Research Article

Synthesis, Characterization and in vitro Anticancer Properties of 1-{5- Aryl-2-[5-(4-Fluoro-Phenyl)-Thiophen-2-yl]-[1,3,4]Oxadiazol-3-yl}-Ethanone

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ABSTRACT

A series of novel 1-{5-aryl-2-[5-(4-fluoro-phenyl)-thiophen-2-yl] [1, 3, 4] oxadiazol-3-yl}-ethanone derivatives **7a-f** was synthesized by convergent synthetic method by using various carbohydrazides and 4-fluorophenyl thiophene-2-carboxaldehyde. The carboxaldehyde was reacted with various hydrazides in presence of catalytic amount of acetic acid and obtained Schiff base derivatives. The Schiff base derivatives were cyclized and acetylated in presence of acetic anhydride and obtained novel ethanone derivatives. The synthesized ethanone derivatives were purified by column-chromatography using silica gel (100-200 mesh). The synthesized compounds were evaluated for their anticancer properties using MTT assay. The 1, 3, 4-oxadiazole compounds have been synthesized from the corresponding Schiff base compounds **6a-f** using acetic anhydride as promoter. The synthesized compounds were characterized on the basis of IR, ^{1}H-NMR, ^{13}C NMR and LCMS analyses. The *in vitro* cytotoxic evaluation of the synthesized heterocycles was carried out against *HepG2*, *HeLa*, *MCF7* and *Caco-2* cell lines. The standard used for the evaluation was 5-fluoro uracil. Most of the compounds in this series showed less cytotoxicity against all the cell lines used. One compound in this series(**7d)**, i.e. 1-{5-[2-(4-fluorophenyl)pyridin-3-yl]-2-[5-(4-fluorophenyl)-thiophen-2-yl] [1, 3, 4] oxadiazol-3-yl}-ethanone was found to be active against breast cancer cell line (*MCF7*) which is comparable to the standard 5-fluorouracil and compounds **7b** and **7e** were moderately active against *HepG2* cell line.

Keywords: Anticancer, 1, 3, 4-oxadiazole, *MCF7*; *HepG2*, cytotoxic, MTT assay

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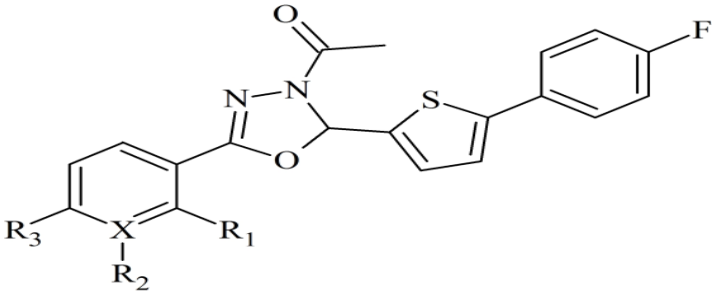
INTRODUCTION

The prevalence of multidrug resistance against cancer is a serious problem in developed and undeveloped countries. Cancer is known as malignant neoplasm involving unregulated cell growth. The development of potent and less cost effective anticancer drug is urgently required due to toxicity and resistance. Many compounds bearing five membered heterocyclic ring containing nitrogen, oxygen and sulphur e.g., oxadiazole, thiadiazole [1, 2] show variety of biological activities like antimicrobial [3, 4], anticonvulsant [5, 6], antitubercular [7, 8], antifungal[9], anti-inflammatory [10] and anticancer [11, 12]. Several ethanone derivatives of 1, 3, 4-oxadiazole exhibit properties such as antimicrobial, anticancer and antitubercular etc. In this connection the authors envisaged that by synthesizing novel ethanone derivatives containing thiophene moiety (**Figure1**), the water insolubility problem of 1, 3, 4-

oxadiazole compounds could be enhanced. The present work involves the synthesis of various carbohydrazide derivatives and reacting these carbohydrazides with 4-fluorophenyl thiophene-2-carboxaldehyde to obtain novel Schiff base compounds **6a-6f**. The Schiff base derivatives were cyclized using acetic anhydride and obtained novel derivatives of 1,3,4-oxadiazole ethanone derivatives. The synthesized compounds were characterized on the basis of spectral (^{1}H-NMR, IR and LCMS) analyses. These compounds were screened against *HeLa*, *MCF7*, *HepG2* and *Caco-2* cell lines using MTT assay. One compound in this series exhibited good inhibition against *MCF7* which is comparable to the standard 5-fluoro uracil.



