaldehyde, thiophene-2-carboxaldehyde and/or 1H-indol-2-carboxaldehyde(0.002 mol) and methylpiperazine (0.2 g , 0.002 mol) was refluxed for 10 h. After cooling, the formed precipitate was filtered and recrystallized from dioxane to give compounds **4a-c** respectively.(Tables 1,2)

2-[4-(1,2,3,4-Tetrahydronaphthalen-6-yl)thiazol-2-ylamino]- isoindoline-1,3-dione (5a), 6-[4-(1,2,3,4-tetrahydronaphthalen-6-yl)thiazol-2-ylamino]-6H-pyrrolo[3,4-b]pyridine-5,7-dione (5b) and 2-[4-(1,2,3,4-tetrahydronaphthalen-6-yl)-thiazol-2-ylamino]-1,8-naphthalimide (5c)

A mixture of compound **2** (0.49 g., 0.002 mol) and the appropriate acid anhydride, namely: phthalic anhydride, 2,3-pyridine dicarboxylic acid anhydride and 1,8-naphthalene dicarboxylic acid anhydride(0.002 mol) in glacial acetic acid (20 ml) , was heated under reflux for 6 h. The reaction mixture cooled and poured onto ice/cold water. The formed precipitate was filtered and recrystallized from dil. AcOH to give compounds **5a-c** respectively. (Tables 1,2)

1-[4-(1,2,3,4-Tetrahydronaphthalen-6-yl) thiazol-2-yl]-3,5-dimethyl-1H-pyrazole (6)

A mixture of compound **2** (0.49 g, 0.002 mol) and acetylacetone (0.2 ml , 0.002 mol) in ethanol (20 ml) was refluxed for 6 h .The solvent was evaporated under reduced pressure and the formed precipitate was washed with petroleum ether, filtered , dried and recrystallized from EtOH/H2O to give compound **6** in 66% yield , m.p. 181-182 ^{o}C.

Analysis, $C_{18}H_{19}N_3S$ (309.4) Calcd. C, 69.86 , H, 6.18, N, 13.57 ; Found C, 70.70, H, 6.53, N, 14.04%. ^{1}HNMR (DMSO-d_6, δ ppm) showed signals at 1.6-1.8 (m, 4H, 2 CH_2 of tetralin), at 2.6-2.8 (m, 10H, 2 CH_3 groups and 2 CH_2 of tetralin), at 4.2(s, 1H,pyrazole) and at 7.1-7.8 (m, 4H, Ar-H and thiazole proton). MS. Showed M+ at m/z 309 (7.5%) and at m/z 104(100%) of C_8H_8 (Ph-CH=CH_2+)

1-[4-(1,2,3,4-Tetrahydronaphthalen-6-yl)thiazol-2-yl]-3-methyl-1H-pyrazol-5(4H)-one (7)

A mixture of compound **2** (0.49 g,0.002 mol) and ethyl acetoacetate (0.26 g, 0.002 mol) in ethanol (20 ml) was refluxed for 5 h. The solvent was evaporated under reduced pressure and the formed precipitate was filtered and recrystallized from EtOH/H_2O to give compound **7** in 60% yield , m.p. 165-166 ^{o}C. Analysis, $C_{17}H_{17}N_3OS$ (311.4) Calcd. C, 65.56, H,5.50, N,13.49 : Found, C, 66.06, H, 5.97, N, 13.80%, ^{1}HNMR($CDCl_3$, δ ppm) showed signals at 1.6-1.8 (m, 4H, 2 CH_2 of tetralin), at 2.3 (s,3H, CH_3), at 2.6-2.8 (m, 4H, 2 CH_2 tetralin), 3.4 (s, 2 H, CH_2) and at 7.1-7.9(m, 4H, Ar-H and thiazole proton); Its MS showed M+ at m/z 311 (9.86%) and the base peak at m/z 157 (100%) of ($C_{10}H_{11}$-CN).

4-Cyclohexyl-1-[4-(1,2,3,4-tetrahydronaphthalen-6-yl)-thiazol-2-yl]semicarbazide (8a), 1-[4-(1,2,3,4-tetrahydronaphthalen-6-yl)thiazol-2-yl]thiosemicarbazide (8b) and its 4-cyclohexyl-, 4-phenyl- and 4-(o-tolyl)- derivatives (8c-e)

A mixture of compound **2** (0.49 g, 0.002 mol) and the appropriate isocyanate and/or isothiocyanate, namely : cyclohexylisocyanate, ammonium thiocyanate, cyclohexylisothio-cyanate, phenylisothiocyanate and/or o-tolylisothiocyanate (0.002 mol) in dry benzene (30 ml) was refluxed for 6 h. The formed precipitate was filtered, dried and recrystallized from ethyl alcohol to give compounds **8a-e** respectively (Tables 1,2).

2-[4-(1,2,3,4-Tetrahydronaphthalen-6-yl)thiazol-2-ylamino] -imino-3-cyclohexyl-(or phenyl)-thiazolidin-4-ones (9a,b)

A mixture of compound **8c** or **8d** (0.01 mol), chloroacetic acid (0.94 g, 0.01 mol) and sodium acetate (0.1 g) in abs. ethanol (20 ml) was refluxed for 10 h. The formed precipitate was filtered, dried and recrystallized from chloroform to give compounds **9a** and/or **9b** respectively (Tables 1,2)

3-[4-(1,2,3,4-Terahydronaphthalen-6-yl) thiazol-2-ylamino]-1-cyclohexyl (or 1-phenyl)-dihydro-2-thioxopyrimidin-4,6 (1H,5H)-diones (10a,b)

A mixture of the thiosemicarbazide **8c** (or **8d**) (0.01 mol) and malonic acid (1g, 0.01 mol) in abs. EtOH (20 ml) was refluxed for 15 h. The reaction mixture was cooled and poured onto ice/cold water with few drops of HCl acid. The formed precipitate was filtered , dried and recrystallized from ethanol to give compounds **10a,b** respectively (Tables 1,2)

2-[3-Cyclohexyl-4-phenyl-or (3,4-diphenyl)-thiazol-2(3H)-ylidene]-1-[4-(1,2,3,4-tetrahydronaphthalen-6-yl)-thiazol-2-yl]-hydrazines (11a,b)

A mixture of the thiosemicarbazide **8c** (or **8d**) (0.01 mol) and phenacyl bromide (1.9 g, 0.01 mol) in abs. EtOH (20 ml) was refluxed for 8 h. Ethanol was evaporated under reduced pressure and the formed precipitate was filtered, washed with $K2CO_3$ solution, dried and recrystallized from ethanol to give compounds **11a,b** respectively. (Tables 1,2).

