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Synthesis, characterization and cytotoxic evaluationof 2-(4-fluorophenyl) substituted pyridine containing 1, 3, 4-oxadiazole moiety

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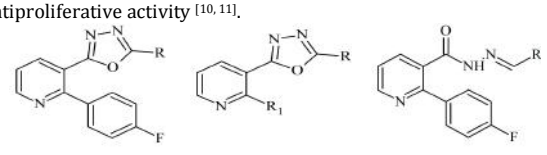
ABSTRACT

A new series of novel 1,3,4-oxadiazole derivativescontaining 4-fluoro phenyl group at C2position of the pyridine ring have been synthesized by linear synthetic method and studied for their cytotoxicity against HeLa (human cervical carcinoma cell line), MCF7 (human breast carcinoma cell line), PANC-1 (human pancreatic carcinoma cell line). The synthesized 1,3,4-oxadiazole derivatives ***6a-e*** *were characterized by spectral ([1]H-NMR,[13]C-NMR, MS and elemental)analyses. The compounds* ***6a-e*** *has been synthesized by the oxidative cyclization of the corresponding Schiff bases* ***5a-e****. The IC_{50} valuesof the synthesized novel 1,3,4-oxadiazole derivatives showed mild cytotoxicity against MCF7 and PANC-1 cell lines. The cytotoxicity of the compounds* ***6(a)*** *and* ***6(d)*** *against MCF7 cell line with IC_{50} of 24.7µM and 21.9µM respectively. The compound* ***6(c)*** *and* ***6(e)*** *showed cytotoxicity against PANC-1 and MCF7 cell lines with IC_{50} of 6.8µM and 8.9µM (****Fig. 1 & 2****) which is comparable with the cytotoxicity of the known standard 5-fluorouracil.*

Key Words*: PANC-1; 1,3,4-Oxadiazoles; Anticancer; Schiff base; MCF7; Cytotoxicity.*

INTRODUCTION

In present work the pyridine substituted with 4-fluorophenyl group at the C2 position of the pyridine ring containing 1,3,4-oxadiazole moiety is the main constituent of the molecular structure (**Fig. 1B**). Different derivatives of pyridine having various substitutions containing 1,3,4-oxadiazole (**Fig. 1B**) ring possess excellent biological properties such as antimicrobial[1], anti-bacterial [2], antituberculosis [3, 4] and anticancer [5] activities. Author envisaged that by substituting 4-fluorophenyl group in the C2 position of pyridine may enhance the biological activity of 1,3,4-oxadiazoles. In order to validate this hypothesis author has synthesizednovel derivatives of 1, 3, 4-oxadiazoles substituted with 4-fluorophenyl group at C2 position of the pyridine ring. All the final compoundswere synthesized by the oxidative cyclization of the corresponding Schiff base [6, 7] derivatives **5a-e** (**Fig. 1C**) by using chloramine-T as promoter [8]. Author has screened these compounds against *HeLa, MCF7, PANC-1* cell lines (*invitro*anti-proliferative activity). The antiproliferative activity of these novel derivatives of 1,3,4-oxadiazoles revealed that by substituting 4-fluorophenyl groupin C2 position of the pyridine ring increases the total polar surface area and makes the 1,3,4-oxadiazole [9] compounds more water soluble thus the molecule to possess excellent antiproliferative activity [10, 11].



A B C

Fig. 1: Structures of pyridine ring containing 2-(4-fluorophenyl)-3-1,3,4-Oxadiazole derivatives (A); Derivatives of pyridine containing 1,3,4-oxadiazoles moiety having different substitution at second position **(B)**; Intermediate **(6)** Schiff base derivatives of pyridine having 2-(4-fluorophenyl) substation**(C)**.

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EXPERIMENTAL

Materials and Methods: All the 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 using F254 grade silica 60 from Merck.IR spectra was recorded by FTIR 1800 series. Whirlpool microwave(genius) was used for microwave reaction.

