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Synthesis, Characterization and biological evaluation of novel Pyrimidine linked 1,2,4-oxadiazoles and substituted pyrazole moieties

^V. Prabhakar*, ^K. Sudhakar Babu, ^L.K. Ravindranath, [+]J. Latha, ^K.Hari naga maddaiah

^Department of Chemistry, Sri Krishnadevaraya University, Anantapuramu, (A P), INDIA.

[+]Department of Bio-technology, Sri Krishnadevaraya University College of Engineering & Technology, S.K.University, Anantapuramu – 515003 (A.P), INDIA.

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ABSTRACT

Objectives: *To synthesize a variety of Pyrimidine analogs, 2, 4, 5, 6, 8 (a-d) and their biological activity was determined.* ***Methods:*** *using 2,4 –di chloro Pyrimidine and hydrazine hydrate, new compounds were synthesized. The structures of all the new compounds are established on the basis of FT-IR, ^{1}H NMR, Mass spectral data. Anti cancer activity was done by Tumor cell count method.* ***Results:*** *All the compounds were synthesized in good yield. Among the new compounds 8a and 8b are found to be most biological activity.* ***Conclusions:*** *The results obtained justify the usage of these compounds from their promising anticancer activity. Therefore, the nature of groups is important for anticancer activity in tumor cell count method.*

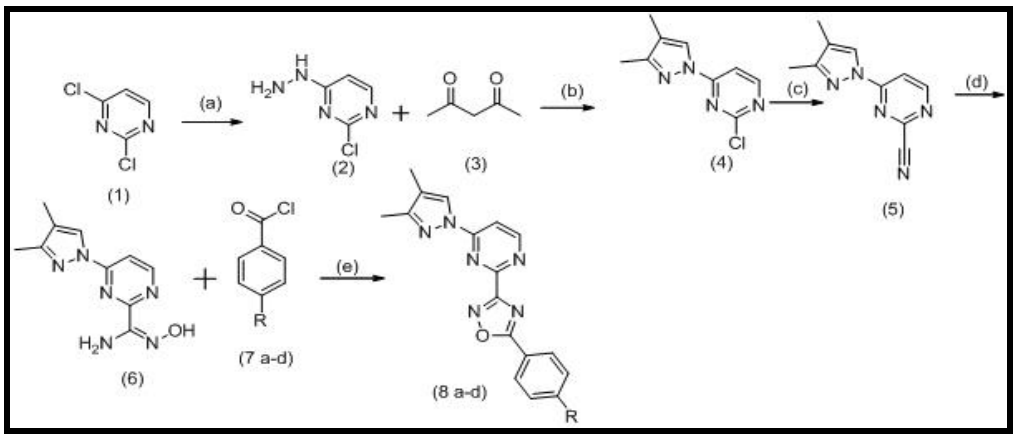
Keywords: *anticancer, 2,4 di chloro Pyrimidine, hydrazine hydrate, 1,2,4-oxa diazole, pyrazoles,*

INTRODUCTION

The five-membered heterocyclic 1,2,4-oxadiazole moitie is synthetic and pharmacological interest. It also forms an important constituent of biologically active compounds including natural products [1]. Sawyer et al. have described such com- pounds as bioisosteres for amides and esters [2], with the 1,2,4-oxadiazoles showing higher hydrolytic and metabolic stability.

To the best of our knowledge, there are only a few examples of natural products with a 1,2,4-oxadiazole core or a structure based on it. The 3-substituted indole alkaloids, phidianidines A and B have been isolated by Carbone et al. from the aeolid opisthobranch Phidiana militaris [3]. They are selective inhibitors of the dopamine transporter DAT and partial agonists of the μ opioid receptor [4]. Moreover, these selective molecules are attractive as CNS targets because neither phidianidine A nor B is cytotoxic. Another example of a natural product with a oxadiazole core is quisqualic acid (**Fig. 1**). This metabolite was obtained from the seeds of Quisqualis indica and Q. fructus [5, 6] and is a strong agonist for AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors and group I metabotropic glutamate receptors [7].

Scheme:



Reagents & Reaction Conditions: (a) Hydrazine hydrate, methanol, reflux, 3hrs; **(b)** Methanol, Reflux, 5hrs; **(c)** DABCO, NaCN, DMSO, Water, RT, 5hrs; **(d)** Hydroxyl amine hydro chloride, TEA, Ethanol, Reflux, 12hrs **(e)** Para substituted benzoyl chlorides, pyridine, RT, 4 hrs

The title compounds) were synthesised in five sequential steps using different reagents and reaction conditions the 8(a-d) were obtained in moderate yields. The structure were established by spectral (IR, ^{1}H-NMR, ^{13}C-NMR and mass) and analytical data.

