

Synthesis, characterization and cytotoxic evaluation of novel derivatives of 1, 3, 4-oxadiazole containing 5-phenyl thiophene moiety.

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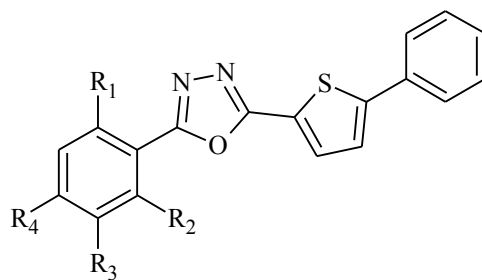
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Abstract: In the present work a series of novel derivatives of 1,3,4-oxadiazoles containing 5-phenyl thiophene moiety has been synthesized by convergent synthetic method and studied their anticancer properties. The synthesized compounds were characterized by spectral (¹H-NMR, ¹³C NMR, MS and elemental) analyses. Three cell lines were used for the cytotoxic evaluation namely, HepG2, Caco-2 and PANC-1. The synthetic chemistry involved conversion of various substituted aromatic acids into ethyl ester **2a-e**. The ethyl ester was converted into corresponding carbohydrazide **3a-e**. Carbohydrazides **3a-e** were reacted with 5-phenyl thiophene-2-carboxaldehyde(**5**) in presence of acetic acid as catalyst and obtained novel Schiff base compounds **6a-e**. The Schiff base derivatives were cyclized using chloramine-T as promoter and obtained novel derivatives of 1,3,4-oxadiazole **7a-e**. Among the synthesised compounds, the cytotoxicity of the compound **7b** i.e. 2-(4'-fluorobiphenyl-3-yl)-5-(5-phenylthiophen-2-yl)-1,3,4-oxadiazole against Caco-2 cell line with IC₅₀ of 5.3 μM. The compound **7e** i.e. 2-(4-methoxyphenyl)-5-(5-phenylthiophen-2-yl)-1,3,4-oxadiazole showed moderate cytotoxicity against HepG2 with IC₅₀ of 28.4 μM. Rest of the compounds showed less cytotoxicity against all the three cell lines.

Key words: PANC-1, Cytotoxicity, 1,3,4-oxadiazole, 5-phenylthiophene, Anticancer

I. Introduction

The development of new anticancer therapeutic agents is one of the fundamental goals in medicinal chemistry. In recent years there has been a concerned search for the discovery and development of potent and selective anticancer agents. The various derivatives of 1,3,4-oxadiazoles substituted with different groups displayed wide spectrum of biological activities such as anti-inflammatory^[1], antimicrobial^[2], analgesic^[3] anti-tuberculosis^[4], anticancer^[5, 6, 7, 8] properties. Author envisage that by introducing 5-phenyl thiophene moiety into the 1,3,4-oxadiazole^[9] ring system (**Fig. 1**) would produce the synergetic effect and increases the water solubility and total polar surface area. The synthetic chemistry involved converting suitably substituted aromatic acid into corresponding ethyl ester **2a-e**. Ethyl ester was further converted into carbohydrazide **3a-e**. The carbohydrazides were reacted with 5-phenyl thiophene^[10, 11] (**5**) and obtained novel Schiff base^[12, 13] compounds **6a-e**. The Schiff base compounds were cyclized using chloramine-T^[14] and obtained novel derivatives of 1,3,4-oxadiazole **7a-e** (**Fig. 1**). The key intermediate 5-phenyl thiophene carbohydrazide (**5**) and 1,3,4-oxadiazole and related compounds have been described as useful building blocks for the synthesis of various heterocyclic rings. A series of 5-phenylthiophene of 1,3,4-oxadiazole^[15] derivatives **7a-e** (**Fig. 1**) have been synthesized and tested their cytotoxicity on human cancer cell lines. Notably, the halogen substitutions were incorporated to improve the solubility of the compounds. Author envisaged that by making Schiff base compounds of various halogens substituted aromatic carbohydrazides with 5-phenylthiophene moiety and cyclizing the Schiff base^[16] compounds using chloramine-T as promoter improves the total polar surface area and increases the water solubility. All the final compounds were characterized by spectral (¹H-NMR, ¹³CNMR, MS and elemental) analyses. Thus it was of interest to implement drug design and to synthesise the novel candidates by joining the 5-phenyl thiophene with different halogen substituted aromatic carbohydrazides and obtained novel derivatives of 1,3,4-oxadiazoles.



