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Synthesis of Fluorinated Thiazolopyrimidine Analogues *via* One Pot Multicomponent Reaction and Evaluation of its Anticancer Activity

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ABSTRACT

In this series fluorine containing thiazolopyrimidine derivative were designed and successfully synthesized using NH_4VO_3 as catalyst through multicomponent reaction and their structures have been confirmed by spectral data. Eight compounds have been selected for screening of in vitro anticancer activity by National Cancer Institute (NCI) USA; against NCI 60 cell line (Single dose analysis) of the synthesized series and results obtained showed significant anticancer activity by compounds SS4, SS5 and SS10. Cancerous cells inhibitory prospective of titled compounds proposed reflected good activity against Leukemia cancer cell lines. If we talk specifically it is found that they are constructively anticancerous for Melanoma LOX IMVI, Leukemia RPMI-8226 and Leukemia MOLT-4 etc. These results of assessment based on present study that fluorinated thiazolopyridine compound exhibit anticancer activity but presence of fluorine with chlorine increases its anticancer activity.

Keywords: Pyrazole, Thiazolopyrimidine, Multicomponent, Anticancer

INTRODUCTION

Multicomponent Reactions (MCRs) have emerged as a powerful tool in organic, combinatorial and medicinal chemistry. MCRs are the most efficient, synthetic route to produce heterocyclic compounds [1-5]. These are simple, atom economic and time-saving methods which make them an important reaction in the synthesis of biologically active compounds such as drugs and agricultural chemicals and many others [6,7].

In recent times halogen-containing compounds (more specific-fluorine, chlorine) have become powerful and common tool for multiuses. It is known that fluorine or trifluoromethyl group at an appropriate position in the molecule can alters results considerably in chemical, pharmacological, and material science research. It is observed that due to presence of fluorine atom there is an increase in oxidative, thermal stability and specific reactivity properties [8,9].

Fluorine containing heterocyclic compounds has great importance in pharmaceuticals and industrial chemicals applications. Fluorinated substitute also have broad potential applications in many areas of agrochemical industry and medicinal sciences [10,11] such as treatment of central nervous systems, cardiovascular and breast cancer cell lines

It is reported that the incorporation of fluorine atom with heterocyclic compounds provides enhanced properties such as fungicidal [12,13], herbicidal activities [14], anticancer [15,16], antidiabetes [17], antimicrobial agent [18], anti-inflammatory [19], it is also seen that fluorine containing pyrazoles exhibited excellent cytotoxicity against cancer cells.

Pyrimidines have widely distinguished history which is extending day by day. The pyrimidine ring is found in vitamins like thiamine, riboflavin and folic acid. During the last two decades, several pyrimidine derivatives have been developed as chemotherapeutic agents and have found wide clinical applications. Thiazoles, represent a class of heterocyclic compounds are of great importance in biological chemistry. Fused pyrimidine containing rings and their therapeutic activities as a anticonvulsant, anticancer, antibacterial and antiviral activity. Since above heterocyclic moieties were found to possess a wide range of activities [20,21], literature survey reveals that thiazoles and pyrimidines combination of rings are very active as antitumour and antimicrobial activity, combination of the two rings is expected to have a synergistic effect on their biological properties. Substituted thiazolopyrimidine ring systems were also reported to possess anticancer [22,23], anti-inflammatory [24], anti-HIV [25,26], antitumor activity [27,28], antioxidant activity [28].

METERIALS AND METHODS

Previously 2H-thiazolo[3,2-a]pyrimidine was synthesized by multistep reactions easily [29,30]. But there are very few reports for the synthesis of 2H-thiazolo[3,2-a]pyrimidine derivatives using catalysts such as Ionic liquid N,N,N',N'-tetramethylguanidinium trifluoroacetate (TMGT) [31] and SMI-SO_3H with the use of solvent free condition (Figure 1) [32].

