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SYNTHESIS AND ANTICANCER ACTIVITY OF NOVEL TETRALIN-6-YLPYRIDINE AND TETRALIN-6-YLPYRIMIDINE DERIVATIVES

KAMELIA M. AMIN[a], MAGDI I. EL-ZAHAR[b] , MANAL M. ANWAR[b], MOHSEN M. KAMEL[b] and MAALY H. MOHAMED[b]

[a] Pharmaceutical Chemistry Department, Faculty of Pharmacy, Cairo University, Egypt
[b] Therapeutic Chemistry Department, National Research Center, Dokki, Cairo, Egypt

Abstract: A series of tetralin-6-ylpyridines and tetralin-6-ylpyrimidines was newly synthesized starting from 1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethanone (**1**). The two groups of derivatives incorporated also different five membered nitrogen-containing heterocycles. The anticancer activity of some of the prepared compounds was evaluated using two human tumor cell lines, representing liver and breast. The compounds tested were, in most of cases, selective towards liver cancer, where the most potent compound showed IC_{50} = 1.01 μg/ mL.

Keywords: tetralin, pyridine, pyrimidine, oxadiazole, triazole, thiadiazole, pyrazoline, thiazolidinone, anticancer activity

Diverse chemotherapeutic activities were ascribed to substituted tetralin (tetrahydronaphthalene)-heterocycles (1-3).

During our previous drug discovery program, different tetralin heterocylic derivatives have been developed and tested as inhibitors of the production of egg masses and carbohydrate metabolism in bilharzia snails (4, 5), antibilharzial (6), antibacterial agents (7, 8), enzyme inhibitors (9), anti HIV and anticancer agents (10). Also, some other derivatives of substituted tetralin-heterocycles were found to possess anti-inflammatory (11) and analgesic activities (12).

In continuation of our previous work and basing on all these findings, it was of interest to synthesize some other safer new tetrahydronaphthalene-nitrogen, oxygen and/or sulfur heterocycles to be evaluated as anticancer agents.

EXPERIMENTAL

Chemistry

All melting points are uncorrected and were taken in open capillary tubes using silicon oil on Gallenkamp apparatus. Elemental microanalyses were performed on Elementar, Vario EL, Microanalytical Unit, National Research Centre, Cairo, Egypt. Infrared spectra were recorded on Jasco FT/IR-330E, Fourier Transform Infrared Spectrometer at cm^{-1} scale using KBr discs.

^{1}H-NMR spectra were determined by using JEOL EX-270 or JEOL ACA500 NMR spectrometers and 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 up by TLC (aluminum 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.

Ethyl 2-(4-aryl-3-cyano-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyridin-2-yloxy)acetate esters (**3a,b**) and 2-(2-oxopropoxy)-4-phenyl-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyridine-3-carbonitrile (**3c**):

A mixture of compound **2a,b** (0.003 mole), 1 g of anhydrous sodium carbonate and the appropriate substituted alkyl halide, namely: ethyl chloroacetate and/or chloroacetone (0.003 mole) in DMF (5 mL) was refluxed for 4 h. The reaction mixture was cooled and poured into ice-cold water acidified with hydrochloric acid. The formed precipitate was filtered off, washed with water and recrystallized from methanol to give compounds **3a-c**, respectively.

* Corresponding author: phone: +20 123571676; fax: +20 33370931; e-mail: melzahar@hotmail.com

2-(4-Aryl-3-cyano-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyridin-2-yloxy)acetohydrazides (**4a,b**)

Compound **3a,b** (0.002 mole) was dissolved in 10 mL of absolute ethanol then an excess of hydrazine hydrate 98% (1 mL) was added and the reaction mixture was refluxed for 3 h. After cooling, the solid produced was filtered off and recrystallized from ethanol to give compounds **4a,b.**

4-Cyclohexyl-1-[2-(4-aryl-3-cyano-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyridin-2-yloxy)acetyl]semicarbazides **(5a,c)** and 4-ethyl-1-[2-(4-aryl-3-cyano-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyridin-2-yloxy)acetyl]thiosemicarbazides **(5b,d)**

A mixture of compound **4a,b** (0.002 mole), the appropriate isocyanate or isothiocyanate, namely; cyclohexyl isocyanate and/or ethyl isothiocyanate (0.002 mole) and few drops of triethylamine in dry benzene (10 mL) was refluxed for 6 h. The solvent was evaporated under reduced pressure. The remaining solid was recrystallized from methanol to give compounds **5a-d**, respectively.

4-Aryl-2-[(5-mercapto-1H-1,2,4-triazol-3-yl)methoxy)]-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyridine-3-carbonitriles **(6a,b)**

A mixture of compound **4a,b** (0.002 mole) and an excess of ammonium thiocyanate (0.5 g; 0.006 mole) was fused in sand bath at 160^{o}C for 1 h. After cooling, the solid product was treated with hot water and filtered off then recrystallized from dilute DMF to give compounds **6a,b,** respectively.

4-(4-Fluorophenyl)-2-[(2,3-dihydro-2-thioxo-1,3,4-oxadiazol-5-yl)methoxy]-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyridine-3-carbonitrile (**7**):

Compound **4b** (4.16 g; 0.01 mole) was dissolved in 2.5% ethanolic potassium hydroxide (30 mL). Then 30 mL of carbon disulfide was added and the mixture was refluxed in water bath at 40^{o}C for 2 h. An excess of carbon disulfide was evaporated under reduced pressure and the residue was poured into ice-cold water acidified with hydrochloric acid. The precipitate formed was filtered off and recrystallized from ethanol to give compound **7**.

4-(4-Fluorophenyl)-2-[(4-amino-4,5-dihydro-5-thioxo-1H-1,2,4-triazol-3-yl)methoxy]-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyridine-3-carbonitrile (**8**)

To a solution of compound **7** (1.37 g; 0.003 mole) in 5 mL DMF, hydrazine hydrate 98% (0.2 g; 0.006 mole) was added dropwise at room temperature with stirring. The mixture was refluxed for 5 h then poured into ice-cold water. The precipitate formed was filtered off, washed with ethanol, and recrystallized from diluted DMF to give compound **8**.

4-(4-Fluorophenyl)-2-[(5,6-dihydro-6-oxothiazolo[3,2-b][1,2,4]triazol-2-yl)methoxy]-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyridine-3-carbonitrile (**9)**

A mixture of compound **6b** (2.28 g; 0.005 mole) and chloroacetic acid (0.47 g; 0.005 mole) in acetic anhydride (25 mL) and acetic acid (50 mL) was refluxed for 6 h. After cooling, the mixture was poured into ice-cold water. The solid produced was filtered off and recrystallized from ethanol to give compound **9.**

4-(4-Fluorophenyl)-2-[(1-substituted-5-mercapto-1H-1,2,4-triazol-3-yl)methoxy]-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyridine-3-carbonitrile **(10a-d)**

A mixture of compound **6b** (0.9 g, 0.002 mole), 0.9 g anhydrous sodium carbonate and the appropriate halide, namely; chloroacetone, benzoyl chloride, methyl iodide and/or ethyl chloroformate (0.002 mole) in 5 mL DMF was refluxed for 7 h. The reaction mixture was cooled then poured into ice-cold water. The solid formed was filtered off and recrystallized from acetic acid to give compounds **10a-d,** respectively.