R₁, R₂, R₃ and R₄ are different substituions

1.1 **Figure 1:** General structures of the 5-phenylthiophene containing 1,3,4-oxadiazole moiety

II. Experimental:

2.1 Materials and Methods: All the reagents, chemicals and solvents were purchased from S-d fine and Spectrochem Ltd, Bengaluru, India. ¹H-NMR and ¹³C-NMR were recorded by Bruker 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.

2.2 Synthesis:

2.2.1 General procedure for synthesis of aromatic ethyl ester 2a-e:

To a mixture of acid **1a-e** (1mol, 1equivalent), ethyl alcohol (50mL) and conc.H₂SO₄ were refluxed at 85°C for 6-8h. Progress of the reaction was monitored by TLC (thin layer chromatography), which indicated completion of the reaction. Ethyl alcohol was completely removed, residue was extracted with ethyl acetate (20 × 3mL), washed with brine (10mL) and dried over Na₂SO₄. Ethyl acetate was concentrated under reduced pressure and obtained colourless syrup. The structure was confirmed by spectral and analytical data.

2.2.2 General procedure for synthesis of aromatic carbohydrazide 3a-e:

To a solution of **2a-e** in ethyl alcohol (50mL) was added with excess of hydrazine hydrate and refluxed at 80°C for 10-12h. Progress of the reaction was monitored by TLC, indicated completion of the reaction. Reaction mixture was concentrated completely under reduced pressure, ice pieces were added and stirred. Precipitate formed was filtered and dried. The structure was confirmed by spectral and analytical data.

2.2.3 Synthesis of 5-phenyl thiophene-2-carboxaldehyde (5):

To a mixture of 5-bromothiophene-2-carboxaldehyde (2g, 0.0104mol 1 equivalent), phenyl boronic acid (1.405g, 0.0115mol), Na₂CO₃ (2.2g, 0.0208mol), tetrakis (triphenylphosphine) palladium(0) (606mg, 0.052mmol) and ethyl alcohol (100mL) were refluxed at 85°C for 10h. Progress of the reaction was monitored by TLC, which indicated the completion of the reaction. Ethyl alcohol was completely removed, residue was extracted with ethyl acetate (25mL × 3), washed with brine (10mL) and dried over Na₂SO₄. The crude product was purified by column-chromatography (silicagel 100-200 mesh), ethyl acetate in hexane (0-15%) as eluent. Yield = 1.85g; m.p-98-123°C; ¹H-NMR (CDCl₃, 400MHz): δ 7.45 (dd, 2H), 7.52 (m, 3H, J = 12.8Hz), 7.62 (d, 2H, J = 6.8Hz), 7.67 (d, 1H), 8.8 (s, 1H); ¹³C-NMR (CDCl₃, 100MHz): 125.5, 126.5, 127, 129, 132, 136, 138, 141, 192.

2.2.4 General procedure for synthesis of Schiff base derivatives 1,3,4-oxadiazole containing 5-phenylthiophene 6a-e:

To a mixture of carbohydrazide **3a-e**, acetic acid (2-5 drops) and 5-phenylthiophene-2-carboxaldehyde (5) (1.1 mmole) were refluxed at 85°C for 2-3h. Progress of the reaction was monitored by TLC, indicated the completion of the reaction. Reaction mixture was concentrate under reduced pressure, ice cold water was added and the precipitate formed was filtered, dried. The structure was confirmed by spectral and analytical methods.

2.2.5 General procedure for synthesis 5-phenylthiophene substituted 1,3,4-oxadiazoles 7a-e:

To a solution of the compound **6a-e** (1mmol) in ethyl alcohol (5mL) and Chloramine-T (1.1mmol) was irradiated with microwave for 60 seconds. Progress of the reaction was monitored by TLC, indicated completion of the reaction. Reaction mixture was extracted with ethyl acetate (25mL × 3), washed with brine (10mL) and dried over Na₂SO₄. The crude product was purified by column-chromatography (silicagel 100-200 mesh), ethyl acetate in hexane (0-75%) as eluent.