Synthesis:

Synthesis of Ethyl 2-chloropyridine-3-carboxylate {2}:

The 2-chloro nicotinic acid **{1}** (10g, 0.0636mol), ethyl alcohol (150mL) and concentrated H_2SO_4 (3-5 drops) were added and refluxed at 80^{0}C for 8 hr. Progress of the reaction was monitored by TLC (Thin layer chromatography) after 8hr, which indicated the completion of the reaction. Ethyl alcohol was concentrated residue was poured over saturated ice cold solution of $NaHCO_3$. Ethyl acetate (25x2mL) was added, washed with brine (10mL) and dried over Na_2SO_4. Ethyl acetate was removed completely under reduced pressure and obtained the colourless liquid. Yield 8.5g, MS-[M+H]- 187; HPLC purity - 96%; TLC-ethyl acetate: hexane (1:9); IR (KBr, cm^{-1}); 2835 (C-H stretching, s), 3026 (C-H stretching, w), 1099 (C-Cl stretching, w), 984 (C-O stretching esters, w); ^{1}H-NMR ($CDCl_3$, 400MHz): δ 1.25 (t, 3H), 3.84 (q, 2H), 7.43(t, 1H), 8.35 (dd, 1H), 8.88 (d, 1H).

Synthesis of ethyl 2-(4-fluorophenyl) pyridine-3-carboxylate {3}:

Ethyl-2-chloropyridine-3-carboxylate (8.5g, 0.0457mol), K_2CO_3 (25.2g, 0.183mol), 4-fluorophenylboronicacid (7.0378g, 0.0502mol), ethanol (100mL) and tetrakis (triphenyl phosphine) palladium (0) (0.263g, 304.8mol) were added and reaction mixture was refluxed at 85^{0}C for 10hr. Progress of the reaction was monitored by TLC after 10 hr, which indicated the completion of the reaction. Ethyl alcohol was removed under reduced pressure residue was extracted with ethyl acetate (20x3mL), washed with brine (10mL) and dried over Na_2SO_4. The crude product was purified by column chromatography using (silica gel 100 to 200mesh), ethyl acetate in hexane (0-15% gradient) as eluent. Yield 4.6g, off white coloured solid; MS-[M+H]-246; M.P-123-128^{0}C; IR (KBr, cm^{-1})- 2935 (C-H stretching, s), 3126 (C-H stretching, w), 1120 (C-O stretching esters, w), 883 (C-F stretching, w); ^{1}H-NMR ($CDCl_3$,

400MHz): δ 0.82 (t, 2H), 3.53 (q, 3H), 7.16 (dd, 2H), 7.66 (q, 2H), 8.67 (m, 1H), 9.11 (q, 2H).

Synthesis of 2-(4-Fluoro-phenyl)-nicotinic acid hydrazide {3}:

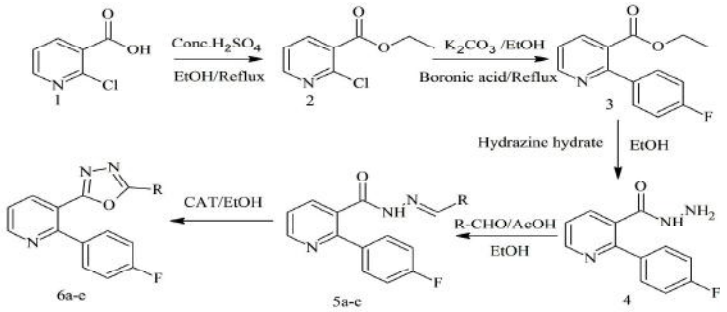
Ethyl-2-(4-Fluorophenyl)pyridine-3-carboxylate **(**4.6g, 0.0186mol) was taken in ethyl alcohol (100mL), hydrazine hydrate (20mL) were added and refluxed at 100°C overnight. Progress of the reaction was monitored byTLC, showed completion of the reaction. Ethyl alcohol was completely removed under reduced pressure, residue was poured over crushed ice and stirred. Precipitates that are separated out was filtered, washed with water (100mL) and dried. Yield 2.3g; white solid; TLC-ethylacetate: Hexane (50:50); MS-[M+1]-231; IR (KBr, cm^{-1}); 2945 (C-H stretching), 3106 (C=Ostretching) 1100 (C-Fstretching), 880 (N-Hstretching); ^{1}H-NMR ($CDCl_3$, 400MHz): δ4.59 (broad s, 2H, *J* = 12.5Hz), 7.29 (dd, 2H), 7.66 (q, 2H, Ar-H), 8.69 (m, 1H), 9.13 (q, 2H).

