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Synthesis, characterization and cytotoxic evaluation of novel derivatives of 1-[2-(aryl substituted)-5-(4'-Fluoro-3-methyl biphenyl-4-yl)-[1, 3, 4] oxadiazole-3-yl]-ethanone

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ABSTRACT

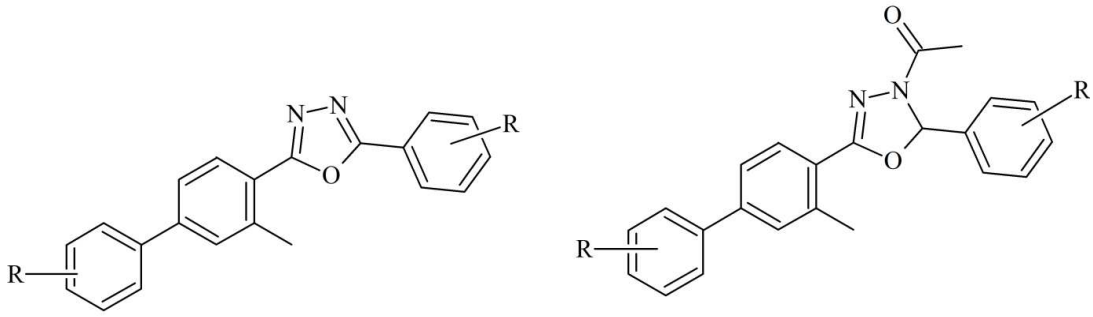
*A series of novel derivatives **6a-6f** of 1, 3, 4-oxadiazole compounds have been synthesized and characterized by ^{1}HNMR, ^{13}CNMR, LCMS and elemental analysis. Synthesis of these novel ethanone derivatives have been synthesized by the 4'-fluoro-3-methylbiphenyl-4-carbohydrazide **4**. The 4'-fluoro-3-methylbiphenyl-4-carbohydrazide was reacted with various aldehydes **(a-f)** in presence of a catalytic amount of acetic acid and obtained the novel Schiff base compounds**5a-5f**. The Schiff base compounds **5a-5f** was acetylated by refluxing with acetic anhydride and obtained the corresponding final derivatives **6a-6f**. All these compounds were screened for their MTT assay on three human carcinoma cell lines, namely HeLa, HepG2 and Caco-2. The antiproliferative activity of these 1, 3, 4-oxadiazole compounds showed good cytotoxicity on Caco-2 cell line. The standard used for the experiment was 5-Fluorouracil and the cytotoxicity of the synthesized compounds was compared with the cytotoxicity exhibited by the standard. Among the synthesized compounds,**6a**and **6e** showed good cytotoxicity on Caco-2 cell line having IC_{50} of**6.3µM** and **4.4µM** respectively. Compounds **6a**, **6b**, **6c** and **6f** showed mild cytotoxicity on all the three cell lines.*

Key words: *Caco-2*, 1, 3, 4-oxadiazole, MTT assay, Anticancer, Acetic anhydride.

INTRODUCTION

The synthesis of novel derivatives of 1,3,4-oxadiazoles **6a-6f**has been prepared on the basis of the fact that 1,3,4-oxadiazoles known from decades a potential molecule possessing various biological properties such as anti-inflammatory[1, 2], antibacterial [3, 4], antituberculer [4]and anticancer [5]. In this research work author has synthesized the novel ethanone derivatives of 1, 3, 4-oxadiazole derivatives (**Figure 1, A**) envisaging that these derivatives showed various biological properties. The biologicalproperties possessed by these novel ethanone derivatives (**Figure 1, B**) include, these 1, 3, 4-oxadiazole compounds have been synthesized by linear synthetic methods the starting material for this synthesis was 4-brormo-2-methyl benzoic acid which is converted into corresponding ester **2**. The ester **2** was treated with 4-fluoro phenyl boronic acid in presence of tetrakis (triphenyl phosphine) palladium (0) to obtain the compound **3**[5, 6].The compound **3** was converted into reactive intermediate carbohydrazide **4** by treating with hydrazine hydrate by refluxing in ethanol. Thus obtained carbohydrazide was reacted with various aldehyde **a-f** in presence of acetic acid as catalyst to get the novel Schiff base derivatives [7, 8]. The Schiff base compounds [8] were refluxed in acetic anhydride yielded the novel ethanone derivatives(**Figure 1, B**) of 1, 3, 4-oxadiazoles **6a-6f**. Intotal six derivatives have been synthesized and evaluated their antiproliferative