7a-f

R_1,R_2,R_3 Different Functional Groups

Figure 1: General Structure of the ethanone derivatives of 1, 3, 4-oxadiazole containing thiophene moiety

EXPERIMENTAL

MATERIALS AND METHODS:

All the reagents, chemicals and solvents were commercially procured from the various chemical units Sigma-Aldrich, CDH, Spectrochem, S-D fine. These solvents and reagents were of LR grade and purified before use. Silica gel (100-200 mesh) was used for analytical column chromatography. TLC was obtained from E-Merck India Ltd and two solvent systems were used viz., Ethyl acetate: Hexane (3:7), Acetone: Benzene (2:8). Whattman No. 42 filter paper was used for vacuum filtration. The proton magnetic resonance (^{1}H-NMR) and ^{13}C spectra were recorded on a Bucker 400MHz instrument using tetra methyl silane as internal standard. Iodine chamber and UV light was used for visualization of the TLC spots. An IR spectrum was recorded in KBr on Perkin-Hammer FTIR. Melting points were recorded by melting point apparatus and are uncorrected. Microwave reactions were carried out using Whirlpool microwave oven.

Synthesis of 5-(4-fluorophenyl) thiophene-2-carbaldehyde: 2

In a mixture of 5-bromothiophene-2-carbaldehyde (1mol), Na_2CO_3 (1mol) & tetrakis(triphenylphosphine)palladium (0)(0.0005mol), 4-fluorophenyl boronic acid (1.2mol) was added with continuous stirring and the reaction mixture was refluxed in ethyl alcohol for 10h. After completion of the reaction, the reaction mixture was concentrated, cooled and poured over ice water. The product was extracted with ethyl acetate (30 × 2mL), washed with brine (10mL) and concentrated under reduced pressure. The residue was recrystallized from ethanol to afford the pale yellow crystals, m.p. 115-123°C; MS (ESI) m/z: 207; IR (KBr, cm^{-1}): (C-H) 2935, (CH, w) 3343, (C-O) 1185, (C-F) 871, (C-S) 1151; ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.48 (dd, 2H), 7.59 (m, 3H, J = 12.8Hz), 7.72 (d, 2H, J = 6.8Hz), 7.87 (d, 1H), 8.92 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100MHz): 125.5, 126.5, 127, 129, 132, 136, 138, 141, and 192.

General Procedure for the Synthesis of Substituted Benzoic/Nicotinic Acid Hydrazide: 4

To a suspension of corresponding acid derivatives (**3a-f**) conc. H_2SO_4 was added and the reaction mixture was refluxed in ethyl alcohol for 8h. After completion of the reaction, the reaction mixture was concentrated, cooled and poured over ice cold water. The aqueous solution was neutralized with NH_4Cl and the product was extracted with ethyl acetate to give the desired compounds (**4a-f**). A mixture of ester derivative (**4a-f**) (1mol) and hydrazine hydrate (5mL) was refluxed in ethyl alcohol for 4h. After completion of the reaction, the reaction mixture was concentrated and poured over ice water; the precipitate so formed was filtered, washed with water, dried and recrystallized with ethanol to give the desired compounds (**5a-f**).