General procedure for the synthesis of Schiff bases derivatives 5a-e:

To a mixture of 2-(4-Fluoro-phenyl)-nicotinic acid hydrazide and substituted aldehydes **(a-e)** were added with ethyl alcohol (20mL), acetic acid (2-5 drops) and refluxed at 80°C for 2-3hr. progress of the reaction was monitored by TLC, indicated completion of the reaction. Solvent was removed, residue was poured over ice water, precipitates that are separated out was filtered, washed with water (10mL) and dried.

General procedure for the synthesis of 2-(4-Fluorophenyl) substituted pyridine containing 1,3,4-oxadiazoles:

To a mixture of corresponding Schiff base derivatives and chloramine-T (1.1equivalent) were added with ethyl alcohol (10mL) and irradiated with a microwave for 2 minutes. Progress of the reaction was monitored by TLC, showed completion of the reaction. Ethylacetate (25mL× 3) was added, washed with brine (10mL) and dried over sodium sulphate. Ethyl acetate was removed completely and crude product was purified by column chromatography (silica gel 100-200mesh), ethyl acetate in hexane (gradient 0-55%) as eluent.



R –
(a): 2-F-Phenyl; (b):5-(4-fluorophenyl)thiophene-2-yl
(c): 5-(phenyl)thiophene-2-yl
(d): Biphenyl-2-yl
(e):4-(4-fluorophenoxy)-3-methoxy phenyl

Scheme 1: Synthesis of novel derivatives of 2-(4-fluorophenyl) substituted pyridine containing 1, 3, 4-oxadiazole moiety

Analytical data of the 2-(4-fluorophenyl) substituted pyridine containing 1, 3, 4-oxadiazole 6a-e:

2-(4-Fluoro-phenyl)-3-[5-(2-fluoro-phenyl)-[1,3,4]oxadiazol-2-yl]-pyridine (a):

white solid; yield 44%; m.p 178-179^{0}C; ^{1}H-NMR ($CDCl_3$, 400MHz): δ7.104 (t,1H, *J* = 17.2Hz), 7.213 (m, 1H), 7.309 (d, 3H, *J* = 8Hz), 7.483 (m, 2H, *J* = 14.4Hz), 7.713 (dt, 1H, *J* = 16.8Hz, Ar-H), 7.8 (d, 3H, *J* = 8Hz); ^{13}CNMR ($CDCl_3$, 100MHz): 21.6, 77.15, 155.55, 117.15, 119.0, 122.3, 124.805, 126.5, 130.19, 133.9, 139.27, 143.6, 151.9, 157.62, 162.2; IR (KBr,cm^{-1}): (C-H) 2925, (C-H, w) 3346, (C-F) 878, (N-H) 3328, (NH-bending) 1553; MS-(ESI) *m/z*: 336 [M+H]$^+$; Anal. Calculated for$C_{19}H_{11}F_2N_3O$; C, 68.06; H, 3.31; F, 11.33; N, 12.53; O, 4.77; found C, 68.08; H, 3.35; F, 11.34; N, 12.55; O, 4.79.

2-(4-Fluoro-phenyl)-3-{5-[5-(4-fluoro-phenyl)-thiophen-2-yl]-[1,3,4]oxadiazol-2-yl}-pyridine(b):

