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RESEARCH ARTICLE

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Adimule Vinayak
Mount Carmel Centre for Scientific and Advanced Research, Mount Carmel College, Vasanth Nagar, Bengaluru-560 052, Karnataka, India
Email: adimulevinayak@yahoo.in

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Design, Synthesis and Cytotoxic evaluation of Novel 2-(4-N, N-Dimethyl) pyridine containing 1, 3, 4-oxadiazole moiety

Adimule Vinayak[a, d], Medapa Sudha[b], Adarsha H. J[c], Kumar S Lalita[d], Rao Prakash Kumar[a*]

[a]Mount Carmel Centre for Scientific and Advanced Research, Mount Carmel College, Vasanth Nagar, Bengaluru-560 052, Karnataka, India
[b]Department of Chemistry, Mount Carmel College (Autonomous), Vasanth Nagar, Bengaluru- 560 052, Karnataka, India.
[c]Department of Inorganic and physical chemistry, IIScBangalore,Karnataka,India
[d]Department of Chemistry,School of Sciences, IGNOU, New-Delhi, India.

Abstract

Anew series of novel 1,3,4-oxadiazoles derivatives have been synthesized by linear synthetic method and screened these compounds for anticancer activity on HeLa, MCF7, Caco-2 cell lines. Final 1, 3, 4-oxadiazoles **6a-6f** were characterized by LCMS,1H NMR,13C, and elemental analysis. Oxidative cyclisation reaction of the corresponding key intermediate Schiff base derivatives **5a-5f** yielded the desired novel 1, 3, 4-oxadiazoles. Most of the compounds in this series showed moderate cytotoxicity on all the cell lines, but compounds **6d** and **6f** is more cytotoxic on Caco-2 and HeLa cell lines respectively. The standard used was 5-FU and cytotoxicity of the compounds were compared with the 5-FU. The IC50 values of compounds **6d** and **6f**is 2.4µM and 5.3µM on Caco-2 and HeLa cell lines respectively.

Keywords: Cytotoxicity, Caco-2, 1, 3, 4-oxadiazoles, pyridine, anticancer

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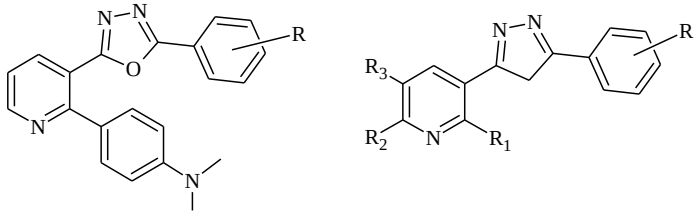
INTRODUCTION

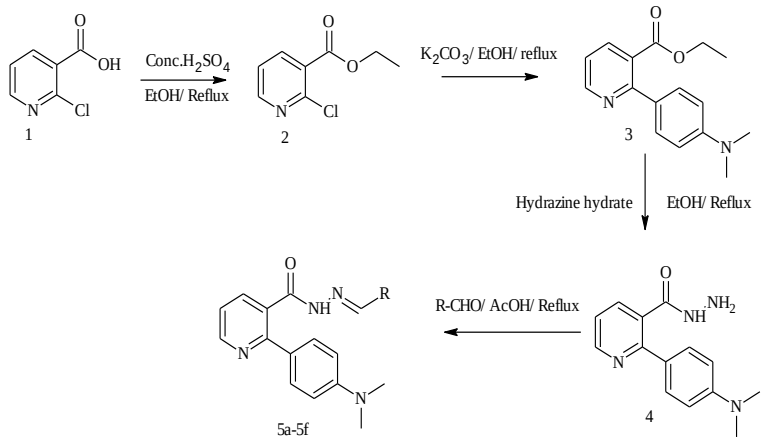
In this research work author synthesized the novel dimethyl amine derivatives of 1, 3, 4-oxadiazoles**6a-6f** and screened these compounds for antiproliferative activity. Pyridine containing 1, 3, 4-oxadiazole moiety has been reported for their anticancer [1], anti-inflammatory[2],anti-microbial [2] and analgesic [3] activities. Author envisaged that by introducing4-N, N-dimethyl phenyl amine group in the second position of the pyridine ring and constructing 1,3,4-oxadiazole ring at the third position may enhance the bioavailability and overcome the water insolubility problem of 1,3,4-oxadiazoles**(Figure 1, (A))**.Pyridine ring having substitutions at different positions containing 1,3,4-oxadiazole ring at the third position**(Figure 1, (B))**possess excellent biological properties4.In order to validate the above hypothesis author has synthesizedsix novelderivatives of pyridine having 4-N, N-dimethyl phenyl amine group attached to the second position and constructed the 1, 3, 4-oxadiazole moiety [5,6]. The N, N-dimethyl phenyl amine group at the second position which may increase the bioavailability of these molecules and may increase the TPSA and overcome the water insolubility. Finalderivatives **6a-6f** were synthesized by the oxidative cyclization [5,6]using CAT (**Chloramine-T**).All the cyclised compounds were purified by column-chromatography and characterized by LCMS,1HNMR,13C spectroscopies. Author has screened these compounds on HeLa,MCF7,Caco-2 cell lines at different concentrations in order to obtain the IC50 values (**Table 1**).The antiproliferative activity[6,7] of these heterocycles showed that by introducing N, N-dimethyl phenyl amine group the cytotoxicity has increased and compounds **6d** and **6f** have showed good inhibition on Caco-2 and HeLa cell lines having IC50of 2.4µM and 5.3µM respectively.



