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Synthesis and Evaluation of Anticancer Activity of Some Imidazothiazolyl, Imidazobenzothiazolyl and Dihydroimidazothiazolyl Coumarins

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Summary

A series of 6-(2H-1-benzopyran-2-one-3-yl)imidazo[2,1-b]thiazoles *(1)*, 2-(2H-1-benzopyran-2-one-3-yl)imidazo[2,1-b]benzothiazoles *(2)* and 3-(2H-1-benzopyran-2-one-3-yl)-5,6-dihydroimidazo[2,1-b]thiazoles *(3)* have been synthesized and evaluated for anticancer activity in vitro. The compounds showed very good activity against different tumor cell lines.

Zusammenfassung

Synthese und Evaluierung der tumorhemmenden Aktivität von Imidazothiazolyl-, Imidazobenzothiazolyl- und Dihydroimidazothiazolyl-Cumarinen

Eine Reihe von 6-(2H-1-Benzopyran-2-one-3-yl)imidazo[2,1-b]thiazolen *(1)*, 2-(2H-1-Benzopyran-2-one-3-yl)imidazo[2,1-b]benzothiazolen *(2)* und 3-(2H-1-Benzopyran-2-one-3-yl]-5,6-dihydroimidazo[2,1-b]thiazolen *(3)* wurden synthisiert und auf tumorhemmende Wirkung geprüft. Die Substanzen zeigten sehr gute Aktivität gegen verschiedene Tumorzelllinien.

Key words

- **2H-Benzopyran-2-ones, anticancer activity in vitro, imidazobenzothiazoles, imidazothiazoles**

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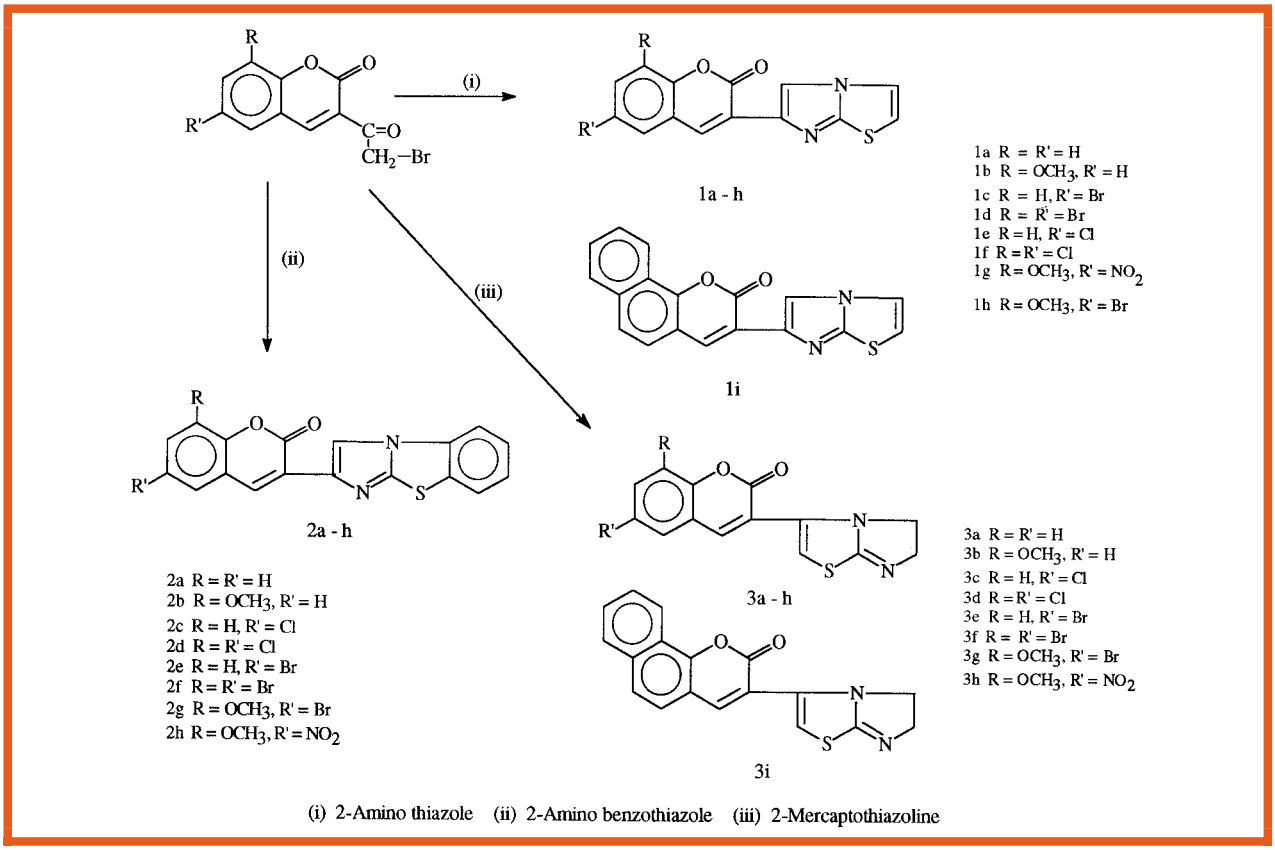