Yellow solid; yield 53%; m.p 148-149^{0}C; ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.11 (t, 2H, *J* = 8.4Hz), 7.140 (t, 3H, *J* = 8.8Hz), 7.211 (d, 1H, *J* = 4Hz), 7.313 (m, 5H, *J* = 13.6Hz), 7.493 (q, 3H, *J* = 14Hz, Ar-H), 7.575 (q, 3H, *J* = 14Hz), 7.806 (d, 4H, *J* = 8Hz), 8.439 (dd, 1H, *J* = 9.2Hz, *J′* = 1.2Hz); ^{13}CNMR ($CDCl_3$, 100MHz):21.6, 77.16, 114.9, 115.524, 116.499, 118.978, 123.170, 126.52, 128.06, 129.7, 130.894, 135.6, 139.3, 143.6, 148.7, 151.89, 157.38, 162.20; IR (KBr, cm^{-1}) : (C-H) 2915, (C-H, w) 3386, (C-F) 879, (N-H) 3327, (NH-bending) 1543; MS-(ESI) *m/z*: 418 [M+H]$^+$; Anal. Calculated for $C_{23}H_{13}F_2N_3OS$; C, 66.18; H, 3.14; F, 9.10; N, 10.07; O, 3.83; S, 7.68; found C, 66.19; H, 3.15; F, 9.13; N, 10.09; O, 3.84; S, 7.69.

2-(4-Fluoro-phenyl)-3-[5-(5-phenyl-thiophen-2-yl)-[1,3,4]oxadiazol-2-yl]-pyridine(c):

Pale yellow solid; yield 63%; m.p 165-169^{0}C; ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.142 (t, 2H, *J* = 17.2Hz), 7.253 (d, 1H, *J* = 3.6Hz), 7.344 (d, 1H, *J* = 4Hz), 7.373 (d, 1H, *J* = 7.2Hz), 7.425 (t, 2H, *J* = 14.8Hz, Ar-H), 7.504 (q, 3H, *J* = 14Hz), 7.620 (t, 2H, *J* = 8.8Hz), 8.442 (dd, 1H, *J* = 9.6Hz, *J′* = 1.6Hz), 8.856 (d, 1H, *J* = 3.6Hz); ^{13}CNMR ($CDCl_3$, 100MHz): 21.6, 77.15, 115.53, 119.0, 122.8, 123.196, 124.14, 126.428, 129.318, 130.885, 133.0, 135.7, 138.55, 143.65, 149.95, 151.87, 157.440, 162.23, 164.708; IR (KBr, cm^{-1}) : (C-H) 2935, (C-H, w) 3356, (C-F) 868, (N-H) 3310, (NH-bending) 1543; MS-(ESI) *m/z*: 399 [M+H]$^+$; Anal. Calculated for $C_{23}H_{14}FN_3OS$; C, 69.16; H, 3.53; F, 4.76; N, 10.52; O, 4.01; S, 8.03; found C, 69.17; H, 3.54; F, 4.77; N, 10.55; O, 4.02; S, 8.06.

3-(5-Biphenyl-2-yl-[1,3,4]oxadiazol-2-yl)-2-(4-fluoro-phenyl)-pyridine(d):

Off white solid; yield 73%; m.p 144-145^{0}C; ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.053 (t, 1H, *J* = 17.2Hz), 7.197 (q, 1H, *J* = 9.6Hz), 7.31 (d, 5H, *J* = 8Hz), 7.347 (t, 2H, *J* = 5.6Hz), 7.60 (m, 1H, *J* = 18Hz, Ar-H), 7.81 (d, 6H, *J* = 8Hz), 8.762 (dd, 1H, *J* = 6.4Hz, *J′*= 1.6Hz); ^{13}CNMR ($CDCl_3$, 100MHz): 21.6, 77.15, 115.4, 118.97, 122.2, 126.5, 127.7, 128.61, 129.8, 130.5, 131.34, 138.28, 139.2, 140.5, 142.3, 143.6, 151.5, 157.49, 163.4, 165.5; IR (KBr, cm^{-1}) : (C-H) 2925, (C-H, w) 3326, (C-F) 888, (N-H) 3320, (NH-bending) 1543; MS-(ESI) *m/z*: 394 [M+H]$^+$; Anal. Calculated for $C_{25}H_{16}FN_3O$; C, 76.32; H, 4.10; F, 4.83; N, 10.68; O, 4.07; found C, 76.34; H, 4.12; F, 4.86; N, 10.69; O, 4.09.