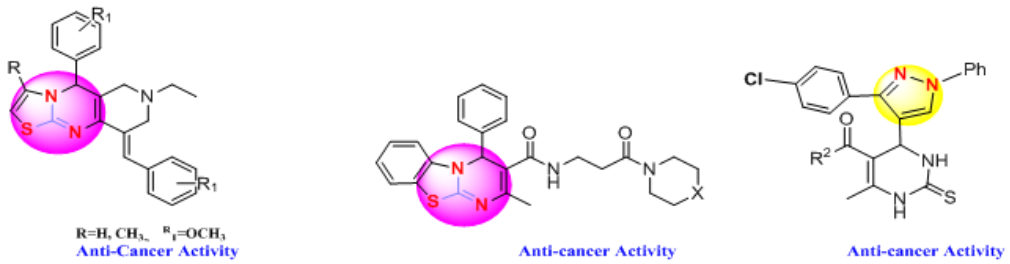


Figure 1: Thiazolopyrimidine and pyrazole structures with anticancer importance

On the basis of above aspects, main motto behind that we have designed some compounds with which some new fluorine group could be located into thiazolopyrimidine and pyrazole Scaffold based compounds. Synthesis of new fused thiazolopyrimidine *via* multicomponent reaction, with eco-friendly 'green' approach [33]. We have used an inorganic acid-ammonium metavanadate (NH_4VO_3) [34] as catalyst for MCRs in solvent free condition. Previously NH_4VO_3 was used for the synthesis of octahydroquinazolinone [35], coumarin [33] and benzimidazole [36] and in industry [37] as a catalyst in good yields. It is easily available, efficient and inexpensive catalyst with solvent free condition is 'green' approach of this reaction. Characterized and continued for cell line based anticancer activity.

RESULTS AND DISCUSSION

Synthesis

General procedure for the synthesis

The expected target synthesis of ethyl 2-(aryl)-5-(3-(aryl)-1-phenyl-1H-pyrazol-4-yl)-7-methyl-8,8a-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate and ethyl 2-(aryl)-5-(3-(aryl)-1H-pyrazol-4-yl)-7-methyl-8,8a-dihydro-5H-thiazolo [3,2-a]pyrimidine-6-carboxylate (SS 1-10) was accomplished in one steps as outlined in Scheme 1. In the reaction, equimolar amounts of ethylacetoacetate (1), 1,3-diphenylpyrazole-4 carboxaldehyde and 3-Arylpyrazole-4-carboxaldehydes (2) [38,39] was refluxed and excess amount of substituted aminothiazole 3 (1.5 eqv.) with catalytic amount of NH_4VO_3 (20 mol%) in solvent free condition. completion of reaction was tested by TLC (EtOAc: Hexane 3:2), after cooling to 25°C, a slurry was obtained washed with cold ethanol then washing with Et_2O (5 ml) and dried to give a final solid compound.

Anticancer activity studies of synthesized compounds

On the basis of their SAR studies, 8 compounds (SS1, SS2, SS3, SS4, SS5, SS7, SS9 and SS10), were selected for one-dose analysis against 60 cancer cell lines and its analysis has been carried out by National Cancer institute, USA. The Anticancer activity of all 8 selected compounds was analysed and studied against 60-cell, evaluated by *in vitro* single dose (1×10^{-5} M) against full NCI 60 cell lines panels. National Cancer Institute (NCI), USA has studied them against full NCI 60 cell lines panel representing all nine human systems breast, prostate, lung, leukemia, melanoma, CNS, brain, ovary and kidney in accordance with their applied protocol (Table 1).

Table 1: *In vitro* anticancer 60-cell line one dose data of the compounds

Panel/Cell line name	Percentage cell growth							
	SS1/NSC-787520	**SS2/NSC 787521**	**SS3/ NSC 787522**	**SS4/NSC 788591**	**SS5/NSC 788594**	**SS7/NSC 787524**	**SS9/NSC 788592**	**SS10/NSC 788593**
Leukemia								
CCRF-CEM	90.17	95.56	89.74	51.10	70.53	92.71	95.53	42.22
HL-60(TB)	96.53	a	102.87	93.81	86.71	106.23	88.32	97.78
K-562	95.38	a	93.02	83.08	72.39	93.78	101.75	94.61
MOLT-4	98.81	a	80.28	54.08	49.68	88.43	78.33	78.40
RPMI-8226	102.71	a	99.35	48.98	61.75	87.12	88.37	48.24
SR	74.08	100.64	65.75	61.56	57.00	94.08	87.97	56.17
Non-Small cell lung cancer								
A549/ATCC	86.42	89.77	90.02	78.98	63.48	80.91	77.82	83.36
EKVX	107.04	a	94.05	94.00	82.70	83.43	88.4	100.4
HOP-62	84.76	86.30	84.34	76.52	71.8	86.87	86.85	78.01
HOP-92	84.25	84.27	88.57	64.24	a	69.24	61.55	58.23