Scheme 1

1. Introduction

The coumarin nucleus is found in a variety of natural products which exert varied pharmacological effects. Numerous reports have appeared in the literature describing HIV protease inhibiting, α-chymotrypsin inhibiting, analgesic and antimicrobial activity [1–4] of 3-heteroaryl coumarins. In an effort to design new compounds as potential anticancer agents we have decided to synthesize the title compounds.

In our ongoing search for potential anticancer agents we present here our results on the design of new 6-(2H-1-benzopyran-2-one-3-yl)imidazo[2,1-b]thiazoles, 2-(2H-1-benzopyran-2-one-3-yl)imidazo[2,1-b]benzothiazoles and 3-(2H-1-benzopyran-2-one-3-yl)-5,6-dihydroimidazo[2,1-b]thiazoles. Some of the title compounds presented here were assayed in vitro for their anticancer activity.

Reaction of 3-(2-bromoacetyl)coumarins with 2-aminothiazole, 2-aminobenzothiazole and 2-mercaptoimidazoline in anhydrous ethanol resulted in the formation of the title compounds **1, 2** and **3,** respectively (Scheme 1).

The 2-aminothiazole and 2-amino benzothiazoles are known to exist in tautomeric forms. During the formation of **1** and **2** in the first step of the reaction, the cyclic secondary nitrogen atom of 2-amino thiazole and 2-aminobenzothiazole replaces the bromine of 3-(2-bromoacetyl)coumarin to give intermediates. This is due to the more basic nature of secondary nitrogen at the 3rd position [5]. These on subsequent cyclodehydration resulted in the formation of the final products **1** and **2.** The compounds **1, 2** and **3** were fully characterized by IR, NMR and mass spectroscopy.

2. Materials and methods

2.1. Chemistry

2.1.1. Chemicals

2-Aminothiazole and 2-aminobenzothiazole were obtained from Merck (Darmstadt, Germany). Salicylaldehyde required for the preparation of 3-acetyl-coumarin was obtained from Loba Chemical Company (Mumbai, India). Ethylacetoacetate was purchased from S.D. Fine Chemicals (Mumbai, India)

2.1.2. General

All melting points were determined in open capillary tubes using sulphuric acid bath and are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer – 282 instrument (USA), ^{1}H-NMR spectra on Varian 200 MHz spectrometer (Darmstadt, Germany) using TMS as internal standard (chemical shifts in δ ppm) and mass spectra on Jeol-JMS-D mass spectrometer at 70 eV.

The various derivatives of 3-(2-bromoacetyl)coumarins were prepared according to our earlier procedure [6]. Repres-

Table 1: Physical data of compounds synthesized.

