Indian Journal of Chemistry
Vol. 44B, October 2005, pp. 2120-2125

Synthesis and biological activity of some 3-imidazo[1,2-*a*]pyridin-2-yl-chromen-2-one and 3-indolizin-2-yl-chromen-2-one

P Vijaya Kumar & V Rajeswar Rao*

Department of Chemistry, National Institute of Technology, Warangal 506 004, India

E-mail: vrajesw@yahoo.com

Received 7 December 2004; accepted (revised) 15 June 2005

Condensation of 3-(2-bromoacetyl)coumarins **1** with various 2-aminopyridines **2** in the solid state under solvent-free conditions yield 3-imidazo[1,2-*a*]pyridin-2-yl-chromen-2-ones **3**. Condensation of **1** with 2-methylpyridines in dry benzene affords N-alkylpyridinium salts **5**. These undergo cyclization reaction when heated with sodium bicarbonate to give indolizines **6**. The structures of newly prepared compounds have been confirmed from analytical and spectral data. Some of the compounds exhibit antitubercular, antiviral and anticancer activities.

Keywords: Coumarins, aminopyridines, cyclization reaction, indolizines, antitubercular, antiviral, anticancer

: Int.Cl.[7] C 07 D 209/04 // A 61 P 31/06, 31/12, 35/00

2-Oxo-2*H*-chromenes and their derivatives have wide applications and are used as uricosuric[1], anti-inflammatory[2-5] and CNS[6] active agents. Similarly, several nitrogen containing heterocyclic systems find a wide variety of therapeutic activities such as anthelmintic[7], antiulcer[8] and antifungal[9]. In the course of our recent work on the synthesis of new poly-heterocyclic systems consisting of coumarin as one of the moieties[10-12], we planned to synthesise pyridinyl and indazolyl chromen-2-ones, which can be exploited as biologically active compounds.

The title compounds pyridinyl-chromen-2-ones **3** have been synthesized by reacting 2-aminopyridine **2** with 3-(2-bromoacetyl)coumarin **1** in the solid state at room temperature (**Scheme I**). 2-Aminopyridine is believed to exist in two tautomeric structures. It has been shown that in 2-aminopyridine, the more nucleophilic cyclic secondary nitrogen[13,14] replaces the bromine of 3-(2-bromoacetyl)coumarin to give the intermediate. This on subsequent cyclodehydration yields the final product **3**. Attempts to isolate the intermediates failed as the final products were directly obtained. The prepared compounds were tested chemically and found to have nitrogen (Lassaigne's test).

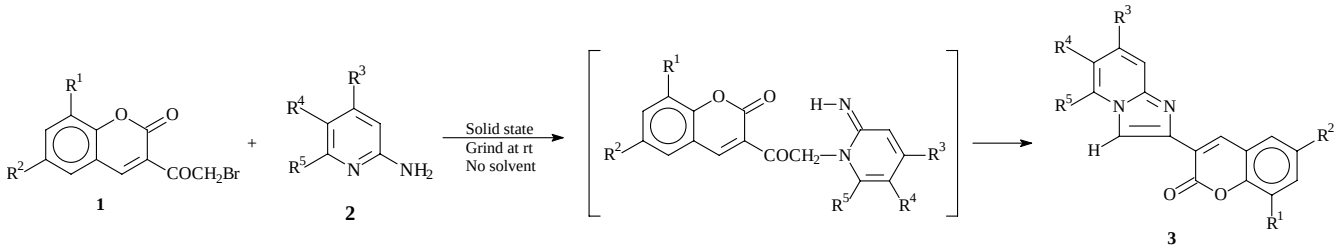
Another possible isomeric structure **4** could be proposed for the prepared compounds. However, the structure **4** can be readily discarded on the basis of the fact that in 2-aminopyridine, the most nucleophilic site is the cyclic secondary 'N' atom at position-1. Hence, the preferential attack will be through this nitrogen on carbon carrying bromine of 3-(2-bromo-acetyl)coumarin leading to the intermediate, followed by dehydration resulting in the formation of **3**.

3-(2-Bromoacetyl)coumarins on reaction with 2-methylpyridines in dry benzene gave corresponding pyridinium salts **5**. These pyridinium salts on refluxing in dry benzene containing sodium bicarbonate resulted in the formation of 3-indolizin-2-yl-chromen-2-ones **6** (**Scheme II**).

The proposed structures of newly synthesized compounds **3, 5** and **6** are in agreement with their spectral (IR, ^{1}H NMR, mass) data and elementary analysis.

The carbonyl stretching of the lactone in the IR spectra of the **3** is observed in the range 1720$\pm$10 cm^{-1}.