NCI-H226	91.28	93.61	93.47	89.22	86.23	86.28	96.44	91.68
NCI-H23	93.67	101.59	99.79	83.70	84.99	90.61	101.83	82.04
NCI-H322M	90.12	99.54	106.63	80.58	82.46	99.00	88.65	100.98
NCI-H460	100.27	100.85	97.11	87.83	86.48	94.38	101.86	85.52
NCI-H522	87.55	82.86	90.04	64.25	69.51	86.35	83.36	56.47
Colon cancer								
COLO 205	95.79	101.50	93.94	104.81	87.02	95.27	106.55	93.71
HCC-2998	98.40	102.44	108.43	106.40	98.79	100.87	105.19	116.0
HCT-116	88.53	94.41	87.36	67.47	68.62	76.05	90.04	61.43
HCT-15	106.12	a	106.17	64.11	91.92	89.10	92.91	70.02
HT29	97.84	98.93	96.6	83.27	85.39	100.71	100.87	83.18
KM12	100.90	100.52	108.91	95.87	90.01	93.70	107.33	91.57
SW-620	89.04	85.44	81.29	90.46	87.01	89.13	100.49	79.93
CNS cancer								
SF-268	92.44	90.66	88.06	76.40	82.24	88.22	92.41	89.32
SF-295	103.48	a	100.45	83.97	65.3	93.73	99.02	81.34
SF-539	89.65	89.10	96.63	89.47	88.99	98.01	100.6	87.65
SNB-19	95.44	96.87	91.45	71.72	80.74	87.13	92.09	82.93
SNB-75	97.11	75.83	77.54	80.90	76.66	73.35	78.24	98.63
U251	91.98	97.45	94.66	75.07	77.48	86.91	87.95	77.25
Melanoma								
LOX IMVI	95.66	98.89	95.22	45.79	78.96	90.76	95.71	38.28
MALME-3M	94.06	101.72	95.73	93.66	78.82	110.61	100.17	72.85
M14	96.63	102.80	99.44	79.77	81.56	93.73	98.64	81.56
MDA-MB-435	97.05	99.77	96.54	90.90	85.63	93.59	94.43	89.56
SK-MEL-2	96.90	93.72	102.09	86.30	75.86	104.54	97.4	94.47
SK-MEL-28	97.95	102.32	102.31	89.07	98.44	107.84	106.15	91.85
SK-MEL-5	96.22	99.50	95.83	79.74	98.09	95.07	96.41	84.28
UACC-257	a	a	a	74.17	65.82	a	81.5	68.59
UACC-62	86.27	76.61	79.88	60.42	56.68	75.15	81.56	69.32
Ovarian cancer								
IGROV1	a	a	a	61.58	65.38	a	96.68	63.18
OVCAR-3	106.82	97.93	99.89	91.30	77.24	97.57	113.52	70.22
OVCAR-4	100.64	102.73	106.0	92.63	100.91	92.38	102.02	85.5
OVCAR-5	99.83	104.87	101.52	100.99	109.96	105.35	91.88	111.66
OVCAR-8	86.35	89.11	76.12	82.48	75.74	95.93	91.98	76.98
NCI/ADR-RES	111.93	118.88	114.99	94.59	102.54	98.95	104.77	97.51
SK-OV-3	93.21	91.65	97.06	91.88	86.65	86.74	87.78	87.46
Renal cancer								
786-0	93.54	93.42	91.9	94.68	92.41	89.35	87.62	95.26
A498	101.38	98.00	100.33	85.38	103.79	102.18	89.73	106.96
ACHN	97.94	100.46	98.85	75.29	73	82.60	101.06	80.76
CAKI-1	85.70	85.52	85.19	75.93	81.25	63.72	84.06	80.32
RXF 393	89.72	101.72	102.54	83.74	87.5	99.57	97.08	85
SN12C	89.38	92.12	88.79	78.98	81.63	82.82	98.6	80.6
TK-10	96.94	95.81	104.03	80.04	108.26	109.44	93.65	94.32
UO-31	86.65	90.21	89.72	61.40	66.25	65.88	85.06	73.01

