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Research Article

SYNTHESIS AND *IN VITRO* ANTICANCER ACTIVITY OF 8-CHLORO-3-CYANO-4-IMINO-2-METHYLTHIO-4H-PYRIMIDO [2, 1-*B*] [1, 3] BENZOTHIAZOLE AND ITS 2-SUBSTITUTED DERIVATIVES

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ABSTRACT:-

8-Chloro-3-cyano-4-imino-2-methylthio-4H-pyrimido [2, 1-*b*] [1, 3] benzothiazole and its 2-substituted derivatives has been prepared and evaluated at National Cancer Institute, Maryland, USA for their *in vitro* anticancer activity towards 60 Human Cancer cell lines, derived from various cancer types. Results revealed that all these compounds displayed remarkable anticancer action across human cancer cell lines. Compounds **3, 4c** and **4e** are selected by NCI for further anticancer activity at five dose concentration level.

Keywords: Benzothiazole, Human cancer cell lines, Anti canceraction.

INTRODUCTION:--

Pyrimidine, iminopyrimidine [1-5] and fused benzothiazole heterocycles [5-6] are reported to be effective pharmacophores. Domino *et.al*. [7] reported the use of 2-benzothiazolamines as central muscle relaxant. Jimonet and his research group [8] reported synthesis and pharmacological activity of 3- substituted-2-imino benzothiazolines which were found to be three times more potent than Riluzole, a blocker of excitatory amino acid mediated neurotransmission. It has been found that small and simple heterocyclic structures surprisingly exhibit complex pharmaceutical properties. M. F.G. Stevens *et.al*. [9-12] reported that benzothiazoles display antitumor properties that are modulated by substitutents at specific positions on the benzothiazole pharmacophore. 2-(4-Amino -3-methyl phenyl) benzothiazole (DF203) and 2-(4-amino phenyl) benzothiazole represent the lead compounds for a recently explored series and possess potent antitumor properties in select breast, ovarian and renal cancer cell lines of the 60 -cell line. E. Brantlsy *et.al*. [13] reported that fluorinated 2-(4-amino-3-methyl phenyl) benzothiazole, induced to CYPIA1 expression, become metabolized and bind to macromolecules in sensitive Human Cancer cells. Recently, Suvarna Kini and her research group [14] synthesized novel benzothiazole derivatives and evaluated against Human Cervical Cancer cell lines.

Biological activities and various applications of pyrimidines, iminopyrimidines, amino and imino benzothiazoles, have stimulated our interest to explore the synthesis of new potential compounds in which pyrimidine / imino pyrimidine pharmacophores are fused with another pharmacophore such as benzothiazole through nitrogen atom. Hence we thought it worthwhile to design and synthesize fused pyrimido benzothiazoles, such as 8-Chloro-3-cyano-4-imino-2-methylthio-4H-pyrimido[2,1-*b*][1,3] benzothiazole and its 2- substituted derivatives and to evaluate at National Cancer Institute, Maryland, USA[15] for their *in vitro* anticancer activity towards 60 human cancer cell lines derived from cancer types like Non-small cell Lung cancer, Colon cancer, Breast cancer, Ovarian cancer, Leukemia, Renal cancer, Melanoma , Prostate cancer and CNS cancer.

EXPERIMENTAL PROCEDURE:

General

Melting points (uncorrected) were determined in open capillary tubes. The purity of compounds was checked by TLC using silica gel .The IR spectra in KBr were recorded on a FTIR-8400S (Shimadzu). The ^{1}H NMR spectra in $CDCl_3$ and ^{13}C NMR spectra in DMSO were recorded on a Gemini 200 MHz spectrometer using TMS as an internal standard. Mass spectra were recorded on a FT VG 7070 H Mass spectrophotometer using EI technique 70 eV.