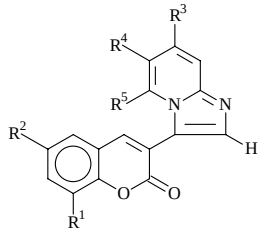
^{1}H NMR spectrum of **3a** showed a characteristic singlet for imidazo-pyridinyl proton at δ 8.95 and another characteristic singlet for C_4 proton of coumarin at δ 8.75. The remaining aromatic protons were observed as multiplet in the usual region. In the IR spectrum **5a** showed a characteristic peak at 1713 $\pm$ 7 due to >C=O stretching of lactone –C=O. The ketone group in the uncyclized compound has been observed at 1690 $\pm$ 4 cm^{-1}. The ^{1}H NMR spectrum of **5a** exhibited a characteristic singlet for –CH_2- protons at δ 6.4. The remaining eight aromatic protons were observed in the usual region.



1 **2** **3**

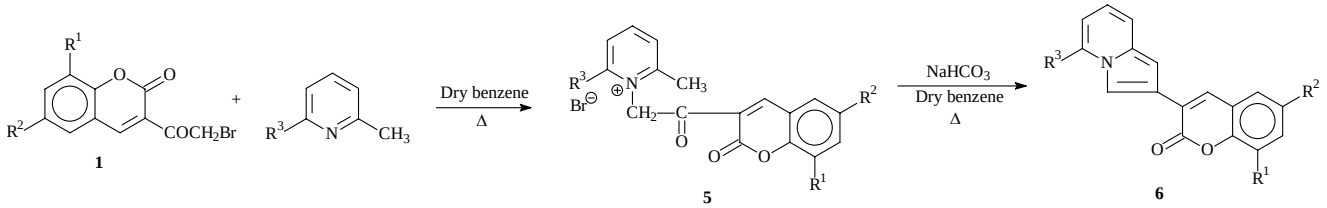
3

a : $R^1 = R^2 = R^3 = R^4 = R^5 = H$
b : $R^1 = OCH_3$, $R^2 = R^3 = R^4 = R^5 = H$
c : $R^1 = H$, $R^2 = Br$, $R^3 = R^4 = R^5 = H$
d : $R^1 = R^2 = Br$, $R^3 = R^4 = R^5 = H$
e : $R^1 = H$, $R^2 = Cl$, $R^3 = R^4 = R^5 = H$
f : $R^1 = R^2 = Cl$, $R^3 = R^4 = R^5 = H$
g : $R^1 = OCH_3$, $R^2 = NO_2$, $R^3 = R^4 = R^5 = H$
h : $R^1 = OCH_3$, $R^2 = Br$, $R^3 = R^4 = R^5 = H$
i : $R^1 = R^2 = H$, $R^3 = CH_3$, $R^4 = H_A$, $R^5 = H_B$ pyridine aromatic $H = H_C$
j : $R^1 = OCH_3$, $R^2 = H$, $R^3 = CH_3$, $R^4 = R^5 = H$
k : $R^1 = H$, $R^2 = Br$, $R^3 = CH_3$, $R^4 = R^5 = H$
l : $R^1 = R^2 = Br$, $R^3 = CH_3$, $R^4 = R^5 = H$
m: $R^1 = H$, $R^2 = Cl$, $R^3 = CH_3$, $R^4 = R^5 = H$
n : $R^1 = R^2 = Cl$, $R^3 = CH_3$, $R^4 = R^5 = H$
o : $R^1 = OCH_3$, $R^2 = Br$, $R^3 = CH_3$, $R^4 = R^5 = H$
p : $R^1 = R^2 = R^3 = H$, $R^4 = Br$, $R^5 = H$
q : $R^1 = OCH_3$, $R^2 = H$, $R^3 = H$, $R^4 = Br$, $R^5 = H$
r : $R^1 = H$, $R^2 = Br$, $R^3 = H$, $R^4 = Br$, $R^5 = H$
s : $R^1 = R^2 = Br$, $R^3 = H$, $R^4 = Br$, $R^5 = H$
t : $R^1 = H$, $R^2 = Cl$, $R^3 = H$, $R^4 = Br$, $R^5 = H$
u : $R^1 = R^2 = Cl$, $R^3 = H$, $R^4 = Br$, $R^5 = H$
v : $R^1 = R^3 = R^4 = R^5 = H$
w : $R^1 = NO_2$, $R^3 = R^4 = R^5 = H$
y : $R^1 = NO_2$, $R^3 = CH_3$, $R^4 = R^5 = H$
z : $R^1 = R^3 = H$, $R^4 = Br$, $R^5 = H$
a$_1$: $R^1 = NO_2$, $R^3 = H$, $R^4 = Br$, $R^5 = H$
a$_2$: $R^1 = NO_2$, $R^3 = R^4 = H$, $R^5 = NH_2$