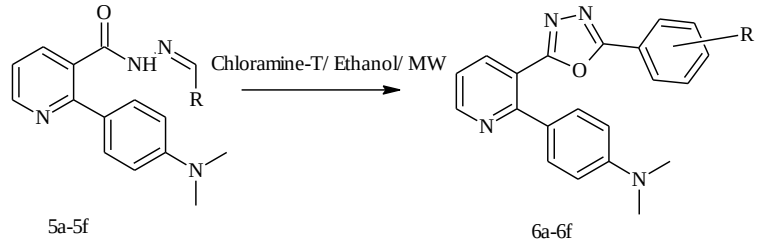
A B

Figure 1: A) Structures of the pyridine containing 2-(4-N, N-Dimethyl amine group at the second position and containing 1, 3, 4-oxadiazole moiety; B) Pyridine ring containing 1, 3, 4-oxadiazole moiety having different substitutions at different positions.

Scheme 1: Linear Synthetic pathway of the synthesis of novel derivatives of Schiff bases compounds of 2-(4-N, N-Dimethyl) pyridine containing 1, 3, 4-oxadiazole moiety.



Scheme 2: Synthetic reaction scheme of novel derivatives of 1, 3, 4-oxadiazole 6a-6f:



Materials and Methods: Allthe reagents, chemicals and solvents were purchased from S-d fine and Spectrochem ltd, Bangalore, india.1H NMR and 13C NMR were recorded by Brucker 400 MHz spectrophotometer. Melting points were 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 1800 series. CEM discoverer (sp-d series) microwave was employed.

EXPERIMENTAL:

Synthesis:

Step 1. Synthesis of Ethyl 2-Chloropyridine-3-Carboxylate 2:

The 2-chloro nicotinic acid 1 (10g, 0.0636mol) was taken in a 500mL single necked round bottom flask. 150mL of ethanol and 3-5 drops of concentrated H2SO4 were added and the reaction mixture was refluxed at 800C for 8 hr. after completion,RM was concentrated under reduced pressure, residue was added with ice cold water and neutralized with saturated solution NaHCO3. The aqueous was extracted with ethyl acetate (30x2mL), washed with brine (15mL) and dried over Na2SO4.The ethyl acetate was removed completely under reduced pressure. Pale yellow liquid; Yield 8.5g; ms(ESI) m/z: [M+H]- 187; TLC-ethyl acetate: hexane (1:8); IR(KBr), νmax/cm-1; 987 (C-O), 1094(C-Cl),2885 (C-H), 3106(C-H), 1HNMR (CDCl3, 400MHz) -δ 1.25(t, 3H), 3.95(q, 2H), 7.53(t, 1H), 8.65 (dd, J 8.6Hz, 1H), 8.91(d,J 7.4Hz, 1H).

Step 2: Synthesis of 2-(4-Dimethylamino-phenyl)-nicotinic acid ethyl ester 3:Ethyl2-chloropyridine-

3-carboxylate(8.5g,
0.0457mol),K2CO3(25.2g,0.183mol),4-N,N-Dimethyl phenyl boronic acid (9.048g, 0.05484mol) and tetrakis (triphenyl phosphine) palladium(0) (0.263g,304.8mol) wereadded to the 1L RB flask containing 250mL of ethanol. RM was refluxed at 850C till thecompletion of the reaction.The solvent was removed under reduced pressure. 200mL of ice cold water was added and the aqueous was extracted with ethyl acetate (30x4mL), washed with brine (20mL), dried over Na2SO4 and ethyl acetate was concentrated. The crude product was purified by column chromatography using silica gel (100-200mesh), gradient (0-15%) ethyl acetate in hexane as the eluent. Yield 4.2g;off white coloured solid ;ms(ESI) m/z:[M+H]-271; m.p-103-1080C; IR(KBr), νmax/cm-1-1100(C-O), 2945(C-H), 2256(C-N), 3106(C-H), 1H-NMR(CDCl3, 400 MHz) -δ 0.8(t,2H), 2.3(s, 6H, 2CH3), 3.5(q,3H), 7.15(dd,J 13.2Hz, 2H), 7.6(q,2H), 8.6(m,1H), 9.1(q,2H)