Syntheses

3*:* A mixture of 2-amino-6-chloro benzothiazole (10mmol), bis (methylthio) methylene malononitrile (10mmol) in N, N-dimethylformamide (15ml) and anhydrous potassium carbonate (10mg) was refluxed for 4-5 h. The mixture was allowed to stand overnight and poured in cold water. The separated crystalline solid was filtered off and washed with ice-cold water and recrystallized from N, N-dimethylformamide-ethyl alcohol mixture to obtain **3**, yield 375 mg, (75%); M.p.: 230^{o}C; IR: (FTIR): υ$^-$ = 3306, 2198; ^{1}H NMR [$CDCl_3$]: δ= 2.7 (s, 3H, SCH_3), 7.4-7.9 (m.3H, Ar-H),9.5(s,1H,=NH);^{13}C NMR: [DMSO]δ= ı□ □ □(C_1,CH3), 115.04 (C_2), 121.83(C_5,Ar-C), 122.49(C_6,Ar-C), 125.87(C_3), 127.39(C_7,Ar-C), 130.86(C_8,Ar-C), 135.40(C_9,Ar-C), 152.56(C_{10},Ar-C), 157(C_4, C=N), 165 (C_{11},C=N) 168 (C_{12}, CN) ; Mass: Ms (70eV): m/z (%) = 308(30) [M+2] 306 (90)[M^+], 259 (80), 232 (20), 206 (10). Found (%):C, 52.40; H, 2.5; N, 20.20. Calc.for C_{12} H_7 N_4 S_2 Cl (%): C, 52.46; H, 2.7; N, 20.39.

4,5,6 *and* ***7*** : A mixture of compound **3** (10mmol) independently with various aromatic amines, heteryl amines, substituted phenols and compounds containing an active methylene group (10mmol) in N,N- dimethylformamide (10ml) and anhydrous potassium carbonate (10mg) was refluxed for 4-6 h. As soon as reaction mixture was cooled to

room temperature and poured into ice cold water, the separated crystalline solid was filtered off and washed with ice cold water to obtain **4**(a-f),**5**(a-d)**, 6**(a-d), **7**(a-d).

4a: yield 60%; M.p.: 220°C; IR (FTIR): υ = 3320, 3190, and 2190; ^{1}H NMR [$CDCl_3$]: δ= 4.5 (br, s, 1H-NH), 7.1-7.7 (m, 8H, Ar-H), 9.3 (s, 1H, =NH); Found (%): C, 57.94; H, 2.80; N, 19.80. Calc. for C_{17} H_{10} N_5 S Cl (%): C, 58.04; H, 2.87; N, 19.91.

4b: yield 67%; M.p.: 180°C; IR (FTIR): υ = 3300, 3170, 2205, 1510, and 1360; ^{1}H NMR [$CDCl_3$]: δ= 4.2 (br, s, 1H,-NH), 7.3-7.9 (m, 7 H, Ar-H), 9.1 (s, 1H, =NH); Found (%): C, 51.30; H, 2.19; N, 21.08. Calc. for C_{17} H_9 N_6 SO_2 Cl (%): C, 51.40; H, 2.29; N, 21.18

4c: yield 70%; M.p.; 140°C; IR(FTIR): υ= 3305, 3110, and 2200; ^{1}H NMR[$CDCl_3$]: δ= 3.3 (s, 3H,-OCH_3), 4.1(br, s, 1H,-NH), 7.2-7.8 (m, 7H, Ar-H), 9.3 (s, 1H, =NH); Found (%): C, 56.52; H, 3.07; N,18.24. Calc.for C_{18} H_{12} N_5 SO Cl (%) C, 56.62; H, 3.17: N, 18.34

4d: yield 60%; M.p.: 170°C; IR (FTIR): υ= 3305, 3111, 2201; ^{1}H NMR [$CDCl_3$]: δ= *2.5* (s, 3H,-Ar-CH_3), 4.6 (br, s, 1H,-NH), 7.1-7.6 (m, 7H, Ar-H), 8. 9 (s, 1H, =NH); Found (%): C, 59.00; H,3.11; N,19.02.Calc.for C_{18} H_{12} N_5 S Cl (%): C,59.10;H,3.31;N,19.14 .

4e: yield 68%; M.p.: 190°C; IR (FTIR): υ= 3320, 3180, 2210. ^{1}H NMR [$CDCl_3$]: δ= 4.2(br, s, 1H,-NH), 7.2-7.8(m, 7H, Ar-H), 9.4 (s, 1H, =NH). Found (%): C, 52.65; H, 2.11; N, 18.02. Calc.for C_{17} H_9 N_5 S Cl_2 (%): C, 52.86; H, 2.35; N, 18.13.