Compd.[a]	tR R'	M.p. (°C)	Yield (%)	Mol. formula (mol. wt.)	Found (Calc.) (%)			
					C	H	N	S
1a	H H	202–204	80	$C_{14}H_8N_2O_2S$ (268)	62.24 (62.69)	2.94 (2.99)	10.40 (10.45)	11.90 (11.94)
1b	OCH_3 H	160–162	75	$C_{15}H_{10}N_2O_3S$ (298)	60.00 (60.40)	3.30 (3.36)	9.21 (9.40)	10.70 (10.74)
1c	H Br	220–222	72	$C_{14}H_7N_2BrO_2S$ (346)	48.50 (48.55)	1.96 (2.02)	7.96 (8.09)	9.20 (9.25)
1d	Br Br	276–278	70	$C_{14}H_6N_2Br_2O_2S$ (426)	39.40 (39.44)	1.37 (1.41)	6.55 (6.57)	7.48 (7.51)
1e	H Cl	172–174	76	$C_{14}H_7N_2ClO_2S$ (302)	55.60 (55.63)	2.27 (2.32)	9.21 (9.27)	10.51 (10.60)
1f	Cl Cl	185–187	78	$C_{14}H_6N_2Cl_2O_2S$ (336)	49.00 (50.00)	1.64 (1.79)	8.30 (8.33)	9.47 (9.52)
1g	OCH_3 NO_2	300–302	74	$C_{15}H_9N_3O_5S$ (343)	52.41 (52.48)	2.54 (2.62)	12.20 (12.24)	9.27 (9.33)
1h	OCH_3 Br	190–192	80	$C_{15}H_9N_2O_3SBr$ (376)	47.80 (47.87)	2.31 (2.39)	7.42 (7.45)	8.50 (8.51)
1i	–	280–282	80	$C_{18}H_{10}N_2O_2S$ (318)	67.69 (67.92)	3.10 (3.14)	8.77 (8.81)	10.00 (10.06)
2a	H H	266–268	78	$C_{18}H_{10}N_2O_2S$ (318)	67.90 (67.92)	3.10 (3.14)	8.70 (8.81)	9.95 (10.06)
2b	OCH_3 H	280–282	80	$C_{19}H_{12}N_2O_3S$ (348)	65.50 (65.52)	3.40 (3.45)	8.00 (8.05)	9.16 (9.20)
2c	H Cl	252–254	75	$C_{18}H_9N_2ClO_2S$ (352)	61.30 (61.36)	2.50 (2.56)	7.90 (7.95)	8.92 (9.09)
2d	Cl Cl	260–262	84	$C_{18}H_8N_2Cl_2O_2S$ (386)	55.90 (55.96)	1.96 (2.07)	7.20 (7.25)	8.20 (8.29)
2e	H Br	200–202	75	$C_{18}H_9N_2BrO_2S$ (396)	54.50 (54.55)	2.23 (2.27)	6.95 (7.07)	7.94 (8.08)
2f	Br Br	230–232	72	$C_{18}H_8N_2Br_2O_2S$ (476)	45.34 (45.38)	1.62 (1.68)	5.80 (5.88)	6.70 (6.72)
2g	OCH_3 Br	250–252	86	$C_{19}H_{11}N_2BrO_3S$ (426)	53.48 (53.52)	2.54 (2.58)	6.51 (6.57)	7.48 (7.51)
2h	OCH_3 NO_2	182–184	72	$C_{19}H_{11}N_3O_5S$ (393)	49.56 (58.02)	2.72 (2.80)	10.62 (10.69)	8.10 (8.14)
3a	H H	270–272	70	$C_{14}H_{10}N_2O_2S$ (270)	62.00 (62.22)	3.63 (3.70)	10.31 (10.37)	11.80 (11.85)
3b	OCH_3 H	268–270	76	$C_{15}H_{12}N_2O_3S$ (300)	59.40 (60.00)	3.90 (4.00)	9.30 (9.33)	10.60 (10.67)
3c	H Cl	270–272	78	$C_{14}H_9N_2ClO_2S$ (304)	55.20 (55.26)	2.90 (2.96)	9.18 (9.21)	10.48 (10.53)
3d	Cl Cl	190–192	81	$C_{14}H_8N_2Cl_2O_2S$ (338)	49.65 (49.70)	2.30 (2.37)	8.20 (8.28)	9.41 (9.47)
3e	H Br	120–122	80	$C_{14}H_9N_2BrO_2S$ (348)	48.00 (48.27)	2.50 (2.59)	7.90 (8.05)	9.10 (9.20)
3f	Br Br	216–218	82	$C_{14}H_8N_2Br_2O_2S$ (426)	39.40 (39.44)	1.85 (1.88)	6.52 (6.57)	7.47 (7.51)
3g	OCH_3 Br	225–227	76	$C_{15}H_{11}N_2BrO_3S$ (378)	47.54 (47.62)	2.88 (2.91)	7.36 (7.41)	8.40 (8.47)
3h	OCH_3 NO_2	210–212	84	$C_{15}H_{11}N_3O_5S$ (345)	52.10 (52.17)	3.10 (3.19)	12.10 (12.17)	9.20 (9.28)
3i	–	268–270	85	$C_{18}H_{12}N_2O_2S$ (320)	67.00 (67.50)	3.70 (3.75)	8.70 (8.75)	9.96 (10.00)

