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Full Length Original Research Paper

Design, Synthesis, Characterization and Anticancer Properties of Novel 2-Chloro-*N*-(Aryl Substituted) Acetamide Derivatives of 5-[2-(4-Methoxyphenyl) Pyridin-3-yl]-1, 3, 4-Oxadiazole-2-Thiol

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Abstract:
In this linear synthesis, novel different 2-chloro N-aryl substitutedacetamide derivatives of 5-(2-(4-methoxyphenyl) pyridin-3-yl)-1, 3, 4-oxadiazole-2-thiol have been synthesized and screened for their cytotoxicity on *PANC-1*, *HepG2* and *MCF7* cell lines and obtained the IC_{50} and CC_{50} values.All the synthesized compounds were characterized by LCMS, IR, ^{1}H and ^{13}C (proton and Carbon 13) spectroscopies and elemental analysis. These compounds were evaluated for *invitro* anticancer activity on three different human leukemic cell lines, namely *PANC-1*,*HepG2* and *MCF7*.In total five compounds were synthesized and studied for their MTT assay. Among five synthesized novel compounds, the compound N-(5-(4-Methoxy-phenyl)-pyridin-2-yl)-2-{5-(2-(4-methoxy-phenyl)-pyridin-3-yl)(1,3,4)oxadiazol-2-ylsulfanyl}-acetamide**6e** is highly cytotoxic on *PANC-1* and *HepG2* cell lines having IC_{50} of 4.6µM and 2.2µM respectively whereas the compound **6c** is moderately cytotoxic on *MCF7* having IC_{50} 15.5µM respectively. Rest all the compounds showed less cytotoxicity on all the three cell lines as compared with the standard 5-FU.

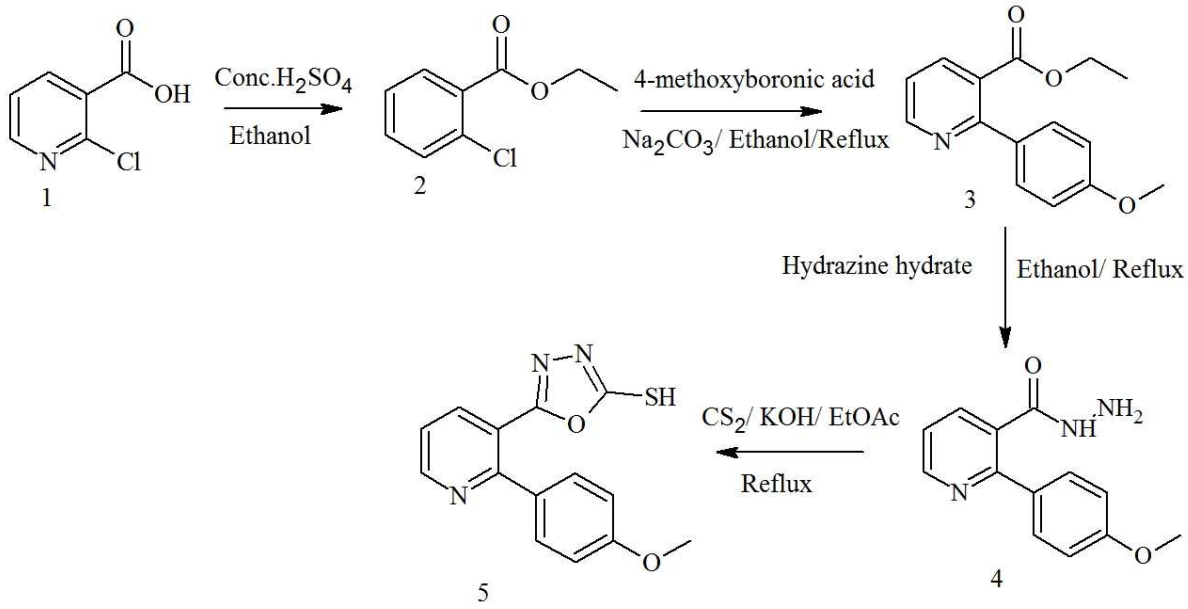
Keywords: *HepG2*, 1, 3, 4-Oxadiazoles, Chloroacetyl chloride, acetamide, MTT assay