4f: yield 68%; M.p.:192°C; IR (FTIR): υ=3423, 3190, 2212; ^{1}H NMR [$CDCl_3$]: δ= 1.5 (t, 6H,-$2CH_3$), 2.9 (q, 4H,-$2CH_2$), 7.1-7.5 (m, 3H, Ar-H), 8.5 (s, 1H, =NH). Found (%): C, 54.35; H, 4.21; N, 21.07.Calc.for $C_{15}H_{14}N_5$ S Cl (%): C, 54.36; H, 4.25, N, 21.11.

5a: yield 65%; M.p.: 180°C; IR (FTIR): υ= 3423, 3190, 2212; ^{1}H NMR [$CDCl_3$]: δ= *2.5* (t, 4 H, -NCH_2), 3.5 (t, 4 H, -OCH_2), 7.2-7.6 (m, 3H, Ar-H), 9.3 (s, 1H, =NH); Found (%): C, 51.96; H, 3.20; N, 20.20. Calc. for $C_{15}H_{12}N_5$OSCl (%): C, 52.10; H, 3.50; N, 20.25.

5b: yield 69%; M.p.: 125°C; IR(FTIR): υ= 3320, 2180 ; ^{1}H NMR [$CDCl_3$]: δ= 2.1(quintet, 4 H,$2CH_2$), 2.5 (quintet, 2H,CH_2,), 2.9 (t, 4 H, -NCH_2), 7.1-7.4 (m, 3H, Ar-H), 9.4(s, 1H, =NH); Found (%): C, 55.56; H, 4.03; N, 20.12. Calc.for C_{16} H_{14} N_5 S Cl (%): C, 55.89; H, 4.10; N, 20.37.

5c: yield 65%; M.p.:180°C; IR (FTIR): υ= 3290, 2185; ^{1}H NMR [$CDCl_3$]: δ= 2.8 (quintet, 4 H, $2CH_2$), 3.6 (t, 4 H, -NCH_2), 7.3-7.7 (m, 3 H, Ar-H), 9.1 (s, 1H, =NH); Found (%): C, 54.31; H, 3.32; N, 21.12. Calc.for C_{15} H_{12} N_5 S Cl (%): C, 54.63; H, 3.67; N, 21.23.

5d: yield 55%; M.p.: 150°C; IR (FTIR): υ= 3310, 3240, 2215 ; ^{1}H NMR[$CDCl_3$]: δ= 2.9 (t, 4 H, -NCH2), 3.5 (t, 4 H, -NCH_2), 7.2-7.7 (m, 3H, Ar-H), 8.8 (s, 1H, -NH), 9.3 (s, 1H, =NH) Found (%): C, 52.12; H, 3.40; N, 23.92. Calc.for C_{15} H_{13} N_6 S Cl (%): C, 52.25; H, 3.80; N, 24.37.

6a: yield 62%; M.p.: 180°C; IR (FTIR): υ=3350, 2210, 1260, 1040; ^{1}H NMR [$CDCl_3$]: δ= 7.2-7.9 (m, 8H, Ar-H), 9.5 (s, 1H, =NH); Found (%): C, 57.52; H, 2.36; N, 15.58. Calc.for C_{17} H_9 N_4 SO Cl (%): C, 57.88; H, 2.57; N, 15.88.

6b: yield 60%; M.p.: 182°C; IR (FTIR): υ= 3290, 2205, 1240, 1010; ^{1}H NMR [$CDCl_3$]: δ= 7.4-8.0 (m, 7H, Ar-H), 9.1 (s, 1H, =NH); Found (%): C, 52.60; H, 2.01; N, 14.27. Calc.for C_{17} H_8 N_4 SO Cl_2 (%): C, 52.73; H, 2.08; N, 14.47.

6c: yield 65%; M.p.: 210°C; IR (FTIR): υ= 3310, 2195, 1530, 1350, 1230, 1030; ^{1}H NMR [$CDCl_3$]: δ= 7.2-7.9 (m, 7 H, Ar-H), 9.3 (s, 1H, =NH); Found (%): C, 51.05; H, 1.98; N, 17.42. Calc.for C_{17} H_8 N_5 SO_3 Cl (%): C, 51.33; H, 2.03; N, 17.61.