Prostate cancer								
PC-3	88.42	86.10	88.11	63.45	54.66	69.45	80.72	68.33
DU-145	116.25	107.48	109.43	89.13	96.72	103.99	103.6	93.07
Breast cancer								
MCF7	98.12	a	90.1	47.13	71.48	62.87	87.19	61.61
MDA-MB-231/ATCC	92.95	87.09	87.96	70.02	59.24	65.09	88.47	77.28
HS 578T	100.39	97.80	94.33	75.06	78.7	88.31	101.15	81.13
BT-549	95.92	94.91	93.53	80.82	93.05	94.99	93.07	76.62
T-47D	91.33	94.78	90.84	62.56	55.67	68.39	79.57	74.58
MDA-MB-468	89.53	93.40	70.68	66.84	81.09	76.24	91.09	62.74

Note: a: Not tested

Anticancer activity of selected 8 compounds was studied. It is tested against 60-cell lines. Some synthesized compounds (SS5, SS4 and SS10) exhibited potential anticancer activity. Compound SS10 showed good anticancer activity against Leukemia cancer (CCRF-CEM, LOX IMVI, RPMI-8226 cell lines) and compound SS5 showed significant anticancer activity against Leukemia cancer (MOLT-4 cell lines) and prostate cancer (PC3 cell lines). Based on Mean growth percentage and most of cell lines inhibition the compounds SS4 showed best activity against Leukemia cancer (CCRF-CEM, MOLT-4, RPMI-8226, LOX IMVI, cell lines) and breast cancer (MCF-7 cell lines) (Table 2 and Figure 2).

Table 2: Percentage cell growth< 55% cell growth reduction following

S. No.	Compound No.	Mean growth percentage	Cancer type/Cell lines					
			Leukemia/CCRF-CEM	Leukemia/MOLT-4	Leukemia/RPMI-8226	Melanoma/LOX IMVI	Breast cancer/MCF-7	Prostate cancer PC-3
1.	SS1/NSC 787520	94.89	90.17	98.81	102.71	95.66	98.12	88.42
2.	SS2/NSC 787521	95.35	95.56	a	100.64	98.89	a	86.1
3.	SS3/NSC 787522	94.06	89.74	80.28	99.35	95.22	90.1	88.11
4.	SS4/NSC 788591	78.46	**51.1**	**54.08**	**48.98**	**45.79**	**47.13**	63.45
5.	SS5/NSC 788594	80.15	70.53	**49.68**	61.75	78.96	71.48	**54.66**
6.	SS7/NSC 787524	89.39	92.71	88.43	87.12	90.76	62.87	69.45
7.	SS9/NSC 788592	93.05	95.53	78.33	88.37	95.71	87.19	80.72
8.	SS10/NSC 788593	80.7	**42.22**	78.4	**48.24**	**38.28**	61.61	68.33

