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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF SOME NEW N[1]-SUBSTITUTED-PYRAZOL-4-CARBALDEHYDE BEARING 2, 4-DICHLORO PHENYL MOIETY

B. Chandrasekhar. Kumar[1]*, K. R. Venugopala Reddy[2], Fasiulla Khan[1]
[1]Department of Chemistry, Manipal Institute of Technology, Manipal University, Udupi, Karnataka, India
[2]Department of Chemistry, Vijayanagara Sri Krishanadevaraya University, Bellary, Karnataka, India
*Corresponding Author Email: muttappa2009@gmail.com
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ABSTRACT
A series of new 3-(2, 4-dichlorophenyl)-1-(2-(substituted phenoxy) acetyl)-1H-pyrazole-4-carbaldehyde were synthesized from substituted simple phenols. Substituted simple phenols were refluxed with ethylchloroacetate in presence of anhydrous potassium carbonate to yield substituted ethyl phenoxy acetate. Further substituted ethyl phenoxy acetate on treatment with hydrazine hydrate in ethanol yielded substituted 2-phenoxyacetohydrazide in turn on refluxing with 2,4-dichloro acetophenones yielded N'-(1-(2,4-dichlorophenyl)ethylidene)-2-(substituted phenoxy) acetohydrazides which on further treatment with DMF and $POCl_3$ undergo Vilsmer - Haack reaction to yield the title compounds i.e. 3-(2,4-dichlorophenyl)-1-(2 (substituted phenoxy)acetyl)-1H-pyrazole-4-carbaldehyde (4a-j). The chemical structures of these compounds were confirmed by various physic-chemical methods viz, IR, ^{1}H NMR, mass spectral data and elemental analysis. Newly synthesized compounds were screened in vitro for their antimicrobial activity against varieties of gram +ve and gram -ve bacterial strains such as *Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli* and fungi strains *Candida albicans* and *Aspergillus niger*. Antimicrobial activity was carried out by cup-plate method; zone of inhibition shown by the compounds against selected microorganisms was measured by using antibiotic zone reader. The minimum inhibitory concentration was carried out for the promising compounds were determined by serial dilution method. The chloro and bromo possessing moiety have shown enhanced biological activity stimulated to synthesize more efficient drug containing more electronegative moiety against pathogenic microorganisms.
Keywords: Hydrazones, pyrazol-4-carbaldehyde, spectral studies, antimicrobial activity.

INTRODUCTION

Five-membered heterocyclic compounds with an additional hetero atom are termed as azoles. Azoles containing two nitrogen atoms; one oxygen and one nitrogen atom; one sulfur and one nitrogen atom in the 1, 2-position are designated as pyrazole, isoxazole and isothiazole respectively. Many of the azoles comprise the ring system of several natural and synthetic compounds which are observed as vital for the humankind as drugs, dyes and pesticides[1]. Pyrazole was first described by Buchner in 1889 during the decomposition of pyrazole 3, 4, 5-carboxylic acid. The dihydro pyrazoles are called pyrazolines and depending on the position of the double bond three forms of pyrazolines are possible. These are 1-pyrazoline, 2- pyrazoline and 1, 3-pyrazoline. Pyrazoles are more stable than pyrazolines and can be converted into the later by mild oxidizing agents like bromine and lead tetra acetate. Pyrazole is a colorless solid with melting point 70°C and is soluble in water. It possesses penetrating smell unlike most of the amines. Pyrazole has a high boiling point (187°C). Pyrazoles can be synthesized by various methods and the most straight forward method involves the reaction between 1, 3-dicarbonyl compound and hydrazine. A simple pyrazole is obtained with 1, 3-dicarbonyl compound such as acetyl acetone and hydrazine hydrate or phenyl hydrazine. Pyrazoles can also be synthesized from α, ß-ethylene carbonyl derivative and hydrazide. α, ß-acetylene carbonyl compounds can also be used. In this case the hydrazine may form hydrazone or add directly to the acetylenic bond. Pyrazole carbaldehydes can be prepared via hydrazones by Vilsmeir-Hack reaction. Vilsmeir-Hack reaction is a cyclic reaction that takes place in presence of $DMF/POCl_3$ often referred as Vilsmeir-Hack reagent[2]. Pyrazoles can be efficiently synthesized on solid supports by using "catch-release"- solid phase strategy[3]. The condensation of the carbonyl function in pyrazole carbaldehydes with some active methylene groups can be carried out under ultrasound irradiation which results in biologically important compounds[4]. Pyrazole and pyrazole carbaldehyde derivatives coupled with other heterocyclic compounds like 1, 8-naphthyridine, benzopyrans, anthracene, pyrimidine, benzofuran, etc are reported to possess antibacterial and antifungal activities[5-12]. The pyrazole derivatives were also reported to possess mono amino oxidase inhibitory activity[13-14]. Pyrazole-related nucleosides were reported to show antiviral, antitumor activities[15]. Pyrazole derivatives were also reported to possess Helicobacter pyrolidihydroorotate dehydrogenase inhibitory activity[16]. 3-(4-phenoxyphenyl) pyrazoles were reported as a novel class of sodium channel blockers[17]. Pyrano [2, 3-c]Pyrazole derivatives were reported with molluscicidal activity[18]. Pyrazoles were also reported to possess cytotoxic[19-20] and cannabinod-1 receptor antagonist[21], Anti convulsant[22] activities. Pyrazole-4-carboxamides were reported to possess anti-leukemic activity[23]. Apart from that pyrazole derivatives were also found to possessAT-1 antagonistic[24], DNA gyrase inhibitory[25] and antileukemic[26] properties. Prompted by the above reports it was contemplated to synthesize and evaluate some pyrazole carbaldehydes carrying 2, 4-dichloro phenyl moiety via hydrazones by Vilsmier - Haack reaction.