1-[4-(1,2,3,4-Tetrahydronaphthalen-6-yl)-thiazol-2-yl]-2-tosyl-hydrazine (12a), 2-chloro-N-[4-(1,2,3,4-tetrahydronaphthalen-6-yl)-thiazol-2-yl]-acetohydrazide(12b), 2-{2-[4-(1,2,3,4-tetrahydronaphthalen-6-yl)-thiazol-2-yl]hydrazinyl}-acetamide (12c) and 1-{2-[4-(1,2,3,4-tetrahydronaphthalen-6-yl)-thiazol-2-yl]-hydrazinyl}-propan-2-one (12d)

General method

A mixture of the starting hydrazine derivative **2** (2.45 g, 0.01 mol) and the appropriate alkyl halide, namely, 4-methylbenzene-1-sulphonylchloride, 2-chloroacetyl chloride, 2-chloroacetamide and chloroacetone (0.01 mol) in abs. EtOH (30 ml) was refluxed for 6h. The reaction mixture was cooled and poured onto ice/cold water. The formed precipitate was filtered , dried and recrystallized from ethanol to give compounds **12a-d** respectively (Tables 1,2).

5-(1,2,3,4-Tetrahydronaphthalen-6-yl)-thiazolo[2,3-c][1,2,4]triazole (13)

A mixture of compound **2** (0.49 g, 0.002 mol) triethylorthoformate (0.29 ml, 0.002 mol) in ethanol (20 ml) was refluxed for 8 h. The solvent was evaporated under reduced pressure. After cooling, the formed precipitate was filtered, dried and recrystallized from ethanol to give compound **13** in 65% yield, m.p. 178-9^{o}C . Analysis: $C_{14}H_{13}N_3S$ (225.3) Calcd., C, 65.85, H, 5.13, N,16.45 , Found, C, 66.19, H, 5.45, N, 16.84%, MS, showed M+ at m/z 255(3.03 %), and the base peak at m/z 128(100%) of C_9H_6N.

5-(1,2,3,4-Tetrahydronaphthalen-6-yl)-3-methylthiazolo[2,3-c][1,2,4]triazole (14)

A mixture of compound **2** (0.49g, 0.002 mol) and acetic anhydride (0.2 ml, 0.002 mol) in abs. EtOH (20 ml) was refluxed for 6h. The reaction mixture was cooled and poured onto ice/cold water with few drops of HCl acid. The formed precipitate was filtered, dried and recrytallized from ethanol/H2O to give compound **14** in 60% yield, m.p. 128-9^{o}C.

Analysis, $C_{15}H_{15}N_3S.H_2O$ (287.4), Calcd., C, 62.68, H, 5.26, N, 14.62., Found, C, 63.03, H, 5.58, N, 15.12%. ^{1}HNMR spectrum ($CDCl_3$, δ ppm) showed signals at 1.6-1.8(m, 4H,2 CH_2), at 2.4(s, 3H, CH_3), at 2.6-2.8 (m, 4H,2 CH_2), and at 7.1-7.9 (m, 4H, Ar-H and thiazole ring protons). Its MS showed the molecular ion peak (the base peak) M+ of ($C_{15}H_{15}N_3S$. H_2O) at m/z 287 (100%).

5-(1,2,3,4-Tetrahydronaphthalen-6-yl)-thiazolo[2,3-c][1,2,4]triazol-3(2H)-one (15)

A mixture of compound **2** (0.49 g, 0.002 mol), and ethyl chloroformate (0.21 ml, 0.002 mol) in pyridine (10 ml) was refluxed for 8 h. The reaction mixture was cooled and poured onto ice/cold water with few drops of HCl acid. The formed precipitate was filtered off, dried and recrystallized from ethanol to give compound **15** in 70 % yield, m.p. 150-1^{o}C.

Analysis, $C_{14}H_{13}N_3OS$ (271.34) , Calcd., C,61.97, H,4.82, N, 15.48, Found, C, 62.36, H,5.05, N,15.95%., IR spectrum (KBr, cm-1), showed bands at 3189 (NH), at 2924 (-CH_2- of tetralin), and at 1687 (C=O, cyclic amide). Its MS showed the molecular ion peak M+ ($C_{14}H_{13}N_3OS$) at m/z 271 (38.23%).

6-(1,2,3,4-Tetrahydronaphthalen-6-yl)-2H-thiazolo[2,3-c][1,2,4]triazin-3,4-dione (16)
A mixture of compound 2 (0.49g, 0.002 mol) and diethyloxalate (0.29 ml, 0.002 mol) in abs. EtOH (20 ml) was refluxed for 10 h. The reaction mixture was cooled, and poured onto ice/cold water with few drops of HCl acid. The formed precipitate was filtered, dried and recrystallized from ethanol to give compound **16** in 80% yield, m.p. 222-3^{o}C. Analysis, $C_{15}H_{13}N_3O_2S$ (299.36) Calcd. C, 60.18, H,4.37, N,14.03, Found, C, 60.60, H, 4.84, N, 14.41%. IR.spectrum (KBr, cm-1) showed bands at 3155 and 3057 (NH), at 2923 (CH_2 of tetralin), at 1739, 1641 (cyclic diketone) and at 1612 (C=N). Its MS showed (M-1)+ of ($C_{15}H_{12}N_3O_2S$) at m/z 298(4.5%).

2-Chloro-4-(1,2,3,4-tetrahydronaphthalen-6-yl)-thiazole (18)
A mixture of 2-amino-4-(1,2,3,4-tetrahyronaphthalen-6-yl) thiazole **(17)** [1, 16], (2.3 g, 0.01 mol) in 20 ml of sulphuric acid, then the solution of 10 g of CuSO4, 4.7 g of NaCl in 25 ml of water was added at 0^{o}C with stirring , then a solution of 1.5 g of sodium nitrite in 5 ml water was added with continous stirring. The reaction mixture was poured onto ice/cold water, the formed precipitate was filtered off, dried and recrystallized from ethyl alcohol to give compound **18** in 65% yield, m.p. 180-1 ^{o}C. Analysis, $C_{13}H_{12}ClNS$ (249.7), Calcd. C, 62.51, H, 4.84, N, 5.60; Found, C, 62.27, H, 4.41, N, 5.24%. Its IR spectrum (KBr, cm-1) showed only bands at 2924 (CH_2 aliphatic) and no bands of amino group while its MS showed the molecular ion peak (the base peak) M+ at m/z 249.5 and 251.5 ($C_{13}H_{12}ClNS$) due to chlorine isotope.