3-{5-[3-(4-Fluoro-phenoxy)-4-methoxy-phenyl]-[1,3,4]oxadiazol-2-yl}-2-(4-fluoro-phenyl)-pyridine(e):

White solid; yield 59%; m.p 167-169^{0}C; ^{1}H-NMR ($CDCl_3$, 400MHz): δ 6.824 (d, 1H, *J* = 8.4Hz), 6.975 (q, 2H, *J* = 13.6Hz), 7.048 (t, 2H, *J* = 17.2Hz), 7.128 (t, 2H, *J* = 17.2Hz), 7.219 (dd, 1H, *J* = 10Hz, J′= 2Hz, Ar-H), 7.316 (d, 1H, *J* = 8Hz), 7.497 (m, 3H, *J* = 22.8Hz), 7.812 (d, 1H, *J* = 8.4Hz), 8.488 (dd, 1H, *J* = 9.6Hz, *J′* = 1.6Hz), 8.852 (t, 1H, *J* = 4.8Hz); ^{13}CNMR ($CDCl_3$, 100MHz): 20.83, 34.81, 56.28, 77.16, 110.6, 115.48, 116.61, 118.821, 119.20, 120.36, 122.507, 126.615, 129.84, 130.941, 136.06, 138.5, 143.72, 151.9, 160.524; IR (KBr, cm^{-1}): (C-H) 2915, (C-H, w) 3336, (C-F) 879, (N-H) 3345, (NH-bending) 1543; MS-(ESI) *m/z*: 458 [M+H]$^+$; Anal. Calculated for $C_{26}H_{17}F_2N_3O_3$; C, 68.27; H, 3.75; F, 8.31; N, 9.19; O, 10.49; found C, 68.28; H, 3.76; F, 8.32; N, 9.20; O, 10.51.

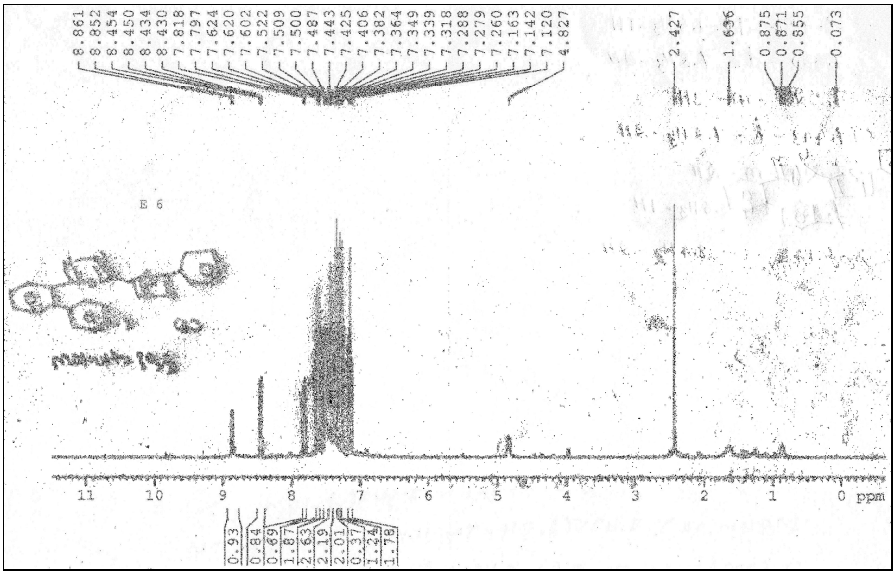


Fig. 2: [1]H-NMR spectra of most potent compound 6(c)