3-Cyano-4-(4-fluorophenyl)-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyridin-2-yloxyacetyl dithiocarbazate potassium salt **(11)**

Compound **4b** (4.16 g, 0.01 mole) was added with stirring to 50 mL of 0.5% ethanolic potassium hydroxide in ice bath. Then carbon disulfide (2 mL) in absolute ethanol (5 mL) was added dropwise with stirring. The reaction mixture was left at room temperature overnight. The solid produced was filtered off, washed with ethanol and recrystallized from ethanol to give compound **11** as potassium salt.

4-(4-Fluorophenyl)-2-[(2,3-dihydro-2-thioxo-1,3,4-thiadiazol-5-yl)methoxy]-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyridine-3-carbonitrile **(12)**

Compound **11** (3.18 g; 0.006 mole) was added portionwise with stirring to ice-cold conc. sulfuric acid (13 mL). After complete addition, the mixture was left overnight then poured into ice-cold water and neutralized with ammonium hydroxide solution. The precipitate formed was filtered off, washed with water and recrystallized from ethanol to give compound **12**.

4-(4-Fluorophenyl)-2-[(2,3-dihydro-3-methyl-2-thioxo-1,3,4-thiadiazol-5-yl)methoxy]-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyridine-3-carbonitrile **(13)**

Compound **12** (0.95 g; 0.002 mole) was added to 4% ethanolic potassium hydroxide solution (15 mL). Then, methyl iodide (2 mL) was added dropwise with stirring at room temperature. The reaction mixture was left overnight, then an excess of solvent was evaporated under reduced pressure. The residue was washed with water and extracted with chloroform. The organic layer was evaporated under reduced pressure and the solid product was recrystallized from isopropanol to give compound **13**.

4-(4-Fluorophenyl)-2-[(2-methylthio-1,3,4-thiadiazol-5-yl)methoxy]-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyridine-3-carbonitrile **(14)**

A mixture of compound **12** (0.95 g; 0.002 mole) and methyl iodide (2 mL) in 4% ethanolic potassium hydroxide solution (15 mL) was heated in water bath at 60^{o}C for 6 h. An excess of solvent was evaporated under reduced pressure and the residue was washed with water and extracted with chloroform. The organic layer was evaporated under reduced pressure and the product was recrystallized from ethanol to give compound **14**.

4-(4-Fluorophenyl)-2-[(3-aminomethyl-2,3-dihydro-2-thioxo-1,3,4-thiadiazol-5-yl)methoxy]-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyridine-3-carbonitriles **(15a,b)**

A mixture of the appropriate secondary amine, namely: piperidine and/or morpholine (0.0006 mole) and paraformaldehyde (0.054 g; 0.0006 mole) was dissolved in hot absolute ethanol (10 mL). A solution of compound **12** (0.28 g, 0.0006 mole) in hot absolute ethanol (10 mL) was added to the previous solution with stirring. The mixture was refluxed for 24 h. Then, an excess of solvent was evaporated under reduced pressure. The residue formed was treated with petroleum ether, collected and recrystallized from ethanol to give compounds **15a,b,** respectively.

1-[4-(4-Fluorophenyl)-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyrimidin-2-yl]hydrazine **(18)**

A mixture of compound **17** (1 g; 0.003 mole) and hydrazine hydrate 98% (1 mL) was refluxed for 6 h. After cooling, the reaction mixture was poured into ice-cold water and neutralized with hydrochloric acid. The solid produced was filtered off, washed with water and recrystallized from ethanol to give compound **18**.

3-Substituted-1-(4-(4-fluorophenyl)-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyrimidin-2-yl)-1H-pyrazol-5(4H)-ones **(19a,b)**

A mixture of compound **18** (1 g; 0.003 mole) and diethyl malonate and/or ethyl acetoacetate (0.003 mole) in hot absolute ethanol (20 mL) was refluxed for 9 h. The solvent was evaporated under reduced pressure and the residual matter was triturated with petroleum ether. The solid produced was filtered off and recrystallized from ethanol to give compounds **19a,b**, respectively.

4-(4-Fluorophenyl)-6-(1,2,3,4-tetrahydronaphthalen-6-yl)-2-(3,5-dimethyl-1H-pyrazol-1-yl)-pyrimidine **(20)**

A mixture of compound **18** (0.5 g; 0.0015 mole) and an excess of acetylacetone (0.5 mL) in absolute ethanol (10 mL) was refluxed for 8 h. Then, the solvent was evaporated under reduced pressure and the residual matter was triturated with benzene. The solid product was filtered off, washed with benzene and recrystallized from methanol to give compound **20**.

2-Arylidene-1-(4-(4-fluorophenyl)-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyrimidin-2-yl)-hydrazines **(21a,b)**

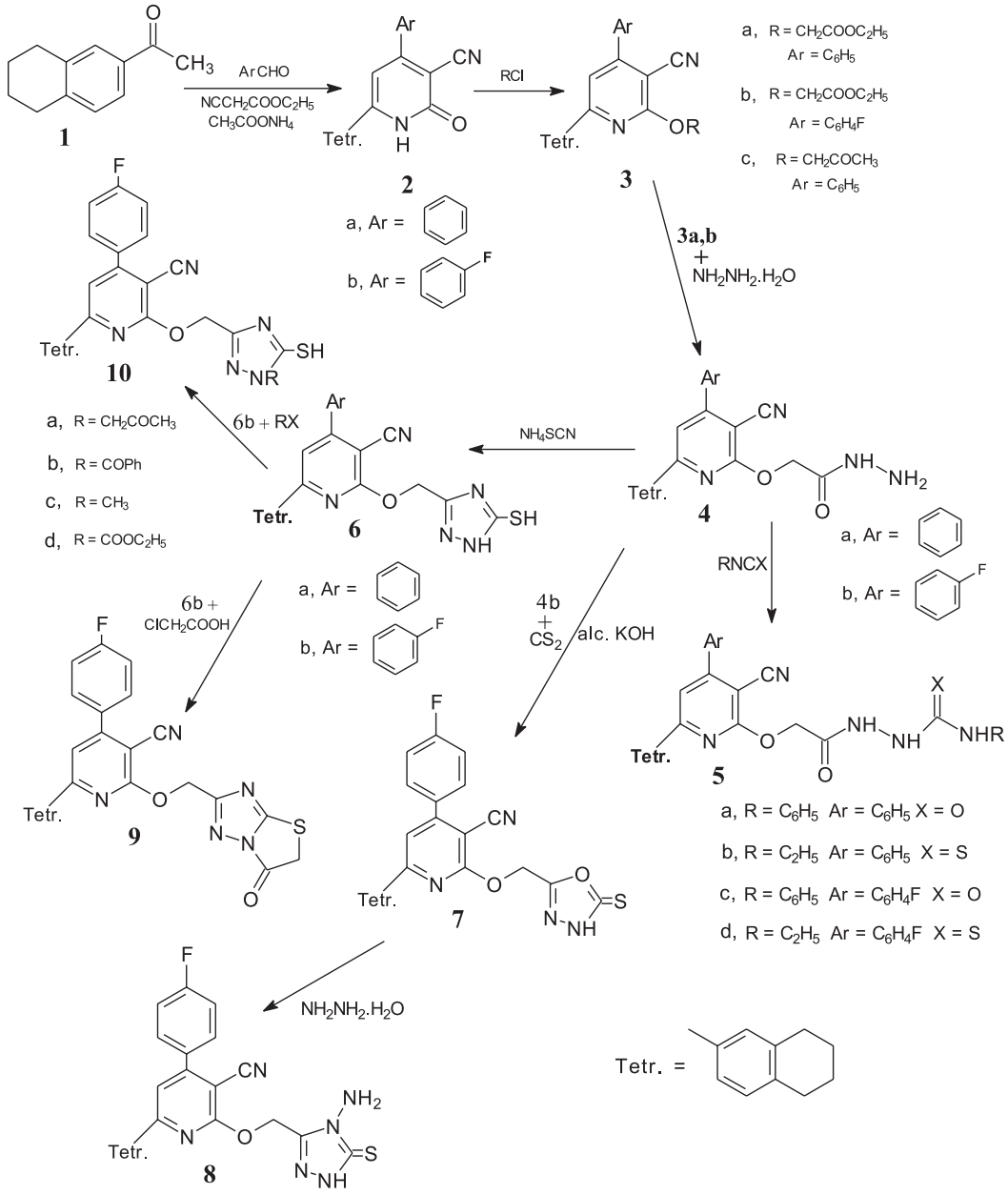
A mixture of compound **18** (0.5 g; 0.0015 mole) and the appropriate aldehyde, namely: benzaldehyde and/or anisaldehyde (0.0015 mole) in glacial acetic acid (10 mL) was refluxed for 10 h. The reaction mixture was poured into ice-cold water and the solid product was filtered off, washed with petroleum ether and recrystallized from benzene to give compounds **21a,b,** respectively.