2.3 Analytical data of the compounds 7a-e:

2.3.1 2-(2,5-Dimethoxy-phenyl)-5-(5-phenyl-thiophen-2-yl)-[1,3,4]oxadiazole (7a):

Pale yellow solid; Yield 45%; m. p 103-106^oC; ¹H- NMR (400MHz, CDCl₃): δ 3.85 (s, 3H, OCH₃), 3.95 (s, 3H, OCH₃), 7.0195 (d, 1H, J = 9.2, Ar-H), 7.082 (dd, 1H, J = 12Hz), 7.298 (d, 3H, J = 8Hz), 7.374 (t, 1H, J = 7.2Hz), 7.435(t, 1H, J = 14.8Hz), 7.534(d, 1H, J = 3.2Hz), 7.675(t, 1H, J = 8.4Hz), 7.799(q, 3H, J = 14.8Hz); ¹³C-NMR (CDCl₃, 100MHz): 21.6, 56.5, 77.16, 113.5, 114.7, 119.4, 124, 126.35, 128.8, 129.53, 130.8, 133.2, 139.3, 143.6, 149.3, 152.4, 153.6, 160.7, 162.7; IR (KBr, cm⁻¹) (C-H) 2935, (CH, w) 3322, (C-O) 1180, (C-F) 874, (C-S) 1151 (CH₂) - 2765, (NH) 3320; MS(ESI) m/z : 365 [M+H]⁺; anal. Calculated for C₂₀H₁₆N₂O₃S; C, 65.92; H, 4.43; N, 7.69; O, 13.17; S, 8.80; found C, 65.96; H, 4.47; N, 7.70; O, 13.18; S, 8.82.

2.3.2 2-(4'-Fluoro-biphenyl-3-yl)-5-(5-phenyl-thiophen-2-yl)-[1,3,4]oxadiazole(7b):

Off white solid; Yield 76%; m. p 112-116^oC; ¹H- NMR (400MHz, CDCl₃): δ 7.374 (q, 2H, J = 15.2Hz), 7.439 (q, 3H, J = 16.8Hz), 7.502 (t, 2H, J = 14.8, Ar-H), 7.610 (t, 1H, J = 15.6Hz), 7.676 (d, 4H, J = 7.6Hz), 7.78 (d, 1H, J = 8Hz), 7.822 (d, 1H, J = 4Hz), 8.104 (d, 1H, J = 8Hz), 8.349 (s, 1H) ; ¹³C-NMR (CDCl₃, 100MHz): 77.6, 123.9, 124.27, 125.7, 126.3, 127.3, 128.5, 129.2, 130.7, 133.24, 140, 142.4, 149.5; IR (KBr, cm⁻¹) (C-H) 2975, (CH, w) 3342, (C-O) 1185, (C-F) 883, (C-S) 1131 (CH₂) - 2785, (NH) 3370; MS(ESI) m/z : 399 [M+H]⁺; anal. Calculated for C₂₄H₁₅FN₂OS; C, 72.34; H, 3.79; F, 4.77; N, 7.03; O, 4.02; S, 8.05; found C, 72.35; H, 3.81; F, 4.79; N, 7.05; O, 4.05; S, 8.07.

2.3.3 2-Biphenyl-3-yl-5-(5-phenyl-thiophen-2-yl)-[1,3,4]oxadiazole(7c):

Pale yellow solid; Yield 66%; m. p 132-133^oC; ¹H- NMR (400MHz, CDCl₃): δ 7.386 (t, 2H, J = 8.4Hz), 7.451 (m, 3H, J = 26.4Hz), 7.613 (t, 1H, J = 15.6, Ar-H), 7.688 (t, 4H, J = 8.4Hz), 7.782 (td, 1H, J = 10.4Hz, J' = 2.8Hz), 7.825(dd, 1H, J = 4Hz, J' = 1.6Hz), 8.351 (t, 1H, J = 3.2Hz); ¹³C-NMR (CDCl₃, 100MHz): 77.15, 123.9, 124.23, 125.75, 126.29, 127.36, 128.5, 129.40, 130.72, 133.24, 140.0, 142.4, 160.9, 164.12; IR (KBr, cm⁻¹) (C-H) 2985, (CH, w) 3352, (C-O) 1195, (C-F) 887, (C-S) 1136 (CH₂) - 2787, (NH) 3374; MS(ESI) m/z : 381 [M+H]⁺; anal. Calculated for C₂₄H₁₆N₂OS; C, 75.77; H, 4.24; N, 7.36; O, 4.21; S, 8.43; found C, 75.78; H, 4.25; N, 7.38; O, 4.24; S, 8.44.