Step 3: Synthesis of 2-(4-Dimethylamino-phenyl)-nicotinic acid hydrazide 4:

2-(4-Dimethylamino-phenyl)-nicotinic acid ethyl ester(4.2g, 0.0155mol) was added with excess of hydrazine hydrate along with 100mL of ethanol and refluxed at 100°C till the completion of the reaction. After completion, solvent was completely removed and residue was poured to ice cold water, precipitates that are separated out was filtered, washed with 100mL of water and dried. Yield 2.3g; white solid; TLC-ethyl acetate: Hexane (50:50);ms(ESI) m/z: [M+H] 257; IR (KBr), νmax/cm-1: 880 (N-H), 2257(C-N), 2945(C-H),3106(C=O); 1H NMR(CDCl3, 400MHz)-δ2.3(s, 6H, CH3), 4.57 (bs,2H,J12.5Hz), 7.35(dd,J 8.3Hz, 2H), 7.78(q,2H,Ar-H), 8.75(m,1H), 9.23(q,2H).

General procedure for the synthesis of Schiff base derivatives of 2-(4-N, N-Dimethyl phenyl amine) pyridine:

100mLsingle necked RB flask containing solvent ethanol, corresponding hydrazide4 and aldehydesa-f were added in the molar ratio of 1:1. Catalytic amount of acetic acid was added to RM and refluxed for 30min-2h.TLC was monitored to check the completion of the reaction and solvent was removed under reduced pressure. The crude product was added with ice water,precipitates that are separated out was filtered,dried and used without purification for the next step.

General procedure for the synthesis of novel 2-(4-N, N-Dimethyl phenyl amine) pyridine containing 1,3,4-oxadiazoles (micro wave reaction):

The CEM microwave flask containing the corresponding Schiff base derivatives5a-5f (1 equivalent), ethanol and Chloramine T(**1.1equivalent**) were irradiated with a microwave for a period of 30 seconds to 2 minutes.TLC was monitored to check the completion of the reaction.After completion, the reaction mixture was diluted with water and the aqueous was extracted with ethyl acetate (25mL × 3), washed with brine (10mL) and dried over sodium sulphate. Ethyl acetate was completely removed under reduced pressure.The crude product was purified by column chromatography,silica gel 100-200mesh eluent started with 100% n-hexane and the polarity was increased upto 50% using ethyl acetate.

Analytical Data of the Novel 2-(4-N, N_dimethyl phenyl amine) pyridine containing 1, 3, 4-Oxadiazole moiety.

Dimethyl-{4-[3-(5-thiophen-2-yl-[1, 3, 4] oxadiazol-2-yl)-pyridin-2-yl]-phenyl}-amine(a):R = Thiophen-2-yl.

yellow solid; yield 43%;m.p 108-1090C;1HNMR(CDCl3, 400MHz): δ 2.25(s, 6H, CH3),7.25(dd,2H), 7.42(m,3H), 7.56(dd,2H), 8.43(d,J 8.6Hz, 2H), 8.65(d,J 12.5Hz, 1H,Ar-H); 13CNMR(CDCl3, 100MHz): 42, 44,77.1, 114., 134, 143, 145;IR(KBr),νmax/cm-1:1556(N-H), 2889(C-H), 3356(N-H), 3234(C-H); ms(ESI) m/z: [M+H]-349; molecular formula C19H16N4OS; anal.calculated C, 65.50; H, 4.63; N, 16.08; O, 4.59; S, 9.20; found C, 65.52; H, 4.65; N, 16.09; O, 4.60; S, 9.22

Dimethyl-(4-{3-[5-(3-methyl-thiophen-2-yl)-[1, 3, 4] oxadiazol-2-yl]-pyridin-2-yl}-phenyl)-amine (b): R = 3-methyl thiophen-2-yl