2-Aryl-3-(4-(4-fluorophenyl)-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyrimidin-2-ylamino)-thiazolidin-4-ones (**22a**,**b**)

A mixture of compound **21a,b** (0.002 mole) and thioglycolic acid (0.14 mL; 0.002 mole) in dry benzene (5 mL) was refluxed for 16 h. The solvent was evaporated under reduced pressure and the residue was treated with petroleum ether. The solid product was filtered off, washed with petroleum ether, then recrystallized from benzene to give compounds **22a,b**, respectively.

Anticancer screening

Fifteen compounds were selected for the screening: **3a**, **3b**, **4a**, **4b**, **5b**, **5d**, **7**, **8**, **9**, **11**, **13**, **15a**, **19a**, **19b** and **22b**. Four concentrations were taken of each compound: 1, 2.5, 5 and 10 mg/ mL.



Scheme 1.

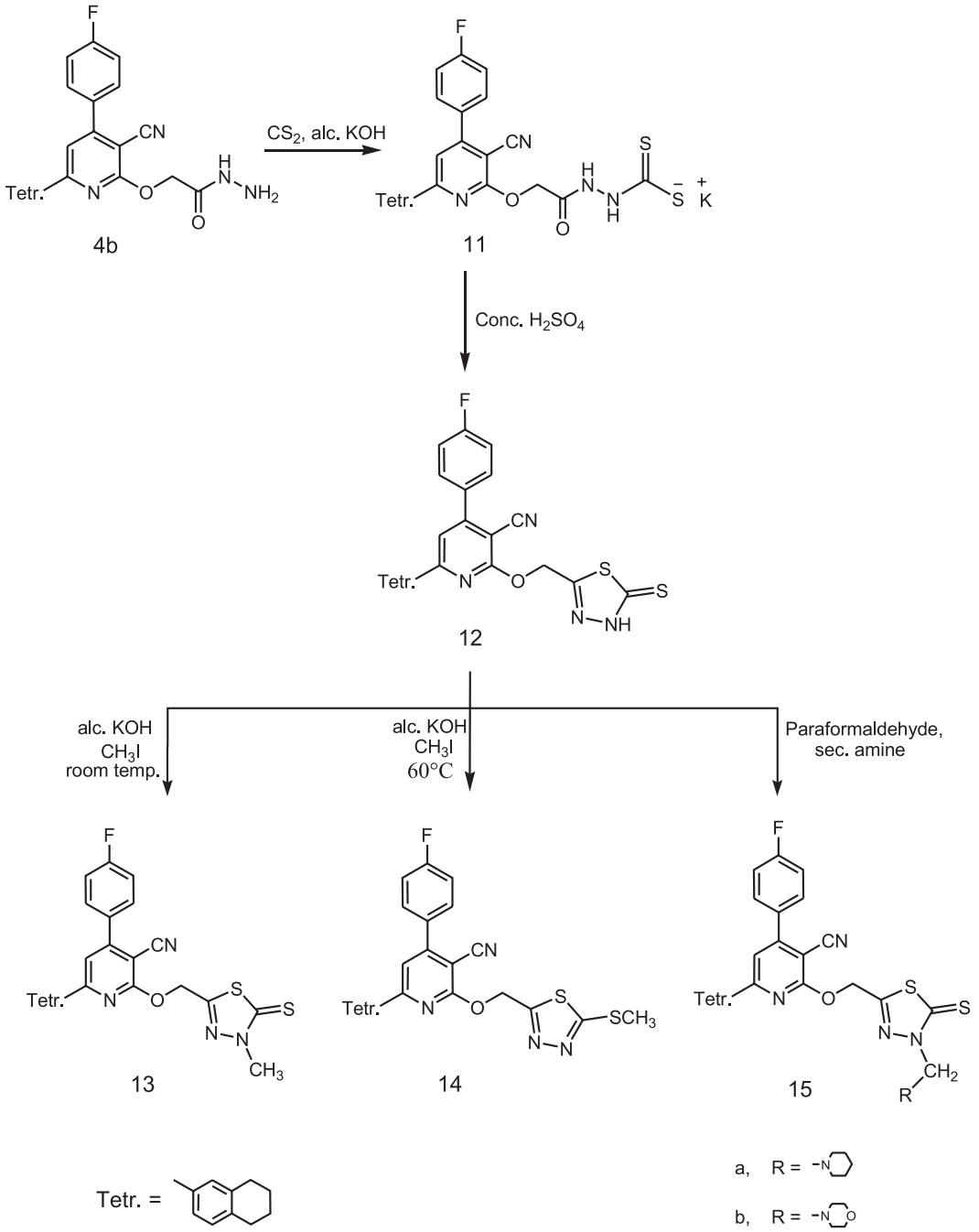
Cells

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 microtiter 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 subtratum were fixed by gently layering 50 mL of cold 50% TCA (4°C) on top of the growth medium in each well to produce a final TCA concentration of 10%. The cultures were incubated at 4°C for one hour and then