Introduction

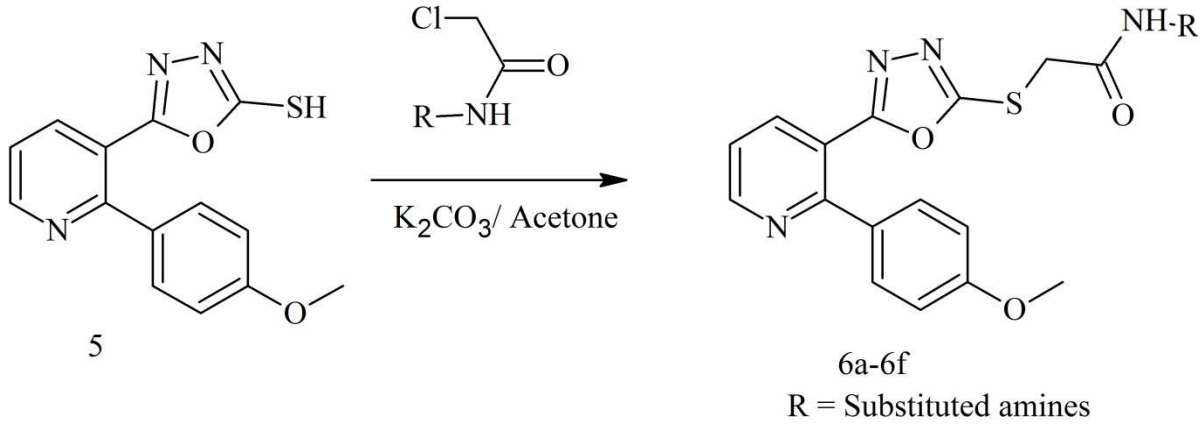
Author has synthesized the novel compounds of 2-chloro (N-aryl substituted)acetamide derivatives of 5-(2-(4-methoxyphenyl) pyridin-3-yl)-1, 3, 4-oxadiazole-2-thiol and screened these compounds for cytotoxicity[1] on three different human leukemic cell lines. Synthetic chemistry was started with 2-chloro nicotinic acid which is converted into ethyl ester and subsequently synthesized the carbohydrazide **4**. The carbohydrazide was cyclised using carbon disulphide and potassium hydroxide and obtained the key intermediate.This kind of novel ring systems not yet studied but few of the derivatives of pyridine containing 1, 3, 4-oxadiazole-thiol moiety have been reported for their potent activity towards anticancer[1] anti-tubercular [3] anti-inflammatory[4, 5, 6] anti-bacterial [7, 8] and kinase[9, 10] inhibition properties. In this connection the author envisaged that by attaching different 2-chloro (N-aryl substituted)acetamides [12] derivatives to the 1, 3, 4-oxadiazole-2- thiol moiety may enhance the Log-P values and thus increasing the potency. In order to validate this hypothesis the author has synthesized five novel 2-chloro(N-aryl substituted) acetamide derivatives of 1, 3, 4-oxadiazole-2-thiol[13] compounds and tested their *invitro* cytotoxicity against cancer cell lines. The study revealed that the different 1, 3, 4-oxadiazole derivatives possesses excellent anticancer activity. In this synthesis compounds

6ehas showed good antiproliferative[13] activity on *PANC-1* and *HepG2* cell lines having IC_{50} of 4.6μM and 2.2μMrespectively.

Scheme 1: Synthesis of 5-(2-(4-methoxyphenyl) pyridin-3-yl)-1, 3, 4-oxadiazole-2-thiol (Intermediate)



Scheme 2: Linear synthetic pathway of synthesis of 2-chloro (N-Aryl substituted) acetamide derivatives of 5-(2-(4-methoxyphenyl) pyridin-3-yl)-1, 3, 4-oxadiazole-2-thiol 6a-6e:



EXPERIMENTAL

Materials and Methods: All reagents, chemicals and solvents were purchased from S-d fine and Spectrochem ltd.Bengaluru.India.^{1}H NMR and ^{13}C NMR were recorded by Brucker 400 MHz spectrophotometer. Melting points are determined using Buchi melting point 545.Mass spectra were recorded by Agilent 1200 series.TLC was done on F254 grade silica 60 from Merck.IR spectra was recorded by FTIR (1800S) series.