4

Scheme I



1 **5** **6**

5 & 6

a : $R^1 = R^2 = R^3 = H$
b : $R^1 = OCH_3$, $R^2 = R^3 = H$
c : $R^1 = H$, $R^2 = Br$, $R^3 = H$
d : $R^1 = R^2 = Br$, $R^3 = H$
e : $R^1 = H$, $R^2 = Cl$, $R^3 = H$
f : $R^1 = R^2 = Cl$, $R^3 = H$
g : $R^1 = R^2 = H$, $R^3 = CH_3$
h : $R^1 = OCH_3$, $R^2 = H$, $R^3 = CH_3$
i : $R^1 = H$, $R^2 = Br$, $R^3 = CH_3$
j : $R^1 = R^2 = Br$, $R^3 = CH_3$
k : $R^1 = H$, $R^2 = Cl$, $R^3 = CH_3$,
l : $R^1 = R^2 = Cl$, $R^3 = CH_3$
m : $R^1 = R^3 = H$
n : $R^1 = NO_2$, $R^3 = H$
o : $R^1 = H$, $R^3 = CH_3$
p : $R^1 = NO_2$, $R^3 = CH_3$

Scheme II

The cyclized compound **6** lacks the >C=O absorption in the region 1690 cm^{-1} in the IR spectra. This readily confirms that a cyclization has occurred during the conversion of **5** into **6**. In the ^1H NMR spectrum compound **6**, showed the absence of $–CH_2$- group adjacent to >C=O. This readily confirms that compound **5** underwent cyclodehydration on refluxing with $NaHCO_3$ in dry benzene. The compound **6a** displayed a characteristic multiplet for eight aromatic protons, a singlet at δ 8.0 for C_4 proton of coumarin and another singlet at δ 8.30 for indolizine proton.

Experimental Section

All melting points were recorded on Cintex melting point apparatus and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 337 spectrophotometer; ^1H NMR spectra on a Varian Gemini 200 MHz spectrometer using TMS as internal standard (chemical shifts in δ, ppm); and mass spectra on a Jeol-JMS-D mass spectrometer at 70 eV.

The various derivatives of 3-(2-bromoacetyl)coumarins were prepared according to literature method[19]. Representative methods of preparation of

compounds **3**, **5** and **6** along with spectral data are described below.

Preparation of 3-imidazo[1,2-*a*]pyridin-2-yl-chromen-2-one 3. General procedure. A mixture of **1** (0.001 mole) and 2-aminopyridine **2** (0.001 mole) was ground in pestle and mortar at room temperature for 10-15 min. The solid thus obtained was treated with water, filtered, dried and recrystallized from acetone to give **3** (**Table I**).

3-Imidazo[1,2-*a*]pyridin-2-yl-chromen-2-one 3a. IR (KBr): 1720 (lactone –C=O), 1654 (-C=C- stretching), 1607 cm^{-1} (-C=N-); ^1H NMR ($CDCl_3$): δ 7.10 – 7.95 (m, 8H), 8.75 (s, 1H, coumarin C_4-H), 8.95 (s, 1H, imidazopyridine); MS: m/z 262 (100%), 234 (60), 205 (20).

3-Imidazo[1,2-*a*]pyridin-2-yl-8-methoxychromen-2-one 3b: IR (KBr): 1730 (lactone –C=O), 1610 cm^{-1} (-C=N-); ^1H NMR ($CDCl_3$): δ 4.00 (s, 3H, OCH_3), 6.9 (s, 1H, d, *J* = 7 Hz, C_7-H of imidazopyridine), 7.26 – 7.28 (m, 5H, Ar-H), 8.2 (d, *J* = 8 Hz, 1H of C_5-H of imidazopyridine), 8.61 (s, 1H, C_4-H of coumarin), 8.91 (s, 1H, C_3-H of imidazopyrimidine); MS: m/z 292.

3-Bromo-3-imidazo[1,2-*a*]pyridin-2-yl-chromen-2-one 3c: IR (KBr): 1605 (–C=N-), 1710 cm^{-1} (lactone, -C=O); ^1H NMR ($CDCl_3$): δ 7.25 – 7.29 (m, 3H, Ar-H), 7.62 – 7.78 (m, 3H, Ar-H), 8.41 (s, 1H, C_4-H of coumarin), 8.70 (s, 1H, C_3-H of imidazopyridine); MS: m/z 341.

6-Nitro-3-imidazo[1,2-*a*]pyridin-2-yl-8-methoxychromen-2-one 3g: IR (KBr): 1734 (lactone, -C=O), 1602 cm^{-1} (-C=N-); ^1H NMR ($CDCl_3$): δ 2.72 (s, 3H, CH_3), 3.98 (s, 3H, OCH_3), 7.20–7.26 (m, 6H, Ar-H), 8.47 (s, 1H, C_4-H of coumarin), 8.75 (s, 1H, C_3-H of imidazopyridine); MS: m/z 337.