6d: yield 59%; M.p.: 290°C; IR (FTIR): υ= 3295, 2185, 1260, 1050; ^{1}H NMR [$CDCl_3$]: δ= 2.1(s, 3 H, Ar-CH_3), 7.2-7.9 (m, 7 H, Ar-H), 9.2 (s, 1H, =NH); Found (%): C, 58.75; H, 3.00; N, 15.02. Calc.for C_{18} H_{11} N_4 SO Cl (%): C, 58.94; H, 3.02; N, 15.27.

7a: yield 65%; M.p.:180°C; IR(FTIR): υ= 3306, 2198, 1728 ; ^{1}H NMR[$CDCl_3$]: δ= 1.2 (t, 3 H, CH_3), 2.1 (s, 3 H, $COCH_3$), 2.6 (s, 1H, CH), 3.4 (q, 2 H, OCH_2), 7.3-7.7 (m, 3H, Ar-H), 9.4 (s, 1H, =NH);Ms, m/z (%):347 [M^{+2}](33),345[M^+](100); Found (%): C, 52.22; H, 3.01; N, 14.25. Calc.for C_{17} H_{13} N_4 SO_3 Cl (%): C, 52.50; H, 3.34; N, 14.41.

7b: yield 70%; M.p.: 184°C; IR(FTIR): υ= 3320, 2180,1740 ; ^{1}H NMR [$CDCl_3$]: δ= 1.1 (t, 6 H, 2 CH_3), 2.8 (s, 1H, CH), 3.6 (q, 4 H, 2 CH_2), 7.2-7.6 (m, 3H, Ar-H), 9.2 (s, 1H, =NH); Found (%): C, 54.27; H, 3.61; N, 14.65. Calc.for C_{19} H_{15} N_4 SO_4 Cl (%): C, 54.54; H, 3.99; N, 14.91.

7c: yield 58%; M.p.: 170°C; IR(FTIR): υ=3280, 2215, 1720; ^{1}H NMR[$CDCl_3$]: δ= 1.3 (t, 3 H, CH_3), 2.6 (s, 1H, CH), 3.0 (q, 2H, OCH_2), 7.1-7.5 (m, 3 H, Ar-H), 9.1 (s, 1H, =NH); Found (%): C, 51.03; H, 2.26; N, 18.25. Calc.for C_{16} H_{10} N_5 SO_2 Cl (%): C, 51.13; H, 2.66; N, 18.64.

7d: yield 64%; M.p.: 190°C; IR (FTIR): υ= 3310, 2115, 1725; ^{1}H NMR [$CDCl_3$]: δ= 2.3 (s, 6 H, 2 $COCH_3$), 3.1(s, 1H, CH), 7.2-7.6 (m, 3H, Ar-H), 9.3 (s, 1H, =NH); Found (%): C, 53.13; H, 3.06; N, 15.32. Calc.for C_{16} $H_{11}N_4SO_2$ Cl (%): C, 53.56; H, 3.09; N, 15.61.

Biological Activity

Out of twenty, fourteen compounds were selected to *in vitro* preliminary screening for anticancer activity. The screening was carried by two stage process. In first stage, all compounds were evaluated against the 60 cell lines at a single dose of 10 µM. The result of anticancer activity from the single dose screen is reported as a mean graph. For second stage screening compounds **3, 4c, 4e** which exhibit significant growth inhibition are selected by NCI for further anticancer activity evaluation against the 60 cell panel at five concentration levels. In graph, referred as 'mean graph', the mean of all cell lines results is considered as zero. This 'mean graph' is developed by plotting positive and negative values generated from a set of GI_{50} values .The positive and negative values are plotted along a vertical line that represents the mean response of all the cell lines in the panel to the test agent. Positive values project to the right of the vertical line and represent celluar sensitivities to the test agent that exceed the mean. Negative values project to the left of the vertical line and represent cell line sensitivities to the test agent that are less than the average value. Compounds with cell lines appearing on positive side of mean graph exhibit high growth inhibition of cancer cells of that particular cancer. The results of *in vitro* anticancer screening are summarized in table 1.