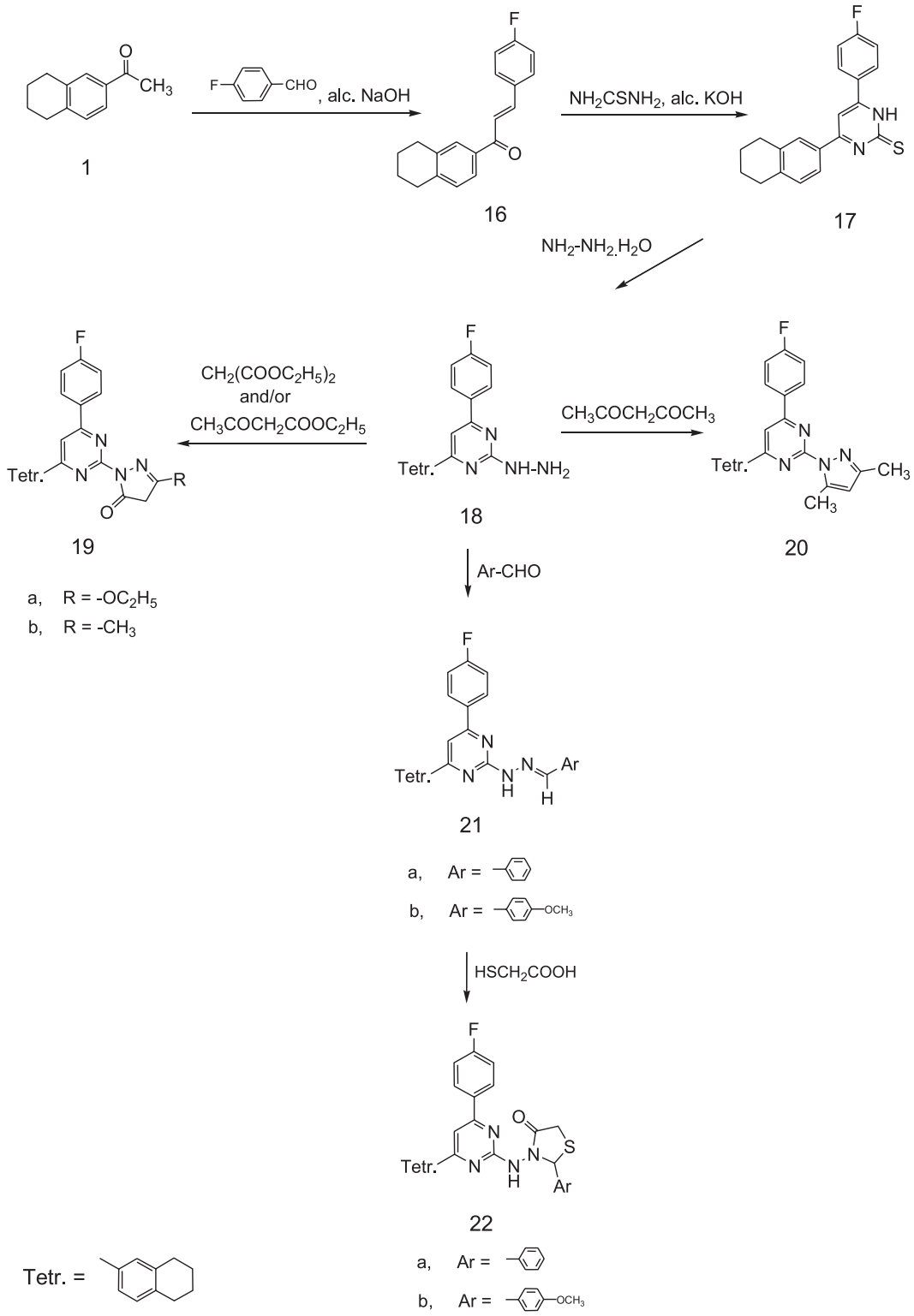


Scheme 2.

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 cell staining and extracted from cells with 10 mM unbuffered Tris base [tris(hydroxymethyl)aminomethane].



Scheme 3.

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 the culture wells from a beaker. This procedure permitted rinsing to be per-

Table 1. Physical and analytical data of all new compounds **3a-22b**

Comp. no.	m.p. (°C) (cryst. solvent)	Yield (%)	Mol. formula (Mol. Wt.)	Analysis (%) Calcd. / Found		
				C	H	N
3a	180 (CH_3OH)	63	$C_{26}H_{24}N_2O_3$ (412.49)	75.70 75.93	5.86 5.60	6.79 6.71
3b	142 (CH_3OH)	64	$C_{26}H_{23}FN_2O_3$ (430.48)	72.54 72.46	5.38 5.20	6.50 6.87
3c	130 (CH_3OH)	60	$C_{25}H_{22}N_2O_2$ (382.46)	78.51 78.19	5.79 5.30	7.32 7.69
4a	186 (C_2H_5OH)	79	$C_{24}H_{22}N_4O_2$ (398.46)	72.34 72.64	5.56 6.11	14.06 14.50
4b	210 (C_2H_5OH)	83	$C_{24}H_{21}FN_4O_2$ (416.46)	69.21 69.11	5.08 5.45	13.45 13.66
5a	150 (CH_3OH)	42	$C_{31}H_{33}N_5O_3$ (523.63)	71.10 70.46	6.35 6.58	13.37 13.57
5b	150 (CH_3OH)	51	$C_{27}H_{27}N_5O_2S$ (485.61)	66.78 67.12	5.60 5.37	14.42 14.60
5c	104 (CH_3OH)	38	$C_{31}H_{32}FN_5O_3$ (541.62)	68.74 68.69	5.95 5.89	12.92 12.80
5d	160 (CH_3OH)	40	$C_{27}H_{26}FN_5O_2S$ (503.61)	64.39 64.74	5.20 5.43	13.90 14.22
6a	262 (DMF)	84	$C_{25}H_{21}N_5OS$ (439.55)	68.31 68.64	4.81 4.56	15.93 15.66
6b	290 (DMF)	76	$C_{25}H_{20}FN_5OS$ (457.54)	65.62 65.15	4.40 4.81	15.30 15.17
7	158 (C_2H_5OH)	37	$C_{25}H_{19}FN_4O_2S$ (458.53)	65.48 65.22	4.17 3.88	12.21 12.43
8	254 (DMF)	45	$C_{25}H_{21}FN_6OS$ (472.56)	63.54 63.80	4.47 4.69	17.78 17.84
9	260 (C_2H_5OH)	32	$C_{27}H_{20}FN_5O_2S$ (497.56)	65.17 65.02	4.05 4.39	14.07 14.42
10a	260 (CH_3COOH)	64	$C_{28}H_{24}FN_5O_2S$ (513.60)	65.48 65.31	4.70 4.49	13.63 13.21
10b	275 (CH_3COOH)	53	$C_{32}H_{24}FN_5O_2S$ (561.64)	68.43 68.62	4.30 4.12	12.46 12.74
10c	90 (CH_3COOH)	74	$C_{26}H_{22}FN_5OS$ (471.56)	66.22 66.49	4.70 4.63	14.85 15.17
10d	240 (CH_3COOH)	71	$C_{28}H_{24}FN_5O_3S$ (529.6)	63.50 63.19	4.56 4.84	13.22 13.05
12	150 (C_2H_5OH)	77	$C_{25}H_{19}FN_4OS_2$ (474.59)	63.27 63.43	4.03 4.11	11.80 11.93
13	85 ($CH_3CH(OH)CH_3$)	30	$C_{26}H_{21}FN_4OS_2$ (488.62)	63.91 64.21	4.33 4.45	11.46 11.73
14	96 (C_2H_5OH)	40	$C_{26}H_{21}FN_4OS_2$ (488.62)	63.91 63.69	4.33 4.59	11.46 11.72
15a	Decomposes at 250 (C_2H_5OH)	76.9	$C_{31}H_{30}FN_5OS_2$ (571.74)	65.12 64.89	5.28 5.16	12.24 12.49
15b	Decomposes at 195 (C_2H_5OH)	65.3	$C_{30}H_{28}FN_5O_2S_2$ (573.71)	62.80 62.92	4.91 4.84	12.20 12.63
18	63 (C_2H_5OH)	90	$C_{20}H_{19}FN_4$ (334.40)	71.83 71.55	5.72 5.93	16.75 16.33
19a	140 (C_2H_5OH)	50	$C_{25}H_{23}FN_4O_2$ (430.49)	69.75 69.89	5.38 5.31	13.01 13.31