3-(7-Methylimidazo[1,2-*a*]pyridin-2-yl)chromen-2-one 3i: IR (KBr): 1724 (lactone –C=O), 1607 cm^{-1} (-C=N); ^1H NMR ($CDCl_3$): δ 2.4 (s, 3H, -CH_3), 6.6

Table I — Physical data of compounds **3a-z** and **$3a_1$, a_2**

Compd 3	Yield (%)	Mol. formula (Mol. wt)	mp °C	Found % (Calcd) C	H	N	Compd 3	Yield (%)	Mol. formula (Mol. wt)	mp °C	Found % (Calcd) C	H	N
a	80	$C_{16}H_{10}N_2O_2$ (262)	225-27	73.23 (73.27	3.80 3.84	10.58 10.68)	**o**	75	$C_{18}H_{13}N_2O_3Br$ (385)	238-40	56.10 (56.12	3.37 3.40	7.25 7.27)
b	82	$C_{17}H_{12}N_2O_3$ (292)	205-07	69.80 (69.86	4.11 4.14	9.53 9.58)	**p**	68	$C_{16}H_9N_2O_2Br$ (341)	185-87	56.30 (56.33	2.63 2.66	8.19 8.21)
c	80	$C_{16}H_9N_2O_2Br$ (341)	192-94	56.29 (56.33	2.61 2.66	8.18 8.21)	**q**	74	$C_{17}H_{11}N_2O_3Br$ (371)	174-76	55.00 (55.01	2.97 2.99	7.52 7.55)
d	78	$C_{16}H_8N_2O_2Br_2$ (420)	198-200	45.71 (45.75	1.89 1.92	6.62 6.67)	**r**	73	$C_{16}H_8N_2O_2Br_2$ (420)	188-90	45.71 (45.75	1.89 1.92	6.64 6.67)
e	70	$C_{16}H_9N_2O_2Cl$ (296)	200-02	64.72 (64.77	3.00 3.06	9.40 9.44)	**s**	78	$C_{16}H_7N_2O_3Br_3$ (499)	195-97	38.48 (38.52	1.39 1.41	5.58 5.61)
f	84	$C_{16}H_8N_2O_2Cl_2$ (330)	202-04	58.00 (58.03	2.40 2.44	8.43 8.46)	**t**	78	$C_{16}H_8N_2O_2ClBr$ (375)	166-68	51.15 (51.16	2.13 2.15	7.43 7.46)
g	85	$C_{17}H_{11}N_3O_5$ (337)	188-90	60.52 (60.54	3.26 3.29	12.44 12.46)	**u**	82	$C_{16}H_7N_2O_2Cl_2Br$ (409)	169-71	46.85 (46.87	1.68 1.72	6.80 6.83)
h	80	$C_{17}H_{11}N_2O_3Br$ (371)	210-12	55.00 (55.01	2.96 2.99	7.52 7.55)	**v**	74	$C_{20}H_{12}N_2O_2$ (312)	176-78	76.89 (76.91	3.83 3.87	8.94 8.97)
i	75	$C_{17}H_{12}N_2O_2$ (276)	235-37	73.88 (73.90	4.35 4.38	10.12 10.14)	**w**	75	$C_{20}H_{11}N_3O_4$ (357)	184-86	67.20 (67.23	3.05 3.10	11.74 11.76)
j	82	$C_{18}H_{14}N_2O_3$ (306)	161-63	70.56 (70.58	4.58 4.61	9.13 9.15	**x**	70	$C_{21}H_{14}N_2O_2$ (326)	248-50	77.26 (77.29	4.29 4.32	8.55 8.58)
k	78	$C_{17}H_{11}N_2O_2Br$ (355)	215-17	51.45 (57.49	3.10 3.12	7.86 7.89)	**y**	72	$C_{21}H_{13}N_3O_4$ (371)	258-60	67.89 (67.92	3.50 3.53	11.29 11.32)
l	80	$C_{17}H_{10}N_2O_2Br_2$ (434)	218-20	47.00 (47.04	2.30 2.32	6.44 6.45)	**z**	85	$C_{20}H_{11}N_2O_2Br$ (391)	181-83	61.37 (61.40	2.80 2.83	7.14 7.16)
m	69	$C_{17}H_{11}N_2O_2Cl$ (310)	184-86	65.69 (65.71	3.52 3.57	9.00 9.01	**a_1**	80	$C_{20}H_{10}N_3O_4Br$ (436)	196-98	55.02 (55.07	2.28 2.31	9.60 9.63)
n	66	$C_{17}H_{10}N_2O_2Cl_2$ (344)	258-60	59.14 (59.15	2.88 2.92	8.08 8.12)	**a_2**	84	$C_{20}H_{12}N_4O_4$ (372)	305-07	64.47 (64.51	3.20 3.22	15.00 15.04)

The compounds **3a-3z** were crystallized from acetone and **$3a_1$** and **$3a_2$** were crystallized from methanol.