Synthesis

Synthesis of Ethyl 2-chloropyridine-3-carboxylate 2

The 2-chloronicotinic acid **1** (10g, 0.0636mol) was taken in a 1L single necked round bottom flask, 200mL of ethanol and concentrated H_2SO_4(3-5 drops) were added, reaction mixture was refluxed at 80°C for 8 h. TLC(Thin layer chromatography) was monitored to check the completion of the reaction. Solvent was evaporated and the residue was neutralized with

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10% $NaHCO_3$solution. Aqueous was extracted with ethyl acetate (35mL x2), washed with brine (20mL) and dried over Na_2SO_4, evaporated. The obtained pale yellow oil was recrystallized form ethanol-water as yellow needles. Yield 8.5g, MS-(M+H)- 187; HPLC purity = 96.7%; TLC-ethyl acetate: hexane (1:9); IR(KBr), vmax/cm^{-1}: 980, 1089, 2845, 3006 ; ^{1}HNMR ($CDCl_3$, 400MHz) : δ 1.18(t, 3H), 3.89(q, 2H), 7.41(t, 1H, *J* 13.4Hz), 8.44(dd, 1H, *J* 8.5Hz), 8.85(d, 1H, *J* 7.8 Hz).

Synthesis of ethyl 2-(4-methoxy phenyl) pyridine-3-carboxylate 3

Ethyl2-chloropyridine-3-carboxylate(8.5g, 0.0457mol),Na_2CO_3(19.37g, 0.182mol),4-methoxy phenylboronicacid (8.335g, 0.0448mol),tetrakis (triphenyl phosphine)palladium (0)(0.263g,304.8mol) were refluxed in 120mL of ethanol for 10h.TLC was monitored to check the completion of the reaction, after completion, the solvent was evaporated,aqueous wasextracted with ethyl acetate (25mL x3), washed with brine (15mL) and dried over Na_2SO_4. Ethyl acetate was evaporated to yield brown oil. The crude product was purified by column chromatography using silica gel(100 to 200mesh), gradient (0-15%) ethyl acetate in hexane as the eluent. Yield 4.6g,off white coloured solid ; MS (ESI) *m/z*: (M+H)-258; m.p-143-148^{0}C; IR(KBr),vmax/cm^{-1} : 1130, 2965,3126; ^{1}H-NMR($CDCl_3$, 400 MHz) : δ 0.9(t,2H), 2.6(s, 3H), 3.7(q,3H), 7.26(dd,*J* 7.8 Hz, 2H), 7.68(q,2H), 8.75(m,*J* 13.2Hz, 1H), 9.34(q,2H).

Synthesis of 2-(4-methoxy phenyl)-nicotinic acid hydrazide:

Ethyl 2-(4-methoxy phenyl) pyridine-3-carboxylate**(**4.6g) was taken in a 250mL single necked round bottom flask added with excess (15mL) of hydrazine hydrateand refluxed in100mL of ethanol overnight.TLC was monitored to check the completion of the reaction, solvent was completely removed under reduced pressure, residue was cooled to 5°C and added ice pieces and stirred. Solids that are separated out were filtered, washed with water (100mL) and dried over sodium sulphate. Yield 2.3g; white solid; TLC-ethylacetate: Hexane (50:50);m.p-162-164°C;MS (ESI) *m/z*: (M+H)-244;IR (KBr), vmax/cm^{-1};1100, 2975, 3176, 3385; ^{1}H NMR($CDCl_3$, 400MHz) δ 2.62(s, 3H), 4.64(bs,2H,NH_2), 7.39(dd,*J* 12.8Hz, 2H), 7.56(q,2H), 8.75(m,*J* 8.5Hz, 1H), 9.23(q,2H).

Synthesis of 5-(2-(4-methoxyphenyl) pyridin-3-yl)-1, 3, 4-oxadiazole-2-thiol.

2-(4-methoxy-phenyl)-nicotinic acid hydrazide (2.3g) was taken in a 100mL single necked RB flask added with carbon disulphide (50mL), 10mL of KOH solution (10%) and solvent ethyl acetate were added. RM was refluxed at 85°C overnight.TLC was monitored to check the completion of the reaction, after completion, solvent was removed RM was poured over 100mL of ice cold water and neutralized with 1N HCl. Solids that are separated out was filtered and dried. The crude product was purified by column chromatographyusing silica gel(100 to 200mesh), gradient (0-15%) ethyl acetate in hexane as the eluent. Yield 4.6g,off white coloured solid ; MS (ESI) *m/z*: (M+H)-286; m.p-183-188^{0}C; IR(KBr),vmax/cm^{-1} : 1100, 2945, 3106 ; ^{1}H-NMR($CDCl_3$, 400 MHz) : δ 2.57(s,3H), 7.15(dd,*J* 7.8 Hz, 2H), 7.6(q,2H), 8.6(m,*J* 13.2Hz, 1H), 9.1(q,2H).