Table 1. cont.

Comp. no.	m.p. (°C) (cryst. solvent)	Yield (%)	Mol. formula (Mol. Wt.)	Analysis (%) Calcd. / Found		
				C	H	N
19b	119 (C_2H_5OH)	54	$C_{24}H_{21}FN_4O$ (400.46)	71.98 72.32	5.28 5.60	13.99 14.36
20	100 (CH_3OH)	58	$C_{25}H_{23}FN_4$ (398.49)	75.35 75.64	5.81 5.98	14.06 14.34
21a	71 (C_6H_6)	50	$C_{27}H_{23}FN_4$ (422.51)	76.75 76.91	5.48 5.66	13.26 13.47
21b	130 (C_6H_6)	62	$C_{28}H_{25}FN_4O$ (452.54)	74.31 74.11	5.56 5.21	12.38 11.98
22a	96 (C_6H_6)	60	$C_{29}H_{25}FN_4OS$ (496.62)	70.13 70.42	5.07 5.33	11.28 11.45
22b	110 (C_6H_6)	66.5	$C_{30}H_{27}FN_4O_2S$ (526.64)	68.42 68.81	5.16 5.10	10.63 10.21

Table 2. Spectral data of the newly synthesized compounds

Comp. No.		MS [m/z (%)], 1H NMR [$CDCl_3$, δ, ppm], IR [KBr; ν cm-1]
3a	MS	412 [M^+] (15), 413 [M^++H] (79), 340 (413-COOEt) (100), 326 [340-CH_2] (16).
3b	MS ^{1}H NMR IR	431 [M^++H] (88.7), 357 [M^+-COOEt] (100), 343 [357-CH_2] (16). 0.9-0.98 (m, 3H, CH_3, ester), 1.5, 2.49 (m, m, 4H, 4H, 4CH_2), 3.8-3.9 (q, CH_2, ester), 4.7 (s, 2H, OCH_2), 6.8 (s, 1H, pyridyl), 6.9-7.4 (m, 7H, Ar). 2932 (CH, alicyclic), 2221 (C≡N), 1748 (C=O, ester), 1589 (C=N), 1223 (C-F).
3c	IR	2929 (CH, alicyclic), 2218 (C=N), 1638 (C=O, ketone, 1593 (C=N).
4a	MS ^{1}H NMR IR	398 [M^+] (47), 397 [M^+-H] (57), 339 [M^+-$CONHNH_2$] (97), 324 [339-CH_2-H] (100). 1.7, 2.5 (m, m, 4H, 4H, 4CH2), 4.3 (s, 2H, NH_2, exchangeable with D_2O), 5 (s, 2H, OCH2), 7.2 (s, 1H, pyridyl), 7.3-7.8 (m, 8H, Ar), 9.2 (s, 1H, NH, exchangeable with D_2O). 3292 (NH, NH_2), 2922 (CH, alicyclic), 2217 (C≡N), 1657 (C=O, amide) and 1590 (C=N).
4b	MS ^{1}H NMR IR	418 [M^++2] (40.3), 387 [418- $NHNH_2$] (63.4), 359 [387-CO] (54), 346 [359-CH_2+H] (100). 1.8, 2.8 (m, m, 4H, 4H, 4CH_2), 3.5 (s, 2H, NH_2, exchangeable with D_2O), 5 (s, 2H, OCH_2), 7.1 (s, 1H, pyridyl), 7.3-7.7 (m, 7H, Ar and 1H, NH, exchangeable with D_2O). 3294 (NH, NH_2), 2918 (CH, alicyclic), 2220 (C≡N), 1676 (C=O, amide), 1583 (C=N) and 1223 (C-F).
5a	MS ^{1}H NMR	442 [M^+-C_6H_{11}-2H] (2), 396 [442- NHCO-H] (100), 338 [396-NHNHCO] (46) and at 324 [338-CH_2] (7.7). 1.2 (m, 6H, cyclohexyl), 1.5-1.8 (m, 4H, cyclohexyl overlapped with 4H, 2CH_2, tetralin), 2.8 (m, 4H, 2CH_2, tetralin), 3.8 (s, 1H, CH-N, cyclohexyl), 5.09 (s, 2H, OCH_2), 7.15 (s, 1H, pyridyl), 7.2-7.73 (m, 8H, Ar and 3H, NH groups).
5b	MS ^{1}H NMR	485 [M^+] (0.25), 339 [M^+- CONHNHCSNHEt] (30), 338 [339-H] (100), 325 [339-CH_2] (55). 1.2 (t, 3H, CH_3), 1.7, 2.7 (m, m, 4H, 4H, 4CH_2), 4.2 (m, 2H, CH_2), 5 (s, 2H, OCH_2), 7 (s, 1H, pyridyl), 7.1-7.4 (m, 8H, Ar and 3H, NH groups).
5c	MS ^{1}H NMR	415 [M^+-C_6H_{11}NHCO] (89), 384 [415-NHNH-H] (25), 356 [384-CO] (100), 343 [356-CH_2+H] (50), 328 [343-O+H] (12). 1.1-1.2 (m, 6H, cyclohexyl), 1.6-1.8 (m, 4H, cyclohexyl overlapped with 4H, 2CH_2, tetralin), 2.8 (m, 4H, 2CH_2, tetralin), 3.8 (s, 1H, CH-N, cyclohexyl), 4.5 (s, 2H, OCH_2), 7.2 (s, 1H, pyridyl), 7.3-7.6 (m, 7H, Ar and 3H, NH groups).
5d	MS ^{1}H NMR	400 [M^+-$C_2H_5NHCSNH$] (18), 358 [400-NHCO+H] (79) and at 344 [358-CH_2] (100). 1.2-1.5 (t, 3H, CH_3), 1.8, 2.8 (m, m, 4H, 4H, 4CH_2), 4-4.3 (m, 2H, CH_2), 4.5 (s, 2H, OCH_2), 7.1 (s, 1H, pyridyl), 7.3-7.8 (m, 7H, Ar and 3H, NH groups).
6a	MS ^{1}H NMR	339 [M^+-$C_2H_2N_3S$] (2), 325 [339-CH_2] (70), 326 [325+H] (100). 1.3 (s, 1H, SH, exchangeable with D_2O), 1.8, 2.8 (m, m, 4H, 4H, 4CH_2), 5.1 (s, 2H, of OCH_2), 6.8 (s, 1H, NH, exchangeable with D_2O), 7.2 (s, 1H, pyridyl) and 7.3-7.6 (m, 8H, Ar).

