Indian Journal of Chemistry
Vol. 42B, August 2003, pp. 1985-1993

# Synthesis of novel tricyclic heterocyclic compounds as potential anticancer agents using chromanone and thiochromanone as synthons

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*Received 23 July 2001; accepted (revised) 1 November 2002*

The arylmethylene of benzopyrane or benzothiopyrane **3,4** have been synthesized and condensed with hydrazine, guanidine and thiourea to yield pyrazole **5-8,** aminopyrimidine **9,10** and thioxopyrimidine derivatives **11,12,** respectively. Compounds **3** or **4** on treatment with malononitrile in the presence of ammonium acetate/acetic acid or in the presence of piperidine/ methanol to yield benzopyrano- and benzothiopyranopyridine **13,14** and benzopyrano- and benzothiopyrane **15,16,** respectively. The oxirane of compound **3** is prepared and condensed with $CS_2$ to yield the tricyclic system, thioxothienobenzopyrane **21**. Ylidenemalononitrile for the ketone **1** and **2** are synthesized and condensed with aromatic aldehyde in presence of ammonium acetate/acetic acid to yield benzopyranopyridine and benzothiopyranopyridine derivatives **24,25,** respectively, which are the isomer of compounds **13,14.** Ylidenemalononitrile on condensation with phenylisothiocyanate yields benzo-pyrano- and benzothiopyranothioxopyridine **28,29**, respectively.

Driven by the increased demand for anticancer and antiviral drugs, the search for new heterocyclic compounds and novel methods of their synthesis is a major topic in contemporary organic synthesis[1,2]. As part of our program in this area, we have synthesized and investigated some reactions of heterocyclic compounds inclouding six[3-6] or seven membered[7-12] ring cyclic or heterocyclic, such as thioxoqunazoline[6], benzothiopenothioxopyrimidine[11] and benzooxipinothioxopyrimidine[10], and other heterocyclic compounds.

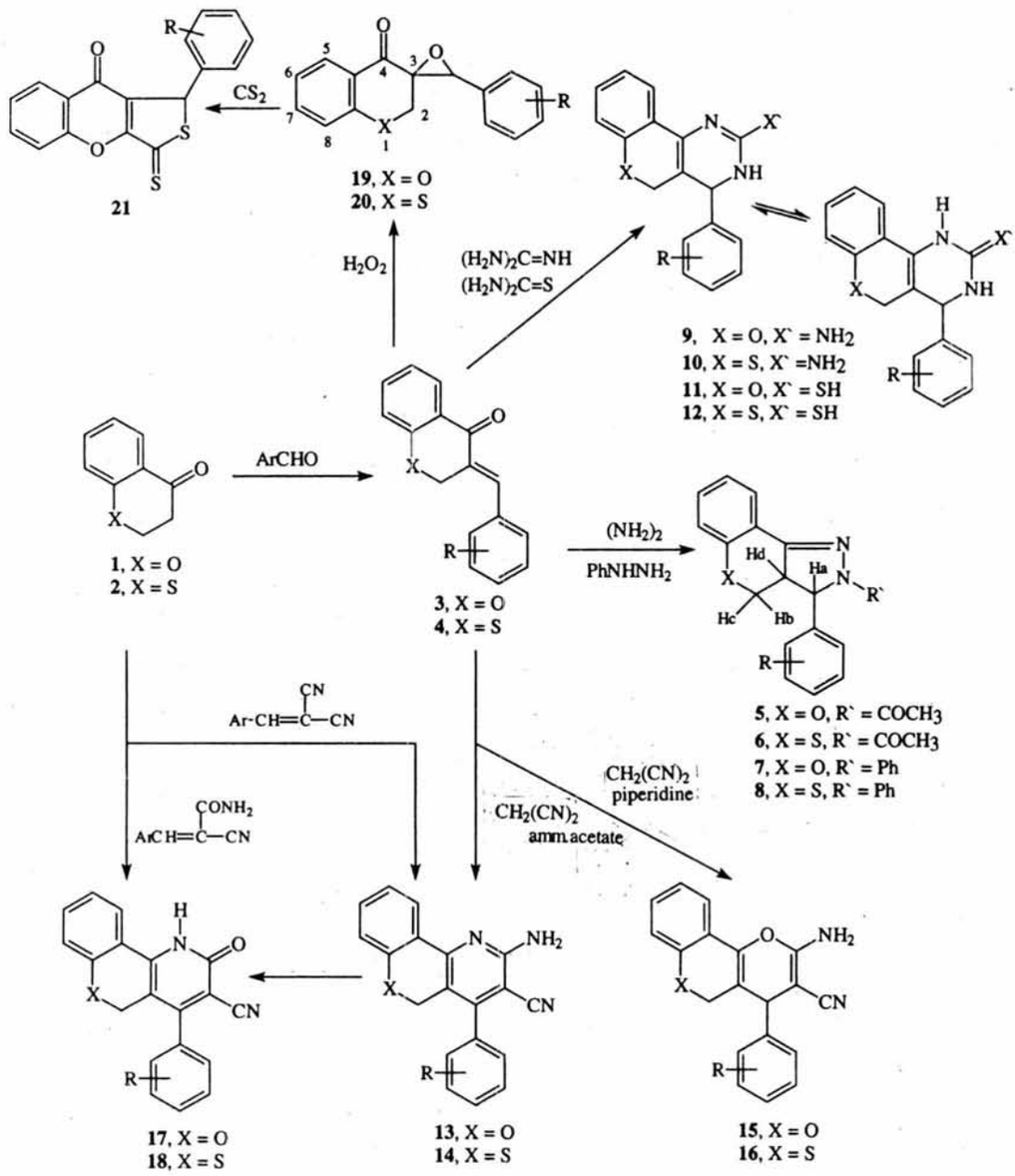
Some of the above synthesized compounds showed anticancer activity[1,2,13,14]. Our current interest lies in a class of tricyclic heterocyclic compounds that contain the benzopyrane and benzothiopyrane ring fused with substituted pyrimidine, pyridine and pyran moiety. In this work we wish to report their synthesis, characterization and the results of screening tests as anticancer.

## Results and Discussion

The assignment of the structures of all the new synthesized compounds were based on elemental analysis and spectral data (IR, mass, $^1$H NMR).

2,3-Dihydro[1]benzopyran-4-one **1** or 2,3-dihydro-[1]benzothiopyran-4-ones **2** were condensed with the proper aromatic aldehyde in the presence of mixed acids as catalyst to yield the corresponding 3-arylmethylene-2,3-dihydro[1]benzopyran-4-ones **3** and 3-arylmethylene-2,3-dihydro[1]benzothiopyran-4-ones **4** respectively in high yield when compared with the reported method[15,16].