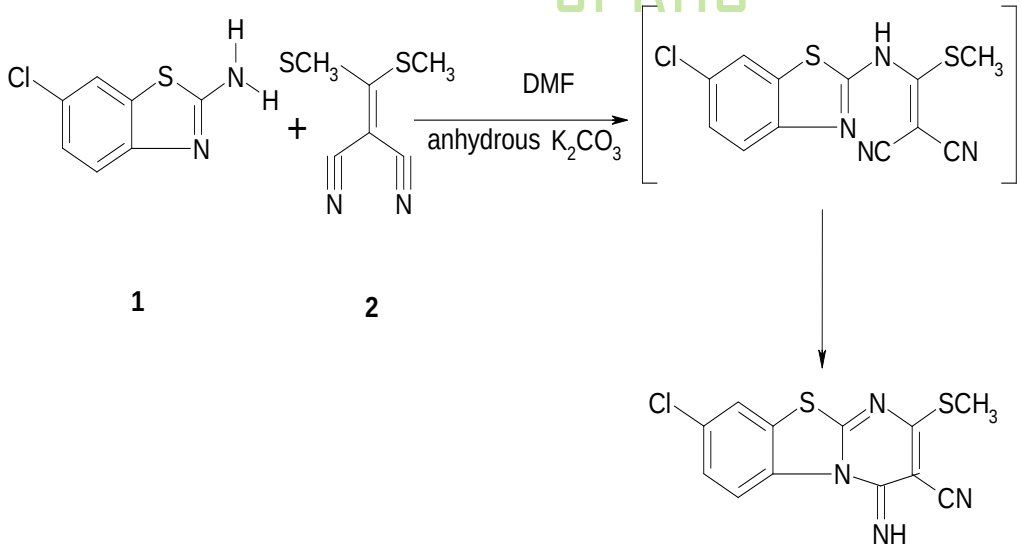
RESULTS AND DISCUSSION:-

In the present work, we report one pot synthesis of new heterocyclic compounds, 8-Chloro3-cyano-4-imino-2-methylthio-4H-pyrimido [2,1-*b*] [1,3] benzothiazole **3** and its 2-substituted derivatives **4,5,6 and 7** .Compound **3** was prepared with 75% yield from the reaction of bis(methylthio)methylene malononitrile **2** with 2-amino-6-chloro-benzothiazole **1** in the presence of N, N-dimethylformamide and a catalytic amount of anhydrous potassium carbonate. The structure of this compound with mp 230^{o}C, was confirmed on the basis of elemental analysis, IR, ^{1}H NMR ,^{13}C-NMR and mass spectral data. Spectral studies of compound **3** show that the compound is stable and does not exhibit any tautomerism. Scheme 1 represents a pathway for the formation of compound **3.**

Compound **3** possesses replaceable methylthio group at 2-position, activated by the ring nitrogen atom and electron withdrawing cyano group at 3- position. Hence, it is surmised that compound **3** would become best precursor for the synthesis of its 2-substitued derivatives. Accordingly 2-substituted derivatives of compound **3** have been prepared by reacting compound **3** with selected N -, O- and C-nucleophiles like aryl /heteryl amines, substituted phenols and compounds containing active methylene group to get corresponding, 2-aryl/heteryl amines, aryloxy, ethyl acetoacetyl, diethyl malonyl, ethyl cyanoacetyl and acetyl acetonyl derivatives **4, 5, 6** and **7 .**

According to this method , compound **3** independently ,on reaction with aniline ,4-nitro aniline ,4-methoxy aniline, 4-methyl aniline, 4-chloro aniline and diethyl amine in N,N-dimethylformamide and a catalytic amount of anhydrous potassium carbonate afforded 8-chloro-3-cyano-4-imino-2-(anilino/4-nitroanilino/ 4-methoxy anilino / 4-methyl anilino / 4-chloroaniline/diethylamino)-4H-pyrimido[2,1-*b*][1,3]benzothiazoles,**4(a-f)** respectively. Under similar experimental conditions, compound **3** was reacted independently with morpholine, piperidine, pyrrolidine and piperazine to obtain 8-chloro-3-cyano-4-imino-2-(morpholino / piperidino / pyrrolidino / piperazino) -4H-pyrimido [2,1-*b*] [1,3] benzothiazoles, **5(a-d)** respectively.