Table 2. cont.

Comp. No.		MS [m/z (%)], 1H NMR [$CDCl_3$, δ, ppm], IR [KBr; ν cm-1]
6b	MS ^{1}H NMR IR	458 [M^++H] (6), 344 [458- $C_2H_2N_3S$-CH_2] (100) and at 328 [344-O] (22). 1.25 (s, 1H, SH, exchangeable with D_2O), 1.8, 2.8 (m, m, 4H, 4H, 4CH_2), 5.1 (s, 2H, of OCH_2), 6.6 (s, 1H, NH, exchangeable with D_2O), 7.2 (s, 1H, pyridyl), 7.3-7.7 (m, 7H, Ar). 3150 (NH), 2933 (CH, alicyclic), 2216 (C≡N), 1603 (C=N), 1223 (C-F).
7	MS	425 [M^+-S-H] (24), 357 [M^+- C_2HN_2OS] (6), 343 [357- CH_2] (41), 342 [343-H] (100).
8	MS IR	343 [M^+-$C_3H_5N_4S$] (80), 289 [343-CN-CO] (36), 187 [343-CN-$C_{10}H_{11}$(tetralin)+H] (91), 145 [$C_3H_5N_4OS$ (4-amino-5-thioxo-1H-1,2,4-triazol-3-ylmethoxy group)] (95) and at 73 [145-CS-CO] (100). 3140 (NH_2), 2929 (CH, alicyclic), 2215 (C≡N), 1641 (C=N) and at 1223 (C-F).
9	MS	496 [M^+-H] (5), 344 [M^+-$C_5H_2N_3OS$-H] (100), 343 [344-H] (5) and at 327 [343-O] (4.5).
10a	MS IR	357 [M^+-$C_5H_6N_3OS$ (5-mercapto-1-(2-oxopropyl)-*1H*-1,2,4-triazol-3-yl group)] (40), 344 [357-CH_2+H] (100), 173 [1-(2,3-dihydro-5-mercapto-3-methyl-1,2,4-triazol-1-yl)propan-2-one] (6) and at 158 [173- CH_3] (20). 2930 (CH, alicyclic), 2218 (C≡N), 1644 (C=O, ketone), 1604 (C=N), 1223 (C-F).
10b	MS IR	560 [M^+-H] (0.2), 344 [M^+-$C_{10}H_8N_3OS$ (3-mercapto-2-phenylcarbonyl-*1H*-1,2,4-triazol-5-ylmethyl)+H] (100), 316 [344-CN-2H] (38). 2933 (CH, alicyclic), 2218 (C≡N), 1640 (C=O, amide), 1604 (C=N), 1221 (C-F).
10c	MS ^{1}H NMR	357 [M^+-$C_3H_4N_3S$ (5-mercapto-1-methyl-*1H*-1,2,4-triazol-3-yl)] (100), 343 [357-CH_2] (60), 344 [343+H] (86). 1.8 (m, 4H, 2CH2), 2.1 (s, 3H, CH_3), 2.8 (m, 4H, 2CH_2), 3.5 (s, 1H, SH, exchangeable with D_2O), 4.2 (s, 2H, OCH_2), 7.2 (s, 1H, pyridyl), 7.3-7.8 (m, 7H, Ar).
10d	MS IR	344 [M^+- $C_6H_8N_3O_2S$ (1-ethoxycarbonyl-5-mercapto-*1H*-1,2,4-triazol-3-ylmethyl)+H] (100), 186 [1-ethoxycarbonyl-5-mercapto-*1H*-1,2,4-triazol-3-ylmethyl] (29) and at 157 [$C_{10}H_{11}CN$ (tetralin+CN from cleavage of pyridine ring)] (31). 2927 (CH, alicyclic), 2219 (C≡N), 1703 (C=O, ester), 1639 (C=N), 1223 (C-F).
12	MS IR	357 [M^+-$C_2HN_2S_2$ (2,3-dihydro-2-thioxo-1,3,4-thiadiazol-5-yl)] (11), 344 [357-CH_2+H] (100) and at 329 [344-O+H] (7). 3189 (NH, thiadiazole), 2929 (CH, alicyclic), 2221 (C≡N), 1589 (C=N), 1223 (C-F).
13	MS ^{1}H NMR IR	488 [M^+] (22), 487 [488-H] (55), 386 [M^+-$C_2H_3NS_2$ (cleavage of thiadiazole ring) +3H] (100), 343 [386-C_2H_3N-2H] (55). 1.8 (m, 4H, 2CH_2), 2.8 (m, 4H, 2CH_2, overlapped with 3H, N-CH_3), 6 (s, 2H, OCH_2), and at 7.2 (s, 1H, pyridyl), 7.3-8.0 (m, 7H, Ar). 2930 (CH, alicyclic), 2220 (C≡N), 1589 (C=N), 1222 (C-F).
14	MS ^{1}H NMR IR	488 [M^+] (15), 487 [488-H] (43), 386 [M^+-$C_2H_3NS_2$ (cleavage of thiadiazole ring) +3H] (85), 343 [386-C_2H_3N-2H] (79), 91 [$C_7H_7^+$] (100). 1.8 (m, 4H, 2CH_2), 2.6 (m, 4H, 2CH_2), 2.7 (s, 3H, S-CH_3), 6 (s, 2H, OCH_2), and at 7.2 (s, 1H, pyridyl), 7.3-8.0 (m, 7H, Ar). 2928 (CH alicyclic), 2219 (C≡N), 1589 (C=N), 1223 (C-F).
15a	MS: ^{1}H NMR (in DMSO)	485 [M^+-$C_5H_{10}N$-2H] (4.5), 344 [485-$C_4H_5N_2S_2$ (3-methyl-2-thioxo-1,3,4-thiadiazol-5-ylmethyl)+H] (65), 115 [($C_5H_{10}N$)CH_2N+3H] (100). 1.6-1.8 (m, 4H, 2CH_2, tetralin and 6H, $(CH_2)_3$, piperidine), 2.8 (m, 4H, 2CH_2, tetralin), 3.4 (m, 4H, CH_2-N-CH_2, piperidine and 2H, N-CH_2-N), 5.1 (s, 2H, OCH_2), 6.9 (s, 1H, pyridyl), 7-8 (m, 7H, Ar).
15b	MS IR	473 [M^+-$C_5H_{10}NO$ (morpholin-4-ylmethyl)] (3.5), 401 [473-CN2S (cleavage of the thiadiazole ring)] (15), 357 [401-CH_2S] (19), 344 [357-CH_2^+H] (100), 99 [(morpholin-4-ylmethyl)-H] (14). 2921 (CH, alicyclic), 2220 (C≡N), 1610 (C=N), 1223 (C-F).
18	MS: IR	334 [M^+] (7), 335 [M^++H] (37), 319 [335-NH_2] (20), 291 [319-CNH-H] (16), 294 [291+3H] (100), 199 [294- C_6H_4F] (60). 3250, 3159 (NH-NH_2), 2927 (CH, alicyclic), 1602 (C≡N), 1220 (C-F).
19a	MS ^{1}H NMR	399 [M^+-C_2H_5-2H] (5), 304 [M^+-$C_5H_7N_2O_2$ (3-ethoxy-5(4H)-oxo-1H-pyrazol-1-yl)+H] (100), 292 [304-C] (85), 95 [C_6H_4F] (17). 1.2 (t, 3H, CH3, ethyl), 1.8-2.8 (m, m, 4H, 4H, 4CH_2), 3.6-3.9 (d, d, 1H, 1H, CH_2, pyrazoline), 4.2 (q, 2H, CH_2, ethyl), 6.9 (s, 1H, pyrimidinyl), 7-8.2 (m, 7H, Ar).
19b	MS IR	400 [M^+] (40), 304 [M^+-$C_4H_5N_2O$ (3-methyl-5(*4H*)-oxo-*1H*-pyrazol-1-yl)+H] (40), 159 [$C_{10}H_{11}CN$ (cleavage of pyrimidine ring)+2H] (100), 95 [C_6H_4F] (30). 2928 (CH, alicyclic), 1733 (C≡O, cyclic amide), 1602 (C=N), 1223 (C-F).