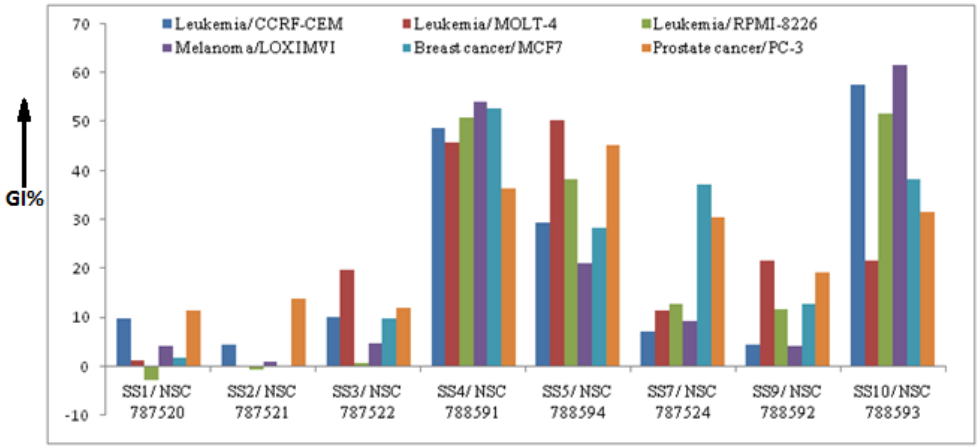
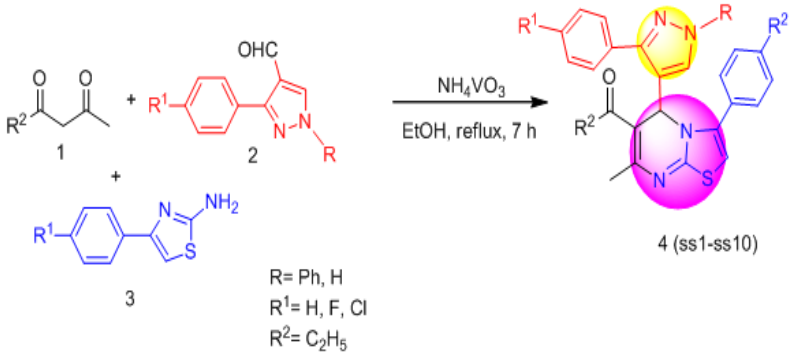


Figure 2: One dose response graph between selected 8 compounds and respect to highest growth inhibition% (GI%) in the anticancer cell lines

Experimental analysis

The completions of reaction of synthesized compounds were checked by Thin Layer Chromatography (TLC) on aluminum plates coated with silica gel $60F_{254}$, 0.25 mm thickness (Merck). Separation of compounds was carried out by column chromatography using silica gel (100-200 mesh). Melting points were determined by open capillary method using a melting point apparatus Buchi Melting Point B-540 apparatus and are uncorrected. IR spectra were recorded as KBr discs (for solids) with a Shimadzu FTIR-8400S instrument and are expressed in cm^{-1}.

NMR spectra were recorded at 25°C with a Bruker Avance III 400 spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C instrument Deuterated Dimethyl Sulfoxide (DMSO-d_6) using as solvent and Tetramethylsilane (TMS) as the internal standard (0.00 ppm). Chemical shifts values were given in δ (ppm) scales.



Scheme 1: Multicomponent synthesis of fluorinated thiazolopyrimidine derivatives

Ethyl 3-(4-fluorophenyl)-5-(3-(4-fluorophenyl)-1H-pyrazol-4-yl)-7-methyl-5H-thiazolo[3,2-a] pyrimidine-6-carboxylate SS1: Light Yellow solid, 62% yield, m.p. 128°C; IR (KBr): 3332, 3151, 3016, 2912, 1734, 1629, 1446, 1367, 1211, ^{1}H-NMR (DMSO-d6, 400 MHz), δ=11.68 (s, 1H), δ=7.54 (d, 2H J=8.0Hz), δ=7.23-7.11 (m, 5H), δ=4.19 (t, 3H J=16 Hz), δ=3.45 (q, 3H, J=20 Hz), δ=3.38 (s, 1H), δ=1.17 (t, 1H J=16 Hz), ^{13}C-NMR (DMSO-d6, 100 MHz), δ=171.38, 159.76, 156.75, 153.49, 150.54, 148.68, 146.56, 144.94, 137.94, 129.05, 129.01, 128.22, 128.06, 127.68, 125.46, 123.01, 120.26, 115.06, 114.85, 40.13, 39.92, 23.53, 20.77, MS (m/z): 478.374 (M^+) Anal. Calcd. for. $C_{25}H_{20}F_2N_4O_2S$.