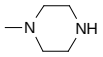
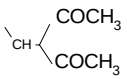
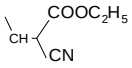
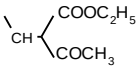
8-Chloro-3-cyano-4-imino-2-(phenoxy / 4-chloro phenoxy / 4-nitro phenoxy / 4-methyl phenoxy) 4H-pyrimido [2,1-*b*] [1,3] benzothiazoles **6(a-d)** were obtained by the condensation of compound **3** independently with phenol, 4- chloro phenol, 4-nitro phenol and 4-methyl phenol in N,N-dimethylformamide and catalytic amount of anhydrous potassium carbonate .Under similar experimental conditions, compound **3** was reacted independently with ethyl acetoacetate, diethyl malonate, ethyl cyanoacetate and acetyl acetone to obtain 8-chloro-3-cyano-4-imino-2-(ethyl acetoacetyl / diethyl malonyl / ethyl cyanoacetyl / acetyl acetonyl) 4H-pyrimido[2,1-*b*] [1,3] benzothiazoles **7(a-d)** respectively. Scheme 2 represents a pathway for the formation of compounds **4(a-f), 5(a-d), 6(a-d),** and **7(a-d).**

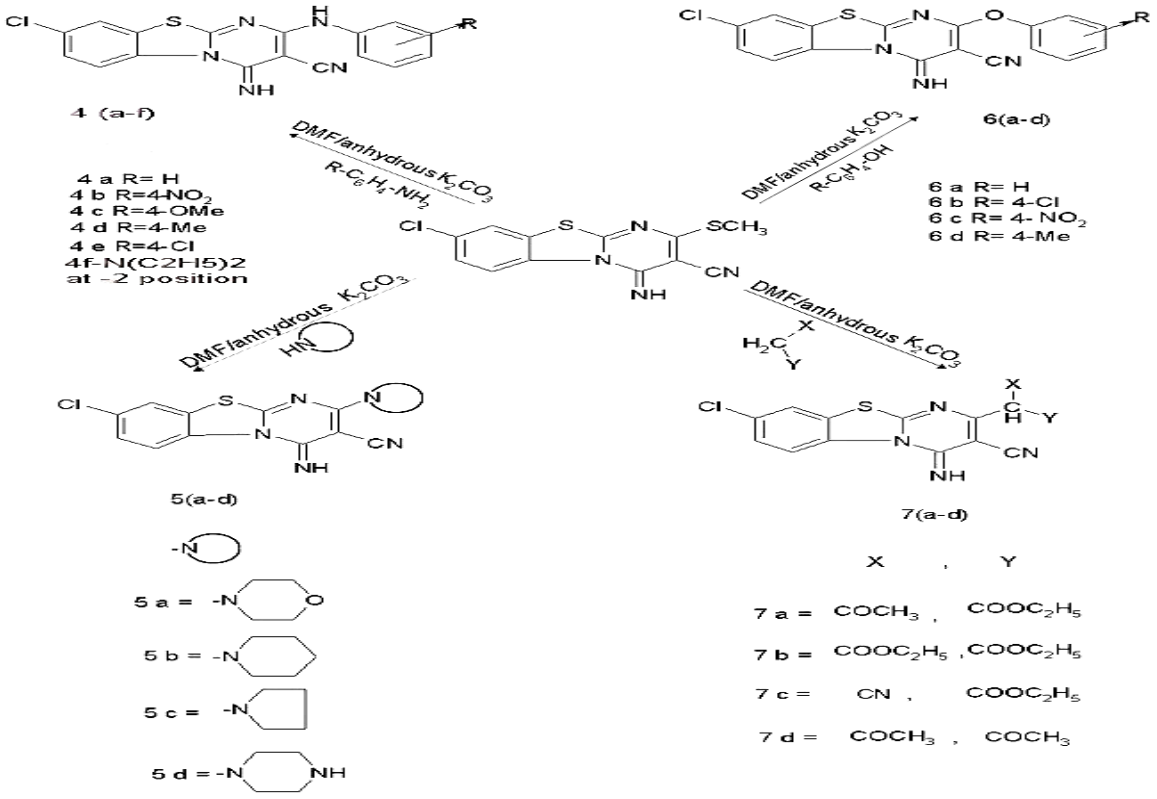


1 **2** **3**

Scheme - 1

Table1. One dose mean graph data in vitro 60-cell drug screening [a] of activity of pyrimido benzothiazole