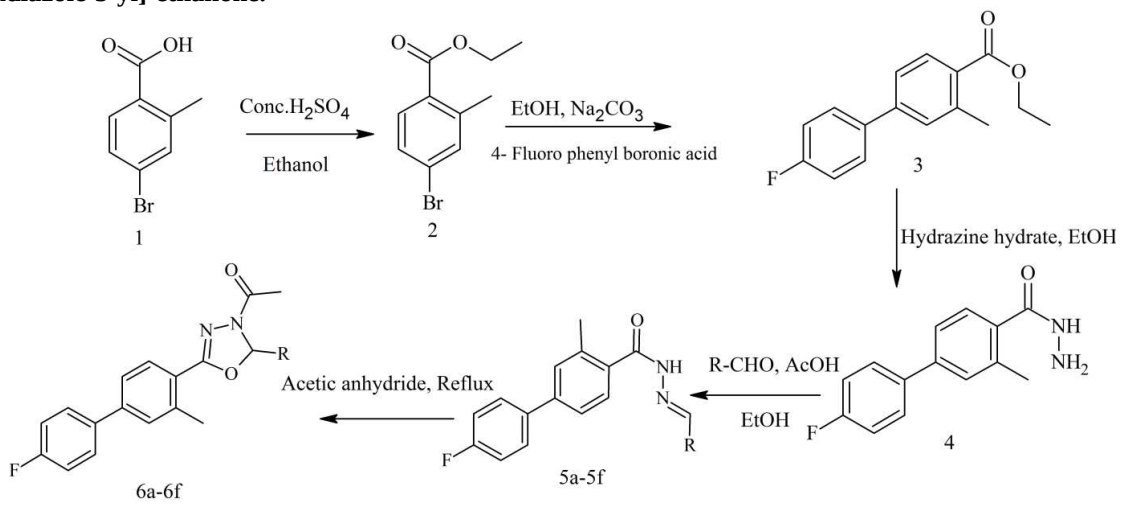
activity [9, 10] on *HeLa*, *HepG2* and *Caco-2* cell line.Most of the compounds in this series showed mild cytotoxicity[10] on all the three cell line but, two compounds**6a** and **6e** showed good cytotoxicity on *Caco-2* cell line having IC_{50} of**6.4µM** and **4.4µM** respectively.



(A) **(B)**

Figure 1: Structures of the 1, 3, 4-oxadiazole containing biphenyl ring system (A); structures of various derivatives of biphenyl substituted 1, 3, 4-oxadiazole ethanone ring (B)

Scheme 1: Synthesis of novel derivatives of 1-[2-(Aryl substituted)-5-(4'-fluoro-3-methyl biphenyl-4-yl)-[1, 3, 4] oxadiazole-3-yl]-ethanone.



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:

Step 1. Synthesis of ethyl 4-bromo-2-methylbenzoate 2:

4-bromo-2-methylbenzoic acid**1**(10g, 0.0465mol) was taken in a 1L single necked round bottom flask, 200mL of ethanol and 10 mL of concentrated H_2SO_4 were added, reaction mixture was refluxed for 6 hr. TLC (Thin layer chromatography) was monitored to check the completion of the reaction. Solvent was evaporated and the residue was neutralized with 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 colourless needles. Yield 8.4g, MS-[M+H]- 216; HPLC purity = 98%; TLC-ethyl acetate: hexane (1:9); IR(KBr), νmax/cm^{-1}: 550, 980, 1089, 1650, 2845, 3006 ; ^{1}HNMR ($CDCl_3$, 400MHz) : δ1.18(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).

Step 2: Synthesis of ethyl 4'-fluoro-3-methylbiphenyl-4-carboxylate 3:

Ethyl 4-bromo-2-methylbenzoate(8.4g, 0.0390mol), Na_2CO_3 (12.402g, 0.117mol), 4-fluoro phenyl boronic acid (6.552g, 0.0468mol), tetrakis (triphenyl phosphine) palladium (0) (0.225g, 1.9480mol) were refluxed in 150mL of ethanol for 10h. TLC was monitored to check the completion of the reaction, after completion, the solvent was evaporated, aqueous was extracted with ethyl acetate (35mL x3), washed with brine (25mL) and dried over Na_2SO_4.