Ethyl 5-(3-(4-fluorophenyl)-1H-pyrazol-4-yl)-7-methyl-3-phenyl-5H-thiazolo[3,2-a] pyrimidine-6-carboxylate SS2: White solid, 71% yield, m.p. 120°C; IR (KBr): 3278, 3186, 3041, 2935, 1723, 1628, 1561, 1383, 1280, ^{1}H-NMR (DMSO-d6, 400 MHz), δ=11.87 (s, 1H), δ=7.70 (d, 2H, J=4.0 Hz), δ=7.54 (d, 2H J=6.0 Hz), δ=7.32-7.21 (m, 5H), δ=5.65 (s, 1H), δ=4.17 (q, 3H, J=17, Hz), δ=2.56 (s, 1H), δ=1.06 (t, 1H J=16 Hz), ^{13}C-NMR (DMSO-d6, 100 MHz), δ=172.19, 166.75, 144.94, 137.94, 129.05, 129.01, 128.22, 128.06, 127.68, 125.46, 123.01, 120.26, 115.06, 114.85, 79.19, 78.87, 78.54, 40.13, 39.92, 39.71, 39.50, 39.28, 39.08, 38.88, 32.30, 20.77, MS (m/z): 460.428 (M^+) Anal. Calcd. For. $C_{25}H_{21}FN_4O_2S$.

Ethyl 3-(4-fluorophenyl)-7-methyl-5-(3-phenyl-1H-pyrazol-4-yl)-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate SS3: White solid, 68% yield, m.p. 132°C; IR (KBr): 3328, 3165, 3021, 2913, 1721, 1625, 1568, 1392, 1276, ^{1}H-NMR (DMSO-d6, 400 MHz), δ=11.19 (s, 1H), δ=7.78 (d, 2H, J=4.0 Hz), δ=7.64 (d, 2H J=5.0 Hz), δ=7.41-7.35 (m, 5H), δ=6.83 (s, 1H), δ=5.33 (s, 1H), δ=3.62 (q, 3H J=16 Hz), δ=2.68 (s, 1H) δ=1.12 (t, 1H, J=5 Hz), ^{13}C-NMR (DMSO-d6, 100 MHz), δ=171.78, 166.75, 144.94, 137.94, 129.05, 129.01, 128.22, 128.06, 127.68, 125.46, 123.01, 120.26, 115.06, 114.85, 79.19, 78.87, 78.54, 40.13, 39.92, 39.71, 39.50, 39.28, 39.08, 38.88, 32.30, 20.77, MS (m/z): 460.261 (M^+) Anal. Calcd. for $C_{25}H_{21}FN_4O_2S$

Ethyl 5-(3-(4-chlorophenyl)-1H-pyrazol-4-yl)-3-(4-fluorophenyl)-7-methyl-5H-thiazolo [3,2-a] pyrimidine-6-carboxylate SS4: White solid, 74% yield, m.p. 138°C; IR (KBr): 3361, 3175, 3061, 2943, 1717, 1622, 1545, 1372, 1270, ^{1}H-NMR (DMSO-d6, 400 MHz), δ=11.78 (s, 1H), δ=7.83 (d, 2H J=4 Hz), δ=7.69 (d, 2H J=7 Hz), δ=7.51-7.45 (m, 5H), δ=5.70 (s, 1H), δ=4.06 (q, 3H, J=18 Hz), δ=2.66 (s, 1H) δ=1.77 (s, 1H), δ=1.10 (t, 3H, J=8 Hz), ^{13}C-NMR (DMSO-d6, 100 MHz), δ=172.90, 166.36, 152.41, 150.82, 145.87, 142.38, 139.71, 139.76, 133.14, 130.09, 128.75, 128.58, 128.34, 128.19, 126.88, 125.77, 125.10, 119.37, 105.77, 73.38, 73.06, 72.74, 56.95, 47.31, 17.54, 14.71 MS (m/z): 494.484 (M^+) Anal. Calcd. for $C_{25}H_{20}ClFN_4O_2S$.