Dark brown solid; yield 61%;m.p 132-1340C;; 1HNMR(CDCl3, 400MHz): δ 2.25(s, 6H, CH3), 3.2(s, 3H, CH3),7.25(dd, 2H), 7.42(m, 3H), 7.56(dd, 2H), 8.43(d, J 8.6Hz, 2H) ; 13CNMR(CDCl3, 100MHz): 42, 44, 77.1, 114., 134, 143, 145; IR(KBr), νmax/cm-1: 891 (C-F), 1556(N-H), 2889(C-H), 3356(N-H), 3234(C-H);IR(KBr), νmax/cm-1 : 1569(N-H), 2265(C-N), 2943(C-H), 3256(C-H), 3370(N-H); ms(ESI) m/z:[M+H] 363; molecular formula C20H18N4OS; anal. calculated for C20H18N4OS; C, 66.28; H, 5.01; N, 15.46; O, 4.41; S, 8.85; found C, 66.29; H, 5.03; N, 15.47; O, 4.43; S, 8.86.

{4-[3-(5-Biphenyl-2-yl-[1,3,4]oxadiazol-2-yl)-pyridin-2-yl]-phenyl}-Dimethyl-amine(c): R = 5-Biphenyl-2yl

White solid; yield 82%;m.p132-1340C;1HNMR(CDCl3, 400MHz): δ 3.15(s, 3H, CH3),7.21(m,3H), 7.35(dd,2H), 7.59(d,J 8.5Hz, 2H), 7.46(m,2H), 7.56(m,3H,Ar-H), 7.92(dd,J 12.7Hz, 2H), 8.2(d,J 12.4Hz, 2H) ;13CNMR(CDCl3, 100MHz): 42, 44, 77.16, 115.8, 117, 122, 124, 126, 132.5, 134.5, 136.3,139.2,141.3,143.6,165.7, 172 ;IR(KBr), νmax/cm-1: 1546(N-H), 2276(C-N),2941(C-H), 3237(C-H), 3345(N-H); ms(ESI) m/z: [M+H]-419; molecular formulaC27H22N4O ;anal. calculated for C27H22N4O; C, 77.49; H, 5.30; N, 13.39; O, 3.82; found C, 77.50; H, 5.33; N, 13.41; O, 3.83.

{4-[3-(5-Biphenyl-3-yl-[1,3,4]oxadiazol-2-yl)-pyridin-2-yl]-phenyl}-Dimethyl-amined:R = 5-Biphenyl-3yl

White solid; yield 55%; m.p 172-1740C; 1HNMR(CDCl3, 400MHz): δ 3.16(s, 3H, CH3),7.25(m, 3H), 7.44(dd, 2H), 7.66(d, J 8.5Hz, 2H), 7.87(m, 2H), 7.90(m, 3H, Ar-H), 7.92(dd, J 12.7Hz, 2H), 8.3(d, J 12.4Hz, 2H) ;13CNMR(CDCl3, 100MHz): 42, 44, 77.16, 115.8, 117, 122, 124, 126, 132.5, 134.5, 141.3, 143.6, 165.7,172 ; IR(KBr), νmax/cm-1: 1565(N-H), 2286(C-N), 2951(C-H), 3267(C-H), 3385(N-H); ms(ESI) m/z: [M+H]-419; molecular formulaC27H22N4O ;anal. calculated for C27H22N4O; C, 77.49; H, 5.30; N, 13.39; O, 3.82; found C, 77.50; H, 5.33; N, 13.41; O, 3.83.

(4-{3-[5-(4'-Fluoro-biphenyl-2-yl)-[1, 3, 4] oxadiazol-2-yl]-pyridin-2-yl}-phenyl)-Dimethyl-amine(e): R = 4'-Fluoro-biphenyl-2-yl

Pale yellow solid; yield 62%; m.p 152-1540C; 1HNMR(CDCl3, 400MHz): δ 3.18(s, 3H, CH3),7.35(dd, 2H), 7.54(dd, 2H), 7.68(d, 2H), 7.87(m, 3H), 7.95(m, 3H, Ar-H), 7.92(dd, J 12.7Hz, 2H), 8.3(d, 1H) ;13CNMR(CDCl3, 100MHz): 42, 44, 77, 116, 118, 124, 126, 126, 132.5, 136, 142, 144, 165.7, 171 ; IR(KBr), νmax/cm-1: 1575(N-H), 2386(C-N), 2961(C-H), 3247(C-H), 3485(N-H); ms(ESI) m/z: [M+H]-437; molecular formula C27H21FN4O ;anal. calculated for C27H21FN4O; C, 74.30; H, 4.85; F, 4.35; N, 12.84; O, 3.67; found C, 74.32; H, 4.87; F, 4.36; N, 12.85; O, 3.68

(4-{3-[5-(4'-Fluoro-biphenyl-4-yl)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-phenyl)-Dimethyl-amine (f): R = 4'-Fluoro-biphenyl-4-yl