Compounds **3** or **4** were reacted with hydrazine hydrate or phenyl-hydrazine in acetic acid to yield 2-acetyl-3-aryl-2,3,3a,4-tetrahydro-(4*H*)-[1]-benzopyrano[4,3-*c*]pyrazoles **5,** 2-acetyl-3-aryl-2,3,3a,4-tetrahydro-(4*H*)-[1]-benzothiopyrano[4,3-*c*]pyrazoles **6,** 2-phenyl-3-aryl-2,3,3a,4-tetrahydro-(4*H*)-[1]-benzopyrano[4,3-*c*]pyrazoles **7** and 3-aryl-2-phenyl-2,3,3a,4-tetrahydro-(4*H*)-[1]-benzopyrano[4,3-*c*]pyrazoles **8**, respectively **(Scheme I)**. The IR spectra of compounds **5** and **6** showed peaks at 1675-1668 (C=O) and 1660-1655 $cm^{-1}$ (C=N). The $^1$H NMR spectrum ($CDCl_3$) of compound **5b** showed signals at δ 6.90-7.49 (8H, m, Ar-H), 4.90 and 5.60 (1H, 2d, H-a, $J$ = 9.56 Hz and $J$ = 10.21 Hz), 4.57 (1H, m, H-b), 4.14 (1H, s, H-c), 3.72 (3H, s, $OCH_3$), 3.40 (1H, m, H-d), and 3.35 (3H, s, $CO\text{-}CH_3$) and its mass spectrum showed peaks of $M^+$ at m/z 322, 77.5%, 280, 79% [$M^+$-$CH_2CO$], 160, 22% [280-$OCH_3C_6H_4CH$], and base peak at 134, 100%. The $^1$H NMR spectrum ($CDCl_3$) of compound **6b** showed signals at 7.1-7.5 (8H, m, Ar-H), 6.0 (1H, d, H-a), 4.6 (1H, m, H-b), 3.5 (1H, m, H-c), 3.1 (1H, m, H-d) and 2.2 (3H, s, $COCH_3$) and its mass spectrum showed peaks of $M^+$ at m/z 387, 18%; m/z 389 [$M^+$+ 2], 17%, due to the presence of Br atom), 344, 63% [$M^+$ - $COCH_3$], and at 161 (344 – $BrC_6H_4CH$=N, 100%).




**Scheme I**

The IR spectra of compounds **7** and **8** showed peaks at 1655-1648 $cm^{-1}$ (C=N). The $^1H$ NMR spectrum (DMSO-$d_6$) of compound **7c** showed signals at 6.90-7.70 (13H, m, Ar-H), 4.90 (1H, d, H-a, $J$ = 12Hz), 4.60 (1H, m, H-b), 4.30 (1H, m, H-c), 3.70 (3H, s, $OCH_3$) and 3.50 (1H, m, H-d) and its mass spectrum showed peaks of $M^+$ at m/z 356 (base peak, 100%), 341, 2% [$M^+$-$CH_3$], 279, 21% [$M^+$-Ph], 264, 3.5% [$M^+$-Ph-NH], and 249, 10% [$M^+$ -$C_6H_4$-$OCH_3$]. The $^1H$ NMR spectrum ($CDCl_3$) of compound **8a** showed signals at 6.90-7.40 (13H, m, Ar-H), 4.8 (1H, d, H-a, $J$ = 12 Hz), 3.90 (3H, s, $OCH_3$), 3.7 (1H, m, H-b), 3.3 (1H, m, H-c) and 3.1 (1H, m, H-d) and its mass spectrum showed peaks of $M^+$ at m/z 372 (base peak, 100%), 280, 41% [$M^+$-PhNH], 251, 13% [$M^+$-$OCH_3$, $C_6H_4$-$CH_2$] and 210, 20% [251-HN-C=$CH_2$].

Compounds **3** or **4** were reacted with guanidine hydrochloride in ethanol and NaOH to yield 2-amino-4-aryl-3,4-dihydro-(5*H*)-[1]benzopyrano[4,3-*d*]-pyrimidine **9** and 2-amino-4-aryl-3,4-dihydro-(5*H*)-[1] benzothiopyrano[4,3-*d*]-pyrimidine **10,** respectively **(Scheme I)**. The IR spectra of compounds **9** and **10**

showed peaks at 3390-3215 ($NH_2$ and NH) and 1665-1663 $cm^{-1}$ (C=N). The $^1H$ NMR spectrum (DMSO-$d_6$) of compound **9d** showed signals at 9.90 (1H, s, NH, exchangeable with $D_2O$), 6.90-8.00 (8H, m, Ar-H), 6.50 (2H, s, $NH_2$, exchangeable with $D_2O$), 5.20 (1H, s, CH-pyrimidine), and 3.70 (2H, s, $CH_2$ of pyran nucleus) and its mass spectrum showed peaks of $M^+$ at m/z 311 (base peak, 100%), at 313 [$M^+$+2] due to presence of Cl atom, 33%, 294, 65% [$M^+$-$NH_3$] and 200, 9.5% [$M^+$ -$C_6H_5$-Cl]. The $^1H$ NMR spectrum (DMSO-$d_6$) of compound **10b** showed signals at 8.2 (1H, s, NH, exchangeable with $D_2O$), 6.8-7.5 (8H, m, Ar-H), 6.60 (2H, s, $NH_2$, exchangeable with $D_2O$), 4.15 (1H, s, CH-pyrimidine) and 3.10 (2H, s, $CH_2$ of thiopyrane nucleus) and its mass spectrum showed peaks of $M^+$ at m/z 372, 27%; 370, 28% [$M^+$-2H], 374, 18%, [$M^+$+2], due to the presence of Br atom; 338, 11% [$M^+$-$H_2S$], 214, 20% [370-$C_6H_4$- Br] and 202, 100% [$M^+$- $CH_2$-$C_6H_4$-Br].

Also, compounds **3** or **4** were condensed with thiourea in ethanol and dry HCl gas to give 4-aryl-1,2,3,4-tetrahydro-(5*H*)-[1]benzopyrano[4,3-*d*]pyrimidine-2-thioxo **11** and 4-aryl-1,2,3,4-tetrahydro-(5*H*)-[1]-benzothiopyrano[4,3-*d*]-pyrimidine-2-thioxo **12,** respectively**.** The IR spectra of compounds **11** and **12** showed peaks at 3434-3259 $cm^{-1}$ (NH). The $^1H$ NMR spectrum (DMSO-$d_6$) of compound **11d** showed signals at 9.80-8.00 (2H, s, 2NH, exchangeable with $D_2O$), 6.90-7.80 (8H, m, Ar-H), 5.30 (1H, s, H-pyrimidine) and 4.60 and 4.80 (2H, 2d, $CH_2$, $J$ = 14.5 Hz, $J$ = 14.49 Hz). The $^{13}$CNMR spectrum (DMSO-$d_6$) of compound **11d** showed signals at 65 ($CH_2$), 106 (CH, pyrimidine), 116, 117, 121, 127, 129.1, 129.2, 129.3, 131, 133, 137, 153 for aromatic carbons and 165 (C=S) and its mass spectrum showed peaks of $M^+$ at m/z 328 [base peak, 100%], 330, 38% [$M^+$+2] due to the presence of Cl atom, 268, 16% [$M^+$-$NH_2$-C=S] and 217, 22% [$M^+$-Cl-$C_6H_4$].