General procedure for the synthesis of 2-chloro (N-Aryl substituted) acetamide derivatives a-e:

The variousamines (**Table 1**) were taken in a 100 mL single necked RB flask to this solvent 100mL of THF was added, 5% NaOH (5-10ML) was then added under stirring and RM was cooled to 0°C. Chloroacetyl chloride was added (2.5-3.5equivalent) drop wiseunder stirring and RM was stirred at R.T for 3-8h.TLC was monitored to

check the completion of the reaction, after completion solvent was removed under reduced pressure residue was added with few ice pieces and solid that is obtained was filtered, washed with water (50mL) and dried.These compounds were pure enough to carry to the next step.

General procedure for the synthesis of novel derivatives of 2-chloro-*N*-(aryl substituted) acetamide of5-(2-(4-methoxyphenyl) pyridin-3-yl)-1, 3, 4-oxadiazole-2-thiol: 6a-6e.

5-(2-(4-methoxyphenyl) pyridin-3-yl)-1, 3, 4-oxadiazole-2-thiolwas taken in a 100 mL single necked RB flask to this solvent 10-15mL of acetone and K_2CO_3 (1.5-2.5 equivalent) were added under stirring. RM was cooled to 0°C. Different 2-chloro (N-aryl substituted) amines (**Table 1**) were added (1.2 equivalent) under stirring to the RM. RM was stirred at R.T for 3-4.5h.TLC was monitored to check the completion of the reaction, If the reaction was not completed RM was warmed to 50°C for 4-6h.TLC was monitored again to check the completion of the reaction, after completion solvent was removed under reduced pressure residue was added with few ice pieces and aqueous was extracted with ethyl acetate,washed with brine,dried over sodium sulphate. The entire final compounds**6a-6e**were purified by column chromatography using silica gel 100-200mesh.Eluent started with 100% n-hexane and polarity was increased to 80% using ethyl acetate.

Analytical data of the final novel derivatives of 2-chloro-(N-aryl substituted) acetamide compounds of 5-(2-(4-Fluorophenyl) Pyridin-3-yl)-1, 3, 4-Oxadiazole-2-Thiol: 6a-6e

2-{5-(2-(4-Fluoro-phenyl)-pyridin-3-yl)-(1, 3, 4) oxadiazol-2-ylsulfanyl}-N-phenyl-acetamide(6a): R = Phenyl acetamide

Off white coloured solid; yield 55.8% ; m.p -165-168^{0}C; IR (KBr), ν_{max}/cm^{-1} : 1123, 2935, 3346, 2765, 3320; ^{1}H-NMR($CDCl_3$, 400MHz): δ 2.53(s, 3H), 2.9 (s, 2H, CH_2), 7.36(dd, *J* 8.5Hz, 2H), 7.67(m, 4H), 7.84(d, *J* 7.2Hz, 2H), 8.34(dd, *J* 12.4Hz, 2H), 9.21(dd, 2H), 10.12(bs, 1H,NH); ^{13}C NMR($CDCl_3$, 100MHz): 65, 116, 124.5, 128.5, 129, 135, 137, 155, 162, 163, 173 ; molecular formula $C_{22}H_{18}N_4O_3S$;MS: (ESI) *m/z*:(M+H)- 419; HPLC 93.4% ;anal. Calculated for $C_{22}H_{18}N_4O_3S$; C, 63.14; H, 4.34; N, 13.39; O, 11.47; S, 7.66; Found C, 63.15; H, 4.35; N, 13.40; O, 11.48; S, 7.67.