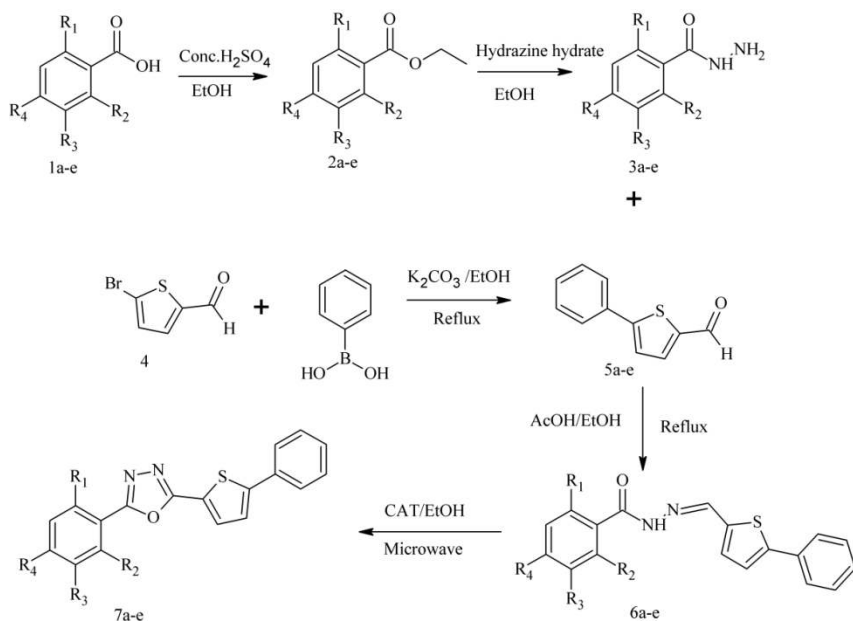
2.3.4 2-(4'-Fluoro-biphenyl-2-yl)-5-(5-phenyl-thiophen-2-yl)-[1,3,4]oxadiazole(7d):

Yellow solid; Yield 66%; m. p 132-133^oC; ¹H- NMR (400MHz, CDCl₃): δ 7.080 (t, 2H, J = 17.6Hz), 7.249 (q, 5H), 7.326 (d, 1H, J = 7.2Hz, Ar-H), 7.392 (q, 3H), 7.497 (t, 1H, J = 14.4 Hz), 7.565(m, 3H, J = 12.4Hz), 7.779 (d, 1H, J = 8Hz), 8.125(d, 1H, J = 7.2Hz); ¹³C-NMR (CDCl₃, 100MHz): 21.6, 77.15, 115.3, 122.6, 123.5, 124.0, 126.3, 128.4, 129.5, 130.42, 131.5, 133.1, 136.7, 137.5, 141.0, 143, 149.4, 161.3, 163.8, 182.9; IR (KBr, cm⁻¹) (C-H) 2965, (CH, w) 3372, (C-O) 1198, (C-F) 889, (C-S) 1146 (CH₂) - 2797, (NH) 3394; MS (ESI) m/z : 399 [M+H]⁺; anal. Calculated for C₂₄H₁₅FN₂OS; C, 72.34; H, 3.79; F, 4.77; N, 7.03; O, 4.02; S, 8.05; found C, 72.36; H, 3.80; F, 4.78; N, 7.06; O, 4.04; S, 8.06.