The $^1H$ NMR spectrum (DMSO-$d_6$) of compound **12b** showed signals at 10.5, 9.5 (2H, s, 2NH, exchangeable with $D_2O$), 7.2-7.6 (8H, m, Ar-H), 5.50 (1H, s, H-pyrimidine) and 3.9 and 3.7 (2H, 2d, $CH_2$) and its mass spectrum showed peaks of $M^+$ at m/z 344 [base peak, 100%], 346, 41% [$M^+$+2], due to the presence of Cl atom, 284, 24% [$M^+$-$NH_2$-C=S] and 233, 13% [$M^+$- $C_6H_4$-Cl].

Compounds **1** or **2** was reacted with α-cyanocinnamonitrile derivatives and ammonium acetate in the presence of ethanol and triethylamine to yield the corresponding 2-amino-4-aryl-(5*H*)-[1]-benzopyrano-[4,3-*b*]pyridine-3-carbo-nitrile **13** and 2-amino-4-aryl-(5*H*)-[1]-benzothiopyrano[4,3-*b*]pyridine-3-carbonitrile **14,** respectively **(Scheme I)**. Also, compounds **13** and **14** could be prepared by the reaction of 3-arylmethylene-2,3-dihydro[1]benzopyran-4-ones **3** or 3-arylmethylene-2,3-dihydro[1]benzothiopyran-4-ones **4** with malononitrile and ammonium acetate in refluxing glacial acetic acid. The IR spectra of compounds **13** and **14** showed peaks at 3404-3344 ($NH_2$) and 2221-2218 $cm^{-1}$ (CN). The $^1H$ NMR spectrum (DMSO-$d_6$) of compound **13c** showed signals at 6.90-7.50 (8H, m, Ar-H), 4.90 (2H, s, $NH_2$, exchangeable with $D_2O$), 4.60 (2H, s, $CH_2$) and 3.70 (3H, s, $OCH_3$) and its mass spectrum showed peaks of $M^+$ at m/z 329, 91%, 330 [$M^+$+1] as base peak, 100%, 299, 21% [$M^+$ - HCHO] and 222, 11% [$M^+$-$C_6H_4$-$OCH_3$].

The $^1H$ NMR spectrum (DMSO-$d_6$) of compound **14b** showed signals at 7.20-7.80 (8H, m, Ar-H), 6.65 (2H, s, $NH_2$, exchangeable with $D_2O$), 3.4 (2H, s, $CH_2$) and its mass spectrum showed peaks of $M^+$ at m/z 394, 91%, 395, 100% [$M^+$+1], 396, 85% [$M^+$+2] due to the presence of Br atom and 238, 17% [$M^+$ - $C_6H_4$- Br].

Compounds **3** and **4** were condensed with malononitrile in a mixture of ethanol and piperidine at room temperature to yield 2-amino-4-aryl-(4*H*),(5*H*)-[1]benzopyrano[4,3-*b*]pyrano-3-carbonitrile **15** and 2-amino-4-aryl-(4*H*),(5*H*)-[1]benzothiopyrano[4,3-*b*]-pyrano-3-carbonitrile **16,** respectively **(Scheme I).** The IR spectra of compounds **15** and **16** showed peaks at 3401-3345 ($NH_2$) and 2223-2219 $cm^{-1}$ (C≡N). The $^1H$ NMR spectrum ($CDCl_3$) of compound **15b** showed signals at 6.70-7.00 (8H, m, Ar-H), 4.70 (2H, s, $NH_2$, exchangeable with $D_2O$), 4.50-4.30 (2H, dd, $CH_2$), 4.00 (1H, s, pyrane proton) and 2.30 (3H, s, $CH_3$), and its mass spectrum showed peaks of $M^+$ at m/z 316, 89%, 299, 10% [$M^+$-$NH_3$], 225, 100% [$M^+$-$C_6H_4$-$CH_3$] and 211, 41% [$M^+$-$CH_2$-$C_6H_4$-$CH_3$].

The $^1H$ NMR spectrum ($CDCl_3$) of compound **16c** showed signals at 7.10-7.50 (8H, m, Ar-H), 4.60 (2H, s, $NH_2$, exchangeable with $D_2O$), 4.10 (1H, s, pyrane proton) and 3.5-3.1 (2H, dd, $CH_2$) and its mass spectrum showed peaks of $M^+$ at m/z 397, 21%, [$M^+$+ 2] at 399, 17% due to the presence of Br atom, 396, 82% [$M^+$- 1] and 241, 100% [$M^+$- Br-$C_6H_4$].

Compounds **1** or **2** were condensed with arylmethylenecyanoacetamide in the presence of triethylamine to yield 4-aryl-1,2-dihydro-(5*H*)-[1]-benzopyrano[4,3-*d*]pyridine-2-one-3-carbonitrile **17** and 4-aryl-1,2-dihydro-(5*H*)-[1]benzothiopyrano[4,3-*d*]pyridine-2-one-3-carbonitrile **18,** respectively **(Scheme I).** The IR spectra of compounds **17** and **18** showed

peaks at 3453-3447 (NH), 2211-2208 (C≡N) and 1698-1639 $cm^{-1}$ (HN-C=O). The $^1H$ NMR spectrum (DMSO-$d_6$) of compound **17e** showed signals at 12.80 (1H, s, NH, exchangeable with $D_2O$), 6.90-7.60 (6H, m, Ar-H), 4.90 (2H, s, $CH_2$) and 3.70 (9H, s, $3OCH_3$) and its mass spectrum showed peaks of $M^+$ at m/z 390 [base peak, 100%], 359, 93% [$M^+$- $OCH_3$], 373, 12% [$M^+$-$NH_3$] and 361, 6% [$M^+$-CH=$NH_2$].

The $^1H$ NMR spectrum (DMSO-$d_6$) of compound **18b** showed signals at 8.10 (1H, s, NH, exchangeable with $D_2O$), 7.1-7.5 (8H, m, Ar-H) and 3.3 (2H, s, $CH_2$) and its mass spectrum showed peaks of $M^+$ at m/z 350 [base peak, 100%], 352, 40% [$M^+$+2] due to the presence of Cl atom, 238, 13% [$M^+$- Cl-$C_6H_4$] and 188, 6% [238 – C≡C-CN].