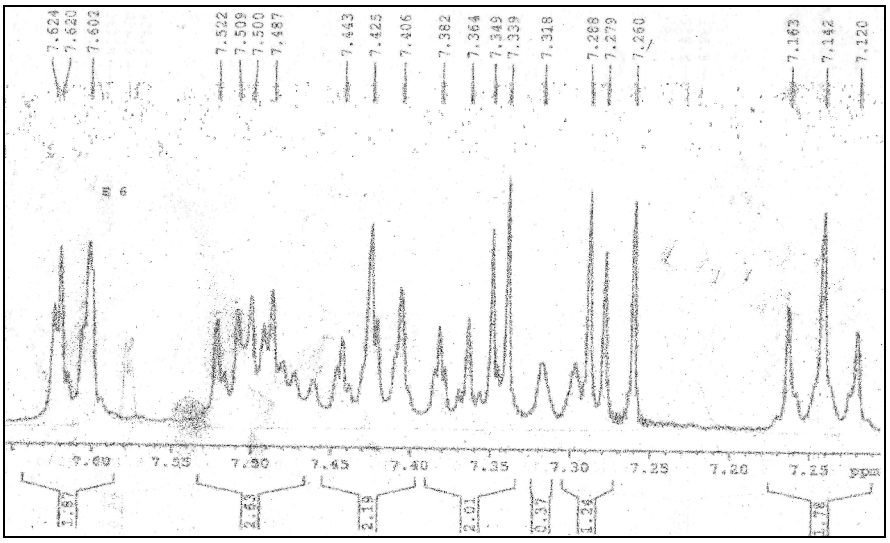


Fig. 3: [1]H-NMR spectra of most potent compound aromatic region expansion 6(c)

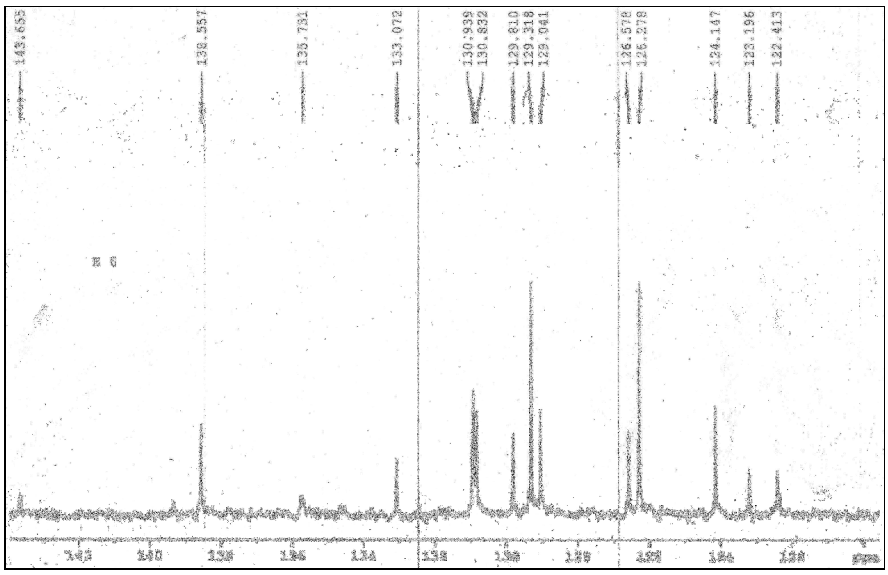


Fig. 4: [13]CNMR spectra of the most potent compound 6(c)