1-{4-[4-(1,2,3,4-Tetrahydronphthalen-6-yl)-thiazol-2-ylamino]phenyl}ethanone (19a) and Ethyl 4-[4-(1,2,3,4-tetrahydronaphthalen-6-yl)thiazol-2-ylamino]benzoate (19b)
General method
A mixture of the chloro derivative **18** (0.49 g, 0.002 mol) and p-aminoacetophenone/or ethyl 4-aminobenzoate (0.002 mol) in ethanol (50 ml) and few drops of HCl acid, was refluxed for 4 h, then the reaction mixture was cooled and poured onto ice/cold water. The formed precipitate was filtered off, dried and recrystallised from the proper solvent. Compound **19a**, 68% yield , m.p. 133-4 ^{o}C, from $CHCl_3$

Analysis, $C_{21}H_{20}N_2OS$ (348.5), Calcd. C, 72.38, H, 5.78, N, 8.03, Found, C, 72.88, H, 6.09, N, 8.42%. Its IR spectrum (KBr, cm-1) showed absorbance bands at 2925 (CH2 of tetralin) and at 1676 (C=O, acetyl). Its ^{1}HNMR spectrum($CDCl_3$, δ ppm) showed signals at 1.6-1.8 (m, 4H, 2 CH_2), at 2.6-2.8(m, 4H, 2 CH_2) ,at 3.5 (s, 3H, CH_3), and at 7.1 -7.9(m, 8H,Ar-H and thiazole protons). Its MS showed M+ at m/z 348 (10.16%) while the base peak appeared at m/z 231 (100%) due to $C_{13}H_{15}N_2S$.

19b, 61% yield, m.p. 173-4 ^{o}C from ethanol
Analysis, $C_{22}H_{22}N_2O_2S$ (378.5), Calcd., C, 69.81, H, 5.85, N, 7.40, Found, C, 70.22, H, 6.35, N, 7.77%. The ^{1}HNMR of 19b ($CDCl_3$, δ ppm) showed signals at 1.3 (t, 3H, CH_3), at 1.6-1.8(m, 4H, 2 CH_2), at 2.6-2.8(m, 4H, 2 CH_2), at 4.3 (q, 2H, CH2 of ethyl) and at 7.1-7.9(m, 8H, Ar-H and thiazole protons). Its MS showed M+ at m/z 378 (100%) for ($C_{22}H_{22}N_2O_2S$).

4-[4-(1,2,3,4-Tetrahydronaphthalen-6-yl)thiazol-2-ylamino]benzohydrazide (20)
The hydrazide derivative of **19b** was prepared by allowing a mixture of (0.38 g, 0.001 mol) of **19b** and hydrazine hydrate (0.035 g, 0.001 mol) in 4 ml of ethanol to reflux for 6 h. The formed precipitate obtained after evaporation of volatile matrials was filtered off, dried and crystallized from chloroform to give compound **20** in 58% yield, m.p. 166-7^{o}C, Analysis, $C_{20}H_{20}N_4OS$ (364.5), C, 65.90, H,5.53, N, 15,37, Found, C, 65.63, H, 5.03, N, 14.99%.

Its IR spectrum (KBr, cm-1) showed absorbance bands at 3271,3186 (NH, NH_2 groups), at 2924 (CH_2 of tetralin) and at 1630(CO-NH). Its MS showed the expected molecular ion peak M+ at m/z 364 (1.7%) and the base peak at m/z 230 (100%) due to $C_{13}H_{14}N_2S$.

1-{4-[4-(1,2,3,4-Tetrahydronaphthalen-6-yl)thiazol-2-ylamino]phenyl}-3-(4-methoxyphenyl)prop-2-en-1-one (21)

A mixture of the ketone **19a** (3.48 g, 0.01 mol), and p-anisaldehyde (1.36 g, 0.01 mol) in 20 ml of ethanolic NaOH soln. 10%, was refluxed for 10 h. The solvent was evaporated under reduced pressure to half its volume and the formed precipitate was filtered off, washed with cold water and recrystallized from ethanol to give 60% yield of **21**, m.p. 147-8^{o}C., Analysis, $C_{29}H_{26}N_2O_2S$ (466.6), Calcd., C, 74.64, H, 5.61, N, 6.00; Found,
C, 74.46, H, 5.11, N, 5.84% . Its IR spectrum(KBr, Cm-1), showed bands at 3426(NH), at 2928(-CH2-), and at 1680 (C=O chalcone), its ^{1}HNMR ($CDCl_3$, δ ppm) showed signals at 1.6-1.8 (m, 4H,2CH_2), at 2.6-2.8(m, 4H, 2CH_2), at 3.8 (s, 3H, OCH_3) and at 7.1-7.9(m, 14H, Ar-H, -CH=CH- and thiazole protons). Its MS showed M+ at m/z 466(39.41%), and the base peak at m/z 186 (100%) for $C_{11}H_8NS$.

N-{4-[4,5-Dihydro-5-(4-methoxyphenyl)-1H (or 1- phenyl) -pyrazol-3-yl]phenyl}-4-(1,2,3,4-tetrahydronaphthalen-6-yl)thiazole-2-amines (22a,b)

General method

A mixture of the chalcone derivative **21** (4.6 g, 0.01 mol) and hydrazine hydrate (99%), (or phenyl hydrazine) (0.01 mol) in 10 ml of abs. ethanol was refluxed for 8 h. The reaction mixture was cooled and poured onto ice/cold water. The formed precipitate was filtered off, dried and crystallised from the proper solvent to give the pyrazoles **22a**,**b** respectively **(Tables 1,2).**

4-{4-[4-(1,2,3,4-Tetrahydronaphthalen-6-yl)thiazol-2-ylamino]phenyl}-5,6-dihydro-6-(4-methoxyphenyl)-pyrimidin-2(1H)thione (23)

A mixture of the chalcone derivative 21 (4.6 g, 0.01 mol) and thiourea (0.76 g, 0.01 mol) in 20 ml of ethanolic NaOH soln. (10%), was refluxed for 8 h. The reaction mixture was cooled and poured onto ice/cold water acidified with few drops of HCl acid. The formed precipitate was filtered off, dried and recystallized from chloroform to give 23 in 72% yield, m.p. 122-4^{o}C. Analysis, $C_{30}H_{28}N_4OS_2$ (524.7), Calcd., 68.67, H, 5.37, N, 10.67, Found, C, 69.05, H, 5.66, N, 11.11%. Its MS showed [M-1]+ at m/z 523 (4.6%) and the base peak at m/z 231 (100%) due to $C_{13}H_{15}N_2S$

4-[4-(1,2,3,4-Tetrahydronaphthalen-6-yl)thiazol-2-ylamino]-sulphanilamides (24a-e)