(d, 1H, H_A, J = 6.8 cps), 7.2–7.6 (m, 5H, Ar-H), 8.0 (d, 1H, Ar-H, H_B, J = 8 cps),. 8.5 (s, 1H, C_4-H of coumarin), 8.8 (s, 1H, C_3-H of imidazopyridine); MS: m/z 276 (M^+), 248 (70%), 247 (10), 220 (17), 205 (3).

3-(6-Bromoimidazo[1,2-*a*]pyridin-2-yl)chromen-2-one 3p: IR (KBr): 726 (C-Br), 1610 (-C=N-); 1710 cm^{-1} (lactone –C=O); ^{1}H NMR ($CDCl_3$): δ 7.30–7.70 (m, 7H, Ar-H), 8.62 (s, 1H, C_4-H of coumarin), 8.90 (s, 1H, C_3-H of imidazopyridine); MS: m/z 341.

3-(6-Bromoimidazo[1,2-*a*]pyridin-2-yl)-8-methoxychromen-2-one 3q: IR (KBr): 1693 (lactone –C=O), 1601 cm^{-1} (-C=N-); ^{1}H NMR ($CDCl_3$): δ 3.99 (s, 3H, OCH_3), 7.24–7.31 (m, 6H, Ar-H), 8.5 (s, 1H, C_4-H of coumarin), 8.60 (s, 1H, C_3-H of imidazopyridine); MS: m/z 371.

6-Bromo-3-(6-bromoimidazo[1,2-*a*]pyridin-2-yl)-chromen-2-one 3r: IR (KBr): 1720 (lactone –C=O), 1610 cm^{-1} (-C=N-); ^{1}H NMR ($CDCl_3$): δ 7.24–7.29 (m, 3H, Ar-H), 7.71–7.78 (m, 3H, Ar-H), 8.40 (s, 1H, C_4-H of coumarin), 8.53 (s, 1H, C_3-H imidazopyridine); MS: m/z 420.

3-(6-Bromoimidazo[1,2-*a*]pyridin-2-yl)-6,8-dichlorochromen-2-one 3u: IR (KBr): 1730 (lactone –C=O), 1605 (-C=N-), 730 (C-Br), 670 cm^{-1} (C-Cl); MS: m/z 409.

Preparation of N-alkylpyridinium salts 5. **General procedure**. A mixture of **1** (0.001 mole) and 2-methylpyridine (0.001 mole) in dry benzene (10 mL) was refluxed for about 6-8 hr. The solid separated was collected by filtration, dried and recrystallised from methanol to get **5** (**Table II**).