Ethyl 3-(4-chlorophenyl)-5-(3-(4-fluorophenyl)-1H-pyrazol-4-yl)-7-methyl-5H-thiazolo [3,2-a] pyrimidine-6-carboxylate SS5: White solid, 77% yield, m.p. 145°C; IR (KBr): 3269, 3188, 3034, 2958, 1731, 1623, 1553, 1353, 1285, ^{1}H-NMR (DMSO-d6, 400 MHz), δ=11.46 (s, 1H), δ=7.84 (d, 2H, J=10 Hz) δ=7.78 (d, 2H, J=7 Hz), δ=7.67 (d, 2H, J=10 Hz), δ=7.51 (d, 2H, J=5 Hz), δ=5.36 (s, 1H), δ=3.80 (q, 3H J=18 Hz), δ=2.22 (s, 1H), δ=1.05 (t, 3H, J=14 Hz), ^{13}C-NMR (DMSO-d6, 100 MHz), δ=173.30, 165.50, 153.33, 150.93, 146.84, 139.78, 132.98, 129.32, 128.80, 128.44, 128.32, 126.69, 126.35, 126.23, 124.23, 119.13, 102.54, 73.74, 73.38, 73.06, 60.57, 46.95, 21.07, 16.06, MS (m/z): 494.378 (M^+) Anal. Calcd. for $C_{25}H_{20}ClFN_4O_2S$.

Ethyl 3-(4-fluorophenyl)-5-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate SS6: Light Yellow, 61% yield, m.p. 163°C; IR (KBr): 3321, 3136, 3029, 2903, 1730, 1635, 1468, 1363, 1234, ^{1}H-NMR ($CDCl_3$, 400 MHz), δ=7.70 (d, 2H, J=8 Hz), δ=7.53 (d, 2H, J=8 Hz) δ=7.50-7.22 (m, 5H), δ=7.15 (d, 2H, J=6 Hz), δ=6.43 (s, 1H), δ=5.54 (s, 1H), δ=3.65 (q, 3H, J=18 Hz), δ=2.05 (s, 1H), δ=0.84 (t, 1H, J=7 Hz), ^{13}C-NMR (DMSO-d6, 100 MHz), δ=174.19, 165.55, 155.67, 152.64, 150.86, 139.86, 136.75, 133.27, 133.09, 132.53, 130.03, 129.14, 129.03, 128.89, 128.77, 128.57, 128.40, 128.32, 126.87, 125.52, 121.96, 121.54, 121.03, 118.98, 118.73, 106.58, 55.60, 47.99, 47.40, 16.15, 11.83, MS (m/z): 554.279 (M^+) Anal. Calcd. for $C_{31}H_{24}F_2N_4O_2S$.

Ethyl 5-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-7-methyl-3-phenyl-5H-thiazolo[3,2-a] pyrimidine-6-carboxylate SS7: White solid, 72% yield, m.p. 155°C; IR (KBr): 3265, 3145, 3067, 2946, 1729, 1643, 1589, 1364, 1271, ^{1}H-NMR (DMSO-d6, 400 MHz), δ=7.53 (d, 2H, J=8.0 Hz), δ=7.49 (d, 2H, J=12 Hz), δ=7.44-6.94 (m, 5H), δ=6.11 (s, 1H), δ=4.15 (s, 1H), δ=3.55 (q, 3H, J=14 Hz), δ=2.05 (s, 1H) δ=0.74 (t, 3H, J=12 Hz), ^{13}C-NMR (DMSO-d6, 100 MHz), δ=173.43, 165.88, 152.40, 149.66, 139.78, 139.43, 137.40, 133.16, 132.14, 130.52, 130.01, 128.99, 128.83, 128.58, 126.92, 125.78, 123.59, 119.85, 106.19, 73.74, 73.38, 73.06, 55.01, 47.41, 18.15, 12.83 MS (m/z): 536.273 (M^+) Anal. Calcd. for $C_{31}H_{25}FN_4O_2S$.