General method

A mixture of the chlorothiazole derivative **18** (0.49g, 0.002 mol) and the appropriate sulfa drug, namely, sulphanilamide, sulphapyridine, sulphadiazine, sulphamethoxazole and/or sulphaisoxazole (0.002 mol) in 20 ml abs. ethanol and a few drops of HCl acid was refluxed for 10 h. The reaction mixture was concentrated under reduced pressure. The formed precipitate obtained on cooling was filtered off , dried and recrystallised from ethanol to give compounds **24a-e** respectively **(Tables 1,2)**

Anticancer screening

Eleven compounds were selected for the screening : **2, 4a, 5b, 7, 8e, 9a, 10b, 12a, 16, 22a** and **24d** Four concentrations were taken of each compound: 1, 2.5, 5 and 10 μg/mL

Cells

Two human cell lines were used in this experiment: **a**. Human liver carcinoma cell line **(HepG2)** and **b.** human breast carcinoma cell line **(MCF7) .**

Stock cultures were grown in **T-75** flasks containing 50 mL of **RP Mi-1640** Medium with glutamine bicarbonate and 5% fetal calf serum. Medium was changed at 48 h intervals. Cells were dissociated with 0.25% trypsin. Experimental cultures were plated in micrititer plates (Costar, Cambridge, **MA**). Containing 0.2 mL of growth medium per well at densities of 1,000-200.000 cells per well.

Cell fixation

Cells attached to the plastic substratum were fixed by gently laying 50 *u*L of cold 50% **TCA** (**4**^{o}C) on top of the growth medium in each well to produce a final **TCA** concentration of 10%. The cultures were incubated at **4**^{o}C for one hour and then washed five times with tap water to remove **TCA**, growth medium and low – molecular weight metabolites, and serum protein. Plates were air dried and then stored until use. Background optical densities were measured in wells incubated with growth medium without cells.

Dying

The anionic dye sulforhodamine **B (SRB, Sigma Chemical Co.)** was dissolved in 1% acetic acid for staining and extracted from cells with 10 mM unbuffered Tris base [tris(hydroxymethyl)aminomethane].

SRB Assay

TCA-fixed cells were stained for 30 min with 0.4% (w/v) **SRB** dissolved in 1% acetic acid . At the end of the staining period, SRB was removed and cultures were quickly rinsed four times with 1% acetic acid to remove unbound dye. The acetic acid was poured directly into permitted rinsing to be performed so quickly that desorption of protein-bound dye did not occur. Residual solution was removed by sharply flicking plates over a sink, which ensured the complete removal of rinsing solution. Because of the strong capillary action in 96-well plates, draining by gravity alone often failed to remove the rinsing solution when plates were simply inverted. After being rinsed, the cultures were air dried until no standing moisture was visible. Bound dye was solubilized with 10 mM unbuffered Tris base (pH 10.5) for 5 min on gyratory shaker.

OD (optical density) was read on a **UVmax** microtiter plate reader (Molecular Devices, Menlo Park, **CA**) at **564** nm for maximum sensitivity.

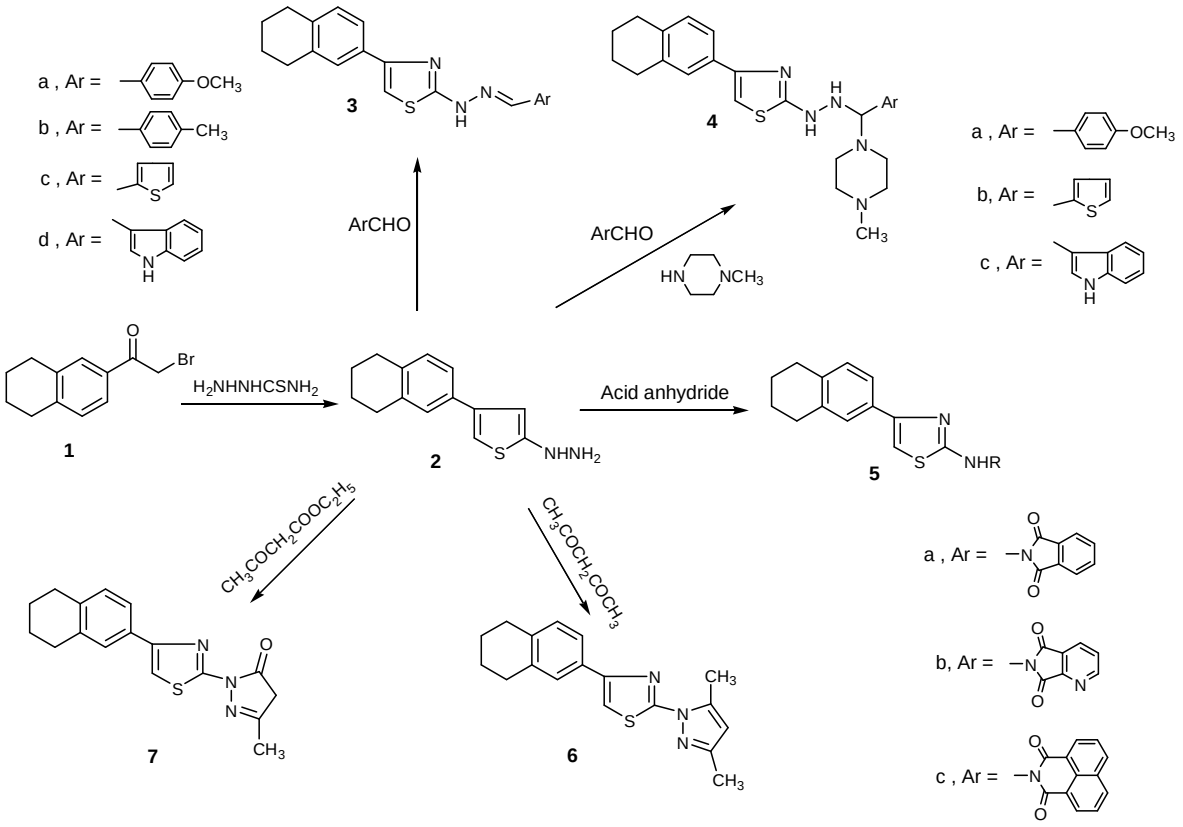
RESULTS AND DISCUSSION

Chemistry

Starting from 2-hydrazino-4-(1,2,3,4-tetrahydronaphthalen-6-yl)-thiazole **(2)** which is prepared by the reaction of 6-bromoacetyl-1,2,3,4-tetrahydronaphthalene**(1)** [16] with thiosemicarbazide, a novel series of tetrahydronaphthalen-6-ylthiazolyl heterocycles , such as pyrazoles, pyrazolones, thiazolidinones, pyrimidinethiones, pyrimidinones, thiazolotriazoles, thiazolotriazines and other related derivatives for the purpose of evaluation of their anticancer activity. Synthesis of the target compounds was achieved by condensation of the hydrazino derivative **2** with different aromatic aldehydes, such as p-anisaldehyde, p-tolualdehyde, thiophene-2-carboxaldehyde and indole-3-carboxaldehyde, to give the corresponding Schiff bases **3a-d** respectively. On the other hand, reaction of compound **2** with different aromatic aldehydes, namely, p-anisaldehyde, thiophene-2-carboxaldehyde and indole-3-carboxaldehyde in presence of methylpiperazine, condensation followed by addition reaction on the azomethene

group took place in one step [17] to give the corresponding 2-aryl-(4-methylpiperazin-1-yl)-1-[4-(1,2,3,4-tetrahydro naphthalen-6-yl) hydrazines **(4a-c)** respectively.