***Corresponding author:**

V. Prabhakar

Department of Chemistry, Sri Krishnadevaraya University, Anantapuramu, (A P), INDIA.; Mobile NO: 8297140295.

**E-Mail: virupakshi.prabhakar@gmail.com*

Compound	8a	8b	8c	8d
R	$-CF_3$	-F	$-NO_2$	$-OCH_3$

1,2,4-oxadiazoles are widely used in synthetic chemistry, e.g., in the search for antitumor agents. Cancer consists of more than one hundred different diseases, all of which are characterized by the uncontrolled growth and spread of abnormal cells. In this context, the identification of drugs acting as apoptosis inducers represents an attractive approach for the discovery of new anticancer agents. 1,2,4-oxadiazole was found to act as an apoptosis agent by a high-throughput screening (HTS) assay [8]. A series of 1,2,4-oxadia-zole-5-

carboxamides B have been synthesized and tested as inhibitors of the glycogen synthase kinase 3 (GSK-3), a key regulator of both differentiation and cellular proliferation [9].

Pyrazoles are five member ring heterocyclic compounds, have some structural features with two nitrogen atoms in adjacent position and are also called as Azoles [10]. Recently Pyrazole derivatives have been found in nature [11], β- [1-pyrazolyl]alanine was isolated from the seeds of water melons [Citurllus lanatus]. The best described property of almost every group of pyrazoles is in the treatment of inflammation and inflammation associated disorders, such as arthritis [12]. Pyrazole derivatives are the subject of many research studies due to their widespread potential biological activities such as antimicrobial [13], antiviral [14], antitumor [15, 16], antihistaminic [17], antidepressant [18], insecticides [18] and ungicides [18].

Several pyrazole derivatives have been found to possess significant activities such as 5-α-red-uctase inhibitor [19], antiproliferative [20], antiparasitic [21], herbicides [22]. A good number of pyrazoles have also been reported to have interesting biological activities like anti-Inflammatory [23] and antiprotozoal [24, 25] which render them valuable active ingredients of medicine and plant protecting agents.

MATERIALS AND METHODS

Materials and physical measurements: Melting points were measured by a Stuart Scientific melting point apparatus in open capillaries and are uncorrected. Infrared spectra (KBr discs) were recorded on a Bruker Alpha (FTIR) Spectrometer. ^{1}H-NMR spectra were recorded on a Bruker spectrometer operating at 400 MHz using DMSO-d6 and CDCl3 as a solvent with TMS as an internal standard. Mass spectra was recorded on an agilent-1100 periods LC-MSD. Elemental analysis was performed using a (EURO EA 3000 instrument). Acme silica gel-G and Merck silica gel (100 to 200, 60 to 120 meshes) were used for analytical TLC and Column chromatography respectively. All other analytical grade chemicals and solvents were obtained from commercial sources and used as received standard procedure.

Experimental Section:

Synthesis of 2-chloro-4-0hydrazinylpyrimidine (2):

A mixture of 2,4 di chloro Pyrimidine (1) (0.01mol) in methanol was taken and cooled to 0-5^0 c in an ice bath,tri ethyl amine (0.01 mol)was added to the cold reaction mixture and then hydrazine hydrate (0.012 mol) was added slowly at 5-10^0 c. The reaction mass was allowed to stir at room temperature for 1hr. The solid thus obtained was filtered ,washed with chilled water and dried to afford compound (2), pale yellow solid. Melting point 140^{0}c-142^{0}c.

^{1}H NMR (DMSO-d6,ppm): δ7.5 (1H, d, j=8HZ), 6 (1H, d, J=8HZ), 2 (2H, S, broad), 3.9 (1H, S, broad).

IR (KBr, cm-1):

700 (C-Cl), 3450 (-NH), 3350 and 3400 (Two peaks indicates-NH_2), 1080 (C-N), 1600 (N-H bending), 3100 (aromatic C-H), 1500 (aromatic C=C).

^{13}C NMR(DMSO-d6,ppm): 155, 160, 105, 170 (4 Aromatic carbons).

Synthesis of 2-chloro-4-(3,4-dimethyl-1H-pyrazol-1-yl) Pyrimidine(4):

To a mixture of compound (2) (0.01 mol) in methanol (50 ml), acetyl acetone (3) (0.01 mol) was added the reaction mixture was refluxed for 5 hrs and then the obtained solid was filtered off, dried and crystallized from ethanol to give compound (4).