Ethyl acetate was evaporated to yield brown semisolid. The crude product was purified by column chromatography using silica gel (100 to 200mesh), gradient (0-25%) ethyl acetate in hexane as the eluent. Yield 4.8g, off white coloured solid ; ms(ESI) *m/z*: [M+H]-271; m.p-145-148^{0}C; IR(KBr),νmax/cm^{-1} : 1130, 1645, 2965, 3126, 3345 ; ^{1}H-NMR($CDCl_3$, 400 MHz) : δ0.9(t, 2H), 2.6(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).

Step 3: Synthesis of 4'-fluoro-3-methylbiphenyl-4-carbohydrazide 4:
Ethyl 4'-fluoro-3-methylbiphenyl-4-carboxylate**(**4.8g) was taken in a 250mL single necked round bottom flask added with excess (25mL) of hydrazine hydrate and refluxed in 100mL of ethanol overnight. TLC was monitored to check the completion of the reaction, solvent was completely removed under reduced pressure and 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 2.4g; white solid; TLC-ethyl acetate: Hexane (50:50); m.p -162-164°C; MS (ESI) *m/z*: [M+H]-257; IR (KBr), νmax/cm^{-1}; 1100, 1679, 2979, 3129, 3179, 3386; ^{1}H-NMR($CDCl_3$, 400MHz) δ1.15(s, CH_3, 3H), 4.64(bs, 2H, NH_2), 7.39(dd, *J* 12.8Hz, 2H), 7.58(q, 2H), 8.78(m, *J* 8.5Hz, 1H), 9.23(q, 2H).

General procedure for the synthesis of Schiff base compounds 5a-5f:
The different substituted aldehydes **(a-f)** and key intermediate carbohydrazide **4**were taken in a 100 mL single necked RB flask to this 25mL of ethanol and 5-8 drops of acetic acid were added and RM was refluxed for 3-5h.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 are separated out was filtered, washed with water (50mL) and dried. These compounds were pure enough to carry over to the next step.

General procedure for the synthesis of novel derivatives of 1-[2-(Aryl substituted)-5-(4'-fluoro-3-methyl biphenyl-4-yl)-[1, 3, 4] oxadiazole-3-yl]-ethanone.6a-6f.
The corresponding Schiff base derivatives **5a-5f** were taken in 100 mL single necked RB flask to this acetic anhydride was added and RM was refluxed for 2-4h. TLC was monitored to check the completion of the reaction. After the completion solvent was removed completely under reduced pressure, residue was added with ice cold water and product was extracted with ethyl acetate (25mL ×3), washed with 10% $NaHCO_3$ solution, washed with brine (10mL) and dried over Na_2SO_4 and concentrated. The all the final compounds **6a-6f**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 1-[2-(Aryl substituted)-5-(4'-fluoro-3-methyl biphenyl-4-yl)-[1, 3, 4] oxadiazole-3-yl]-ethanone: 6a-6f
1-[5-(4'-Fluoro-3-methyl-biphenyl-4-yl)-2-(2-fluoro-phenyl)-[1,3,4]oxadiazol-3-yl]-ethanone (**6a**):
R = 2-Fluoro Benzaldehhyde
White coloured solid; yield 54.8% ; m.p -165-168^{0}C; IR (KBr), ν_{max}/cm^{-1} : 1123, 1642, 2936, 3347, 2764, 3325; ^{1}H-NMR($CDCl_3$, 400MHz): δ1.05(s, CH_3, 3H), 2.2(S, 3H), 6.7(s, 1H), 7.13(dd, *J* 8.5Hz, 2H), 7.32(m, 3H), 7.56(m, *J* 7.2Hz, 2H), 7.7(dd, *J* 12.4Hz, 2H), 8.9(dd,*J* 12.5Hz, 1H); ^{13}C NMR($CDCl_3$, 100MHz): 114.5, 115.5, 123, 124, 128.5, 130, 134, 136.5, 150, 159, 163, 177; molecular formula $C_{23}H_{18}F_2N_2O_2$; MS: (ESI) *m/z*:[M+H]- 393; HPLC 94.4% ;anal. Calculated for $C_{23}H_{18}F_2N_2O_2$; C, 70.40; H, 4.62; F, 9.68; N, 7.14; O, 8.15; Found C, 70.41; H, 4.63; F, 9.69; N, 7.15; O, 8.16.