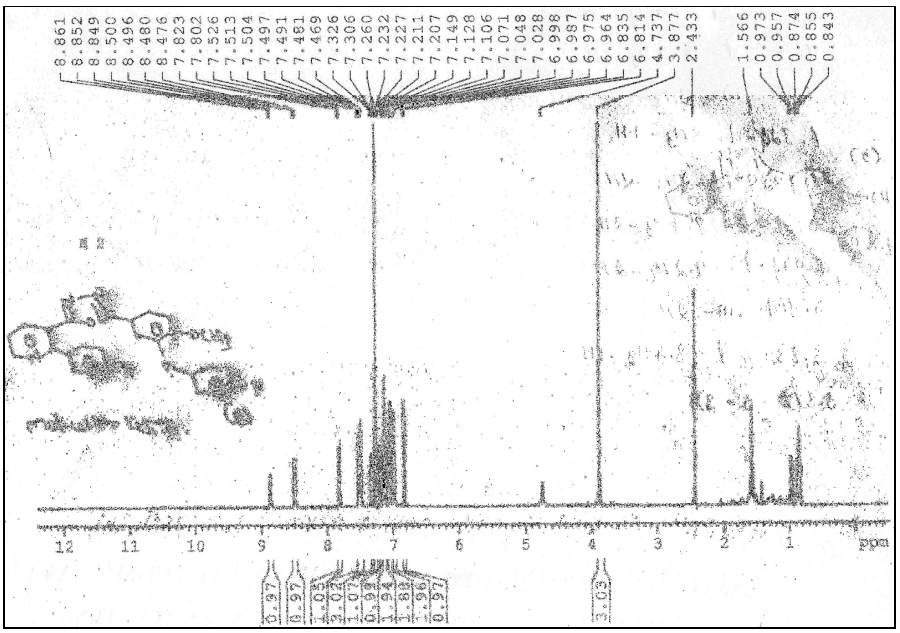


Fig. 5: ^{1}H-NMR spectra of the most potent compound 6(e)

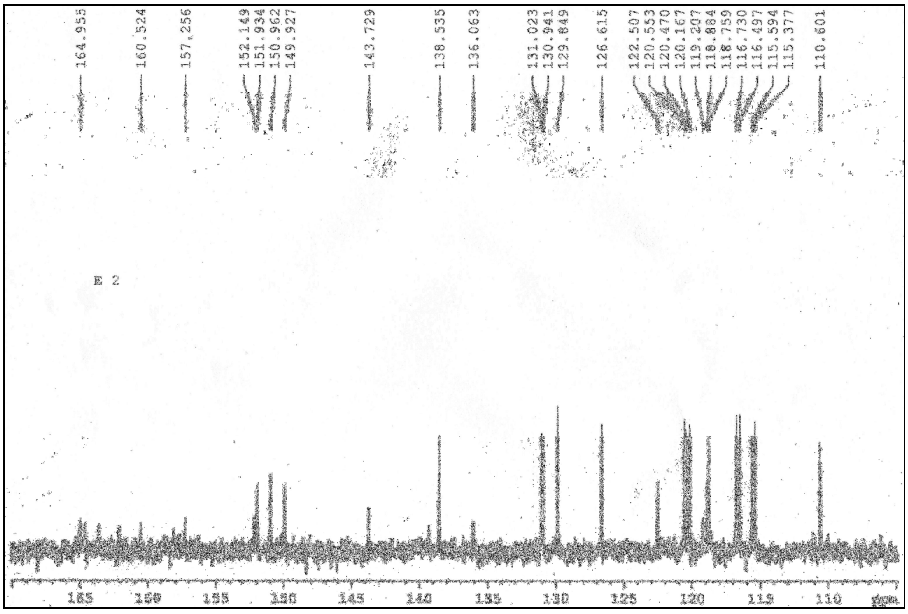


Fig. 6: ^{13}CNMR spectra of the most potent compound 6(e)

Table No. 1: IC_{50} values novel 2-(4-fluoro phenyl) substituted derivatives of 1, 3, 4-oxadiazoles

IC_{50} values of the novel derivatives of 2-(4-Fluorophenyl) substituted pyridine containing 1, 3, 4-oxadiazole: 6a-6e			
Compounds	***HeLa* (µM)***	***MCF7*(µM)***	***PANC-1*(µM)***
6a	190.2	24.7	18.2
6b	112.9	76.9	43.8
6c	275.4	68.9	**6.8[1]**
6d	187.6	21.9	56.3
6e	89.9	**8.9**	28.2
5-FU	7.6	6.8	8.3

5-FU: 5-fluorouracil (standard); IC_{50}: Inhibitory concentration of the compound at 50% of the cells.*Average values of the mean of the experiment, n = 4.

Cytotoxic Evaluation:

MTT assay and Anti proliferative activity:

The *invitro* anti-proliferative study was carried out at genelon institute of life sciences. Three human carcinoma cell lines were used namely, *HeLa*, *MCF-7* and *PANC-1*. All the cell lines were procured form NCCS, Pune, India and were grown in DMEM-HG supplemented with 10% heat-inactivated FBS, 2% Penicillin-Streptomycin and 2.5 µg/mL, Amphotericin-B solution (All from HI Media Labs, Mumbai, India).Cell lines were incubated at 37°C in a humidified atmosphere of 95% air, 5% CO_2. The adherent cells were detached using Trypsin-EDTA solution (HI Media Labs, Mumbai, India) after 48hr of incubation. Cell count was done using the Luna automated cell counter (Logos Biosystems, India) based on trypan blue dye exclusion method. Cytotoxicity of the novel 1, 3, 4-oxadiazole compounds **6a-e**have been determined using MTT 3-(4, 5-Dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide) assay.