Table 2. cont.

Comp. No.		MS [m/z (%)], 1H NMR [$CDCl_3$, δ, ppm], IR [KBr; ν cm-1]
20	MS 1H NMR	396 [M^+-2] (1), 159 [$C_{10}H_{11}CN$ (cleavage of pyrimidine ring)+2H] (41), 78 [C_6H_6] (87), 62 [C_5H_2] (100). 1.8 (m, 4H, $2CH_2$), 2.4 (s, 6H, $2CH_3$, pyrazole), 2.7 (m, 4H, $2CH_2$), 6.1 (d, 1H, pyrazole), 7 (s, 1H, pyrimidinyl), 7.1-8.2 (m, 7H, Ar).
21a	MS	318 [M^+-C_6H_5CHN] (15), 294 [318-CNH+3H] (55), 159 [$C_{10}H_{11}CN$ (cleavage of pyrimidine ring)+2H] (100).
21b	MS	319 [M^+-$CH_3OC_6H_4CHN$] (15), 294 [319-CNH+2H] (30), 159 [$C_{10}H_{11}CN$ (cleavage of pyrimidine ring)+2H] (100).
22a	MS	495 [M^+-H] (1), 319 [M^+-C_9H_8NOS (2-phenyl-4-oxothiazolidin-3-yl)+H] (95), 304 [319-NH] (40), 119 [(3-aminothiazolidin-4-one)+H] (100).
22b	MS IR	526 [M^+] (1), 319 [M^+-$C_{10}H_{10}NO_2S$ (2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)+H] (17), at 280 [319-$NCNH_2$ (cleavage of pyrimidine ring) +3H] (100). 3182 (NH), 2929 (CH, alicyclic), 1718 (C=O, cyclic amide), 1603 (C=N), 1223 (C-F).

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

Compound	IC_{50} (μg/mL)	
	HepG2	MCF7
3a	-	-
3b	-	-
4a	-	-
4b	-	-
5b	-	-
5d	4.90	-
7	5.37	-
8	1.01	-
9	-	5.03
11	3.22	-
13	6.05	-
15a	-	-
19a	8.66	-
19b	5.50	7.29
22b	7.11	-

IC_{50}: Dose of the compound that reduces the surviving cells by 50%

formed 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 UV_{max} microtiter plate reader (Molecular Devices, Menlo Park, CA) at 564 nm for maximum sensitivity.

RESULTS AND DISCUSSION

Chemistry

Starting from 1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethanone (1), which is prepared according to the method of Newman and Zahm (13), cyclocondensation reaction with ethyl cyanoacetate and the appropriate aromatic aldehyde in the presence of excess ammonium acetate in *n*-butanol gave the corresponding 4-substituted-6-(1,2,3,4-tetrahydronaphthalen-6-yl)-2-oxo-1,2-dihydropyridine-3-carbonitriles **2a** (14) and **2b** (15) in one pot reaction, according to our method firstly reported in (12). Two different alkoxy side chains were introduced into the 2-position of the pyridine moiety *via* condensation of **2a** and/or **2b** with ethyl chloroacetate and/or chloroacetone according to the reported method (16) to give the corresponding ethyl 2-(4-aryl-3-cyano-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyridin-2-yloxy)acetate esters **3a,b** and/or 2-(2-oxopropoxy)-4-phenyl-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyridine-3-carbonitrile 3c, respectively.

Reaction of **3a,b** with excess hydrazine hydrate in ethanol (17) gave the corresponding pyridin-2-yloxyacetohydrazides **4a,b,** which upon treatment with the appropriate semicarbazide and thiosemicarbazide, namely: cyclohexyl isocyanate and ethyl isothiocyanate, using the reported method (18), afforded the corresponding 4-cyclohexyl (or ethyl)-

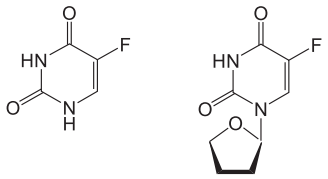
1-[2-(pyridin-2-yloxyacetyl)] semi (or thiosemi)carbazide derivatives **5a-d**, respectively.

On the other hand, according to the known chemotherapeutic activities of 1,2,4-triazoles as antiviral, antifungal (19) and anticancer agents (20-22), it was of interest to incorporate such moiety into the parent tetralin-6-yl pyridine backbone to obtain more active and less toxic anticancer agents. So, fusion of the acetohydrazides **4a,b** with ammonium thiocyanate according to a reported method (18) afforded the desired (5-mercapto-*1H*-1,2,4-triazol-3-yl)methoxypyridine-3-carbonitriles **6a,b,** respectively. Heating **4b** with CS_2 in ethanolic KOH gave the corresponding 1,3,4-oxadiazol-2-thione derivative **7**, which when treated with hydrazine hydrate (18), gave the 4-amino-4,5-dihydro-5-thioxo-*1H*-1,2,4-triazole **8**. Treatment of **6b** with chloroacetic acid in the presence of acetic acid and acetic anhydride afforded the corresponding binary system, namely 4-(4-fluorophenyl)-2-[(5,6-dihydro-6-oxothiazolo[3,2-b][1,2,4]triazol-2-yl)methoxy]-6-(1,2,3,4-tetrahydronaphthalen-6-yl)pyridine-3-carbonitrile **9**. Also the reaction of **6b** with different halo compounds, namely: chloroacetone, benzoyl chloride, methyl iodide and/or ethyl chloroformate, afforded the corresponding 1-substituted-5-mercapto-*1H*-1,2,4-triazoles **10a-d,** respectively (Scheme 1).