1-[2-(4'-Fluoro-biphenyl-3-yl)-5-(4'-fluoro-3-methyl-biphenyl-4-yl)-[1,3,4]oxadiazol-3-yl]-ethanone (**6b**):
R = 4-Fluoro biphenyl 3-aldehyde
Yellow coloured solid; yield 68.7% ; m.p -183-184^{0}C; IR (KBr), ν_{max}/cm^{-1} : 780,1128, 1660, 2955, 3376, 2785, 3340; ^{1}H-NMR($CDCl_3$, 400MHz): δ 0.8 (s, CH_3, 3H), 2.3(s, CH_3, 3H), 6.45(s, 1H), 7.25(dd, *J* 12.5Hz, 2H), 7.35(dd, 2H), 7.7(m, *J* 7.2Hz, 3H), 7.8(m, *J* 12.4Hz, 3H), 8.05(dd, *J* 7.5Hz, 2H), 8.1(dd, *J* 7.6, 2H); ^{13}C NMR ($CDCl_3$, 100MHz): 65, 114.5, 116, 123, 125, 127, 128.5, 129, 134, 137, 141, 150, 159, 162, 163, 177; molecular formula $C_{29}H_{22}F_2N_2O_2$; MS: (ESI) *m/z*:[M+H]-469; HPLC 94.7% ; anal. Calculated for $C_{29}H_{22}F_2N_2O_2$; C, 74.35; H, 4.73; F, 8.11; N, 5.98; O, 6.83; Found C, 74.36; H, 4.74; F, 8.12; N, 5.99; O, 6.84.

1-[2-Biphenyl-2-yl-5-(4'-fluoro-3-methyl-biphenyl-4-yl)-[1,3,4]oxadiazol-3-yl]-ethanone (6c):
R = 2-Biphenyl 3-aldehyde
Off white coloured solid; yield 67.8%; IR (KBr), ν_{max}/cm^{-1} : 768, 1215, 1632,2786, 2856, 3350, 3356; ^{1}H-NMR($CDCl_3$, 400MHz): δ 0.8 (s, CH_3, 3H), 2.32(s, CH_3, 3H), 6.45(s, 1H), 7.2(dd, *J* 12.5Hz, 2H), 7.6(m, 3H), 7.7(m, 3H), 7.8(m, *J* 12.4Hz, 3H), 8.15(dd, *J* 7.5Hz, 2H), 8.8 (dd, J 7.6, 2H), 9.1(dd, 1H); ^{13}C NMR($CDCl_3$, 100MHz): 65, 90, 114.5, 122.5, 127.5, 128.5, 129, 134, 136.5, 150.5, 159, 162, 177; molecular formula $C_{29}H_{23}FN_2O_2$; MS: (ESI) *m/z*:[M+H]- 451; HPLC 95.2% ; anal. Calculated for $C_{29}H_{23}FN_2O_2$; C, 77.32; H, 5.15; F, 4.22; N, 6.22; O, 7.10; Found C, 77.33; H, 5.16; F, 4.23; N, 6.23; O, 7.11.

1-[2-(2,5-Dimethoxy-phenyl)-5-(4'-fluoro-3-methyl-biphenyl-4-yl)-[1,3,4]oxadiazol-3-yl]-ethanone (6d): R = 2, 5-Dimethoxy benzaldehyde