Compounds **17** and **18** were prepared also by passing HCl gas into compounds **15** and **16** in ethanol[17,18] at 0°C. The structures were confirmed by m.p., mixed m.p. and TLC by comparison with authentic sample.

Compounds **3** or **4** in methanol/acetone mixture was reacted with hydrogen peroxide in the presence of 10% sodium hydroxide at 0°C to yield 3′-aryl-(3′*H*)-(2*H*)-spiroxariane[2′,3]benzopyran-4-one **19** and 3′-aryl-(3′*H*)-(2*H*)-spiroxariane[2′,3]benzothiopyran-4-one **20**, respectively **(Scheme I)**. The IR spectra of compounds **19** and **20** showed peaks at 1679,1685 $cm^{-1}$ (C=O). The $^1H$ NMR spectrum (DMSO-$d_6$) of compound **19b** showed signals at 7.5-7.8 (8H, m, Ar-H), 4.75 (1H, d, H-a, $J$ = 12.3 Hz), 4.55 (1H, s, H-b), 4.10 (1H, d, H-c, $J$ = 12.3 Hz) and 2.30 (3H, s, $CH_3$). The $^{13}$CNMR spectrum (DMSO-$d_6$) of **19b** showed signals at 21.2 ($CH_3$); 60.15 ($CH_2$); 65 (CH); 118, 121, 122, 126, 127, 129.3, 129.6, 136.6, 138.7 (aromatic carbons); 161.4 (spiro carbon) and at 188.5 (C=O) and its mass spectrum showed peaks of $M^+$ at m/z 266 [base peak, 100%], 249, 6% [$M^+$-OH], 146, 9% [249-$C_8H_7$].

The $^1H$ NMR spectrum (DMSO-$d_6$) of compound **20b** showed signals at 7.4-8.0 (8H, m, Ar-H), 4.0 (1H, d, H-a), 4.5 (1H, s, H-b) and 2.6 (1H, d, H-c) and its mass spectrum showed peaks of $M^+$ at m/z 347, 5%; 349, 4.5% [$M^+$+2], due to the presence of Br atom, 329, 4% [$M^+$-HOH], 162, 64% [$M^+$-CHO-$C_6H_4$-Br] and at m/z 185, base peak, 100%.

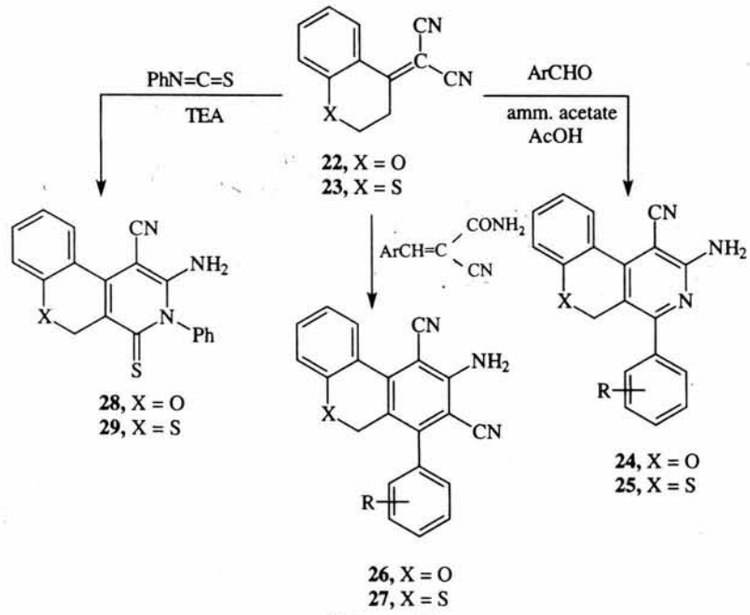
Compounds **19** was reacted with carbon disulfide in the presence of ethanolic sodium hydroxide to yield 4-aryl-2-thioxo-(4*H*)-thieno[3,4-*b*]-benzopyran-4-one **21**. The IR spectra of compounds **21** showed peaks at 1675-1670 $cm^{-1}$ (C=O). The $^1H$ NMR spectrum ($CDCl_3$) of compound **21b** showed signals at 7.0-7.9 (8H, m, Ar-H), 5.30 (1H, s, CH) and 3.80 (3H, s, $OCH_3$) and its mass spectrum showed $M^+$ at m/z [340, 11%], 325, 12% [$M^+$-$CH_3$], 281, 10% [325-C=S] and at m/z 69 (b.p. 100%).

On the other hand, condensation of compounds **1** or **2** with malononitrile gave ylidenemalononitrile derivatives **22** and **23,** respectively. 2-amino-4-aryl-(5*H*)-[1]benzopyrano[3,4-*c*]pyridine-1-carbonitrile **24** and 2-Amino-4-aryl-(5*H*)-[1]benzothiopyrano[3,4-*c*]-pyridine-1-carbonitrile **25** were prepared by the reaction of compounds **22** or **23** with aromatic aldehydes in the presence of ammonium acetate **(Scheme II)**. The IR spectra of compounds **24** showed peaks at 3355-3461 ($NH_2$) and 2219-2215 $cm^{-1}$ (C≡N). The $^1H$ NMR spectrum ($CDCl_3$) of compound **24c** showed signals at 6.90-7.80 (8H, m, Ar-H), 5.50 (2H, s, $NH_2$, exchangeable with $D_2O$), 4.90 (2H, s, $CH_2$) and 3.60 (3H, s, $OCH_3$) and its mass spectrum showed peaks of $M^+$ at m/z 329, base peak, 100%, 314, 11% [$M^+$-$CH_3$], 222, 15%[$M^+$-$C_6H_4$-$OCH_3$] and 195, 26% [222-HCN].

The IR spectra of compounds **25** showed peaks at 3470-3417 ($NH_2$) and 2210-2202 $cm^{-1}$ (C≡N). The $^1H$ NMR spectrum (DMSO-$d_6$) of compound **25b** showed signals at 7.30-7.80 (8H, m, Ar-H), 7.01 (2H, s, $NH_2$, which exchangeable with $D_2O$) and 3.70 (2H, s, $CH_2$) and its mass spectrum showed peaks of $M^+$ at m/z 394, 52%, 396, 23% [$M^+$+2] due to the presence of bromine atom, 395, 100% [$M^+$+1], 238, 8% [$M^+$-$C_6H_4$-Br] and 211, 16% [238 – HCN].