[a] Compounds **1a** to **2h** and **3a, 3c, 3g, 3h** were recrystallised from aqueous dimethylformamide. Remaining compounds were recrystallised from dimethyl sulphoxide.

entative methods of preparations of compounds **1, 2** and **3** along with spectral data are described below.

2.1.3. Preparation of 6-(2H-1-benzopyran-2-one-3-yl)imidazo[2,1-b]thiazole, 1a

A mixture of 0.267 g (0.001 mol/l) 3-(2-bromoacetyl) coumarin and 0.10 g (0.001 mol/l) of 2-aminothiazole was dissolved in absolute ethanol (20 ml) and refluxed for 1 h. The solid separated was filtered to give the title compound. The crude product was crystallised from aqueous dimethyl formamide to yield **1a.** Yield 80 %; m.p. 202–204 °C.

IR (KBr, ν_{max}, cm^{-1}): 1600 (–C=N–), 1700 (lactone –C=O), ^{1}H-NMR (200 MHz) $CDCl_3$ + DMSO-d_6 δ: 7.2–7.65 (m, 6H, Ar-H of coumarin and thiazole), 8.45 (s, 1H, imidazole); 8.65 (s, 1H, H_4 of coumarin); MS: m/z 268 (100 %), 240 (62), 211 (15) and 173 (8).

2.1.4. Preparation of 2-(2H-1-benzopyran-2-one-3-yl)imidazo[2,1-b] benzothiazole, 2a

A mixture of 0.267 g (0.001 mol/l) of 3-(2-bromoacetyl) coumarin and 0.150 g (0.001 mol/l) 2-amino benzothiazole was dissolved in absolute ethanol (20 ml) and refluxed for 1 h. The solid separted was filtered and recrystallised from aqueous dimethyl formamide to yield **2a.** Yield 78 %, m.p. 266–268 °C.

IR (KBr, ν_{max}, cm^{-1}) 1600 (–C=N–) and 1710 (lactone –C=O). ^{1}H NMR (200 MHz) $CDCl_3$ + DMSO-d_6 δ; 6.9–7.4 (m, 8H, Ar-

Table 2: Anticancer activity of different compounds tested against different cell lines.