2-{5-(2-(4-Fluoro-phenyl)-pyridin-3-yl)-(1, 3, 4) oxadiazol-2-ylsulfanyl}-N-pyridin-2-yl-acetamide(6b): R = Pyridin-2yl

Pale yellow coloured solid; yield 67% ; m.p -123-124^{0}C; IR (KBr), ν_{max}/cm^{-1} : 1235, 2985, 3356, 2865, 3310; ^{1}H-NMR($CDCl_3$, 400MHz): ^{1}H-NMR ($CDCl_3$, 400MHz): δ2.53(s, 3H),2.87 (s, 2H, CH_2), 7.34(dd, *J* 8.2Hz, 2H), 7.56(dd, *J* 8.5Hz, 2H), 7.75(m, 3H), 7.89(dd, *J* 13.4Hz, 2H), 9.05(dd, *J* 8.5Hz, 2H), 10.03(bs, 1H,NH); ^{13}C NMR($CDCl_3$, 100MHz): 65, 113.5, 116, 123.2, 124, 129, 135, 136, 137, 144, 150, 155, 163, 173; molecular formula $C_{21}H_{17}N_5O_3S$; MS: (ESI) *m/z*:(M+H)-420; HPLC 94.7% ; anal. Calculated for $C_{21}H_{17}N_5O_3S$; C, 60.13; H, 4.09; N, 16.70; O, 11.44; S, 7.64; Found C, 60.14; H, 4.10; N, 16.72; O, 11.45; S, 7.65.

N-(5-Bromo-pyridin-2-yl)-2-{5-(2-(4-fluoro-phenyl)-pyridin-3-yl)-(1, 3, 4) oxadiazol-2-ylsulfanyl}-acetamide (6c): R = 5-Bromo-pyridin-2yl.

Off white coloured solid; yield 47%; IR (KBr), ν_{max}/cm^{-1} : 1215, 2965, 3356,2786, 2815, 3350; ^{1}H-NMR($CDCl_3$, 400MHz): 2.53(s, 3H),δ 3.1 (s, 2H, CH_2), 7.23(dd, *J* 13.2Hz, 2H), 7.34(dd, *J* 8.3Hz, 2H), 7.87(m, 3H), 7.91(dd, 2H), 9.23 (dd, *J* 6.8Hz, 2H), 10.23(bs, 1H,NH); ^{13}C NMR($CDCl_3$, 100MHz): 65, 115, 116, 118, 124, 129, 135, 137, 139, 148, 150, 153,

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155, 162, 163, 173;molecular formula $C_{21}H_{16}BrN_5O_3S$; MS: (ESI) *m/z*(M+H)- 498; HPLC 95.2% ; anal. Calculated for $C_{21}H_{16}BrN_5O_3S$; C, 50.61; H, 3.24; Br, 16.03; N, 14.05; O, 9.63; S, 6.43; Found C, 50.62; H, 3.25; Br, 16.04; N, 14.07; O, 9.64; S, 6.44.

N-(5-(4-Fluoro-phenyl)-pyridin-2-yl)-2-{5-(2-(4-fluoro-phenyl)-pyridin-3-yl)-(1, 3, 4) oxadiazol-2-ylsulfanyl}-acetamide(6d): R = 4-Fluoro-phenyl)-pyridin-2-yl

White coloured solid; yield 56%; m.p- 122-126°C ; IR (KBr), ν_{max}/cm^{-1} : 1235, 2935, 3396,2886, 2815, 3250; ^{1}H-NMR($CDCl_3$, 400MHz): δ2.53(s, 3H), 2.65 (s, 2H, CH_2), 7.45(dd, 2H), 7.53(dd, *J* 8.5Hz, 2H), 7.78(m, 3H), 7.89(dd, *J* 7.8Hz, 2H), 8.43 (dd, *J* 12.4Hz, 2H), 9.13(dd, *J* 13.4, 2H), 9.34(dd, 1H), 10.23(bs, 1H,NH); ^{13}C NMR($CDCl_3$, 100MHz): 65, 114, 116, 124, 129, 135, 137, 144.5, 149, 151, 163, 173; molecular formula $C_{27}H_{20}FN_5O_3S$;MS: (ESI) *m/z*:(M+H)- 514; HPLC 96% ;anal. Calculated for $C_{27}H_{20}FN_5O_3S$; C, 63.15; H, 3.93; F, 3.70; N, 13.64; O, 9.35; S, 6.24; Found C, 63.16; H, 3.94; F, 3.71; N, 13.65; O, 9.36; S, 6.25.

2-{5-(2-(4-Fluoro-phenyl)-pyridin-3-yl)-(1, 3, 4) oxadiazol-2-ylsulfanyl}-N-(5-(4-methoxy-phenyl)-pyridin-2-yl)-acetamide(6e): R = 4-methoxyphenyl)-pyridin-2yl.