Ethyl 5-(1,3-diphenyl-1H-pyrazol-4-yl)-3-(4-fluorophenyl)-7-methyl-5H-thiazolo[3,2-a] pyrimidine-6-carboxylate SS8: Light yellow solid, 69% yield, m.p. 172°C; IR (KBr): 3342, 3143, 3043, 2924, 1736, 1621, 1574, 1336, 1266, ^{1}H-NMR (DMSO-d6, 400 MHz), δ=7.44 (d, 1H J=8Hz), δ=7.40-7.06 (m, 5H) δ=7.03 (d, 1H, J=6 Hz), δ=6.60 (s, 1H), δ=5.30 (s, 1H), δ=3.95 (q, 3H, J=16 Hz), δ=2.46 (s, 1H), δ=0.96 (t, 1H, J=11 Hz), ^{13}C-NMR (DMSO-d6, 100 MHz), δ=171.38, 164.52, 148.62, 146.49, 138.86, 138.23, 137.05, 136.67, 136.13, 135.74, 135.27, 131.73, 127.83, 127.41, 126.71, 126.31, 122.93, 116.53, 106.11, 74.24, 73.98, 73.69, 54.89, 47.13, 17.68, 11.45, MS (m/z): 536.541 (M^+) Anal. Calcd. for $C_{31}H_{25}FN_4O_2S$.

Ethyl 5-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(4-fluorophenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate SS9: White solid, 71% yield, m.p. 185°C; IR (KBr): 3378, 3167, 3075, 2962, 1738, 1632, 1548, 1356, 1277, ^{1}H-NMR (DMSO-d6, 400 MHz), δ=7.86 (d, 1H, J=6 Hz), δ=7.71 (d, 2H, J=6 Hz), δ=7.53-7.46 (m, 5H), δ=7.33 (t, 1H, J=16 Hz), δ=6.79 (d, 2H, J=8 Hz), δ=6.07 (s, 1H), δ=5.65 (s, 1H), δ=4.25 (q, 3H, J=16 Hz), δ=2.56 (s, 1H), δ=1.24 (t, 1H, J=8 Hz), ^{13}C-NMR (DMSO-d6, 100 MHz), δ= 172.64, 165.84, 150.32, 148.54, 144.12, 143.42, 142.56, 141.55, 139.43, 138.99, 137.77, 133.34, 132.85, 132.52, 130.78, 130.23, 122.67, 117.93, 106.19, 76.74, 76.55, 76.44, 76.20, 56.53, 48.32, 18.12, 11.68, MS (m/z): 4 570.267 (M^+) Anal. Calcd. for $C_{31}H_{24}ClFN_4O_2S$.

Ethyl 3-(4-chlorophenyl)-5-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate SS10: White solid, 78% yield, m.p. 161°C; IR (KBr): 3269, 3157, 3041, 2962, 1737, 1631, 1557, 1392, 1264, ^{1}H-NMR (DMSO-d6, 400 MHz), δ=8.99 (s, 1H), δ=7.78 (d, 2H, J=7 Hz), δ=7.54-7.50 (m, 5H, J=16 Hz), δ=5.33 (s, 1H), δ=3.81 (q, 3H, J=18 Hz), δ=2.51 (s, 1H), δ=0.84 (t, 3H, J=14 Hz) ^{13}C-NMR (DMSO-d6, 100 MHz), δ=172.89, 165.95, 151.44, 149.76, 144.29, 143.86, 143.52, 142.67, 139.72, 139.65, 138.84, 135.63, 133.56, 133.21, 131.67, 131.36, 123.56, 117.45, 106.45, 77.70, 77.46, 77.34, 77.12, 56.76, 48.67, 18.51, 12.09. MS (m/z): 570.423 (M^+) Anal. Calcd. for $C_{31}H_{24}ClFN_4O_2S$.

CONCLUSION

In present study we have successfully synthesized new fluorine-containing thiazolopyrimidine-6-carboxylate derivatives (SS1-SS10) using NH_4VO_3 as a Catalyst in MCRs. Some synthesized compounds (SS5, SS4 and SS10) exhibited potential anticancer activity. Compound showed good anticancer activity against Leukemia, prostate cancer and breast cancer. On the basis of present anticancer activities it can be concluded that fluorine containing compound exhibit good anticancer activity and presence of chlorine boost its anticancer activity. The compound ss10 may be a potential lead candidate with respect further biological exploration.

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