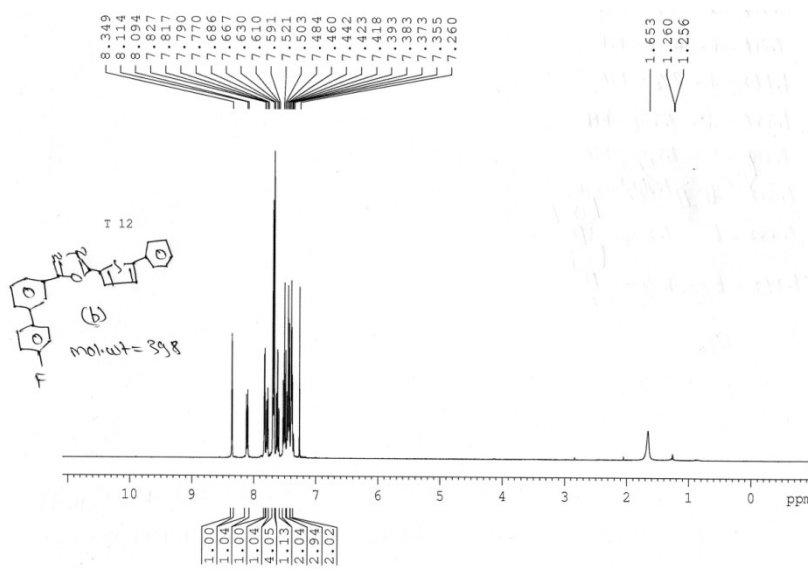
2.3.5 2-(4-Methoxy-phenyl)-5-(5-phenyl-thiophen-2-yl)-[1,3,4]oxadiazole(7e):

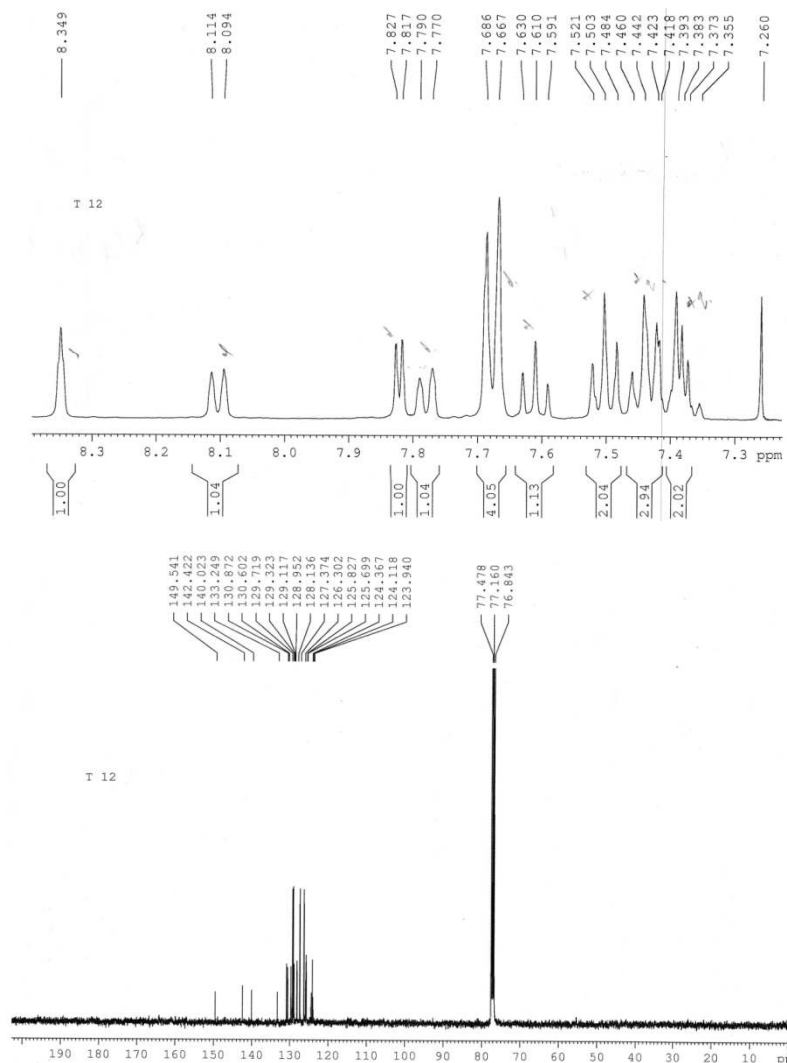
Yellow solid; Yield 56%; m. p 142-148^oC; ¹H- NMR (400MHz, CDCl₃): δ 3.893 (s, 3H, OCH₃), 7.030 (d, 2H, J = 9.2Hz), 7.303 (d, 2H, J = 8.4 Hz, Ar-H), 7.37 (d, 1H, J = 4Hz), 7.430 (q, 2H, J = 14.8 Hz), 7.662 (d, 2H, J = 7.2Hz), 7.77 (d, 1H, J = 3.6Hz), 7.811(d, 2H, J = 8.4Hz), 8.059(d, 2H, J = 8.8Hz); ¹³C-NMR (CDCl₃, 100MHz): 21.6, 55.6, 77.15, 114.6, 116.2, 124.0, 126.39, 128.8, 129.5, 130.5, 133.2, 139.2, 143.6, 149.1, 162.5; IR (KBr, cm⁻¹) (C-H) 2965, (CH, w) 3372, (C-O) 1198, (C-F) 889, (C-S) 1146 (CH₂) - 2797, (NH) 3394; MS (ESI) m/z : 399 [M+H]⁺; anal. Calculated for C₁₉H₁₄N₂O₂S; C, 68.24; H, 4.22; N, 8.38; O, 9.57; S, 9.59; found C, 68.26; H, 4.24; N, 8.39; O, 9.58; S, 9.60.