Brown coloured solid; yield 67% ; m.p: 139-141^{0}C IR (KBr), ν_{max}/cm^{-1} : 1285, 2945, 3326,2916, 2835, 3240; ^{1}H-NMR($CDCl_3$, 400MHz): δ 2.05 (s, 3H, O-CH_3),2.45(s, 3H), 2.65 (s,2H,CH_2), 7.32(dd, *J* 12.4, 2H), 7.56(m, 3H), 7.87(m, 3H), 7.82(dd, *J* 7.8Hz, 2H), 8.32 (dd, *J* 13.4Hz, 2H), 9.25(dd, *J* 13.4, 2H), 10.05(bs, 1H,NH); ^{13}C NMR($CDCl_3$, 100MHz): 65, 67, 114, 116, 124, 128.5, 129, 134, 135, 137, 145, 149, 150.5, 155, 159, 162, 163, 173; molecular formula $C_{28}H_{23}N_5O_4S$; MS: (ESI) *m/z*:(M+H)- 526; HPLC 96% ; anal. Calculated for $C_{28}H_{23}N_5O_4S$; C, 63.99; H, 4.41; N, 13.33; O, 12.18; S, 6.10; Found C, 63.99; H, 4.41; N, 13.33; O, 12.18; S, 6.10.

Table 1: Structures of amine and 2-chloro (N-aryl substituted) acetamide derivativesa-e.

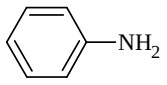
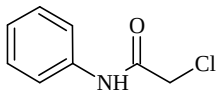
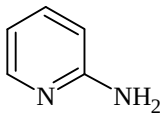
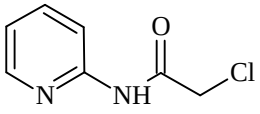
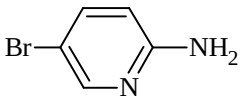
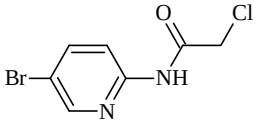
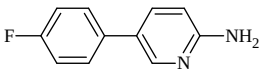
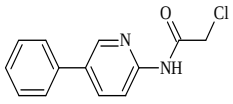
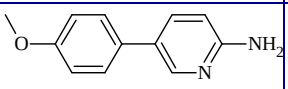
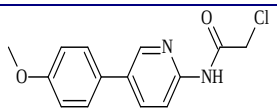
Entry	Amines	2-chloro (N-aryl substituted) acetamides
1	 A1	 **a**
2	 B1	 **b**
3	 C1	 c
4	 D1	 **d**
5	 E1	 **e**

Table 2: IC_{50} and CC_{50} values of the novel 2-chloro (N-aryl substituted) acetamidederivatives of 5-(2-(4-methoxyphenyl) pyridin-3-yl)-1, 3, 4-oxadiazole-2-thiol.

Compounds	IC_{50} and CC_{50} values of 1, 3, 4-oxadiazoles		
	PANC-1	*HepG2*	*MCF7*
6a	34.4(68.9)	64.6(54.8)	108.8(55.7)
6b	49.8(78.9)	55.6(66.8)	38.2(46.7)
6c	47.5(43.3)	78.9(**>150**)	15.5(**>200**)
6d	29.8(45.8)	45.08(34.4)	56.8(32.2)
6e	4.6(**>150**)	2.2(23.4)	37.8(45.6)
5-FU	7.8(39.9)	6.9(36.8)	8.2(45.8)

IC_{50}- Is the concentration that induces 50% of the growth inhibition as compared to untreated cells.CC_{50}- Is the concentration of the 50% of the remaining cells after inhibition. 5-Fluoro uracil, standard used in the experiment.

CYTOTOXIC EVALUATION

Cell Lines fixation and Culture Conditions:

The *invitro* anti-proliferative study was carried out on three human carcinoma cell lines namely *PANC-1*, *HepG2* and *MCF7*.All the cell lines were grown in DMEM-HG supplemented with 10% heat-inactivated FBS, 2% Penicillin-Streptomycin and 2.5 µg/mL Amphotericin-B solutions (All from HI Media Labs, Mumbai, India).Cell lines were incubated at 37°C in a humidified atmosphere of 95% air, 5% CO_2. Following 24-48 hr.of incubation period, the adherent cells were detached using Trypsin-EDTA solution (HI Media Labs, Mumbai, India). Cell count was done using the Luna automated cell counter (Logos Bio systems, India) based on trypan blue dye exclusion method. Cytotoxicity of the novel acetamidederivatives of 1, 3, 4-oxadiazoles have been determined using MTT 3-(4, 5-Dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide) assay.