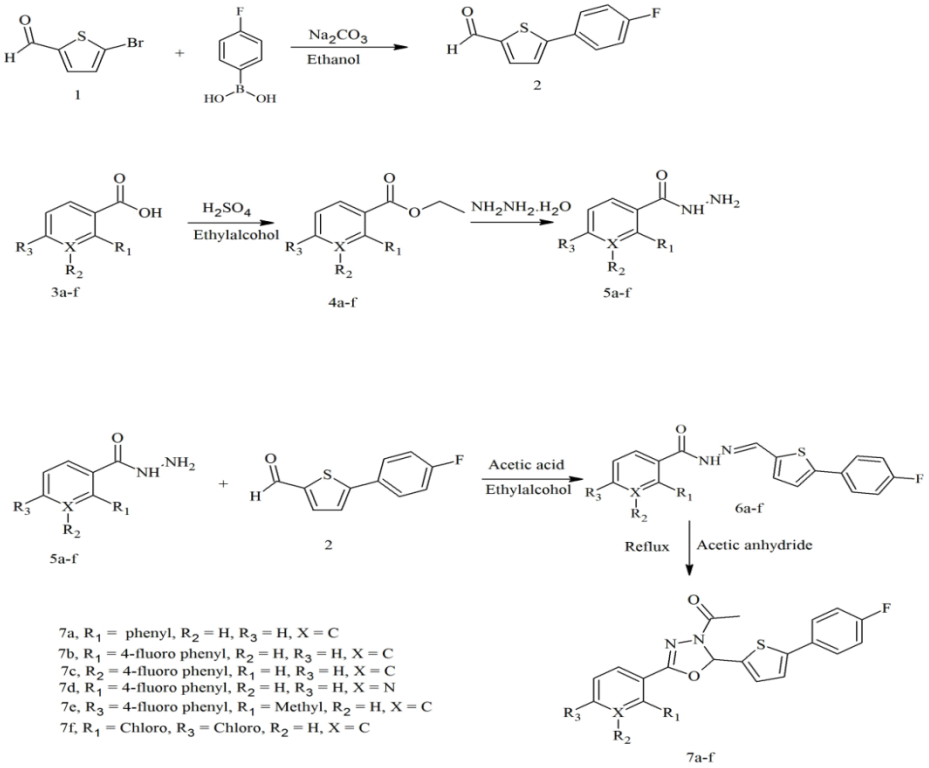
General Procedure for the Synthesis of Schiff Base Derivatives (6a-f):

A mixture of respective carbohydrazide derivatives (**5a-f**) (1mol) and 5-(4-fluorophenyl)thiophene-2-carbaldehyde (1mol) in ethyl alcohol (10mL) and few drops of glacial acetic acid was refluxed for 4h. After completion of the reaction, the reaction mixture was concentrated and poured over ice water. The separated out precipitate was filtered, dried and recrystallized in ethanol to give the desired Schiff base compounds (**6a-f**).

General Procedure for the Synthesis of 1-{5- Aryl-2-[5-(4-Fluorophenyl)-Thiophen-2-yl]-[1, 3, 4] Oxadiazol-3-yl}-Ethanone: 7a-f

A suspension of corresponding Schiff base derivatives **6a-f** (100mg each) and acetic anhydride (2-5mL) was refluxed for 3h. After completion of the reaction, the reaction mixture was concentrated to three fourth of its volume and poured over crashed ice. Precipitate thus separated out was filtered, washed with water, and dried. The solid was recrystallized from ethanol to give desired 1-{5-aryl-2-[5-(4-fluorophenyl) thiophen-2-yl]-[1,3,4]oxadia-zol-3-yl} ethanone (**7a-f**).

Reaction Scheme 1: Synthetic Reaction pathway for the novel derivatives of 1, 3, 4-oxadiazole ethanone



Analytical Data of the Compounds 7a-7f

Synthesis of 1-{5-Biphenyl-2-yl-2-[5-(4-Fluorophenyl)-Thiophen-2-yl]-[1,3,4]Oxadiazol-3-yl}-Ethanone (7a).