Compounds **22** or **23** were condensed with arylmethylenecyano-acetamide in ethanol, the presence of triethylamine to yield 2-amino-4-aryl-(5*H*)-dibenzo[*b,d*]pyran-1,3-dicarbonitrile **26** and 2-amino-4-aryl-(5*H*)-dibenzo[*b,d*]thiopyran-1,3-dicarbonitrile **27 (Scheme II).** The IR spectra of compounds **26** showed peaks at 3445-3360 ($NH_2$) and 2212 $cm^{-1}$ (C≡N). The $^1H$ NMR spectrum ($CD_3COCD_3$) of compound **26e** showed signals at 7.1-7.5 (4H, m, Ar-H), 6.8 (2H, s, Ar-H), 6.25 (2H, s, $NH_2$, exchangeable with $D_2O$), 4.70 (2H, s, $CH_2$) and 3.80 (9H, s, $3OCH_3$) and its mass spectrum showed peaks of $M^+$ at m/z 413 [base peak, 100%], 398, 56% [$M^+$-$CH_3$], 382, 98% [$M^+$-$OCH_3$] and 246, 14% [$M^+$-$C_6H_2$-$(OCH_3)_3$].

The IR spectra of compounds **27** showed peaks at 3415-3375 ($NH_2$) and 2221-2214 $cm^{-1}$ (C≡N). The $^1H$ NMR spectrum (DMSO-$d_6$) of compound **27a** showed signals at 7.20-8.00 (8H, m, Ar-H), 6.60 (2H, s, $NH_2$, exchangeable with $D_2O$), 3.80 (2H, s, $CH_2$) and 3.60 (3H, s, $OCH_3$) and its mass spectrum showed peaks of $M^+$ at m/z 369 [base peak, 100%], 293, 5% [$M^+$-$C_6H_4$] and 261, 23% [$M^+$- $C_6H_5$-$OCH_3$].




**Scheme II**

Compounds **22** or **23** was reacted with phenyl-isothiocyanate in DMF in the presence of triethyl-amine at 50°C to yield 2-amino-3-phenyl-4-thioxo-(5*H*)-[1]benzopyran[3,4-*c*]pyridine-1-carbonitrile **28** and 2-amino-3-phenyl-4-thioxo-(5*H*)-[1]benzothio-pyran[3,4-*c*]pyridine-1-carbonitrile **29 (Scheme II)**. The IR spectra of compounds **28** showed peaks at 3375-3058 ($NH_2$) and 2212 $cm^{-1}$ (C≡N). The $^1H$ NMR spectrum (DMSO-$d_6$) of compound **28** showed signals at δ, ppm: 6.5-7.6 (m, 9H Ar-H), 5.4 (dd, 2H, $CH_2$) and 4.3 (s, 2H, $NH_2$, exchangeable with $D_2O$) and its mass spectrum showed peaks of $M^+$ at m/z 331 [base peak, 100%], 305, 21% [$M^+$-CN], 254, 43% [$M^+$-Ph], 239, 30% [254-NH].

The IR spectra of compounds **29** showed peaks at 3472-3417 ($NH_2$) and 2226 $cm^{-1}$ (C≡N). The $^1H$ NMR spectrum of compound **29** (DMSO-$d_6$) showed signals at δ, ppm: 7.10-7.60 (m, 9H Ar-H), 6.80 (2H, s, $NH_2$, exchangeable with $D_2O$) and 3.50 (2H, s, $CH_2$) and at and its mas s spectrum showed peaks of $M^+$ at m/z 347, 81%; 314, 100% [$M^+$-SH]$^7$ 0, 285 10% [314-$CHNH_2$], 270, 16% [314-C=S] and 237, 9% [314- Ph].

**Table I**— Growth Percentage

| Compd. | CNS | Breast | Lung | Activity |
|---|---|---|---|---|
| 5c | -25 | -11 | -5 | Active |
| 7c | 15 | -25 | -30 | Active |
| 7d | 49 | 48 | 54 | Inactive |
| 9d | -5 | -40 | -10 | Active |
| 11d | 92 | 76 | 91 | Inactive |
| 15b | 11 | 44 | 53 | Active |
| 15d | -10 | 25 | 24 | Active |
| 17c | 54 | 50 | 53 | Inactive |
| 17e | -24 | 15 | 7 | Active |
| 19c | 38 | 37 | 51 | Inactive |
| 19d | -24 | -38 | -74 | Active |
| 19e | 55 | 28 | 27 | Active |
| 26b | 18 | 55 | 22 | Active |
| 26e | -16 | 55 | 66 | Active |

## Biological Evaluation

The selected compounds listed below (**Table I**) have been evaluated in the three cell line (Lung, Breast and CNS), one dose primary anticancer assay. The compounds which reduced the growth of any one of cell line to approximately 32% or less (negative numbers indicate cell kill) are passed on for evaluation in the full panel of 60 cell lines over a 5-log dose range.

The above biological evaluation was carried in National Cancer Institute in Maryland U.S.A.

## Experimental Section

Melting points are uncorrected and were taken on Electrothermal IA 9000 SERIES Digital Melting Point Apparatus. Microanalyses were performed by the Central Services Laboratory, NRC. IR spectra were recorded on Carlzeise Spectrophotometer model "UR 10" using KBr, $^1H$ NMR spectra on Varian Gem-

ini 200 Mhz using tetramethyl silane as an internal standard and mass spectra (MS) on a finnigan SSQ 7000 mass spectrometer.

**3-Arylmethylene-2,3-dihydro[1]benzopyran-4-ones 3 and 3-aryl-methylene-2,3-dihydro[1]benzothiopyran-4-ones 4**

**Method A: (reported method)**[15,16] To a mixture of 2,3-dihydro[1]benzopyran-4-one **1** or 2,3-dihydro[1]benzothiopyran-4-one **2** (0.03 mole) and appropriate aromatic aldehydes (0.03 mole) in absolute ethanol (50 mL), conc. HCl (4.5 mL) was added. The reaction mixture was heated under reflux for 4 hr, the solid formed was filtered off, dried and crystallized from the proper solvent (**Table II**).

**Method B:** To a solution of compounds **1** or **2** (0.03 mole) and appropiate aromatic aldehydes (0.03 mole) in glacial acetic acid (20 mL), conc. $H_2SO_4$ (6 mL) was added. The reaction mixture was stirred at room temperature for 20 min. the solid formed was collected by filteration, dried and crystallized from the proper solvent (**Table II**).

**Method C:** To solution of compounds **1** or **2** (0.03 mole), aromatic aldehydes (0.03 mole) in glacial acetic acid (20 mL), was added 20 mL conc. HCl. The mixture was stirred at room temperature for 20 min, the solid formed was collected and crystallized from the proper solvent (**Table II**). Method B: gives better yield than Method C.

**2-Acetyl-3-aryl-2,3,3a,4-tetrahydro-(4*H*)-[1]benzopyrano[4,3-*c*]pyrazole 5 and 2-acetyl-3-aryl-2,3,3a,4-tetrahydro-(4*H*)-[1]benzothiopyrano[4,3-*c*]-pyrazole 6**. A mixture of **3** or **4** (0.01 mole) and hydrazine hydrate (0.01 mole) in glacial acetic acid (15 mL), was refluxed for 3 hr, allowed to cool, and poured into cold water. The solid formed was filtered off, washed with water and crystallized from the proper solvent (**Table II**).

