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Synthesis and Anticancer Activity of 3-[5-Amino-6-(2,3-dichlorophenyl)-[1,2,4] triazin-3-yl]-6,8-dibromo-2-substituted-3H-quinazolin-4-one

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A series of novel 6,8-dibromo-2,3-disubstituted quinazolin-4(3H)-ones have been synthesized by condensing the primary amino group of lamotrigine with benzoxazin-4-one. The structure of the synthesized compounds was elucidated by spectral analysis (IR, NMR and mass). Investigation of anticancer activity was done against nine types of human cancer in 60 different strains of tumour cell line.

Key Words: Synthesis, Anticancer activity, Quinazolin-4(3H)-one, Lamotrigine.

INTRODUCTION

Quinazolin-4(3H)-one is a versatile lead molecule for designing potential bioactive agents. 2,3-disubstituted quinazolin-4(3H)-one derivatives have been evaluated for a wide spectrum of biological activities such as sedative[1], anticonvulsant[2], antifungal and antibacterial[3–6], anti-HIV[4, 7, 8], antiviral[9, 10] and anticancer activities[11, 12]. The objective of the study was to synthesize a series of hitherto unreported 6,8-dibromo-2,3-disubstituted quinazolin-4(3H)-ones and the synthesized compounds were screened for anticancer activity against 60 cell line of nine types of human cancer.

Anthranillic acid/3,5-dibromo anthranilic acid reacts with acetic anhydride, propionic anhydride and benzoyl chloride to form corresponding 2-methyl/-ethyl/-phenyl benzoxazin-4-one by N-acylation followed by dehydrative cyclization mechanism[13]. 2-substituted/6,8-dibromo derivatives of benzoxazin-4-one were condensed with the primary amino group of lamotrigine to afford 6,8-dibromo-2,3-disubstitued benzoxazin-4-one **(Scheme-1).** IR and NMR spectra were consistent with the assigned structure.

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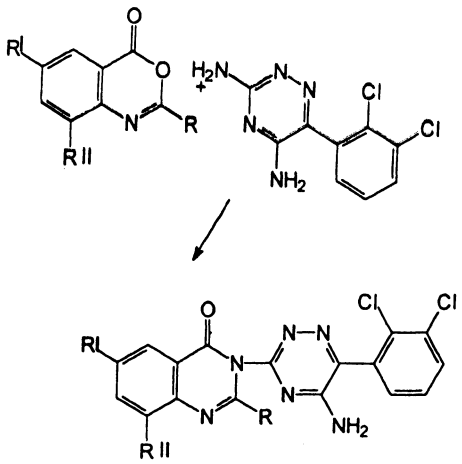

R = CH_3,C_2H_5,C_6H_5

R^I,R^{II} = H,Br

Scheme 1. Synthetic Protocol of the Compounds

EXPERIMENTAL

Melting points were determined by using Thomas melting point apparatus and are uncorrected. The purity was checked by TLC using silica gel G as stationary phase. The structures of the synthesized compounds were elucidated by using Perkin-Elmer FT-IR in KBr disc and PMR was taken on the Bruker AMX-(400 MHz) FT-NMR. Mass spectra were obtained on Varian Atlas CH-7 mass spectrometer at 70 eV.

3-[5-Amino-6-(2,3-dichlorophenyl)-[1,2,4] triazin-3-yl]-6,8-dibromo-2-substituted-3H-quinazolin-4-one

An equimolar (0.10 mol) mixture of 6,8-dibromo-2-substituted-1,3-benzoxazin-4-one and lamotrigine was refluxed for 6 h in 10 mL of glacial acetic acid. The mixture was cooled to room temperature and poured into crushed ice; the solid obtained was recrystallized from ethanol.

3-[5-Amino-6-(2,3-dichlorophenyl)-[1,2,4] triazin-3-yl]-6,8-dibromo-2-methyl-3H-quinazolin-4-one (SPC-IBr): yield 69%, m.p. 130°C, IR (KBr, cm^{-1}) : 3216 ν(NH), 1698 ν(C=O), 1556 ν(C=N), 1440 ν(N=N); PMR (DMSO-d_6) δ ppm: 1.3 (s, 3H, —CH_3), 4.8 (b, 2H, —NH_2), 7.3 (m, 3H, Ar—H), 7.8 (t, 1H, Q-7H), 8 (d, 1H, Q-5H); EI-MS (m/e): 557.031.