Pale brown solid; yield 61%; M.P.-149-152^{0}C; ^{1}H-NMR (400MHz, $CDCl_3$): δ 1.1 (s, 3H, CH_3), 6.8 (s, 1H, NH), 7.21 (dd, 2H, Ar-H, J = 8.2Hz), 7.32 (dd, 2H, J = 6.4Hz), 7.51 (t, 2H, J = 13.2Hz), 7.7 (dd, 3H, J = 13.5Hz); ^{13}C-NMR ($CDCl_3$, 100MHz):18, 90, 115.5, 116.4, 124.1, 126.3, 127.6, 130.1, 136, 137.3, 162, 163, 177; IR (KBr, cm^{-1}) (C-H) 2955, (CH, w) 3386, (C-O) 1169, (C-F) 884; (CH_2) - 2785, (NH) 3390; MS(ESI): $[M+H]^+$ 423; Anal. Calcd. for $C_{26}H_{19}FN_2O_2S$: C, 70.57; H, 4.33; F, 4.29; N, 6.33; O, 7.23; S, 7.25; Found: C, 70.58; H, 4.34; F, 4.30; N, 6.34; O, 7.24; S, 7.26.

1-{5-(4'-Fluorobiphenyl-2-yl)-2-[5-(4-Fluorophenyl)-Thiophen-2-yl]-[1,3,4]Oxadiazol-3-yl}-Ethanone (7b)

Brown solid; yield 57%; M.P-109-112^{0}C; ^{1}H- NMR (400MHz, $CDCl_3$): δ 1.12 (s, 3H, CH_3), 6.82 (s, 1H, NH), 7.3 (dd, 2H, Ar-H, J = 8.5Hz), 7.32 (d, 2H, J = 6.4Hz), 7.51 (t, 2H, J = 13.8Hz), 7.7 (dd, 3H, J = 13.8Hz); ^{13}C-NMR ($CDCl_3$, 100MHz)- 18, 90, 115.5, 116.4, 124.1, 126.3, 127.6, 130.1, 132, 135, 136, 137.3, 162, 163, 177, 179.; IR (KBr, cm^{-1}) (C-H) 2959, (CH, w) 3376, (C-O) 1269, (C-F) 874; (CH_2) - 2780, (NH) 3399; MS(ESI): $[M+H]^+$461; Anal. Calcd. for $C_{26}H_{18}F_2N_2O_2S$: C, 67.81; H, 3.94; F, 8.25; N, 6.08; O, 6.95; S, 6.96. Found: C, 67.82; H, 3.95; F, 8.26; N, 6.09; O, 6.96; S, 6.97.

1-{5-(4'-Fluorobiphenyl-3-yl)-2-[5-(4-Fluorophenyl)-thiophen-2-yl]-[1,3,4]Oxadiazol-3-yl}-Ethanone (7c).

Off white solid; yield 59%; M.P-119-121^{0}C; ^{1}H- NMR (400MHz, $CDCl_3$): δ 1.13 (s, 3H, CH_3), 6.84 (s, 1H, NH), 7.33 (dd, 2H, Ar-H, J = 8.5Hz), 7.43 (d, 2H, J = 6.4Hz), 7.61 (t, 2H, J = 13.8Hz), 7.74 (dd, 3H, J = 13.8Hz); ^{13}C-NMR ($CDCl_3$, 100MHz):90, 115.5, 116.4, 118, 124.1, 126.3, 127.6, 130.1, 132, 135, 136, 137.3, 162, 163, 177, 179.; IR (KBr, cm^{-1}) (C-H) 2969, (CH, w) 3356, (C-O) 1249, (C-F) 879; (CH_2) - 2781, (NH) 3398 ; MS(ESI): [M+H]461; Anal. Calcd. for $C_{26}H_{18}F_2N_2O_2S$: C, 67.81; H, 3.94; F, 8.25; N, 6.08; O, 6.95; S, 6.96. Found: C, 67.82; H, 3.95; F, 8.26; N, 6.09; O, 6.96; S, 6.97.

1-{5-[2-(4-Fluorophenyl)-Pyridin-3-yl]-2-[5-(4-Fluorophenyl)Thiophen-2-yl]-[1,3,4]Oxadiazol-3-yl}-Ethanone(7d).

