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Research Article

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 1,3,4-oxadiazole derivatives **6a-6f** have been synthesized and characterized by ^{1}H-NMR, ^{13}CNMR, LCMS and elemental analysis. The key intermediate compound4'-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** wereacetylated by refluxing with acetic anhydride and obtained the final derivatives **6a-6f**. All these compounds were evaluated for their MTT assay on three human cancer cell lines namely, *HeLa*, *HepG2* and *Caco-2*. The antiproliferative activity of 1, 3, 4-oxadiazole compounds showed good cytotoxicity on *Caco-2* cell line. 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.

Keywords: *Caco-2*, 1, 3, 4-oxadiazole, MTT assay, Anticancer, Acetic anhydride

1. Introduction

The synthesis of novel derivatives of 1,3,4-oxadiazoles **6a-6f**has been synthesized on the basis of the fact that 1,3,4-oxadiazoles known from decades as a potential molecule possessing various biological properties such as anti-inflammatory[1,2], antibacterial[3,4], antitubercular [4] and anticancer[5]. In this research work author has synthesized the novel ethanone derivatives of 1, 3, 4-oxadiazole compounds (Figure 1, A).The 1, 3, 4-oxadiazole compounds have been synthesized by linear synthetic method the starting material for this synthesis was 4-brormo-2-methyl benzoic acid which is converted into corresponding ester **2**. The ester **2** was reacted with 4-fluoro phenyl boronic acid in presence of tetrakis (triphenyl phosphine) palladium (0) and 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**. In total 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.

2. 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.

2.1Synthesis:

2.1.1. 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 h. TLC (Thin layer chromatography) was monitored showed completion of the reaction. Solvent was evaporated and the residue was neutralized with 10% $NaHCO_3$ solution. Aqueous was extracted with ethyl acetate (35x2mL), 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}H-NMR ($CDCl_3$, 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).

2.1.2. 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. After completion, the solvent was evaporated, aqueous was extracted with ethyl acetate (35x3mL), 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).

2.1.3. 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-

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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).

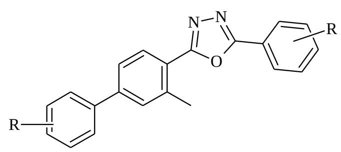
2.1.4. General procedure for the synthesis of Schiff base compounds 5a-5f:

To a mixture of various substituted aldehydes **(a-f)** and the 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. After completion solvent was removed under reduced pressure. Ice cold water was added to the residue and the precipitates that are separated out was filtered, washed with water (50mL) and dried.

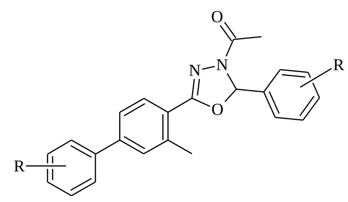
2.1.5. General procedure for the synthesis of novel derivatives of 1-[2-(Aryl substituted)-5-(4'-fluoro-3-methyl biphenyl-4-yl)-[1, 3, 4] oxadiazole-3-yl]-ethanone.6a-6f.

The corresponding various Schiff base derivatives **5a-5f** were reacted with 5-10mL acetic anhydride and reaction mixture was refluxed for 2-4h. TLC was monitored to check the completion of the reaction. After completion, solvent was removed completely under reduced pressure, residue was added with ice cold water and product was extracted with ethyl acetate (25×3), washed with 10% $NaHCO_3$ solution, washed with brine (10mL) and dried. All the final compounds **6a-6f** was purified by column chromatography using silica gel 100-200mesh. Eluent started with 100% n-hexane and polarity was increased to 80% using ethyl acetate.

2.1.6. 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).



(A)



(B)

2.3 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

2.3.1.*1-[5-(4'-Fluoro-3-methyl-biphenyl-4-yl)-2-(2-fluoro-phenyl)-[1,3,4]oxadiazol-3-yl]-ethanone (6a):*R = 2-Fluoro benzaldehyde .
white coloured solid; yield 54.8% ; m.p -165-168^{0}C; IR (KBr), ν_{max}/cm^{-1} : 1123, 1642, 2764,2936, 3325, 3347; ^{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.

2.3.2.*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, 2785, 2955, 3340, 3376; ^{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}CNMR ($CDCl_3$, 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.

2.3.3.*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.

2.3.4.*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.

*2.3.5.1-{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, 1920,2824,2887, 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.

*2.3.6.1-[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), 7.7(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 1: IC_{50} and CC_{50} values of the novel derivatives of 1-[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)

2.4 Cytotoxic Evaluation

2.4.1. Cell Lines fixation and Culture Conditions: The *in vitro* anti-proliferative study was carried out on three human cancer 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.

2.4.2. InvitroCell 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, 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%].

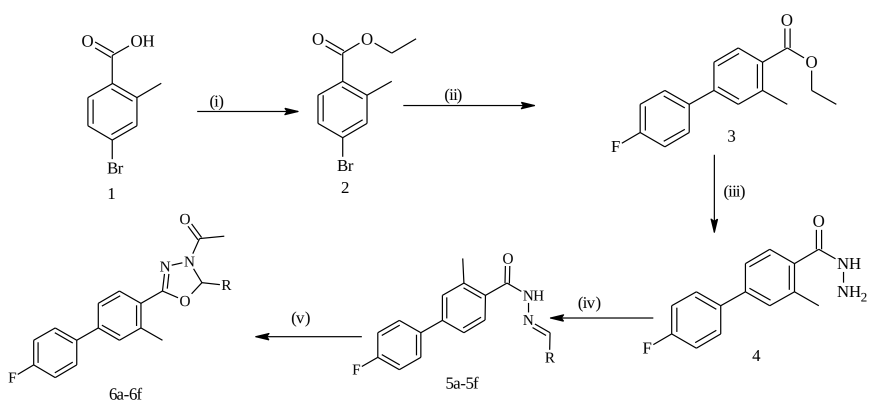
3. Results and Discussions

3.1. Chemistry (Scheme 1): The synthetic chemistry of novel ethanone derivatives of 1, 3, 4-oxadiazole compounds started with the synthesis of ethyl 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 group increases the Log-P as well as TPSA of the 1,3,4-oxadiazole molecules. The intermediate **3** was reacted with hydrazine hydrate and ethyl alcohol in order to obtain 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 yielded a series of novel Schiff base derivatives **5a-5f**. The reactive novel Schiff base derivative **5a-5f** were refluxed in acetic anhydride and obtained 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].

3.1.2SAR: 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 forth position and constructing biphenyl ring enhances further the Log-P values as well as increases the TPSA of the molecules. Author envisaged that by reacting with various aldehydes and further cyclizing the intermediate obtained novel derivatives of 1, 3, 4-oxadiazole ethanone moiety[13].

3.1.3. Biology: The obtained series of novel 1, 3, 4-oxadiazole derivatives **6a-6f** have been screened for cytotoxicity[13] on three different human cancer cell lines namely, *HeLa*, *HepG2* and *Caco-2* and obtain the IC_{50} and CC_{50} of the molecules. 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 good cytotoxicity on *Caco-2*cell lines having IC_{50} of 6.4**µM** and **4.4µM** respectively. Rest all the compounds showed moderate cytotoxicity as in the (**Table 1**).

3.1.4. 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.



Reagents and Conditions:(i) Ethyl alcohol, Conc. H2SO4; (ii) 4-Fluoro phenyl boronic acid; (iii) Hydrazine hydrate/reflux ; (iv) Acetic acid/ various aldehydes; (v) Acetic anhydride/ reflux

4. Conclusions

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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