MATERIALS AND METHODS

Melting points were taken in open capillaries and are uncorrected. Infra-red spectra (KBr in cm^{-1}) were recorded on 8400S, Shimadzu FT-IR spectrophotometer. ^{1}H-NMR spectra were measured by Bruker Ascend-TM 400MHz-NMR spectrometer, deuterated solvents such as dimethyl-sulphoxide (DMSO-d_6), methanol (CD_3OD) and also chloroform ($CDCl_3$) were used as solvents and the chemical

shifts were quoted as δ-value relative to tetramethyl silane (TMS, δ=O) as an internal standard. Mass spectra were recorded on LC-MS Schimadzu 2010A spectrometer. The elemental analysis was carried out on a Perkin Elmer C, H, N analyzer. The purity of the compounds was monitored by thin layer chromatography on silica gel plates and iodine was used as a visualizing agent.

Synthesis

General procedure for the synthesis of orthoandpara substituted ethyl phenoxy acetate (1a-j)

A mixture of phenol (0.05 mol), ethylchloroacetate (0.05 mol) was refluxed in dry acetone in presence of potassium carbonate for 24 hours on water bath. The reaction mixture was cooled and filtered, the excess solvent was distilled and the solid thus separated was recrystallized from ethanol.

General procedure for the synthesis of 2-phenoxyacetohydrazide (2a-j)

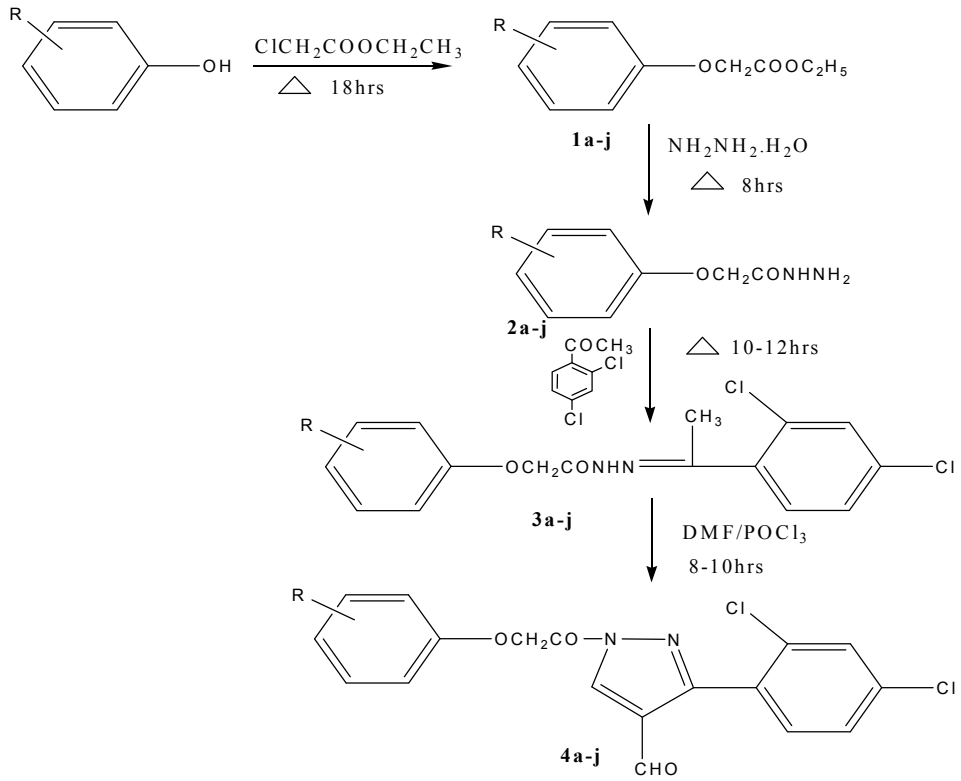
A mixture of compounds (1a-j) (0.05 mol), hydrazine hydrate (0.07 mol) in ethanol were refluxed for 6 hours. The excess of solvent is distilled off and the solid thus separated was recrystallized from ethanol.