Table II — Physical data of compounds **5** and **6**

Compd	Yield (%)	Mol. formula (Mol. wt)	mp °C	Found % (Calcd) C	H	N	Compd	Yield (%)	Mol. formula (Mol. wt)	mp °C	Found % (Calcd) C	H	N
5a	80	$C_{17}H_{14}NO_3Br$ (359)	235-37	56.80 (56.82	3.86 3.89	3.87 3.89)	**6a**	82	$C_{17}H_{11}NO_2$ (261)	200-02	78.14 (78.15	4.20 4.24	5.34 5.36)
5b	82	$C_{18}H_{16}NO_4Br$ (389)	258-60	55.49 (55.52	4.06 4.11	3.58 3.59)	**6b**	85	$C_{18}H_{13}NO_3$ (291)	152-54	74.18 (74.22	4.46 4.50	4.78 4.81)
5c	84	$C_{17}H_{13}NO_3Br_2$ (437)	264-66	46.67 (46.68	2.96 2.97	3.19 3.20)	**6c**	77	$C_{17}H_{10}NO_2Br$ (340)	175-77	60.00 (60.02	2.92 2.96	4.10 4.12)
5d	84	$C_{17}H_{12}NO_3Br_3$ (515)	283-85	39.60 (39.61	2.32 2.33	2.69 2.71)	**6d**	76	$C_{17}H_9NO_2Br_2$ (419)	262-64	48.70 (48.72	2.13 2.16	3.32 3.34)
5e	80	$C_{17}H_{13}NO_3ClBr$ (393)	244-46	51.88 (51.90	3.28 3.30	3.54 3.56)	**6e**	75	$C_{17}H_{10}NO_2Cl$ (295)	221-22	60.01 (60.05	3.38 3.41	4.70 4.74)
5f	77	$C_{17}H_{12}NO_3Cl_2Br$ (428)	255-57	47.64 (47.66	2.78 2.80	3.26 3.27)	**6f**	74	$C_{17}H_9NO_2Cl_2$ (329)	238-40	61.82 (61.84	2.73 2.75	4.22 4.24)
5g	72	$C_{18}H_{16}NO_3Br$ (373)	152-54	57.87 (57.90	4.26 4.28	3.74 3.75)	**6g**	76	$C_{18}H_{13}NO_2$ (275)	118-20	78.50 (78.53	4.73 4.76	5.04 5.09)
5h	75	$C_{19}H_{18}NO_4Br$ (403)	203-05	56.54 (56.57	4.45 4.46	3.45 3.47)	**6h**	78	$C_{19}H_{15}NO_3$ (305)	197-99	74.72 (74.74	4.94 4.95	4.56 4.59)
5i	74	$C_{18}H_{15}NO_3Br_2$ (451)	234-36	47.87 (47.89	3.30 3.32	3.10 3.10)	**6i**	82	$C_{18}H_{12}NO_2Br$ (354)	208-10	61.00 (61.04	3.38 3.41	3.94 3.95)
5j	78	$C_{18}H_{14}NO_3Br_3$ (529)	238-40	40.81 (40.83	2.62 2.64	2.63 2.64)	**6j**	85	$C_{18}H_{11}NO_2Br_2$ (433)	214-16	49.89 (49.92	2.54 2.56	3.20 3.23)
5k	77	$C_{18}H_{15}NO_3ClBr$ (407)	210-12	53.03 (53.07	3.66 3.68	3.41 3.43)	**6k**	72	$C_{18}H_{12}NO_2Cl$ (309)	192-94	69.78 (69.80	3.88 3.90	4.49 4.52)
5l	76	$C_{18}H_{14}NO_3Cl_2Br$ (442)	224-26	48.84 (48.86	3.12 3.16	3.15 3.16)	**6l**	74	$C_{18}H_{11}NO_2Cl_2$ (343)	204-06	62.78 (62.81	3.19 3.22	4.04 4.07)
5m	76	$C_{21}H_{16}NO_3$ (409)	292-94	61.59 (61.61	3.90 3.91	3.40 3.42)	**6m**	72	$C_{21}H_{13}NO_2$ (311)	247-49	81.00 (81.01	4.19 4.21	4.47 4.50)
5n	75	$C_{21}H_{15}N_2O_5Br$ (454)	> 300	55.47 (55.50	3.28 3.30	6.15 6.16)	**6n**	71	$C_{21}H_{12}N_2O_4$ (356)	263-65	70.76 (70.78	3.36 3.39	7.84 7.86)
5o	79	$C_{22}H_{18}NO_3Br$ (423)	232-34	62.39 (62.41	4.21 4.25	3.28 3.30)	**6o**	72	$C_{22}H_{15}NO_2$ (325)	210-12	81.19 (81.21	4.62 4.65	4.28 4.30)
5p	72	$C_{22}H_{17}N_2O_5Br$ (468)	266-68	56.40 (56.41	3.60 3.63	5.96 5.98)	**6p**	76	$C_{22}H_{14}N_2O_4$ (370)	219-21	71.32 (71.35	3.80 3.81	7.54 7.56)

The compounds **5** and **6** were crystallized from methanol.

2-(2-Methyl-1-pyridiniumyl)-1-(2-oxo-2*H*-3-chromenyl)-1-ethanone-bromide 5a: IR (KBr): 1726 (lactone –C=O), 1696 (ketone), 1603 cm^{-1} (-C=N-); ^1H NMR ($CDCl_3$): δ 2.5 (s, 3H, $-CH_3$ at C_2 of pyridine), 6.4 (s, 2H, $-CH_2-$), 7.2–7.4 (m, 2H, Ar-H), 7.7–8.1 (m, 4H, Ar-H), 8.45–8.55 (m, 1H, Ar-H), 8.80 (s, 1H, C_4-H of coumarin), 9.1 (d, 1H, Ar-H); MS: m/z 359.

2-(2,6-Dimethyl-1-pyridiniumyl)-1-(2-oxo-2*H*-3-chromenyl)-1-ethanone-bromide 5g: IR (KBr): 1605 (-C=N-), 1695 (-C=O), 1730 cm^{-1} (lactone –C=O); ^1H NMR ($CDCl_3$): δ 2.70 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 4.71 (s, 2H, $-CH_2-CO-$), 7.28–7.35 (m, 5H, Ar-H), 8.65 (s, 1H, C_4-H of coumarin); MS: m/z 373.