IR (KBr, cm-1): 2940 (C-H), 1655 (C=N), 1500 (C=C), 728 (C-Cl).

^{1}H NMR (DMSO-d6,ppm): δ2 (6H, S, 2×CH_3), 7.5 (S, 1H, pyrazoleproton), 7.3 (1H, d, J=7HZ), 8.4 (1H, d, J=7HZ).

Synthesis of 4-(3,4-dimethyl-1H-pyrazol-1-yl)pyrimidine-2-carbonitrile (5):

To a solution of compound 4 (0.6mmol) and DABCO (0.6mmol) in DMSO and water (9:1, 6mL) was added potassium cyanide (0.9mmol). The solution was stirred for 5h at room temperature. Then the mixture was poured into ice water (30mL) and extracted with ethyl acetate (2x30mL). The combined organic phases were washed with saturated solution of sodium bicarbonate (30mL), dried over sodium sulfate, filtered and concentrated. Purification by flash chromatography gave the pure compound (5) as a white solid with 45% yield. (All labware in contact with potassium cyanide was decontaminated with bleach)

IR (KBr, cm-1): 2940 (C-H), 1655 (C=N), 1500 (C=C), 2200 (Presence of nitrile gp).

^{1}H NMR (DMSO-d6,ppm): δ2 (6H, S, 2×CH_3), 7.5 (S, 1H, pyrazole proton), 7.8 (1H, d, J=7HZ), 8.9 (1H, d, J=7HZ).

^{13}C-NMR (DMSO-d_6, δ, ppm): 110 TO 165 (7 aromatic carbons), 118 (indicates presence of Nitrile gp).

Synthesis of 4-(3,4-dimethyl-1H-pyrazol-1-yl)-N'-hydroxypyrimidine-2-carboximidamide (6):

A mixture of compound (5) (0.01 mol) in ethanol (10v), hydroxyl amine hydro chloride (0.025mol) and tri ethyl amine (0.05 mol) was added. The resultant solution was stirred and refluxed for 12hrs. reaction was progress was monitored by TLC. after completion of starting material, cool to rt, the ethanol was evaporated and then the mixture was poured in cool water and left to overnight, the solid crystal was was filtered and dried.

Yield: 80% colourless crystals, **mp**117-118^{0}c

IR (KBr, cm-1): 3488 (-OH str), 3400 (-NH_2), 1600 (Ar C=C), 3150 (Ar C-H), 1650 (C=N), 1370 (C-N).

^{1}H NMR (DMSO-d6,ppm): δ2 (6H, S, 2×CH_3), 7.5 (S, 1H, pyrazoleproton), 7.3 (1H, d, J=7HZ), 8.4 (1H, d, J=7HZ), 7 (2H, S, -NH_2), 2 (1H, S).

Synthesis of 3-(4-(3,4-dimethyl-1H-pyrazol-1-yl)pyrimidin-2-yl)-5-(4-(trifluoromethyl/Fluoro/nitro/methoxy)phenyl)-1,2,4-oxadiazole(8a-d):

In a clean and dry RBF compound (6) (0.01mol) in pyridine (7v) was taken, to this a prepared solution of Para substituted benzoyl chlorides(0.012mol) (7 a-d) was added. Then the mixture was stirred at RT for 4 hrs. pyridine was removed under vacuum. The solid was obtained was purified by column chromatography over silica gel with a mixture of hexane/ethyl acetate as eluant. to get compound 8 (a-d)

3-(4-(3,4-dimethyl-1H-pyrazol-1-yl)pyrimidin-2-yl)-5-(4-(trifluoromethyl) phenyl)-1,2,4-oxadiazole (8a):

Yield: 48% (colourless crystals)
Melting Point: 110^{0}c-112^{0}c
R_f value: 0.6

IR (KBr, cm-1): 1600 (Ar C=C), 3150 (Ar C-H), 1650 (C=N), 1370 (C-N), 1200 (C-F).

^{1}H NMR (DMSO-d6,ppm): δ2 (6H, S, 2×CH_3), 7.5 (S, 1H, pyrazoleproton), 7.3 (1H, d, J=7HZ), 8.4 (1H, d, J=7HZ), 7.5 (1H, d, j=8HZ), 7.8 (1H, d, j=8HZ).

^{13}C-NMR (DMSO-d_6, δ, ppm): 110 to 175 (16 aromatic carbons), 20 (2×CH_3, aliphatic carbons).