Also, reaction of **2** with different acid anhydrides, namely, phthalic anhydride, 2,3-pyridine dicarboxylic acid anhydride and 1,8-naphthalene dicarboxylic acid anhydride , afforded the corresponding cyclic imides **5a-c,** respectively according to reported method [10] . Moreover, reaction of **2** with a B-diketone (e.g. acetylacetone), or a B-ketonic ester (e.g. ethyl acetoacetate), afforded the corresponding dimethyl- pyrazole derivative **6** or the pyrazolone derivative **7** respectively. **(Scheme 1)**



Scheme 1

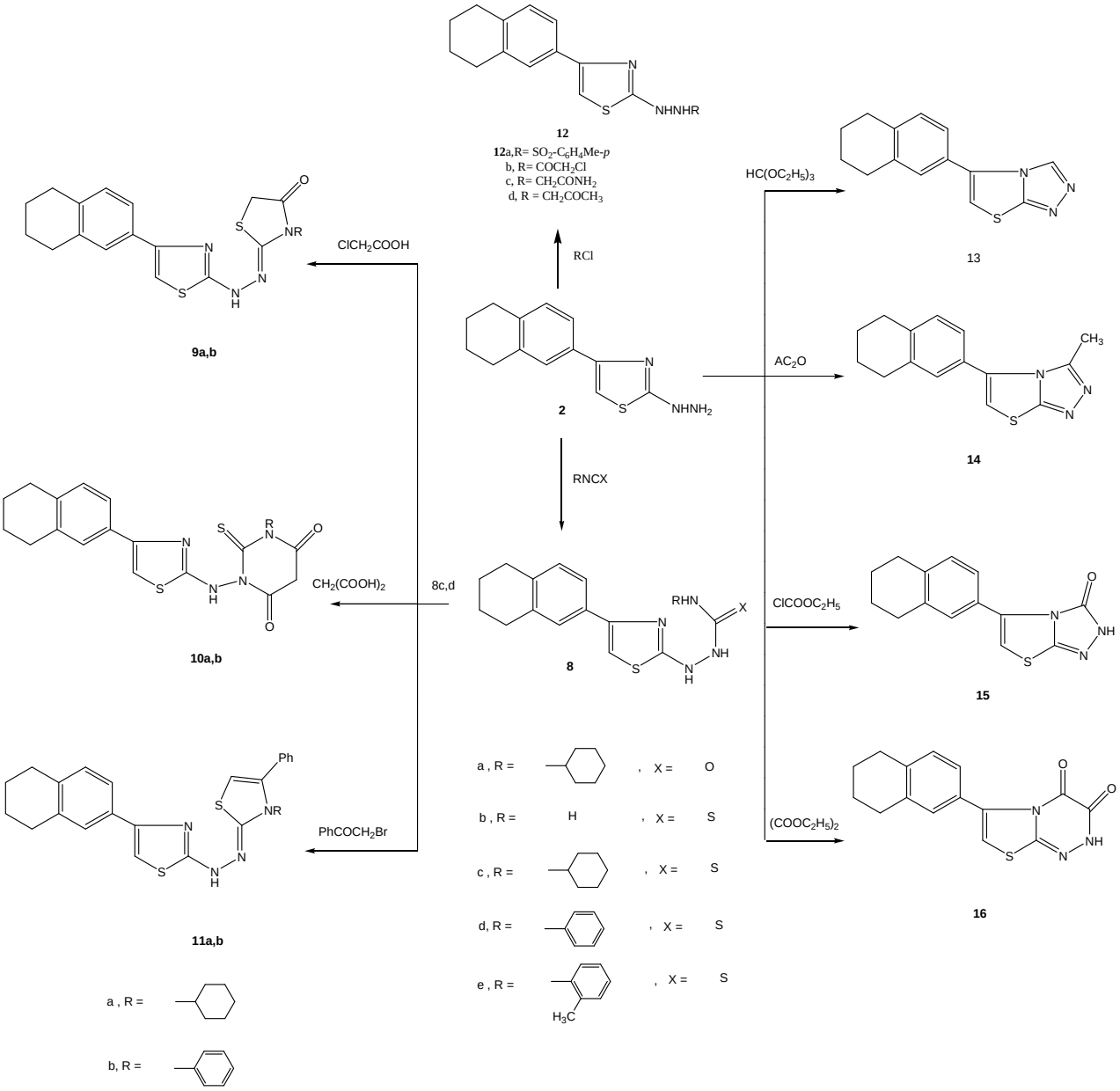
It has been reported that several chemotherapeutic activities were ascribed to certain substituted semicarbazides and thiosemicarbazides especially as antimicrobial[18-22] or antineoplastic agents [23-25], besides its reactivity as intermediates for the synthesis of different heterocycles of biological importance [26]. In this work, it was of our interest to incorporate both of semi and thiosemicarbazide moieties to the parent hydrazino derivative **2** in order to obtain another series of safer anticancer agents. Thus, condensation of the hydrazine derivative **2** with cyclohexyl- isocyanate, ammonium thiocyanate, cyclohexyl, phenyl and/ or o-tolylisothiocyanates, afforded the corresponding thiazol-2-ylsemicarbazide **8a** and/ or thiazol-2-ylthiosemicarbazides **8b-e** respectively.

Upon reaction of the thiosemicarbazides **8c** and/or **8d** with chloroacetic acid, cyclocondensation reaction took place to give the iminothiazolidinone derivatives **9a,b** respectively, while their cyclocondensation with malonic acid, afforded the corresponding dihydro-2-thioxopyrimidin-4,6-(1H,5H)-diones **10a,b** respectively. Also, reaction of **8c** or **8d**

with phenacyl bromide, gave the corresponding (4-phenyl- thiazol-2(3H)-ylidene)-hydrazine derivatives **11a,b** respectively. **(Scheme 2)**

On the other hand, reaction of the hydrazino derivative **2** with different halides,namely, p-toluene sulphonylchloride, chloroacetyl chloride, chloro acetamide and/or chloro acetone , afforded the corresponding substituted hydrazines **12a-d** respectively.