White solid; yield 49%; M.P.-154-155^{0}C; ^{1}H- NMR (400MHz, $CDCl_3$): δ 1.16 (s, 3H, CH_3), 6.88 (s, 1H, NH), 7.33 (d, 2H, Ar-H, J = 8.8Hz), 7.48 (m, 2H, J = 12.5Hz), 7.67 (t, 2H, J = 13.5Hz), 7.74 (dd, 2H, J = 13.8Hz); ^{13}C-NMR ($CDCl_3$, 100MHz)- 90, 115.5, 116.4, 118, 124.1, 126.3, 127.6, 130.1, 132, 135, 136, 137.3, 162, 163, 177, 179.; IR (KBr, cm^{-1}) (C-H) 2968, (CH, w) 3345, (C-O) 1249, (C-F) 879; (CH_2) - 2771, (NH) 3397; MS(ESI): $[M+H]^+$462 ; Anal. Calcd. for $C_{25}H_{17}F_2N_3O_2S$: C, 65.07; H, 3.71; F, 8.23; N, 9.11; O, 6.93; S, 6.95. Found: C, 65.08; H, 3.72; F, 8.24; N, 9.12; O, 6.94; S, 6.96.

1-{5-(4'-Fluoro-3-Methylbiphenyl-4-yl)-2-[5-(4-Fluorophenyl)Thiophen-2-yl][1,3,4]Oxadiazol-3-yl}-Ethanone (7e)

White solid; yield 42%; M.P.-104-105^{0}C; ^{1}H- NMR (400MHz, $CDCl_3$): δ 1.16 (s, 3H, CH_3), 1.8 (s, CH_3, 3H), 6.9 (s, 1H, NH), 7.33 (dd, 4H, Ar-H, J = 8.4Hz), 7.48 (m, 3H, J = 12.4Hz), 7.67 (t, 3H, J = 13.6Hz), 7.74 (dd, 2H, J = 13.8Hz); ^{13}C-NMR ($CDCl_3$, 100MHz): 90, 115.5, 116.4, 118, 125., 126, 127, 130, 132, 135, 136, 162, 163, 177, 179; IR (KBr, cm^{-1}): (C-H) 2967, (CH, w), 3345, (C-O) 1249, (C-F) 878; (CH_2) 2751, (NH) 3245; MS(ESI): [M+H] 423; Anal. Calcd. 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-(2,4-Dichlorophenyl)-2-[5-(4-Fluorophenyl)-Thiophen-2-yl]-[1,3,4]Oxadiazol-3-yl}-Ethanone (7f)

Yellow solid; yield 71%; M.P.-184-185^{0}C; ^{1}H- NMR (400MHz, $CDCl_3$): δ 1.16 (s, 3H, CH_3), 6.56 (s, 1H, NH), 7.45 (d, 2H, Ar-H, J = 8.1 Hz), 7.48 (m, 3H, J = 12.4Hz), 7.67 (dd, 2H, J = 8.6Hz), 7.74 (dd, 2H, J = 13.8Hz); ^{13}C-NMR ($CDCl_3$, 100MHz: 90, 115, 116.4, 119, 125., 126, 127, 130, 132, 135, 136, 162, 163, 177, 179.; IR (KBr, cm^{-1}): (C-H) 2947, (CH, w) 3335, (C-O) 1289, (C-F) 898; (CH_2) - 2778, (NH) 3245; MS(ESI): [M+H] 436; Anal. Calcd. for $C_{20}H_{13}Cl_2FN_2O_2S$: C, 55.18; H, 3.01; Cl, 16.29; F, 4.36; N, 6.44; O, 7.35; S, 7.37.