Chemical Formula: $C_{18}H_{13}F_3N_6O$
Molecular Weight: 386.33
MS m/z: 386.11 (100.0%), 387.11 (21.7%),

Elemental Analysis:
Calculated C, 55.96; H, 3.39; N, 21.75;
Found: C, 55.94; H, 3.37; N, 21.70;

3-(4-(3,4-dimethyl-1H-pyrazol-1-yl)pyrimidin-2-yl)-5-(4-fluorophenyl)-1,2,4-oxadiazole (8b):

Yield: 47 %(colourless crystals).
Melting Point: 130^{0}c-132^{0}c.
R_f value: 0.7.

IR (KBr, cm-1): 1600 (Ar C=C), 3150 (Ar C-H), 1650 (C=N), 1370 (C-N), 1200 (C-F).

^{1}H NMR (DMSO-d6,ppm): δ2 (6H, S, 2×CH_3), 7.5 (S, 1H, pyrazoleproton), 7.3 (1H, d, J=7HZ), 8.4 (1H, d, J=7HZ), 8.5 (1H, d, j=8HZ), 7.2 (1H, d, j=8HZ).

^{13}C-NMR (DMSO-d_6, δ, ppm): 110 to 175 (15 aromatic carbons), 20 (2×CH_3, aliphatic carbons).

Chemical Formula: $C_{17}H_{13}FN_6O$
Molecular Weight: 336.32
MS m/z: 336.11 (100.0%), 337.12 (18.6%),
Elemental Analysis: Calculated: C, 60.71; H, 3.90; N, 24.99(%)
Found: C, 60.68, H, 3.88; N, 24.97;

3-(4-(3,4-dimethyl-1H-pyrazol-1-yl)pyrimidin-2-yl)-5-(4-nitrophenyl)-1,2,4-oxadiazole (8c):

Yield: 57% (colourless crystals)
Melting Point: 140^{0}c-142^{0}c
R_f value: 0.8

IR (KBr, cm-1): 1600 (Ar C=C), 3150 (Ar C-H), 1650 (C=N), 1370 (C-N), 1530 and 1350 (N-O stret, two bands).

^{1}H NMR (DMSO-d6,ppm): δ2 (6H, S, 2×CH_3), 7.5 (S, 1H, pyrazoleproton), 7.3 (1H, d, J=7HZ), 8.4 (1H, d, J=7HZ), 8.4 (1H, d, j=8HZ), 8.2 (1H, d, j=8HZ).

^{13}C-NMR (DMSO-d_6, δ, ppm): 110 to 175 (15 aromatic carbons), 20 (2×CH_3, aliphatic carbons).

Chemical Formula: $C_{17}H_{13}N_7O_3$
Molecular Weight: 363.33
MS m/z: 363.11 (100.0%), 364.11 (21.2%)

Elemental Analysis:
Calculated: C, 56.20; H, 3.61; N, 26.99;
Found: C, 56.18; H, 3.60; N, 26.97

3-(4-(3,4-dimethyl-1H-pyrazol-1-yl)pyrimidin-2-yl)-5-(4-methoxyphenyl)-1,2,4-oxadiazole(8d):
1,2,4-oxadiazole(8 c):

Yield: 47% (colourless crystals)
Melting Point: 150^{0}c-152^{0}c
R_f value: 0.72

IR (KBr, cm-1): 1600 (Ar C=C), 3150 (Ar C-H), 1650 (C=N), 1370 (C-N), 1530 and 1150 (C-O Stret).

^{1}H NMR (DMSO-d6,ppm): δ2 (6H, S, 2×CH_3), 7.5 (S, 1H, pyrazoleproton), 7.3 (1H, d, J=7HZ), 8.4 (1H, d, J=7HZ), 8.0 (1H, d, j=8HZ), 6.9 (1H, d, j=8HZ), 3.8 (3H, S, -OCH_3).

^{13}C-NMR (DMSO-d_6, δ, ppm): 110 to 175 (15 aromatic carbons), 20 (2×CH_3, aliphatic carbons), 55 (-O**C**H_3 carbon)

Chemical Formula: $C_{18}H_{16}N_6O_2$
Molecular Weight: 348.36
MS m/z: 348.13 (100.0%), 349.14 (19.7%),

Elemental Analysis:
Calculated C, 62.06; H, 4.63; N, 24.12; O, 9.19
Found: C, 62.04; H, 4.60; N, 24.10; O, 9.16

Biological Evaluation:

The synthesized compounds were subject to assessment of anticancer activity. The test compounds (5, 8(a-d)) 25mg/kg body weight and standard drug 5-flurouracil 5mg/kg body weight were used.