**2-Phenyl-3-aryl-2,3,3a,4-tetrahydro-(4*H*)-[1]benzopyrano[4,3-*c*]pyrazole 7 and 2-phenyl-3-aryl-2,3,3a,4-tetrahydro-(4*H*)-[1]benzothiopyrano[4,3-*c*]-pyrazole 8.** A mixture of **3** or **4** (0.01 mole) and phenylhydrazine (0.01 mole) in glacial acetic acid (15 mL) was refluxed for 6 hr allowed to cool, and poured into cold water. The solid formed was filtered off, washed with water and crystallized from the proper solvent (**Table II**).

**2-Amino-4-aryl-3,4-dihydro-(5*H*)-[1]benzopyrano-[4,3-*d*]-pyrimidine 9 and 2-amino-4-aryl-3,4-dihydro-(5*H*)-[1]benzothiopyrano[4,3-*d*]pyrimidine 10**. Guanidine hydrochloride (0.01 mole) was added to a solution of compound **3** or **4** (0.01 mole) in absolute ethanol containing 0.5g NaOH (25 mL). The reaction mixture was refluxed for 4 hr. and then poured gradually with stirring onto cold water. The solid formed was collected by filteration, washed with water and crystallized from the proper solvent (**Table II**).

**4-Aryl-1,2,3,4-tetrahydro-(5*H*)-[1]benzopyrano-[4,3-*d*]-pyrimidine-2-thioxo 11 and 4-aryl-1,2,3,4-tetrahydro-(5*H*)-[1]benzothiopyrano[4,3-*d*]-pyrimidine-2-thioxo 12.** Dry hydrogen chloride gas was passed through a mixture of compound **3** or **4** (0.01 mole) and thiourea (0.01 mole) in absolute ethanol (25 mL) at room temperature for 6 hr. The reaction mixture was poured gradually with stirring onto cold water. The solid formed was filtered off, washed with water and crystallized from the proper solvent (**Table II**).

**2-Amino-4-aryl-(5*H*)-[1]benzopyrano[4,3-*b*]-pyridine-3-carbonitrile 13 and 2-amino-4-aryl-(5*H*)-[1]benzothiopyrano[4,3-*b*]pyridine-3-carbonitrile 14:**

**Method A:** A mixture of **3** or **4** (0.01 mole), malononitrile (0.01 mole) and ammonium acetate (0.08 mole) in glacial acetic acid (25 mL) was heated under reflux for 8 hr, left to cool, then poured onto cold water. The solid formed was filtered off, washed with water, and crystallized from the proper solvent **(Table II).**

**Method B:** A mixture of **1** or **2** (0.01 mole), α-cyanocinnamonitrile (0.01 mole) and ammonium acetate (0.08 mole) in absolute ethanol (50 mL) was heated under reflux for 10 hr, left to cool, then poured onto cold water. The solid formed was filtered off, washed with water, and crystallized from the proper solvent (**Table II**). It was identified by m.p. and mixed m.p. with samples obtained from Method A.

Method A gives better yield.

**2-Amino-4-aryl-(4*H*),(5*H*)-[1]benzopyrano-[4,3-*b*]pyrane-3-carbonitrile 15 and 2-amino-4-aryl-(4*H*),(5*H*)-[1]benzothiopyrano[4,3-*b*]pyrane-3-carbonitrile 16.** A solution of **3** or **4** (0.01 mole) and malononitrile (0.01 mole) in ethanol (100 mL) in the presence of piperidine (20 mL) was stirred at room temperature for 1 hr. The solvent was concentrated by evaporation under reduced pressure, the solid formed was filtered off, washed with water and crystallized from the proper solvent (**Table II**).

**4-Aryl-1,2-dihydro-(5*H*)-[1]benzopyrano[4,3-*b*]-pyridine-2-one-3-carbonitrile 17 and 4-aryl-1,2-dihydro-(5*H*)-[1]benzothiopyrano[4,3-*b*]pyridine-2-one-3-carbonitrile 18**.