White coloured solid; yield 66%; m.p- 124-126°C ; IR (KBr), ν_{max}/cm^{-1} : 812, 1235,1742,1890, 2287, 2815, 2935, 3255, 3396; ^{1}H-NMR($CDCl_3$, 400MHz): δ1.11 (s, CH_3, 3H),2.2(s, 3H), 2.6(s, OCH_3, 6H), 6.7(s, 1H), 7.05(m, *J* 12.5Hz, 3H), 7.11(dd, 2H), 7.6(t, *J* 7.2Hz, 2H), 7.75 (dd, *J* 12.4Hz, 2H), 8.9(dd, *J* 7.5Hz, 1H); ^{13}C NMR ($CDCl_3$, 100MHz): 19, 65, 90, 114.5, 115, 122.5, 128.5, 134, 136, 150, 152, 159, 163, 177; molecular formula $C_{25}H_{23}FN_2O_4$ MS: (ESI) *m/z*:[M+H]- 435; HPLC 96% ;anal. Calculated for $C_{25}H_{23}FN_2O_4$; C, 69.11; H, 5.34; F, 4.37; N, 6.45; O, 14.73; Found C, 69.12; H, 5.35; F, 4.38; N, 6.46; O, 14.74.

1-{5-(4'-Fluoro-3-methyl-biphenyl-4-yl)-2-[5-(4-fluoro-phenyl)-thiophen-2-yl]-[1,3,4]oxadiazol-3-yl}-ethanone (6e): R = 4-Fluoro-phenyl)-thiophen-2-aldehyde

Pale yellow coloured solid; yield 56.9%; m.p- 152-156°C ; IR (KBr), ν_{max}/cm^{-1} : 776, 987, 1235, 1716, 1920, 2887, 2824, 2945, 3256, 3396; ^{1}H-NMR($CDCl_3$, 400MHz): δ 0.8 (s, CH_3, 3H), 2.3(s, CH_3, 3H), 6.4(s, 1H), 7.2(dd, *J* 12.5Hz, 2H), 7.3(dd, J 7.12, 2H), 7.6(dd, *J* 7.2Hz, 2H), 7.7(t, *J* 12.4Hz, 3H), 7.8(m, 3H), 9.03 (dd, 2H); ^{13}C NMR ($CDCl_3$, 100MHz): 90, 114.5, 116, 122.5, 128.5, 129, 134, 136, 137, 150, 159, 162,163, 177; molecular formula $C_{27}H_{20}F_2N_2O_2S$;MS: (ESI) *m/z*:[M+H]- 475; HPLC 96% ;anal. Calculated for $C_{27}H_{20}F_2N_2O_2S$; C, 68.34; H, 4.25; F, 8.01; N, 5.90; O, 6.74; S, 6.76; Found C, 68.35; H, 4.26; F, 8.02; N, 5.91; O, 6.75; S, 6.77.

1-[5-(4'-Fluoro-3-methyl-biphenyl-4-yl)-2-(5-phenyl-thiophen-2-yl)-[1,3,4]oxadiazol-3-yl]-ethanone (6f): R = 5- Phenyl thiophene-2-carboxaldehyde

Yellow coloured solid; yield 76%; m.p- 172-176°C ; IR (KBr), ν_{max}/cm^{-1} : 785, 1235, 1768, 2886, 2935, 3256, 3396; ^{1}H-NMR($CDCl_3$, 400MHz):): δ 0.8 (s, CH_3, 3H), 2.3(s, CH_3, 3H), 6.42(s, 1H), 7.25(dd, *J* 12.5Hz, 2H), 7.45(dd, J 7.12, 2H), 7.6(dd, *J* 7.2Hz, 2H), 7.7(m, *J* 12.4Hz, 4H), 8.05(dd, J 12.6, 2H), 9.1(dd, J 11.8, 2H); ^{13}C NMR($CDCl_3$, 100MHz): 90, 114.5, 122.5, 125, 126, 127.5, 128.5, 134, 136, 137, 141.5, 150, 159, 162, 163, 177; molecular formula $C_{27}H_{21}FN_2O_2S$ MS: (ESI) *m/z*:[M+H]- 457; HPLC 96% ;anal. Calculated for $C_{27}H_{21}FN_2O_2S$; C, 71.03; H, 4.64; F, 4.16; N, 6.14; O, 7.01; S, 7.02; Found C, 71.04; H, 4.65; F, 4.17; N, 6.15; O, 7.02; S, 7.03.