General procedure for the synthesis of 2-(substituted phenoxy)-*N*'-[1-(2, 4-dichlorophenyl) ethylidene] aceto hydrazide 3(a-j)

A mixture of (2a-j) (0.01mol) and 2, 4-disubstituted acetophenone (0.01 mol) was refluxed along with a few drops of glacial acetic acid for 10- 12 hours. The reaction mixture was cooled and then poured on to crushed ice and stirred well. The separated solid was filtered and recrystallized from ethanol.

Synthesis of 1-[(substituted phenoxy)acetyl]-3-(2,4-dichlorophenyl)-1H-pyrazole-4-carbaldehyde 4(a-j)

Compounds (3a-j), (0.005 mol) were dissolved in Vilsmeier - Haack reagent (DMF – 10 ml and $POCl_3$ – 2 ml) and stirred at room temperature for 8-10 hours. The contents were poured onto crushed ice and neutralized with $NaHCO_3$; the solid thus separated was filtered, washed with cold water, dried and recrystallized from DMF.



Scheme 1: Preparation of 1-[(substituted phenoxy)acetyl]-3-(2,4-dichlorophenyl)-1H-pyrazole-4-carbaldehyde (4a-j)

3-(2, 4-dichlorophenyl)-1-(2-phenoxyacetyl)-1H-pyrazole-4-carbaldehyde (4a)

IR(KBr)(cm^{-1})

3013.89(Ar-H str), 1667.81(C=O str) 1594.23 (C=N of ring str.), 1484.00 (Ar-C=C str), 1198.07 (C-O-C str), 756.09(C-Cl str). **^{1}H-NMR (400 MHz, ppm):** 9.3(s, 1H, -CHO), 8.0-6.5(m, 9H, Ar-H), 5.3(s, 2H, OCH_2) **MS (m/z):** 376 (M^+); Anal. Calcd (found) for $C_{18}H_{12}Cl_2N_2O_3$, C, 57.60 (56.56); H, 3.20(3.07); N, 6.40(6.36)

1-(2-(2-chlorophenoxy) acetyl)-3-(2, 4-dichlorophenyl)-1H-pyrazole-4-carbaldehyde(4b)

IR(KBr)(cm^{-1})

3085.89(Ar-H str), 1681.81(C=O str) 1589.23 (C=N of ring str.), 1480.00 (Ar-C=C str), 1188.07 (C-O-C str), 750.00(C-Cl str). **^{1}H-NMR (400 MHz, ppm):** 9.3(s, 1H, -CHO), 8.0-6.5(m, 8H, Ar-H), 5.3(s, 2H, OCH_2). **MS (m/z):** 410 (M^+); Anal. Calcd (found) for $C_{18}H_{11}Cl_3N_2O_3$, C, 52.81(51.77); H, 2.68(2.65); N, 5.86(5.83)

3-(2, 4-dichlorophenyl)-1-(2-(2, 4, 6-trichlorophenoxy)acetyl)-1H-pyrazole-4-carbaldehyde(4c)
IR(KBr)(cm^{-1}): 3043.89(Ar-H str), 1691.81(C=O str) 1556.23 (C=N of ring str.), 1483.00 (Ar-C=C str), 1198.07 (C-O-C str), 756.37(C-Cl str). **^{1}H-NMR (400 MHz, ppm):** 9.3(s, 1H, -CHO), 8.0-6.5(m, 6H, Ar-H), 5.3(s, 2H, OCH_2). **MS (m/z):** 479 (M^+); Anal. Calcd (found) for $C_{18}H_9Cl_5N_2O_3$, C, 45.18(44.15); H, 1.88(1.00); N, 5.02(5.00)