***Invitro* Cell Viability Assay (MTT Assay):**200µL cell suspension was seeded in 96-well micro plates (Corning®, USA**)** at a density of 25,000 cells/well and incubated for 24hrs, all cells were seeded in duplicates with novel compounds **6a-6e.**Having range of concentrations from 50µM-500µM, incubated in a CO_2 incubator at 37°C.Treated cells were thereafter incubated with 10% MTT (5mg/ml; HI Media Labs, Mumbai, India) for 3 h.The culture medium was then aspirated and 200µL dimethyl sulfoxide (DMSO; Sigma-Aldrich, India) was added. 5-fluorouracil was used as control. Cell viability was determined by measuring the absorbance on a micro plate reader (SPECTRO STAR NANO, BMG LABTECH, Germany) at 570nm. Cell viability was calculated as a percentage of viable cells at different test concentrations relative to the control (5-FU) cells (% cell viability = (A_{570} of treated cells / A_{570} of control cells) ×100%).

RESULTS AND DISCUSSIONS

Chemistry (Figure 1&2): The synthetic chemistry of novel 1, 3, 4-oxadiazole compounds started with the synthesis of key intermediate 5-(2-(4-Fluorophenyl) Pyridin-3-yl)-1, 3, 4-Oxadiazole-2-Thiol[13]**5**. This intermediate was obtained by reacting compound **4** with carbon disulphide and potassium hydroxide. 2-chloro-(N-aryl substituted) acetamide**a-e** were synthesized by treating corresponding amines with chloroacetyl chloride. Final compounds **6a-6e** were synthesized by reacting different acetamides [13, 14]**a-e** with **5**-(2-(4-methoxyphenyl) pyridin-3-yl)-1, 3, 4-oxadiazole-2-thiol.The final compounds **6a-6e** were synthesized by fusing different 2-chloro-(N-aryl substituted) acetamides [13, 14] to the key intermediate **5**-(2-(4-methoxyphenyl) pyridin-3-yl)-1, 3, 4-oxadiazole-2-thiol in presence of K_2CO_3 and solvent acetone.Author envisaged that by introducing 4-methoxy phenyl boronic acid group at the second position of the pyridine ring may enhance the Log-P and TPSA values of 1, 3, 4-oxadaizoles and thus increasing the more bioavailability of the compounds.

a) **SAR: Structural Activity Relationship**: Studies related to SAR of these 1, 3, 4-oxadiazoles -2-thiol showed that the 2-chloro (N-aryl substituted) acetamidederivatives coupled with the cyclised key intermediate **5**-(2-(4-methoxyphenyl) pyridin-3-yl)-1, 3, 4-oxadiazole-2-thiol ring enhances the water solubility and thereby more bio available molecules. By introducing the 4-methoxy phenyl group at the second position of the pyridine enhances further the Log-P values as well as increases the TPSA of the molecules. Author

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envisaged that by coupling different 2-Chloro-(N-aryl substituted) acetamide group to the 1, 3, 4-oxadiazole thiolmoiety may further enhance the bioavailability of these molecules and thus increasing its potency.

b) **Biology**: The obtained series of novel 1, 3, 4-oxadiazole derivatives **6a-6e** have been screened for cytotoxicity[14, 15] on three different human leukemic cell lines to obtain the IC_{50} and CC_{50} of the molecules. The cancer cell lines used was *PANC-1*, *HepG2* and *MCF7*.The MTT assay of the novel 1, 3, 4-oxadaizoles[14] have been screened for these cell lines and obtained the interesting data (Table2).Compound **6e** showed greater cytotoxicity on *PANC-1* and *HepG2* cell lines having IC_{50} of 4.6µM and 2.2µM respectively. Rest all the compounds showed moderate cytotoxicity as in the (Table 2).

Conclusions

In this research author has synthesized five novel derivatives of 1, 3, 4-oxadiazole and screened for MTT assay.Compound **6e** showed good antiproliferative activity on *PANC-1* and *HepG2* cell lines having IC_{50} 4.6µM and 2.2µM of respectively.Compound **6c** showed moderate inhibition on *MCF7* cell lines having IC_{50} 15.5µM. Rest all the compounds showed moderate to low cytotoxicity on all the three cell lines as compared with the standard 5-FU.

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