Table 2: **IC_{50} and CC_{50} values of the novel1-[2-(Aryl substituted)-5-(4'-fluoro-biphenyl-4-yl)-[1, 3, 4] oxadiazole-3-yl]-ethanone**

Compounds	IC_{50} and CC_{50} values of 1, 3, 4-oxadiazoles in µM		
	HeLa	*HepG2*	*Caco-2*
6a	34.4(68.9)	64.6(54.8)	**6.4(55.7)**
6b	49.8(68.9)	55.6(56.8)	38.2(36.7)
6c	47.5(53.3)	78.9(>100)	15.5(>200)
6d	29.8(55.8)	45.08(44.4)	66.8(32.2)
6e	43.6(>100)	23.2(29.4)	**4.4(45.6)**
6f	44.5(65.6)	23.4(56.7)	77.6(123.5)
5-FU	7.8(48.9)	6.9(36.8)	8.2(45.8)

IC_{50}- The concentration that induces 50% of the growth inhibition as compared to untreated cells. CC_{50}- The concentration of the 50% of the remaining cells after inhibition. 5-FU- 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 *HeLa*, *HepG2* and *Caco-2*. 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 ethanone derivatives 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-6f.** Having range of concentrations from 50µM-500µM, inαubated 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 DISCUSSION

Chemistry (Scheme 1): The synthetic chemistry of novel ethanone derivatives of 1, 3, 4-oxadiazole compounds started with the synthesis ofethyl 4-bromo-2-methylbenzoate **2** which is coupled with 4-fluoro phenyl boronic acid(Suzuki coupling).The introduction of the 4-fluoro phenyl boronic acid increases the Log-P as well as TPSA of the 1,3,4-oxadiazole molecules. The intermediate **3** was reacted with hydrazine hydrate in presence of ethanol solvent and obtained the corresponding carbohydrazide **4**. The key intermediate4'-fluoro-3-methylbiphenyl-4-carbohydrazide was reacted with various substituted aldehydes **a-f** in presence of a catalytic amount of acetic acid, obtained a series of novel Schiff base derivatives **5a-5f**. The reactive novel Schiff base derivative**5a-5f** was refluxed in acetic anhydride and yielded a series of novel derivatives of 1-[2-(Aryl substituted)-5-(4'-fluoro-3-methyl biphenyl-4-yl)-[1, 3, 4] oxadiazole-3-yl]-ethanone [11, 12]. Author envisaged that by introducing 4-fluoro phenyl boronic acid group at the second position of the pyridine ring may enhance the Log-P and TPSA values of 1, 3, 4-oxadiazoles [12, 13] and thus increasing the more bioavailability of the novel ethanone derivatives of 1, 3, 4-oxadiazole compounds [13].

SAR: Structural Activity Relationship: Studies related to SAR of these 1, 3, 4-oxadiazole ethanone derivatives showed that the substitution of different aryl derivatives in the oxadiazole ring enhances the water solubility and thereby more bio available molecules. By introducing the 4-fluoro phenyl group at the para position and constructing biphenyl ring enhances further the Log-P values as well as increases the TPSA of the molecules. Author envisaged that by coupling different aldehydes and cyclizing and acetylating to yield the different novel derivatives of 1, 3, 4-oxadiazole ethanone moiety [13] 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-6f** have been screened for cytotoxicity [13] on three different human leukemic cell lines to obtain the IC_{50} and CC_{50} of the molecules. The cancer cell lines used was *HeLa*, *HepG2* and *Caco-2*. The MTT assay of the novel 1, 3, 4-oxadaizoles [13] have been screened for these cell lines and obtained the interesting data (**Table1**). Compound **6a**and **6e** showed greater cytotoxicity on *Caco-2*cell lines having IC_{50} of **6.4µM** and **4.4µM** respectively. Rest all the compounds showed moderate cytotoxicity as in the (**Table 1**).

CONCLUSION

In this research author has synthesized six novel derivatives of 1, 3, 4-oxadiazole and screened for MTT assay. Compound **6a**and **6e** showed good antiproliferative activity on *Caco-2*cell lines having IC_{50}**6.4µM** and **4.4µM** of respectively. The obtained IC_{50} values are better than the one obtained with the standard 5-FU. The compounds **6a** and **6e** can act as potent compound for the antiproliferative activity. The remaining compounds showed moderate to low cytotoxicity on all the three cell lines as compared with the standard 5-FU.

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