Found: C, 55.19; H, 3.02; Cl, 16.30; F, 4.37; N, 6.45; O, 7.36; S, 7.38

Table1: IC_{50} Values of the Synthesized Novel Ethanone Derivatives of 1,3,4-Oxadiazole Ethanone Containing Thiophene Moiety

Compounds **7a-7f**	IC_{50} values of the synthesized novel 1,3,4-oxadiazole containing ethanone derivatives (μM)			
	HeLa	***Hep-G2***	***MCF- 7***	***Caco-2***
7a	96.5	350.4	123.5	112.4
7b	405.7	**54.3**	108.9	234.4
7c	232.4	213.6	459.6	453.3
7d	561	156.5	**8.6**	656.3
7e	567.8	**23.6**	89.9	543.3
7f	212.5	223.3	126.7	234.2
5-FU[1]	8.2	7.4	8.2	9.3

Antiproliferative Activity:

Cell lines and culture conditions: Human cancer cell lines namely, *HeLa* (Human cervical cancer cells), *HepG2*(Hepatic cancer cells), *MCF7*(Human breast adenocarcinoma cell line) and *Caco-2*(Human colorectal cancer cells) were grown in RPMI 1640 medium supplemented with 10% foetal bovine serum(FBS), 10U penicillin and 100μg/mL streptomycin at 37°C and 5% CO_2 humidified atmosphere. *HeLa* and *MCF7* cells were also grown in DMEM medium supplemented with antibiotics as described above. Fresh medium was supplemented on the day before the experiment and cells were passaged at densities using 0.05% trypsin and 0.5 mM EDTA.

MTT Assay and Data Analysis: The in vitro anticancer activity was measured by MTT assay. Growing cells were harvested and plated in 96 well plates at concentration of 1×10^4 cells/well and kept for incubation at 37°C, 5% CO_2 for 24h. Cells in the wells were treated with target test compounds (**7a-7f)** at various concentrations for 24h (DMSO concentration was kept 1%). A solution of 3-(4,5-dimethyl thiazol-2-yl)-2,5-tetrazolium bromide was prepared at 5mg/mL in phosphate buffer (1.6mM KH_2PO_4, 6.8mM Na_2HPO_4, 150mM NaCl, 25mM KCl), pH 7.5 and added to each well. After 4h of incubation at 37°C, 5% CO_2 humidified atmosphere; the medium and MTT was removed, formazan crystals were dissolved in 100μL of DMSO per well.The absorbance of the wells was read with the micro platereader (Bio-Rad instrument) at 570nm. The survival cells were calculated using the formula % cell viability = [absorbance of the treated cells- absorbance of the culture medium] / [Absorbance of the untreated cells-absorbance of the culture medium] × 100. The experiment was done in triplicate and the minimum inhibitory concentration (IC_{50}) was calculated from dose response curve. Evaluation was done using mean values of the IC_{50} i.e. minimum concentration of the test compounds that reduced the absorbance of the treated cells by 50%.

RESULTS AND DISCUSSION: The synthetic chemistry involved the synthesis of the key carboxaldehyde i.e. 4-fluorophenyl thiophene-2-carbaldehyde **(2)**. Six novel different Schiff base derivatives [13]**6a-6f** were obtained by treating carbaldehyde with various substituted carboxaldehyde in presence of catalytic amount of acetic acid. The physical data of the Schiff base derivatives **6a-6f is** shown in analytical data. The Schiff base derivatives were cyclized and acetylated using anhydrous acetic anhydride and obtained a series of ethanone derivatives [14] **7a-7f**. All the compounds were purified by column chromatography using silica gel (100-200 mesh) and ethyl acetate and hexane (gradient 75:15) as eluent. All the synthesized compounds were screened for their cytotoxicity using MTT assay[15]. The standard used for the evaluation was 5-FU. The results indicate that anticancer activity or cytotoxicity varies with the structural modifications.

CONCLUSION

Six novel ethanone derivatives containing 1,3,4-oxadiazole moiety have been synthesized and studied their cytotoxicity using MTT assay. The test compounds were tested as growth inhibitors of *HeLa*, *MCF7*, *HepG2* and *Caco-2* cell lines. Among six derivatives, one compound i.e. 1-{5-[2-(4-

fluorophenyl)-pyridin-3-yl]-2-[5-(4-fluorophenyl)-thiophen-2-yl] [1, 3, 4] oxadiazol-3-yl} ethanone showed IC_{50} of **8.6µM** against *MCF7* which is comparable to the standard used. These results indicate that different ethanone derivatives may be useful leads for the anticancer drug development in the future.

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