Moreover, cyclocondensation reaction of **2** with triethyl- orthoformate, acetic anhydride, ethyl chloro formate and/or diethyl oxalate, afforded the corresponding fused binary systems, thiazolo[2,3-c][1,2,4]triazoles **13,14,** thiazolo[2,3-c][1,2,4]triazol-3(2H)-one **15** and/or the thiazolo[2,3-c][1,2,4]triazine-3,4-dione **16,** derivatives respectively**. (Scheme 2)**



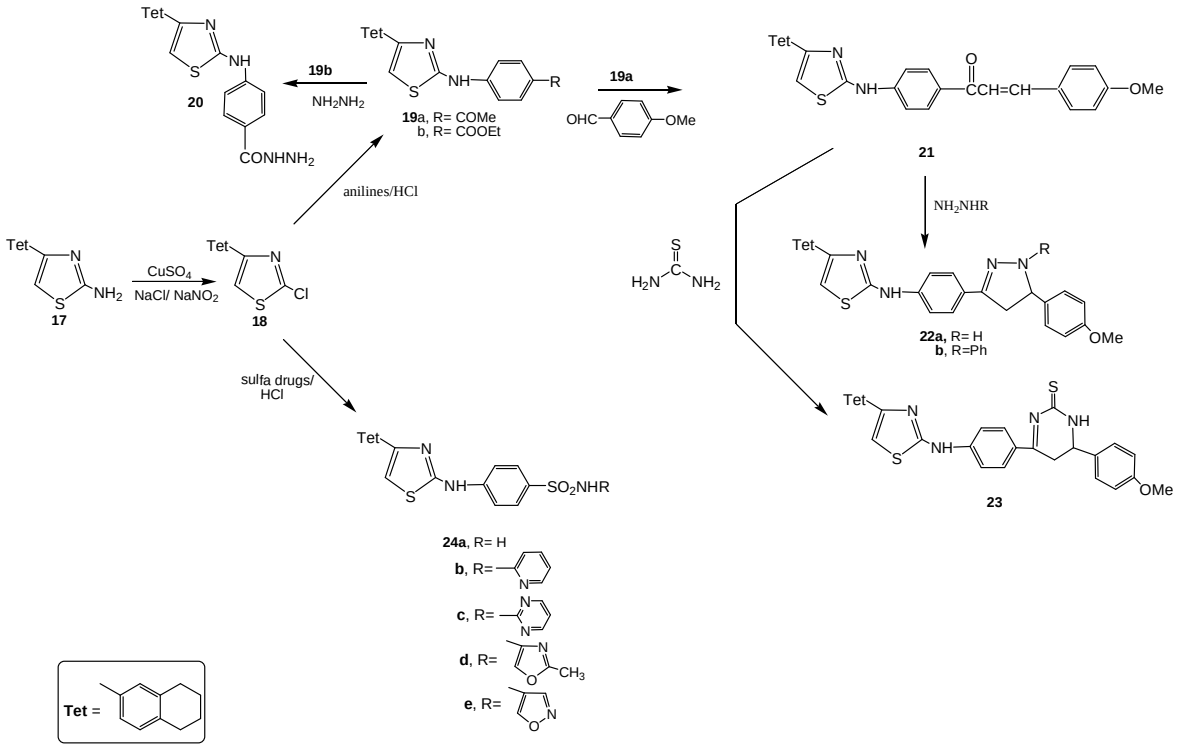
Scheme 2

Moreover**,** it was of interest to synthesize another related derivatives of the tetrahydronaphthylthiazoles series starting from the new 2-chloro-4-(1,2,3,4-

tetrahydronaphthalen-6-yl)thiazole **(18),** obtained from the known 2-amino derivative **17** [1,16] via Sand-Mayer reaction **.** Reaction of **18** with p-aminoacetophenone and/or ethyl-p-aminobenzoate in presence of HCl, afforded the corresponding 2-(p-substituted anilino)thiazole **19a** and/or **19b** respectively. The benzohydrazide **20** was obtained by reaction of the benzoic acid ester **19b** with hydrazine hydrate **(Scheme 3).**

Reaction of the acetyl derivative **19a** with p-anisaldehyde afforded the corresponding propenone (chalcone) derivative **21** which upon reaction with hydrazines gave the corresponding pyrazoline derivatives **22a,b**, while upon its reaction with thiourea , it gave the corresponding pyrimidin-thione derivative **23**.

Furthermore, reaction of the chlorothiazole derivative 18 with different sulpha drugs in presence of HCl, afforded the corresponding 4-[4-(1,2,3,4-tetrahydronaphthelen-6-yl)thiazol-2-ylamino]-sulphanilamides (24a-e). **(Scheme 3)**



Scheme 3

All compounds were subjected to microchemical and spectral analyses (IR, ^{1}HNMR and MS)

Tables 1 and 2.

Anticancer screening

Anticancer activity

Eleven compounds, number 2, 4a, 5b, 7, 8e, 9a , 10b, 12a, 16, 22a and 24d were selected for testing for their anticancer activity, at the Department of Tumor Pathology, National Cancer Institute, Cairo, Egypt. Two cell lines were used for the evaluation (human liver carcinoma cell line HePG2 and human breast carcinoma cell line MCF7) according to the method described by Skehan et al. [27]

The results are expressed in the form of the concentration of compound that causes 50% inhibition of cells growth. The *in vitro* evaluation revealed the tested compounds exhibit

significant anticancer activities against both of the liver cancer and the breast cancer at specified concentrations. The data of the selected eleven tetralin-6-ylthiazoles evidenced that compounds **2** and **8e** were the most effective against **HepG2** carcinoma cell lines showing IC_{50} of 0.47 μg/mL for each one, and compounds **7**, **9b** and **16** are less active showing IC50 of 54 ug/mL, whereas compounds **4a**, **5b**, **9a** and **16** were the most effective against **MCF7** carcinoma cell line showing IC50 of 0.40 μg/mL for each one and compounds **2**, **8e** and **10b** were less active showing IC50 of 0.47 μg/mL. All other compounds are moderately active. (Table 3)