Male and female mixed Swiss albino mice of about 8 weeks of age with an average body weight of 15-18g were used for the Experiment. The animals were acclimatized to laboratory condition with 12hr/12hr cycles of light and dark at 25^{0}c for 10 days before commencement of the experiment. they were fed standard pellet diet were given fresh water adlibium.

EAC Cells were maintained in vivo in swiss albino mouse by pass aging every 10 days.EAC Cells that were 9 days old was used for screening of the synthesized compounds.

The evaluation of the test drug was carried out by comparing the cell count of the test with that of the control. The percentage inhibition of cell count is obtained by the following expression:

Percentage inhibition of Ascetic cells (TCI)= (1-T/C)×100

Where T is the average no of the ascetic cells per ml in test animals and C is the average no of the ascetic cells per ml in control animals.

Survival time in days and percentage increase of life span of test animals in comparison to control animal is obtained by the following expression

% increase of life span = (1-C/T) X100

Where C is the survival time in days of control animals is the survival time in days for the test animal.

The antitumor activities of the compounds were measured in EAC animals with respect to the following parameters such as:

Tumor weight: The mice were dissected and the ascetic fluid was collected from the peritoneal cavity. The tumour weight was calculated from the difference in weight of mice before dissection and after collection of ascetic fluid after dissection.

Tumor Cell Count: The ascetic fluid was taken in a WBC Pipette and diluted 100 times. Then a drop of the diluted cell suspention was placed on the neubauer counting chamber and the no of cells in the 64 small squares were counted.

Table No. 1: Anti cancer activity of synthesized compounds on Swiss albino mice

Group	Dose of drug mg/kg	Average tumour weight (g)	%TWI	Average cell – count (Number)	Average cell count/ml fluid	%TCI
I	-	-	-	-	-	-
II	-	4	0.00	45	2.68X10^8	0.00
III	24	1.8	45.6	27	1.75X10^8	35.5
IV	24	2.5	37.00	30	1.87X10^8	30.2
V	5	0.00	100	0	-	100

Table No. 2: Survival time determination of the test animal

Group	Survival time(Days)	% increase of life spam
II	16	-
III	30	45
IV	25	31

From the above experiments shows the compounds 8a to 8c compounds shown more potent activity and 5 shows moderate activity.

RESULTS AND DISCUSSION

Spectral studies: Hydrazino Pyrimidine (2) was synthesised according to the reported procedure [26]. The reaction of 2,4 di chloro Pyrimidine with hydrazinehydrate in methanol to afford the corresponding hydrazine Pyrimidine (2) which was reacted with acetyl acetone as per the reportrd procedure [26] to afford 2-chloro4-(3,4-dimethyl-1H-pyrazol-1-yl)Pyrimidine (4).

Which was reacted with sodium cynide to afford 4-(3,4-dimethyl-1H-pyrazol-1-yl)pyrimidine-2-carbonitrile (5) according to the reported procedure [27], which was reacted with hydroxyl amine hydrochloride in ethanol to afford 4-(3,4-dimethyl-1H-pyrazol-1-yl)-N'-hydroxypyrimidine-2-carboximidamide(6) according to the reported procedure [28], which was reacted with para substituted benzoyl chlorides to afford as Title compounds (8 a-d) according to the repored procedure [28].

The structural elucidation of the newly synthesized compounds 2, 4 and 5,6,8(a-d) was done on the basis of spectral and analytical data. The appearance of IR spectral values for newly

synthesized compounds near1600(Ar C=C),3150(Ar C-H),1650(C=N),1370(C-N),1530 and 1150(C-O Stret) 2200(-Cyno group stret) respectively. The appearance of ^{1}H-NMR signals for newly synthesized compounds near 2 (6H, S, 2×CH_3), 7.5 (S, 1H, pyrazoleproton), 7.3 (1H), 8.4 (1H), 8.0 (1H), 6.9 (1H), 3.8 (3H, S, -OCH_3) respectively.

Readily available starting materials and simple synthesizing procedures make this method is very attractive and convenient for the synthesis of various Pyrimidines. Formation of products was confirmed by recording their Elemental analysis, ^{1}H NMR, FT-IR and mass spectra. The Elemental analysis data showed good agreement between the experimentally determined values and the theoretically calculated values with in ±0.4%

CONCLUSION

In conclusion, a series of new Pyrimidine analogs, 2,4,5,6,8(a-d) were synthesized in good yield, characterized by different spectral studies and their anti cancer activity have been evaluated. Various derivatives of Pyrimidine showed potent anticancer activity ,like compounds with electron withdrawing groups. Among the synthesized compounds 8a and 8b showed excellent anticancer activity. Electron donating methoxy group in 8d less activity when compared to other compounds in the series.

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