2-(2,6-Dimethyl-1-pyridiniumyl)-1-(8-methoxy-2-oxo-2*H*-3-chromenyl)-1-ethanone-bromide 5h: IR (KBr): 1601 (-C=N-), 1691 (ketone), 1734 cm^{-1} (lactone –C=O); ^1H NMR ($CDCl_3$): δ 2.75 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 3.99 (s, 3H, OCH_3), 4.76 (s, 2H, $-CH_2-CO-$), 7.24–7.28 (m, 7H, Ar-H), 8.61 (s, 1H, C_4-H of coumarin); MS: m/z 403.

Preparation of 3-indolizin-2-yl-chromen-2-one 6. General procedure. A mixture of **5** (0.001 mole) and sodium bicarbonate (0.001 mole) in dry benzene (10 mL) was refluxed for about 6-8 hr. The solid separated was filtered, dried and recrystallized from methanol to give **6** (**Table II**).

3-Indolizin-2-yl-chromen-2-one 6a: IR (KBr): 1713 cm^{-1} (lactone –C=O); ^1H NMR ($CDCl_3$): δ 6.4-6.70 (m, 3H, Ar-H), 7.20–7.59 (m, 5H, Ar-H), 7.90 (d, 1H, C_6–H of indolizine), 8.0 (s, 1H, C_4-H of coumarin), 8.30 (s, 1H, C_8-H of indolizine); MS: m/z 261.

3-(5-Methyl-indolizin-2-yl)chromen-2-one 6g: IR (KBr): 1725 cm^{-1} (lactone –C=O); ^1H NMR ($CDCl_3$): δ 2.39 (s, 3H, CH_3), 6.73–7.28 (m, 5H, Ar-H), 7.57 (s, 1H, C_4-H of coumarin), 7.68 (s, 1H, indolizine proton); MS: m/z 275.

8-Methoxy-3-(5-methyl-indolizin-2-yl)chromen-2-one 6h: IR (KBr):1720 cm^{-1} (lactone –C=O); ^1H NMR ($CDCl_3$): δ 1.20 (s, 3H, CH_3), 4.00 (s, 3H, OCH_3), 7.25–7.53 (m, 6H, Ar-H), 7.93 (s, 1H, C_4-H of coumarin), 8.30 (s, 1H, indolizine proton); MS: m/z 305.

Biological Evaluation

Antitubercular activity. Twenty four compounds from **3** series have been subjected for their tuberculosis inhibition activity. Primary screening was conducted at 6.25 μg/mL (or molar equivalent of highest molecular weight compound in a series of congeners) against mycobacterium tuberculosis H_{37} RV in BA CTEC 12B medium using a broth microdilution assay, the micro plate Alamar Blue Assay[15] (MABA). Out of 24 compounds only two compounds **3y** and **$3a_2$** were found to be producing 100% inhibitory activity while others showed activity varying from 0-59%. The details are shown in **Table III**.

Anticancer activity[16-18]. Compounds **3** were tested for their biological activities in various tumor cell lines. As can be seen from **Table IV**, compounds **3w** and **3y** exhibited pronounced cytostatic activity, as these compounds proved inhibitory to the proliferation of all three tumor cell lines within the IC_{50} (50% inhibitory concentration) range of 1-10

Table III – Tuberculosis inhibition test results

Compd **3**	MIC[a] (μg/mL^{-1})	Inhibition (%)	Activity[b]
a	> 6.25	0	--
b	> 6.25	0	--
c	> 6.25	5	--
d	> 6.25	7	--
f	> 6.25	10	--
g	> 6.25	0	--
h	> 6.25	37	--
i	> 6.25	0	--
j	> 6.25	8	--
k	> 6.25	3	--
l	> 6.25	17	--
m	> 6.25	9	--
n	> 6.25	20	--
o	> 6.25	57	--
p	> 6.25	0	--
q	> 6.25	0	--
r	> 6.25	0	--
s	> 6.25	17	--
w	> 6.25	21	--
x	> 6.25	7	--
y	< 6.25	100	+
z	> 6.25	6	--
a_1	> 6.25	0	--
a_2	< 6.25	100	+

[a]MIC is found by using MABA in BACTEC 12B medium against mycobacterium tuberculosis H 37 RV (ATC 27294). [b]Compounds demonstrating at least 90% inhibition in the primary screening are called "active" and these compounds can be tested further.