Cell Viability Assay (MTT Assay): The MTT assay was carried out in Genelon Institute of Life Sciences Pvt. Ltd. 200µL cell suspension was seeded in 96-well microplates (Corning®, USA**)** at a density of 25,000 cells/well and incubated for 24hr, all cells were seeded in duplicates with novel compounds **6a-e** 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 hr.The culture medium was then aspirated and 200µL dimethyl sulfoxide (DMSO; Sigma-Aldrich, India) was added. 5-Fluorouracil was used as standard. 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 using the formula as [% cell viability = (A_{570} of treated cells / A_{570} of control cells) ×100%].

RESULTS AND DISCUSSION

Chemistry: The novel derivatives of 1,3,4-oxadiazole compounds were synthesized and studied for their *invitro* anticancer properties against *HeLa*, *MCF7* and *PANC-1* cell lines. Synthetic chemistry involved the conversion of 2-chloronicotinic acid [11, 12] (IR absorbance at 1187 cm^{-1}) into 2-chloronicotinic ethyl ester (IR absorbance 1120 cm^{-1}) **(2)**. 2-chloronicotinic acid ethyl ester was coupled with 4-fluorophenyl boronic acid and obtained ethyl 2-(4-fluorophenyl)pyridine-3-carboxylate [12, 13]. Ethyl 2-(4-fluorophenyl)pyridine-3-carboxylate was further converted into carbohydrazide **(4)** by refluxing with hydrazine hydrate [13, 14]. The carbohydrazide was reacted with different aldehydes **(a-e)** in presence of acetic acid and obtained corresponding Schiff base derivatives **5a-e**. The novel Schiff bases [15, 16] were cyclized using Chloramine-T as promoter and obtained the potent 1,3,4-oxadiazole derivatives **6a-e.**

In this work author synthesized pyridine containing1,3,4-oxadiazole derivatives and screened for their*invitro* cytotoxicity.Various derivatives of pyridine containing 1,3,4-oxadiazole ring possessesexcellent biological activities. Introducing 4-fluoro phenyl group at the C2 position of the pyridine ring enhances the water solubility of the 1,3,4- oxadiazole derivatives and increases the total polar surface area.

b) Biology: All the test compounds were screened for *invitro* cytotoxic evaluation on *HeLa*, *MCF7* and *PANC-1* cell lines and obtained the IC_{50} values. The cytotoxicity of the compounds **6(a)** and **6(d)** against *MCF7* cell line with IC_{50} of 24.7µM and 21.9µM respectively. The cytotoxicity of the compounds **6(c) (Fig. 2 & 3)** and **6 (e) (Fig. 5)** against *PANC-1* and *MCF7* cell lines with IC_{50} of 6.8µM and 8.9µM which is comparable with the cytotoxicity of the known standard 5-fluorouracil. Compound **6(a)** showed moderate cytotoxicity of 18.2µM against *PANC-1* cell line.

CONCLUSION

The synthesized 1, 3, 4-oxadiazoles showed moderate cytotoxicity on *MCF7* and *PANC-1* cell lines. In this series the compounds **6(a)** and **6(d)** showed moderatecytotoxicity on *MCF7* and *PANC-1* cell linewith IC_{50} of 24.7µMand 21.9µM respectively.The compounds **6(c) (Fig 2 & 3)** and **6(e) (Fig. 5&6)** showed grater cytotoxicity on*PANC-1* and *MCF7* cell lines with IC_{50} of 6.8µM and 8.9µM which is comparable with the cytotoxicity of the known standard 5-fluorouracil. Further screening of these compounds on other carcinoma cell lines and apoptosis mechanism were in progress.

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