The potassium dithiocarbazate salt **11**, prepared from compound **4b,** was cyclized in conc. H_2SO_4 to afford the thiadiazole-2-thione derivative **12** (23), which upon methylation using methyl iodide in ethanolic KOH, according to a reported method (23, 24), yielded the 3-methyl thiadiazole-2-thione derivative **13**, while its methylation using the same reactants at 60°C, according to a reported method (23-25), gave the S-methyl thiadiazole derivative **14**.

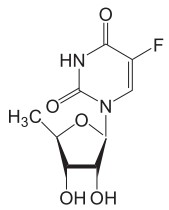
Also, compound **12** was allowed to undergo the Mannich reaction with paraformaldehyde and the appropriate secondary amines in absolute ethanol to give the corresponding Mannich bases **15a**,**b**, in which the alkylaminomethyl grouping was attached to the nitrogen of position 3 of the thiadiazole ring (23). The presence of this Mannich side chain might overcome the water insolubility problem of such compounds, thus increasing their bioavailability (26, 27) (Scheme 2).

On the other hand, since many pyrimidine derivatives possess anticancer activity, e.g.: 5-fluorouracil, ftorafur, floxuridine and capecitabine (28):

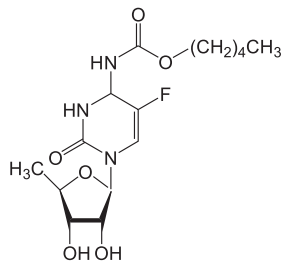


5-Fluorouracil

Ftorafur



Floxuridine



Capecitabine

it was of interest to synthesize some new pyrimidines incorporated into the tetralin moiety and other important heterocyclic systems to obtain more active and less toxic anticancer agents.

The reaction of 1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethanone (**1**) with 4-fluorobenzaldehyde (15) followed by cyclization of the resulting α,β-unsaturated ketone (chalcone **16**) with thiourea in alcoholic KOH afforded the corresponding pyrimidine-2-thione derivative: 6-(4-fluorophenyl)-4-(1,2,3,4-tetrahydronaphthalen-6-yl)pyrimidine-2(*1H*)-thione **17** (15). Treatment of **17** with 98% hydrazine hydrate afforded the hydrazinopyrimidine derivative **18** acc. to (29). Reaction of **18** with the appropriate β-ketonic ester, e.g. diethyl malonate and/or ethyl acetoacetate, afforded the corresponding pyrazolones **19a,b**, respectively, while its reaction with acetylacetone gave the corresponding (3,5-dimethyl-*1H*-pyrazol-1-yl)pyrimidine derivative 20 according to the method described by Ebeid et al. (30).

Moreover, treatment of **18** with aromatic aldehydes followed by cyclization of the resulting Schiff's bases **21a,b** with thioglycolic acid (5, 10) afforded the corresponding (4-oxothiazolidin-3-yl)aminopyrimidines **22a,b**, respectively (Scheme 3).

All compounds were subjected to microchemical and spectral analyses (IR, ^{1}HNMR and MS) (Tables 1 and 2).

Anticancer screening

Anticancer activity

Fifteen compounds were selected for testing at the Department of Tumor Pathology, National Cancer Institute, Cairo, Egypt.

Two cell lines were used for the evaluation (human liver carcinoma cell line and human braest carcinoma cell line) according to the method described by Skehan et al. (31).

The results are expressed in the form of the concentration of compound that causes 50% inhibition of cells growth. The *in vitro* evaluation revealed that the activity of the tested compounds was higher towards the liver cancer than the breast cancer. A single compound (**19b**) showed dual effect, while compounds **5d, 7, 8, 11, 13, 19a** and **22b** were selective towards the liver cancer. Compound **9** was the only compound selective towards the breast cancer.

The results of the anticancer screening of the tested compounds are illustrated in Table 3.

Structure-activity relationship (SAR)

The data of the selected tetralylpyridine-3-carbonitriles **3a**,**b**, **4a**,**b**, **5b**,**d**, **7**-**9**, **11**, **13** and **15a** and the tetralylpyrimidines **19a**,**b** and **22b** evidenced that compounds **8** and **11** were the most effective against the liver carcinoma cell line (HepG2) showing IC_{50} of 1.01 and 3.22 μg/mL, respectively, whereas compounds **3a**, **3b**, **4a**, **4b**, **5b**, **9** and **15a** were non toxic against the same cell line. All the tested compounds were also inactive against the breast carcinoma cell line (MCF7) except compounds **9** and **19b**, showing IC_{50} of 5.03 and 7.29 μg/mL, respectively.

The activity of the tested compounds could be correlated with structure variation and modification as follows:

Tetralin-6-ylpyridines

In case of tetralylpyridines bearing a heterocyclic substituent at C2-pyridine:

- The activity order of the compounds against HepG2 was the triazole **8** (the most active; IC_{50} = 1.01 μg/mL) > the oxadiazole **7** (IC_{50} = 5.37 μg/mL) > the thiadiazole **13** (IC_{50} = 6.05 μg/mL). Interestingly, when the triazole ring is fused to a thiazole one (in compound **9**) it was found that the compound acquires a significant antitumor activity against MCF7 cells with IC_{50} = 5.03 μg/mL and loses its activity towards HepG2 cells.
- The activity of the thiadiazole compound **13** (IC_{50} = 6.05 μg/mL towards liver cancer) is found to be due to the small size of the N-alkyl group, as compound **15**, bearing a large N-alkyl substituent [N-(piperidin-1-ylmethyl)] is devoid of cytotoxic activity.

In case of tetralylpyridines with acyclic side chain substituent:

The effect of groups seems to be correlated and not depending on certain group alone. For example, the esters **3a**,**b**, the hydrazides **4a**,**b** and the thiosemicarbazide **5b** showed no cytotoxic activity, whereas compounds **5d** and **11** incorporating thiosemicarbazide and dithiocarbazate substituents, respectively, along with the 4-fluorophenyl moiety, showed activity against HepG2 cell line with IC_{50} = 4.90 and 3.22 μg/mL, respectively.

Tetralin-6-ylpyrimidines

In this class, compounds **19a** and **22b** were active against liver cancer cells (HepG2) with IC_{50} = 8.66 and 7.11 μg/mL, respectively, while compound **19b** showed dual activity (IC_{50} = 5.50 and 7.29 μg/mL for liver and breast cancers, respectively).

The wide variation of cytotoxic spectrum and activity between the two closely related derivatives **19a** and **19b** indicates that the dual activity and potency can be obtained, in this class of compounds, by attaching small alkyl group in position 3 of pyrazoline ring, as in compound **19b** (CH_3), rather than the larger groups (as OC_2H_5 in **19a**).

Tetralin-6-ylpyridines and tetralin-6-ylpyrimidines

The presence of the 4-fluoro substituent in the phenyl group is essential for activity. All the active compounds incorporate, in addition to other necessary groups, a fluorine atom in position 4 of the phenyl ring.

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