Table IV — Inhibitory effects of compounds, the proliferation of murine leukemia cells (L 1210/0) and human T-lymphocyte cells (Molt 4 / C_8, CEM/0)

Compd **3**	IC_{50} (μg/mL)		
	L 1210/0	Molt 4/C_8	CEM/0
a	69 ± 4	3.4 ± 0.2	4.4 ± 0.5
b	> 200	> 200	102 ± 14
c	69 ± 2	44 ± 2	26 ± 7
d	90 ± 0	92 ± 11	79 ± 1
g	20 ± 5	86 ± 6	25 ± 6
h	33 ± 18	21 ± 5	18 ± 5
i	95 ± 9	144 ± 30	86 ± 12
j	80 ± 7	81 ± 6	64 ± 20
k	81 ± 6	44 ± 13	44 ± 11
l	84 ± 0	57 ± 7	25 ± 9
m	61 ± 9	75 ± 1	42 ± 1
n	156 ± 35	≥ 200	122 ± 6
p	87 ± 11	132 ± 33	87 ± 5
r	18 ± 4	18 ± 3	14 ± 0
s	23 ± 6	24 ± 11	14 ± 3
v	74 ± 18	130 ± 27	94 ± 11
w	0.60 ± 0.09	0.79 ± 0.12	1.7 ± 0.9
x	91 ± 9	120 ± 36	95 ± 0
y	1.3 ± 0.9	1.9 ± 1.1	3.2 ± 0.1
z	99 ± 12	112 ± 59	87 ± 4
a_1	14 ± 2	16 ± 4	12 ± 2
a_2	3.7 ± 0.8	7.3 ± 3.6	8.4 ± 2.8
6g	97 ± 2	83 ± 8	83 ± 0

[a]50% inhibitory concentration.

μg/mL. In particular **3w** being the most potent of this series (**Table IV**).

Acknowledgement

The authors are thankful to Dr E Declereq, Rega Medical Institute for Research, Katholieke Universitsit, Leuven, Belgium for anticancer activity. Further, authors thank the UGC, New Delhi for the financial support (No. F-12-106/2001 (SR-I)).

References

1 Baker W & Howese C S, *J Chem Soc*, 119, **1953**.
2 Chakravarthy B K, Rao Y N, Gombir S S & God K D, *Planta Med*, 43, **1981,** 64.
3 Romen R, *Res Commun Pathol Pharmaco*, 11, **1975**, 552.
4 Singh I P, Kumar A, Gurtus S, Sinha J N & Shanker, *Arch Pharm (Weinlinin)*, 317, **1984**, 984.
5 Dutta P K, Sen A K, Sarkar K K & Banerji N, *Indian J Chem*, 26B, **1987**, 281-282.
6 Nakabayshi T, Miyazaki H & Tokaroyana T, *J Pharm Soc Japan*, 13, **1953**, 565j; *Chem Abstr*, 48, **1954**, 5187e.
7 Labanauskers L K, Braklis A B, Gaidelis P G, Buchin Sklaite V A, Undernaite L B & Panhas V K, *Pharm Chem J*, 34, **2001**, 353.
8 Fischilli A, Krasso A & Szente A, *Eur Pat Appl E P*, 304, **1989**, 624; *Chem Abstr*, 111, **1989**, 194761C.
9 Fsahin C, Sajak & Ertan M, *FABAB Farm Org*, 13, **1988**, 365; Steering I T & Worthington P A, PCT/N/APP/WO, 93, 08, **1991**, 180; *Chem Abstr*, 119, **1993**, 180765K.
10 Rajeswar Rao V, Rao M S & Padmanabha Rao, *Colln Czech Chem Commun*, 51, **1986**, 2214.
11 Rajeswar Rao V, Ravindar P & Padmanabha Rao, *Colln Czech Chem Commun*, 33, **1988**, 326.
12 Rajeswar Rao V & Adityavardhan I, *Indian J Chem*, 36B, **1997**, 1085.
13 Adolf, Sitte, Paul H & Guenter H, *Z Chem*, 7, **1967**, 341.
14 Paul M, Sitte A & Wessl K, *Monatsch Chem*, 108, **1977**, 665.
15 Collins L & Franzblan S G, Microplate Alamar Blue Assay versus BACTEC 460 system for High-throughput screening of compounds against mycobacterium tuberculosis and mycobacterium avium, *Antimicrob Agents Chemother*, 41, **1997,** 1004.
16 De Clereq E, Balzarini J, Torrence P F, Mertes M P, Schmidt C L, Sugar D, Barr P J, Jones A S, Verhelst G & Walker R T, *Mol Pharmacol*, 19, **1981,** 321.
17 Balzarini J, Karlsson A, Wang, Bohman C, Harska K, Votruba J, Fridland A, Van Aerschot A A, Her dewijn P & De Clercq E, *J Biol Chem*, 268, **1993**, 24591.
18 Balzarini J, Bohman C & De Clereq E, *J Biol Chem*, 268, **1993**, 6332.
19 (a) Koelsch C F, *J Am Chem Soc*, 72, **1950**, 2993.
(b) Rajeswar Rao V & Padmanabha Rao T V, *Indian J Chem*, 25B, **1986**, 413.