Sr.No (NSC No.) [d]	Comp No.	R	GI_{50} (μ M) in cell lines[b]						
			HCC-2998	HL-60(TB)	TK-10	MALME 3M	Du-145	SF-539	Mean[c] GI_{50}
1(745689)2(745676)3(745677)	3	$-SCH_3$	18.01	52.21	15.08	-28.63	21.38	1.34	68.76
	4b	$4\text{-}NHC_6H_4\text{-}NO_2$	55	26.84	58.78	1.44	18.30	17.41	89.16
	4c	$4\text{-}NHC_6H_4\text{-}CH_3$	23.63	47.14	45.65	5.50	33.42	31.20	71.86
4(745678)	4e	$4\text{-}NHC_6H_4\text{-}Cl$-	35.55	45.07	36.15	13.58	25.90	31.02	71.77
5(745679)	4f	$N(C_2H_5)_2$	21.60	29.04	77.19	514.94	17.41	21.52	85.45
6(745680)	6b	$4\text{-}O\text{-}C_6H_4\text{-}Cl$	31.84	11.07	44.96	13.90	16.84	49.48	96.91
7(745681)	6c	$4\text{-}O\text{-}C_6H_4\text{-}NO_2$	39.10	72.62	-28.47	-88.98	26.95	27.64	78.37
8 (745682)	5a		26.76	11.78	64.91	22.22	23.08	13.08	95.00
9 (745683)	5b		30.45	13.10	58.46	5.75	6.8	6.39	96.85
10 (745684)	5c		56.15	33.84	-8.93	-1.95	10.67	112.4	96.48
11 (745685)	5d		16.8	29.79	57.04	15.21	9.78	6.27	100.96
12 (745086)	7d		4.90	29.79	105.60	12.60	14.95	12.94	82.59
13 (745087)	7c		6.61	7.20	67.97	542.42	26.02		102.90
14 (745688)	7a		48.12		15.80	-30.81	21.38	-3.60	83.33
				32.01				16.53	
									



Scheme - 2

CONCLUSION

In this paper, an easy and useful method to obtain biological active, 8-Chloro3-cyano-4-imino-2-methylthio-4H-pyrimido [2,1-*b*] [1,3] benzothiazole **3** and its 2-substituted derivatives **4, 5,6 and 7** has been presented. The parent compound **3** exhibits cytotoxic activity against HL-60(TB) cell line (Leukemia).

From the point of structure activity relationship, results obtained by first stage screening revealed that replacement of methylthio group at 2- position by 4-methoxy aniline **4c**, 4-chloro aniline **4e**, 4- nitro phenoxy **6c** and ethyl acetoacetyl **7a** were found to be cytotoxic against HL-60(TB) cell line (Leukemia). However amoungst these compounds, compound **6c** with 4- nitro phenoxy substituent was found to be most potent.

Compounds obtained by the replacement of methylthio group at 2- position by 4-nitro aniline **4b**, diethyl amino **4f**, morpholino **5a**, piperidino **5b**, piperazino **5d**, ethyl cynoacetyl **7c** and acetyl acetonyl **7d** groups revealed anticancer activity against TK-10 cell line(Renal cancer). However the presence of acetyl acetonyl group at 2- position **7d** makes this compound most anticancer amoungst these compounds.

Compounds with substituents diethyl amino and ethyl cyno acetyl **4f, 7c** respectively exhibited remarkable inhibitory effects against MALME-3M cell line (Melanoma). Compounds having 4-nitro aniline, pyrolidino, ethyl acetoacetynl substituent at 2- position **4b**, **5c, 7a** respectively showed antitumor activity against HCC-2998 cell line (Colon cancer) and **6b, 5c** exhibited inhibitory cytotoxicity against SF-539 cell line (CNS).

All these compounds displayed cytyotoxicity response across cell lines, sensitive cell lines exhibit GI_{50} values $<10^{-8}$ M and insensitive cell lines $>10^{-4}$ M. For second stage screening compounds **3, 4c** and **4e** exhibit significant growth inhibition are selected by NCI for further cytotoxicity by evaluation against 60 cell panels at five dose concentration levels.

Fused pyrimido benzothiazoles of the type **3, 4, 5, 6** and **7** demonstrate cytotoxic properties justifying further investigation as the potential anticancer agents and may be used as a basis for the design of new non- toxic anticancer drugs.

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