**Table II**—Physical data of prepared compound

| Compd | R | m.p. °C solvent | Yield (%) | Mol. formula (M.Wt) | Compd | R | m.p. °C solvent | Yield (%) | Mol. formula (M.Wt) |
|---|---|---|---|---|---|---|---|---|---|
| **3a** | H | 110 MeOH | 85 | $C_{16}H_{12}O_2$ 236.3 | **8a** | 4-$OCH_3$ | 196 AcOH | 65 | $C_{23}H_{20}N_2OS$ 372.49 |
| **3b** | 4-$CH_3$ | 118 MeOH | 87 | $C_{17}H_{14}O_2$ 250.3 | **8b** | 4-Br | 149 EtOH | 82 | $C_{22}H_{17}BrN_2S$ (421.36) |
| **3c** | 4-$OCH_3$ | 132 MeOH | 88 | $C_{17}H_{14}O_3$ 266.3 | **9a** | H | 272 EtOH | 75 | $C_{17}H_{15}N_3O$ 277.3 |
| **3d** | 4-Cl | 168 EtOH | 95 | $C_{16}H_{11}ClO_2$ 270.7 | **9b** | 4-$CH_3$ | 184 EtOH | 72 | $C_{18}H_{17}N_3O$ 291.4 |
| **3e** | 4-$NO_2$ | 223 EtOH | 90 | $C_{16}H_{11}NO_4$ 281.3 | **9c** | 4-$OCH_3$ | 182 MeOH | 70 | $C_{18}H_{17}N_3O_2$ 307.4 |
| **3f** | 3,4-($OCH_3$) | 128 EtOH | 91 | $C_{18}H_{16}O_4$ 296.3 | **9d** | 4-Cl | 186 EtOH | 65 | $C_{17}H_{14}ClN_3O$ 311.8 |
| **3g** | 4-Br | 174 EtOH | 94 | $C_{16}H_{11}BrO_2$ 315.2 | **9e** | 4-Br | 112 EtOH | 69 | $C_{17}H_{14}BrN_3O$ 356.2 |
| **3h** | 3,4,5-($OCH_3$) | 107 EtOH | 91 | $C_{19}H_{18}O_5$ 326.3 | **10a** | 4-$OCH_3$ | 101 EtOH/$H_2O$ | 61 | $C_{18}H_{17}N_3OS$ 323.4 |
| **4a** | 4-$CH_3$ | 107 MeOH | 89 | $C_{17}H_{14}OS$ 266.4 | **10b** | 4-Br | 126 EtOH | 62 | $C_{17}H_{14}BrN_3S$ (372.3) |
| **4b** | 4-$OCH_3$ | 113 MeH | 91 | $C_{17}H_{14}O_2S$ 282.4 | **11a** | H | 272 EtOH/$H_2O$ | 70 | $C_{17}H_{14}N_2OS$ 294.4 |
| **4c** | 4-Cl | 135 EtOH | 85 | $C_{16}H_{11}ClOS$ 286.8 | **11b** | 4-$CH_3$ | 241 MeOH | 73 | $C_{18}H_{16}N_2OS$ 308.4 |
| **4d** | 4-Br | 149 EtOH | 90 | $C_{16}H_{11}BrOS$ 331.2 | **11c** | 4-$OCH_3$ | 213 EtOH | 79 | $C_{18}H_{16}N_2O_2S$ 324.4 |
| **5a** | H | 139-41 EtOH | 88 | $C_{18}H_{16}N_2O_2$ 292.3 | **11d** | 4-Cl | 246 dioxane | 85 | $C_{17}H_{13}ClN_2OS$ 328.8 |
| **5b** | 4-$OCH_3$ | 124-6 EtOH | 78 | $C_{19}H_{18}N_2O_3$ 322.4 | **11e** | 4-Br | 248 EtOH | 72 | $C_{17}H_{13}BrN_2OS$ 373.3 |
| **5c** | 4-Cl | 149-51 AcOH | 76 | $C_{18}H_{15}ClN_2O_2$ 326.8 | **12a** | 4-$OCH_3$ | 141 dioxane | 65 | $C_{18}H_{16}N_2OS_2$ 340.50 |
| **5d** | 4-$NO_2$ | 214 MeOH | 74 | $C_{18}H_{15}N_3O_4$ 337.3 | **12b** | 4-Cl | 199 AcOEt | 61 | $C_{17}H_{13}ClN_2S_2$ 344.89 |
| **5e** | 4-Br | 164 EtOH | 71 | $C_{18}H_{15}BrN_2O_2$ 371.2 | **12c** | 4-Br | 157 dioxane | 71 | $C_{17}H_{13}BrN_2S_2$ 389.34 |
| **6a** | 4-$OCH_3$ | 140 MeOH | 82 | $C_{19}H_{18}N_2O_2S$ 338.4 | **13a** | H | 327 EtOH/$H_2O$ | 67 | $C_{19}H_{13}N_3O$ 299.3 |
| **6b** | 4-Br | 143 AcOH | 80 | $C_{18}H_{15}BrN_2OS$ 387.3 | **13b** | 4-$CH_3$ | 302 MeOH | 60 | $C_{20}H_{15}N_3O$ 313.4 |
| **7a** | H | 152 EtOH | 70 | $C_{22}H_{18}N_2O$ 326.4 | **13c** | 4-$OCH_3$ | 285 EtOH | 72 | $C_{20}H_{15}N_3O_2$ 329.4 |
| **7b** | 4-$CH_3$ | 140 MeOH | 65 | $C_{23}H_{20}N_2O$ 340.43 | **13d** | 4-Cl | 352 EtOH | 65 | $C_{19}H_{12}ClN_3O$ 333.8 |
| **7c** | 4-$OCH_3$ | 165 MeOH | 76 | $C_{23}H_{20}N_2O_2$ 356.43 | **13e** | 4-Br | 348 AcOH/$H_2O$ | 71 | $C_{19}H_{12}BrN_3O$ 378.2 |
| **7d** | 4-Cl | 103 EtOH/$H_2O$ | 71 | $C_{22}H_{17}ClN_2O$ 360.84 | **14a** | 4-$CH_3$ | 115 MeOH | 60 | $C_{20}H_{15}N_3S$ 329.4 |
| **7e** | 4-Br | 110 EtOH/$H_2O$ | 73 | $C_{22}H_{17}BrN_2O$ 405.3 | **14b** | 4-Br | 130-4 MeOH | | $C_{19}H_{12}BrN_3S$ 394.3 |

*—Contd*

**Table II**—Physical data of prepared compound—*Contd*

| Compd | R | m.p. °C solvent | Yield (%) | Mol. formula (M.Wt) | Compd | R | m.p. °C solvent | Yield (%) | Mol. formula (M.Wt) |
|---|---|---|---|---|---|---|---|---|---|
| **15a** | H | 211 EtOH | 67 | $C_{19}H_{14}N_2O_2$ 302.3 | **20b** | 4-Br | 143 MeOH | 68 | $C_{16}H_{11}BrO_2S$ 347.2 |
| **15b** | 4-$CH_3$ | 215 EtOH | 75 | $C_{20}H_{16}N_2O_2$ 316.4 | **21a** | 4-$CH_3$ | 122 MeOH | 60 | $C_{18}H_{12}O_2S_2$ 324.4 |
| **15c** | 4-$OCH_3$ | 234 MeOH | 72 | $C_{20}H_{16}N_2O_3$ 332.4 | **21b** | 4-$OCH_3$ | 133 EtOH | 61 | $C_{18}H_{12}O_3S_2$ 340.4 |
| **15d** | 4-Cl | 226 EtOH | 70 | $C_{19}H_{13}ClN_2O_2$ 336.8 | **21c** | 4-Cl | 230 MeOH | 51 | $C_{17}H_9ClO_2S_2$ 344.8 |
| **15e** | 4-Br | 342 EtOH/dioxane | 81 | $C_{19}H_{13}BrN_2O_2$ 381.2 | **24a** | H | 118-20 EtOH | 60 | $C_{19}H_{13}N_3O$ 299.3 |
| **16a** | 4-$CH_3$ | 195-7 MeOH | 65 | $C_{20}H_{16}N_2OS$ 332.43 | **24b** | 4-$CH_3$ | 202 EtOH | 63 | $C_{20}H_{15}N_3O$ 313.4 |
| **16b** | 4-$OCH_3$ | 160-4 MeOH | 68 | $C_{20}H_{16}N_2O_2S$ 348.43 | **24c** | 4-$OCH_3$ | 185-8 dioxane/$H_2O$ | 60 | $C_{20}H_{15}N_3O_2$ 329.4 |
| **16c** | 4-Br | 205 EtOH | 63 | $C_{19}H_{13}BrN_2OS$ 397.30 | **24d** | 4-Cl | 178-80 EtOH | 62 | $C_{19}H_{12}ClN_3O$ 333.8 |
| **17a** | 4-$CH_3$ | >300 EtOH | 72 | $C_{20}H_{14}N_2O_2$ 314.3 | **24e** | 4-Br | 293-6 EtOH | 67 | $C_{19}H_{12}BrN_3O$ 378.2 |
| **17b** | 4-$OCH_3$ | >300 EtOH | 65 | $C_{20}H_{14}N_2O_3$ 330.3 | **25a** | 4-$OCH_3$ | 179 MeOH/$H_2O$ | 59 | $C_{20}H_{15}N_3OS$ 345.43 |
| **17c** | 4-Cl | >300 dioxane | 71 | $C_{19}H_{11}ClN_2O_2$ 334.8 | **25b** | 4-Br | 262 dioxane | 69 | $C_{19}H_{12}BrN_3S$ 394.30 |
| **17d** | 4-Br | >300 EtOH | 70 | $C_{19}H_{11}BrN_2O_2$ 379.2 | **26a** | H | 263 EtOH | 72 | $C_{21}H_{13}N_3O$ 323.4 |
| **17e** | 3,4,5-($OCH_3$) | 287 EtOH | 73 | $C_{22}H_{18}N_2O_5$ 390.4 | **26b** | 4-Cl | 239 EtOH | 74 | $C_{21}H_{12}ClN_3O$ 357.8 |
| **18a** | 4-$OCH_3$ | 212 EtOH | 82 | $C_{20}H_{14}N_2O_2S$ 346.4 | **26c** | 3,4-($OCH_3$) | 290 EtOH | 70 | $C_{23}H_{17}N_3O_3$ 383.4 |
| **18b** | 4-Cl | >300 AcOH | 65 | $C_{19}H_{11}ClN_2OS$ 350.8 | **26d** | 4-Br | 242 EtOH | 71 | $C_{21}H_{12}BrN_3O$ 402.3 |
| **19a** | H | 128 MeOH | 71 | $C_{16}H_{12}O_3$ 252.3 | **26e** | 3,4,5-($OCH_3$) | 254 MeOH | 68 | $C_{24}H_{19}N_3O_4$ 413.4 |
| **19b** | 4-$CH_3$ | 129 EtOH | 70 | $C_{17}H_{14}O_3$ 266.3 | **27a** | 4-$OCH_3$ | 248 EtOH/dioxane | 62 | $C_{22}H_{15}N_3OS$ 369.4 |
| **19c** | 4-$OCH_3$ | 115 EtOH | 72 | $C_{17}H_{14}O_4$ 282.3 | **27b** | 4-Cl | 227-29 EtOH | 72 | $C_{21}H_{12}ClN_3S$ 373.90 |
| **19d** | 4-Cl | 116 EtOH | 75 | $C_{16}H_{11}ClO_3$ 286.7 | **28** | - | 203-5 MeOH | 73 | $C_{19}H_{13}N_3OS$ 331.4 |
| **19e** | 3,4,5-($OCH_3$) | 137 EtOH | 71 | $C_{19}H_{18}O_6$ 342.3 | **29** | - | 200-4 dioxane | 71 | $C_{19}H_{13}N_3S_2$ 347.5 |
| **20a** | 4-$CH_3$ | 109-111 MeOH | 68 | $C_{17}H_{14}O_2S$ 282.4 | All compounds gave satisfactory (C, H, N, S and halogen) analysis | | | | |