3-[5-Amino-6-(2,3-dichlorophenyl)-[1,2,4] triazin-3-yl]-6,8-dibromo-2-ethyl-3H-quinazolin-4-one (SPC–IIBr): yield 64%, m.p. 165°C. IR (KBr, cm^{-1}): 3245 ν(NH), 1672 ν(C=O), 1508 ν(C=N), 1442 ν(N=N); PMR (DMSO-d_6) δ ppm : 1.3 (t, 3H, —CH_3), 2.5 (q, 2H, —CH_2), 6.8 (m, 3H, Ar—H), 7.3 (d, 1H, Q-7H, 8.0 (s, 1H, Q-5H); EI-MS (m/e): 571.057.

3-[5-Amino-6-(2,3-dichlorophenyl)-[1,2,4] triazin-3-yl]-6,8-dibromo-2-phenyl- 3H-quinazolin-4-one (SPC-IIIBr): yield 71%, m.p. 158°C. IR (KBr, cm^{-1}): 3222 ν(NH), 1541 ν(C=N), 1655 ν(C=O), 1443 ν(N=N); PMR (DMSO-d_6)

δ ppm: 4.5 (s, 2H, —NH_2), 7.6 (m, 7H, Ar—H), (t, 1H, Q-7H), 8.0 (d, 1H, Q-5H); EI-MS (m/e): 619.101.

In vitro anticancer screening

All the compounds were submitted for NCI-60 cell anticancer screening programme. Among the three derivatives, two compounds were selected for in *vitro* anticancer activity in 60 cell line of nine type of human cancer by three cell line prescreen high throughoutput technique[15–17]. The results of anticancer activity expressed as $\log_{10} GI_{50}$—the concentration required for 50% growth inhibition. The anticancer data are presented in Tables 1 and 2. All the compounds inhibit the growth of cancer cells and inhibitory effect ($\log_{10} GI_{50}$) range from 4–6 molar concentrations.

TABLE-1
IN VITRO ANTICANCER ACTIVITY DATA OF THE COMPOUNDS

Type of cancer	Cell line	$\log_{10} GI_{50}$	
		SPC-IIIBr	SPC-IBr
Leukemia	CCRF-CEM	5.27	4.71
	K-562	5 .33	5.47
	MOLT-4	4.60	4.82
	RPMI-8226	5.22	5.03
Non-small cell lung cancer	A549/ATCC	5.13	4.59
	EKVK	4.69	4.66
	HOP-62	5.55	5.15
	HOP-92	4.41	4.37
	NCI-H226	4.62	4.67
	NCI-H23	4.81	4.63
	NCI-H322M	5.61	4.83
	NCI-H460	5.16	4.69
	NCI-H522	4.68	4.89
Colon cancer	COLO-205	5.05	4.48
	HCC-2998	5.47	4.75
	HCT-116	5.61	4.89
	HCT-15	5.51	4.81
	HT29	5.32	4.52
	KM12	5.42	4.92
	SW-620	5.29	4.47
CNS cancer	SF-268	4.69	4.34
	SF-295	4.95	4.88
	SF-539	5.11	4.67
	SNB-19	4.52	4.38
	SNB-75	5.06	4.47

Type of cancer	Cell line	$\log_{10}$ GI_{50}	
		SPC-IIIBr	SPC-IBr
	U251	5.16	4.66
Melanoma	LOX IMVI	5.39	4.89
	M14	5.58	5.32
	SK-MEL-2	4.08	4.56
	SK-MEL-28	4.00	4.18
	SK-MEL-5	5.33	4.76
	UACC-257	4.65	4.61
	UACC-62	5.15	4.87

$\log_{10}$ GI_{50}: the concentration required for 50% growth inhibition

TABLE-2
IN VITRO ANTICANCER ACTIVITY DATA OF THE COMPOUNDS

Type of Cancer	Cell Line	$\log_{10}$ GI_{50}	
		SPC-IIIBr	SPC-IBr
Ovarian cancer	IGROVI	4.89	4.82
	OVCAR-3	5.16	4.73
	OVCAR-4	4.29	4.07
	OVCAR-5	5.21	4.57
	OVCAR-8	4.76	4.73
	SK-OV-3	4.57	4.60
Renal cancer	786-0	4.95	4.74
	A498	4.81	4.50
	ACHN	4.92	4.71
	CAKI-1	4.77	4.55
	RXF 393	4.84	4.58
	SN12C	4.73	4.72
	TK-10	5.40	4.70
	UO-31	4.40	4.51
Prostate cancer	PC-3	4.58	4.63
	DU-145	4.56	4.56
Breast cancer	MCF7	5.31	4.57
	NCI/ADR-RES	5.70	4.90
	MDA-MB-231	5.38	4.20
	HS-578T	5.30	4.80
	MDA-MB-435	5.66	4.60
	BT-549	4.72	4.60
	T-47D	4.0	4.70

$\log_{10}$ GI_{50}: the concentration required for 50% growth inhibition.

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