Table 1. **Physical and analytical data of the new synthesized compounds**

Comp. No.	**m.p.(°C)** (Cryst.solvent)	**Yield** (%)	**Mol. Formula** (Mol. Wt.)	**Analysis (%)** Calcd. / Found		
				C	**H**	**N**
3a	140-1	70	$C_{21}H_{21}N_3OS$	69.39	5.82	11.56
	(EtOH)		(363.49)	69.76	6.16	12.02
3b	163-4	88	$C_{21}H_{21}N_3S$	72.58	6.09	12.09
	(EtOH)		(347.49)	72.72	6.49	12.22
3c	148-9	87	$C_{18}H_{17}N_3S_2$	63.68	5.04	12.37
	(EtOH)		(339.48)	63.34	4.66	12.02
3d	152-4	84	$C22H_{20}N_4S$	70.93	5.41	15.04
	(EtOH)		(372.50)	70.43	5.15	14.74
4a	121-2	80	$C_{26}H_{33}N_5OS$	67.35	7.17	15.10
	(Dioxane)		(463.65)	67.67	7.53	15.40
4b	155-7	60	$C_{23}H_{29}N_5S_2$	62.83	6.64	15.92
	(Dioxane)		(439.64)	62.62	6.16	15.55
4c	141-2	76	$C_{27}H_{32}N_6S$	68.61	6.82	17.78
	(Dioxane)		(472.66)	69.11	7.22	18.08
5a	120-1	70	$C_{21}H_{17}N_3O_2S$	67.18	4.56	11.19
	(dil.AcOH)		(375.45)	66.86	4.09	10.69
5b	133-4	60	$C_{20}H_{16}N_4O_2S$	63.81	4.28	14.88
	(dil. AcOH)		(376.45)	64.31	4.54	15.09
5c	146-7	81	$C_{25}H_{19}N_3O_2S$	70.56	4.50	9.87
	(dil. AcOH)		(425.52)	70.22	4.33	9.69
8a	164-5	60	$C_{20}H_{26}N_4OS$	64.83	7.07	15.12
	(EtOH)		(370.53)	64.44	6.86	14.62
8b	125-6	70	$C_{14}H_{16}N_4S_2$	55.23	5.29	18.40
	(EtOH)		(304.44)	55.55	5.46	18.88
8c	205-7	65	$C_{20}H_{26}N_4S_2$	62.13	6.77	14.49
	(EtOH)		(386.59)	62. 47	7.17	14.99
8d	185-7	73	$C_{20}H_{20}N_4S_2$	63.12	5.29	14.72
	(EtOH)		(380.54)	63.36	5.57	15.15
8e	190-2	78	$C_{21}H_{22}N_4S_2$	63.92	5.61	14.20
	(EtOH)		(394.56)	63.77	5.11	13.83
9a	178-8	60	$C_{22}H_{26}N_4OS_2$	61.93	6.14	13.13
	($CHCl_3$)		(426.61)	62.43	6.46	13.33

9b	145-6	55	$C_{22}H_{20}N_4OS_2$	62.83	4.79	13.32
	($CHCl_3$)		(420.56)	62.33	4.44	12.82
10a	190-1	68	$C_{23}H_{26}N_4O_2S2$	60.76	5.76	12.32
	(EtOH)		(454.62)	60.26	5.26	12.12
10b	178-9	70	$C_{23}H_{20}N_4O_2S_2$	61.58	4.49	12.49
	(EtOH)		(448.57)	61.12	3.99	12.02
11a	134-5	56	$C_{28}H_{30}N_4S_2$	69.09	6.21	11.51
	(EtOH)		(486.71)	68.59	5.88	11.11
11b	125-6	63	$C_{28}H24N4S2$	69.96	5.03	11.65
	(EtOH)		(480.66)	70.46	5.33	12.05
12a	160-1	85	$C_{20}H_{21}N_3O_2S_2$	60.12	5.29	10.51
	(EtOH)		(399.54)	60.60	5.55	10.91
12b	131-2	64	$C_{15}H_{16}ClN_3OS$	55.98	5.01	13.05
	(EtOH)		(321.84)	55.77	4.89	12.55
12c	146-7	70	$C_{15}H_{18}N_4OS$	59.57	5.99	18.52
	(EtOH)		(302.41)	59.09	5.65	18.36
12d	156-8	73	$C_{16}H_{19}N_3OS$	63.75	6.35	13.94
	(EtOH)		(301.42)	64.16	6.64	14.20
22a	134-5	76	$C_{29}H_{28}N_4OS$	72.47	5.87	11.65
	(dil AcOH)		(480.5)	72.22	5.37	11.15
22b	136-7	66	$C_{35}H_{32}N_4OS$	75.50	5.79	10.06
	($CHCl_3$)		(556.7)	76.00	5.99	10.36
24a	115-6	83	$C_{19}H_{19}N_3O_2S_2$	59.19	4.96	10.89
	(EtOH)		(385.51)	59.43	5.35	11.06
24b	132-4	63	$C_{24}H_{22}N_4O_2S_2$	62.31	4.79	12.11
	(EtOH)		(462.59)	62.59	5.05	12.61
24c	196-7	75	$C_{23}H_{21}N_5O_2S_2$	59.59	4.56	15.10
	(EtOH)		(463.58)	60.09	5.00	15.55
24d	160-2	60	$C_{23}H_{22}N_4O_3S_2$	59.20	4.75	12.00
	(EtOH)		(466.58)	59.66	5.25	12.33
24e	146-7	58	$C_{22}H_{20}N_4O_3S_2$	58.38	4.45	12.38
	(EtOH)		(452.56)	57.90	3.95	11.91

Table 2. Spectral data of the new synthesized compounds

Comp. No.		MS [m/z (%)]; ^{1}H NMR[solvent] , δ ppm; IR [KBr, v cm^{-1}]
3a	MS	365 [M+2]+ (5), 160 (C_9H_6NS) (100)
	^{1}HNMR	[$CDCl_3$], 1.60-1.80(m,4H, 2 CH_2 of tetralin), 2.64-2.80 (m, 4H, 2 CH_2 of tetralin), 3.80(s, 3H, OCH_3), 6.90-7.90 (m, 9H, Ar-H, thiazole and CH=N protons)
3b	^{1}HNMR	[DMSO-d_6], 1.60-1.80(m,4H, 2 CH_2 of tetralin), 2.60 (s, 3H, CH_3), 2.70-2.80(m, 4H, 2CH_2 of tetralin), 4.2(s, 1H, NH),7.10-7.80 (m, 9H, thiazole, Ar-H and CH=N).
	IR	3157,3072 (NH), 2924 (CH_2 of tetralin) , 1644 (C=N)
3c	MS	339 [M+] (25), 213 ($C_{12}H_{11}NS$)(100)
3d	MS	371 [M-1]+ (5%), 146 (C_9H_6S) (100%)
	IR	3161-3046(NH), 2926 (CH2 of tetralin), 1630(C=N)