Pale yellow solid; yield 52%; m.p 136-1380C; 1HNMR(CDCl3, 400MHz): δ 3.19(s, 3H, CH3),7.45(dd, 2H), 7.55(dd, 2H), 7.65(d, 2H), 7.87(m, 3H), 7.95(m, 3H, Ar-H), 7.92(dd, J 12.7Hz, 2H), 8.3(d, 1H) ;13CNMR(CDCl3, 100MHz): 42, 44, 77, 116, 118, 124, 126, 126, 132.5, 136, 142, 144, 165.7, 171 ; IR(KBr), νmax/cm-1: 1565(N-H), 2396(C-N), 2978(C-H), 3267(C-H), 3489(N-H); ms(ESI) m/z: [M+H]-437; molecular formula C27H21FN4O ;anal. calculated for C27H21FN4O; C, 74.30; H, 4.85; F, 4.35; N, 12.84; O, 3.67; found C, 74.32; H, 4.87; F, 4.36; N, 12.85; O, 3.68.

Cytotoxic Evaluation:

MTT assay and Anti proliferative activity:

Theinvitro anti-proliferative activity was carried out on three human carcinoma cell lines namely HeLa, MCF-7 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% CO2. Following 24-48 h.of incubation period, the adherent cells were detached using Trypsin-EDTA solution (HI Media Labs, Mumbai, India). Cell count was determined 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.

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 24hrs, all cells were seeded in duplicates with novel compounds **6a-6f** 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 microplate reader (SPECTROstar 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 = (A570 of treated cells / A570 of control cells) ×100%].

Serial No	Compounds No	IC_{50} values of 1,3,4-oxadiazole in µM		
		HeLa	*MCF7*	*Caco-2*
1	**6a**	23.3	24.6	45.7
2	**6b**	43.5	53.5	32.2
3	**6c**	66.5	102.6	112.3
4	**6d**	123.3	34.4	2.4[1]
5	**6e**	26.9	43.4	18.5
6	**6f**	5.3	41.2	56.3
7	5-FU[2]	6.9	7.5	8.8

Table 1: IC50 values of the novel derivatives of 2-(4-N, N-Dimethyl) pyridine containing 1, 3, 4-oxadiazole moiety.

RESULTS AND DISCUSSION

Chemistry: In this research work sixnovel 1, 3, 4-oxadiazole compounds havebeen synthesized and screenedfor anticancer [6,7,8] activity by MTT procedure invitro on HeLa, MCF7 and Caco-2 cell lines [8,9,10]. Syntheticreactions started with 2-Chloronicotinic acid [12] which is converted

[1]Potent Molecule
[2]Standard

intocorresponding ethyl ester **2**.The ethyl ester of **2**was coupled with 4-N, N-dimethyl phenyl boronic acid and obtained product **3**[12].The intermediate 3[12,13]was refluxed with hydrazine hydrate and synthesized the key intermediate **4**.Carbohydrazide **4**[13,14] was reacted with various aldehydesa-f in presence of acetic acid to get corresponding Schiff base compounds5a-5f. All compounds **5a-5f** were cyclisedusing CAT (Chloramine T) [13,14,15]and synthesized the final1,3,4-oxadiazoles **6a-6f**.

b) Biology: The synthesized 1, 3, 4-oxadiazoles **6a-6f** were evaluated their cytotoxicity on HeLa,MCF7 and Caco2 cell lines16(50µM -500µM)in orderto obtain the effective concentration at 50% of the inhibited cells. The results are expressed as 50% of the total available cells inhibited after 72 h. of incubation. All the compounds in this series showed moderate cytotoxicity on all the three cell lines. The compounds **6d** and **6f** showed good cytotoxicity [16,17] having IC50 of 2.4µM and 5.3µM on Caco-2 and HeLa cell lines respectively.The results of the MTT assay [16,17] of these compounds were compared with the results of the standard 5-FU. Anticancer activity of the 1, 3, 4-oxadiazoles were compared with the standard 5-FU.

CONCLUSION: The six set of novel derivatives of 1, 3, 4-oxadiazoles have been synthesized and evaluated their cytotoxicity by MTT assay. Most of the compounds in this series showed showed moderate cytotoxicity on all the three cell lines.The compound 6d is highly cytotoxic on Caco-2 cell lines having IC502.4µM whereas, compound 6f if highly cytotoxic on HeLa cell lines having IC50 5.3µM. Both these compounds showed very good cytotocicity as compared with the cytotoxicity exhibited by 5-FU. Further screening of these compounds with few of the other carcinoma cell lines and apoptosis mechanism is in progress.

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