1.4 Scheme 1: Synthesis of novel derivatives of 1,3,4-oxadiazole containing 5-phenylthiophene moiety 7a-e:

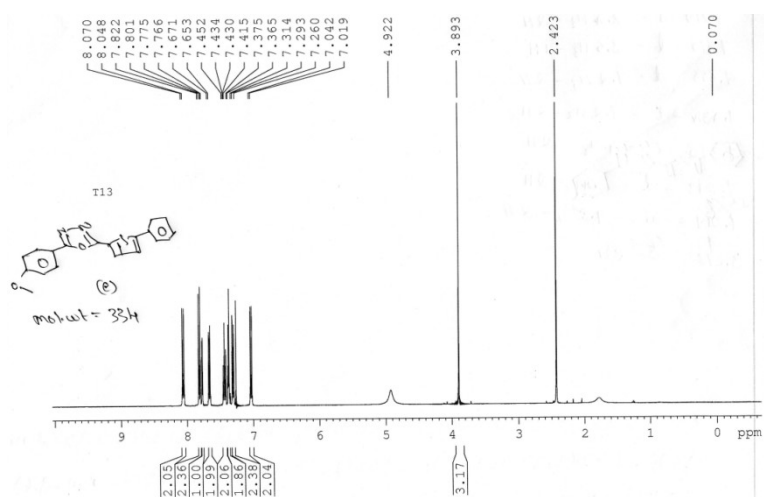


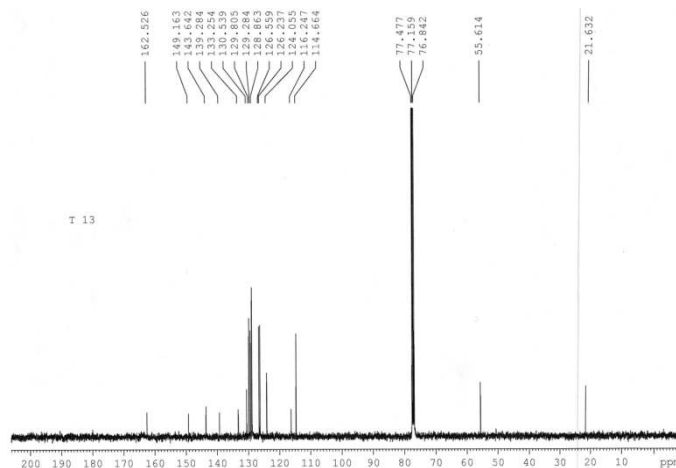
- (a): R₁ = OCH₃, R₂ = H, R₃ = OCH₃, R₄ = H
- (b): R₁ = H, R₂ = H, R₃ = Ph-F, R₄ = H
- (c): R₁ = H, R₂ = H, R₃ = Ph, R₄ = H
- (d): R₁ = H, R₂ = Ph-F, R₃ = H, R₄ = H
- (e): R₁ = H, R₂ = H, R₃ = H, R₄ = OCH₃





1.4.1 Figure 2: ¹H-NMR and ¹³C NMR spectra of the most active compound on Caco-2, 7(b).





2.4.2 Figure 3: ¹H-NMR and ¹³CNMR spectra of the moderately active compound 7 (e):

Table 1: IC₅₀ Values of the Novel Derivatives of 1,3,4-Oxadiazole (7a-e) Containing 5-Phenyl Thiophene Moiety:

Sl. No	Compounds	IC ₅₀ Values of 1,3,4-Oxadiazoles 7a-e (μM)		
		HepG2 (μM)*	Caco-2 (μM)*	PANC-1(μM)*
1	7a	67.8	78.9	112.3
2	7b	78.9	5.3*	34.5
3	7c	125.6	56.6	56.8
4	7d	234.5	78.5	123.6
5	7e	28.4	156.7	234.6
6	5-fluouracil	6.7	8.6	7.3

5-fluorouracil-standard used; *potent molecule; IC₅₀: Inhibitory concentration of the compound at 50% of the cells.

III. Cytotoxic Evaluation (Table 1):

3.1.1 Cell Lines fixation and Culture Conditions:

The in vitro anti-proliferative study was carried out on three human cancer cell lines namely HepG2, Caco-2 and PANC-1. 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% CO₂. Following 24-48 hrs 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 Biosystems, India) based on trypan blue dye exclusion method. Cytotoxicity of the novel 1, 3, 4-oxadiazoles have been determined using MTT 3-(4, 5-Dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide) assay.

3.1.2 Cell Viability Assay (MTT Assay): The MTT assay was carried out at 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 24hrs, all cells were seeded in duplicate with novel compounds **7a-e** having range of concentrations from 50μM-500μM, incubated in a CO₂ incubator at 37°C. Treated cells were thereafter incubated with 10% MTT (5mg/ml; HI Media Labs, Mumbai, India) for 3 hrs. The culture medium was then aspirated and 200μL dimethyl sulfoxide (DMSO; Sigma-Aldrich, India) was added. 5-Fluoro uracil (5-FU) 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 [% cell viability = (A₅₇₀ of treated cells / A₅₇₀ of control cells) × 100%].

IV. Results And Discussions:

4.1 Chemistry (Scheme 1): In the present work novel derivatives of 1, 3, 4-oxadiazoles **7a-e** were synthesized, characterized and evaluated for their cytotoxicity against HepG2, Caco-2 and PANC-1 cell lines. Synthetic chemistry involved the conversion of substituted acids into corresponding ester **2a-e**. The ester compound was further converted into corresponding carbonylhydrazide (IR absorbance of NH 3345 cm⁻¹) **3a-e**. The carbonylhydrazide **3a-e** was reacted with 5-phenylthiophene carboxaldehyde and obtained Schiff base^[17] compounds **6a-e**. The Schiff base compounds were cyclized in presence of chloramine-T as promoter and obtained the novel series of 1,3,4-oxadiazoles **7a-e**. The synthesized novel derivatives of 1,3,4-oxadiazole compounds were evaluated for their cytotoxicity^[17, 18] against HepG2, Caco-2 and PANC-1 cell lines using MTT assay.

4.2 b) Anticancer activity (Table 1): The synthesized compounds were screened for in vitro anticancer activity against three human cancer cell lines^[18, 19] namely, HepG2, Caco-2 and PANC-1. The results were expressed in the form of IC₅₀ (Inhibitory concentration of the compound at 50%). The 5-fluorouracil was used as a standard. The compound **(7b) (Fig. 2)** showed cytotoxicity against human colorectal carcinoma cell line (**Caco-2**) with IC₅₀ of **5.3 μM** which is comparable to that of known standard 5-fluorouracil. The compound **7(e) (Fig. 3)** showed moderate cytotoxicity^[20] against HepG2 cell line with IC₅₀ of 28.4 μM.

V. Conclusion:

The cytotoxicity of the synthesized 1,3,4-oxadiazole compounds **7a-e** were compared with the cytotoxicity of the known standard, 5-fluorouracil. Cytotoxicity of the compound **7b (Fig. 2)** against Caco-2 cell line with IC₅₀ of 5.3 μM which is comparable with the cytotoxicity of the known standard 5-fluorouracil. The compound **7e (Fig. 3)** showed moderate cytotoxicity against HepG2 cell line whose IC₅₀ value is 28.4 μM. The authors are interested to study the various biological activities and apoptosis mechanism in their further research.

Acknowledgements

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