4a	^{1}HNMR	[$CDCl_3$], 1.60-1.80 (m, 4H, 2 CH_2 of tetralin), 2.3 (s, 3H, CH_3), 2.40-3.00 (m, 13 H, methylene protons of tetralin and methyl piperazine), 3.80 (s, 3H, OCH3), 4.00(s, 1H, CH-N), 6.80-7.90(m, 8H, thiazole and Ar-H protons).
4b	MS	440 [M+1]+ (1.7), 213 ($C_{13}H_{11}NS$) (100).
	IR	3413,3157 (NH), 2923 (CH_2 of tetralin) 1683 (C=N
4c	MS	472 [M+] (2.85), 159 (C9H5NS) (100)
	IR	3410 (NH), 2923 (CH_2 of tetralin), 1612 (C=N)
5a	MS	376 [M+1]+ (5), 213 ($C_{13}H_{11}NS$)(100)
	IR	3168 (NH), 2926 (CH2 of tetralin), 1787, 1729 (CO-cyclic amide) , 1664 (C=N)
5b	MS	376 [M+] (1.7), 213 ($C_{13}H_{11}NS$) (100)
	IR	3307 (NH), 2928 (CH_2 of tetralin), 1769, 1702(CO – cyclic amide), 1660 (C=N)
5c	MS	425 [M+] (55.88), 393 ($C_{25}H_{19}N_3O_2$) (100)
8a	MS	370 [M+] (1.76), 159 (C_9H_5NS) (100)
8b	MS	304 [M-1]+ (7.3), 157 ($C_{11}H_{11}N$) (100)
8c	MS	386 [M+] (7.87), 230 ($C_{13}H_{14}N_2S$) (100)
9a	MS	426 [M+] (64.70), 212, $C_{13}H_{10}NS$ (100)
9b	MS	420 [M+] (42.94), 159 (C_9H_5NS) (100)
	^{1}HNMR	[DMSO-d6], 1.60-1.80 (m, 4H, 2 CH2 of tetralin), 2.4 (s, 2H, CH_2 of thiazolidinone), 2.60-2.80 (m, 4H, 2 CH_2 0f tetralin, 7.10-7.90 (m, 9H, aromatic and thiazole protons)
	IR	3417 (NH), 2924 (CH_2), 1721 (CO, cyclic amide)
10a	MS	454 [M+] (1.69), 231 ($C_{13}H_{15}N_2S$)(100)
	IR	3107-3011 (NH), 2926 (CH_2 of tetralin), 1726 (CO, cyclic amide)
10b	MS	449 [M+1]+ (2.94), 231 ($C_{13}H_{15}N_2S$)(100)
	^{1}HNMR	[DMSO-d6], 1.60-1.80 (m, 4H, 2CH_2 of tetralin), 2.60-2.80 (m, 4H, 2CH2 of tetralin), 3.6(s, 2H, CH_2), 7.1-7.9(m,9H, Ar-H, thiazole protons)
	IR	3396(NH),2927(CH_2,tetralin),1721(CO,cyclic amide),1619(C=N)
11a	MS	487 [M+1]+ (3.0) **,** 229 ($C_{13}H_{13}$N2S) (100)
	IR	3274 (NH), 2923 (CH_2 ,tetralin), 1604 (C=N)
11b	MS	481 [M+1]+ (7.05), 309 ($C_{16}H_{11}N_3S_2$)(100)
	IR	3422, 3354 (NH), 2927 (CH_2, tetralin), 1628 (C=N)
12a	MS	401 [M+2]+ (76), 91 (C_7H_7) (100)
	^{1}HNMR	[DMSO-d6], 1.6-1.8 (m, 4H, 2 CH_2), 2.3 (s, 3H, CH_3), 2.6-2.8 (m,4H, 2 CH_2), 7.10-7.80 (m, 8H , Ar-H and thiazole protons)
12b	IR	3352, 3139 (NH), 2924 (CH_2 of tetralin), 1665 (C=O)
12c	MS	302 [M+] (65)
	^{1}HNMR	[$CDCl_3$], 1.6-1.8 (m, 4H, 2 CH_2), 2.6-2.80 (m, 4H, 2 CH_2), 3.60(s, 2H, CH_2),7.10-7.90 (m, 5H, Ar-H and thiazole protons)
	IR	3278, 3116 (NH_2), 2923 (CH2 of tetralin) , 1611(C=O, amide)
12d	MS	301 [M+] (5), 230 ($C_{13}H_{14}N_2S$) (100)
	^{1}HNMR	[$CDCl_3$] , 1.60-1.80 (m, 4H, 2 CH2), 2.4 (s, 3H, CH3), 2.6-3.0 (m, 6H, 2 CH2, N-CH2), 7.10-7.90 (m, 5H, Ar-H and thiazole)
	IR	3012 (NH), 2926 (CH2 of tetralin), 1613 (C=O)

22a	MS	480 [M+] (10), 340 ($C_{22}H_{16}N_2S$) (100)
	1HNMR	[$CDCl_3$], 1.6-1.8(m, 4H, 2 CH_2),2.6-2.8(m, 4H, 2CH_2),3-3.5 (2dd, 1H-4cis,1H-4trans, pyrazoline),3.7(s, 3H, OCH_3), 5.6(dd, 1H-5, pyrazoline) , 7.1-7.9(m, 12H, Ar-H and thiazole proton)
22b	MS	555 [M-1]+ (1.6), 230 ($C_{13}H_{14}N_2S$)(100)
24a	MS	385 [M+] (22.59), 230 ($C_{13}H_{14}N_2S$) (100)
	IR	3262,3104(NH), 2927 (CH_2 of tetralin)
24b	MS	462 [M+] (1.7), 231($C_{13}H_{15}N_2S$) (100)
24c	MS	463 [M+] (2.8), 159(C_9H_5NS) (100)
	IR	3422,3353 (NH), 2928 (CH_2 of tetralin)
24d	MS	466 [M+] (18.8), 305 ($C_{13}H_{17}N_2S$) (100)

Table 3 Effect of the selected compounds on liver carcinoma cell line (HepG2) and breast carcinoma cell line (MCF7)

Compound	IC50 (µg/mL)	
	HepG2	MCF7
2	0.47 µg/mL	0.47 µg/mL
4a	0.60 µg/mL	0.40 µg/mL
5b	0.87 µg/mL	0.40 µg/mL
7	0.54 µg/mL	0.87 µg/mL
8e	0.47 µg/mL	0.47 µg/mL
9a	0.60 µg/mL	0.40 µg/mL
10b	0.54 µg/mL	0.47 µg/mL
12a	0.94 µg/mL	3.69 µg/mL
16	0.54 µg/mL	0.40 µg/mL
22a	0.87 µg/mL	0.40 µg/mL
24d	0.60 µg/mL	0.60 µg/mL

IC50 : Dose of the compound that reduces the surviving cells by 50%

Acknowlegement
The authors express deep thanks to pharmacological unit of national cancer institute for performing the anticancer screening .

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