Cell line Name – Type	Mean $GI_{50\%}$ ± SD (mol/l)								
	1e	**1h**	**1i**	**2d**	**2g**	**3c**	**3d**	**3g**	**3i**
Leukemia CCRF-CEM HL-60 (TB) K-562 MOLT-4 RPMI-8226 SR	3.04 ± 0.67	3.12 ± 0.32	3.54 ± 3.00	2.06 ± 0.23	1.90 ± 0.35	1.93 ± 0.18	3.91 ± 1.06	2.44 ± 0.35	3.50 ± 0.40
NS Lung A549/ATCC EKVX HOP-62 HOP-92 NCI-H23 NCI-H322M NCI-H460 NCI-H522	4.16 ± 1.57	2.97 ± 0.83	3.84 ± 2.90	7.21 ± 2.54	2.21 ± 0.86	2.41 ± 0.77	4.94 ± 1.46	1.91 ± 0.15	3.40 ± 0.85
Colon COLO-205 HCC-2998 HCT-116 HCT-15 HT29 KM12 SW-620	4.24 ± 1.00	4.05 ± 1.85	1.74 ± 0.17	5.35 ± 3.27	2.74 ± 0.68	1.92 ± 0.32	5.75 ± 2.34	2.00 ± 0.29	4.14 ± 0.93
CNS SF-268 SF-295 SF-539 SNB-19 SNB-75 U251	6.30 ± 2.93	3.16 ± 0.33	6.59 ± 3.53	8.75 ± 1.95	2.58 ± 0.60	2.71 ± 0.92	6.06 ± 3.15	1.93 ± 0.12	5.98 ± 2.40
Melanoma LOX IMVI MALME-3M M14 SK-MEL-2 SK-MEL-28 SK-MEL-5 UACC-257 UACC-62	6.65 ± 2.73	4.42 ± 2.35	3.04 ± 2.84	7.68 ± 2.81	2.58 ± 0.70	2.61 ± 0.70	6.30 ± 2.73	2.19 ± 0.42	6.20 ± 2.45
Ovarian IGROV1 OVCAR-3 OVCAR-4 OVCAR-5 OVCAR-8 SK-OV-3	4.14 ± 2.46	4.23 ± 1.66	4.10 ± 3.40	6.84 ± 3.08	2.64 ± 0.84	2.82 ± 1.32	6.32 ± 3.10	2.03 ± 0.44	4.61 ± 1.51
Renal 786-O A498 ACHN CAKI-1 RXF 393 SN12C TK-10 UO-31	4.41 ± 1.77	3.63 ± 1.42	1.94 ± 0.49	5.79 ± 2.56	2.71 ± 0.91	2.67 ± 1.04	4.73 ± 1.44	2.21 ± 0.67	4.41 ± 1.77
Prostate PC-3 DU-145	7.41 ± 3.04	2.79 ± 0.38	2.33 ± 0.48	6.05 ± 1.90	1.70 ± 0.10	2.05 ± 0.17	4.11 ± 0.14	1.81 ± 0.04	4.90 ± 3.17
Breast MCF7 NCI/ADR-RES MDA-MB-231/ ATCC HS578T MDA-N MDA-MB-435 BT-549 T-47D	3.89 ± 2.14	3.09 ± 1.87	2.40 ± 1.06	5.35 ± 2.96	2.56 ± 0.65	2.54 ± 0.87	3.83 ± 1.87	2.56 ± 1.79	4.64 ± 2.05

H), 8.2 (s, 1H, imidazole) and 8.3 (s, 1H, H_4 of coumarin); MS: m/z 318 (100 %), 290 (50), 261 (20) and 173 (10).

2.1.5. Preparation of 3-(2H-1-benzopyran-2-one-3-yl)-5,6-dihydroimidazo[2,1-b] thiazole, 3a

A mixture of 2-mercapto imidazoline (0.01 mol/l) and 3-(2-bromoacetylcoumarin (0.01 mol/l) in anhydrous ethanol was refluxed for 30 min. The solid that separated was filtered, washed with water and recrystallised from suitable solvent (Table 1). Compound **3a**: yield 70 %, m.p. 228–230 °C (aqueous dimethyl formamide).

IR (KBr, ν_{max} cm^{-1}), 1600 (–C=N–) and 1740 (lactone –C=O); ^{1}H-NMR (300MHz)DMSO-d_6 δ: 4.1 (s, 2 CH_2), 7.0 (s, 1H, thiazole), 7.40–7.48 (m, 2H, H_6 and H_8 of coumarin), 7.67–7.2 (m, 1H, H_7 of coumarin), 7.83–7.86 (d, 1H, J = 8Hz, H_5) and 8.37 (s, 1H, H_4 of coumarin), MS: m/z 270 (100 %), 2.17 (5), 170 (25), 142 (20) and 115 (5).

2.2. Pharmacology

The synthesized compounds were screened for anticancer activity against 60 different cell lines of 9 different types of human cancers, namely leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, overian cancer, renal cancer, prostate cancer and breast cancer, at the National Cancer Institute, Bethesda, MD (USA). Results are expressed as $GI_{50\,\%}$, which is the drug concentration (mol/l) producing 50 % inhibition of cell growth. No reference compound was used for testing activity along with the synthesized compounds. The mean (± SD) activities of different compounds against these cell lines are given in Table 2.

3. Results

It is very evident from the results that all compounds tested showed very good anticancer activity. All 9 compounds (**1c, 1h, 1i, 2d, 2g, 3c, 3d, 3g, 3i**) exhibited potent activity against leukemia cell lines. Amoungst the screened compounds **2g, 3c** and **3g** showed greatest and uniform activity against all the cell lines employed. In all these cases the compounds inhibited 50 % growth at a concentration less than 3×10^{-5} mol/l. Out of the remaining 6 compounds, compound **(1i)** also showed very good inhibitory activity against colon, renal, prostate and breast cancer cell lines.

4. References

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