**Method A:** To a mixture of **1** or **2** (0.01 mole), arylmethylene-cyanoacetamide (0.01 mole) in absolute ethanol (50 mL) was added few drops of triethylamine. The mixture was refluxed for 9 hr, left at room-temperature, then poured onto cold water. The solid formed was filtered off, washed with water, and crystallized from the proper solvent (**Table II**).

**Method B:** Compound **15** or **16** (0.01 mole) was suspended in 100 mL ethanol, then a current of HCl gas was passed at 0°C till saturation, the reaction mixture was left overnight, then ethanol was evaporated

under reduced pressure, the solid formed was filtered off, washed with water, and crystallized from the proper solvent (**Table II**) and identified by m.p. and mixed m.p. experiment with the samples obtained from method A.

**3-Aryl-(3′*H*)-(2*H*)-spiroxarane[2′,3]benzopyran-4-one 19 and 3-aryl-(3′*H*)-(2*H*)-spiroxarane[2′,3]-benzothiopyran-4-one 20.** Hydrogen peroxide (10 mL, 30%) was added portion-wise to a mixture of 3 or 4 (0.01 mole) and 10% NaOH (3 mL) in methanol/acetone (30:10 mL) as solvent. The mixture was stirred in ice-bath for 8 hr, then left overnight at room temperature. The white solid formed was collected by filteration and crystallized from the proper solvent (**Table II**).

**4-Aryl-2-thioxo-(4*H*)-thieno[3,4-*b*]benzopyran-5-one 21.** A mixture of **19** (0.01 mole), carbon disulfide (3 mL), NaOH (1 g) in ethanol (50 mL) was refluxed for 4 hr. The solvent was evaporated under reduced pressure, the product was extracted with chloroform, dried over anhyd. $Na_2SO_4$, evaporated and solidified with diethyl ether. The solid formed was filtered off and crystallized from the proper solvent (**Table II**).

**2-Amino-4-aryl-(5*H*)-[1]benzopyrano[3,4-*c*]-pyridine-1-carbonitrile 24 and 2-amino-4-aryl-(5*H*)-[1]benzothiopyrano[3,4-*c*]-pyridine-1-carbonitrile 25.** A mixture of 2,3-dihydro[1]benzopyran-4(2*H*)yielidinemalononitrile **22** or 2,3-dihydro[1]benzothiopyran-4(2*H*)yielidinemalononitrile **23** (0.01 mole), aromatic aldehydes (0.01 mole) and ammonium acetate (0.08 mole) in glacial acetic acid (50 mL) was heated under reflux for 10 hr., allowed to cool, then poured onto cold water. The solid formed was filtered off, washed with water, and crystallized from the proper solvent (**Table II**).

**2-Amino-4-aryl-(5*H*)-dibenzo[b,d]pyran-1,3-dicarbonitrile 26 and 2-amino-4-aryl-(5*H*)-dibenzo-[b,d]thiopyran-1,3-dicarbonitrile 27.** To a mixture of **22** or **23** (0.01 mole), arylmethylenecyanoacetamide (0.01 mole) in ethanol (50 mL), few drops of triethylamine was added, the mixture was heated under reflux for 9 hr, allowed to cool, then poured onto cold water. The solid formed was filtered off, washed with water, and crystallized from the proper solvent (**Table II**).

**2-Amino-3-phenyl-4-thioxo-(5*H*)-[1]benzopyrano[3,4-*c*]pyridine-1-carbonitrile 28 and 2-amino-3-phenyl-4-thioxo-(5*H*)-[1]benzothiopyrano[3,4-*c*]-pyridine-1-carbonitrile 29.** To a mixture of 22 or 23 (0.05 mole) and phenyl-isothiocyanate (0.05 mole) in dimethylformamide (10 mL), triethyl-amine (4 mL) was added. After stirring for 2 hr at 50°C, methanol (20 mL) was added. The mixture was left overnight. The solid formed was filtered off and crystallized from the proper solvent (**Table II**).

## Acknowledgement

Authors thank Dr V L Narayanan and his groups, National Institute of Health, Meryland, USA, for anticancer screening.

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