3-(2, 4-dichlorophenyl)-1-(2-(4-hydroxyphenoxy)acetyl)-1H-pyrazole-4-carbaldehyde(4d)
IR(KBr)(cm^{-1}): 3304.07(OH str), 3009.89(Ar-H str), 1698.81(C=O str) 1589.07 (C=N of ring str.), 1488.84 (Ar-C=C str), 1194.07 (C-O-C str), 756.78 (C-Cl str). **^{1}H-NMR (400 MHz, ppm):** 11.3 (s, 1H, OH), 9.4(s, 1H, -CHO), 8.0-6.5(m, 8H, Ar-H), 5.3(s, 2H, OCH_2). **MS (m/z):** 392 (M^+); Anal. Calcd (found) for $C_{18}H_{12}Cl_2N_2O_4$, C, 55.24(54.22); H, 3.06(3.00); N, 6.13(6.11)

3-(2, 4-dichlorophenyl)-1-(2-(4-nitrophenoxy)acetyl)-1H-pyrazole-4-carbaldehyde(4e)
IR(KBr)(cm^{-1}): 3006.37 (Ar-H str), 1698.81(C=O str) 1573.23 (C=N of ring str.), 1434.08 (Ar-C=C str), 1197.07 (C-O-C str), 756.05(C-Cl str). **^{1}H-NMR (400 MHz, ppm):** 9.6(s, 1H, -CHO), 8.0-6.5(m, 8H, Ar-H), 5.2(s, 2H, OCH_2). **MS (m/z):** 421 (M^+); Anal. Calcd (found) for $C_{18}H_{11}Cl_2N_3O_5$, C, 51.42(50.30); H, 2.61(2.58); N, 10.00(9.68)

1-(2-(4-bromophenoxy)acetyl)-3-(2,4-dichlorophenyl)-1H-pyrazole-4-carbaldehyde(4f)
IR(KBr)(cm^{-1}): 3005.89 (Ar-H str), 1698.81(C=O str) 1568.23 (C=N of ring str.), 1473.00 (Ar-C=C str), 1156.07 (C-O-C str), 758.88 (C-Cl str). **^{1}H-NMR (400 MHz, ppm):** 9.4(s, 1H, -CHO), 8.0-6.5 (m, 8H, Ar-H), 5.3 (s, 2H, OCH_2). **MS (m/z):** 455 (M^+); Anal. Calcd (found) for $C_{18}H_{11}BrCl_2N_2O_3$, C, 47.57(46.55); H, 2.42(2.40); N, 5.28(5.26)

3-(2,4-dichlorophenyl)-1-(2-(4-methoxyphenoxy)acetyl)-1H-pyrazole-4-carbaldehyde(4g)
IR(KBr)(cm^{-1}): 3085.89(Ar-H str), 1691.81(C=O str) 1589.23 (C=N of ring str.), 1487.00 (Ar-C=C str), 1108.07 (C-O-C str), 755.05(C-Cl str). **^{1}H-NMR (400 MHz, ppm):** 9.5(1H, s, -CHO), 8.0-6.5(m, 8H, Ar-H), 5.2(s, 2H, OCH_2) 3.8(s, 3H, OCH_3). **MS (m/z):** 406 (M^+); Anal. Calcd (found) for $C_{19}H_{14}Cl_2N_2O_4$, , C, 56.29(55.25); H, 3.45(3.43); N, 3.45(3.44)

1-(2-(2,4-dichlorophenoxy)acetyl)-3-(2,4-dichlorophenyl)-1H-pyrazole-4-carbaldehyde(4h)
IR(KBr)(cm^{-1}): 3097.89 (Ar-H str), 1694.81(C=O str) 1571.23 (C=N of ring str.), 1488.00 (Ar-C=C str), 1183.07 (C-O-C str), 751.05(C-Cl str). **^{1}H-NMR (400 MHz, ppm):** 9.7(s, 1H, -CHO), 8.0-6.5(m, 7H, Ar-H), 5.3(s, 2H, OCH_2). **MS (m/z):** 445 (M^+); Anal. Calcd (found) for $C_{18}H_{10}Cl_4N_2O_3$, C, 48.64(47.62); H, 2.25(2.23); N, 5.40(5.39)

3-(2,4-dichlorophenyl)-1-(2-(2-hydroxyphenoxy)acetyl)-1H-pyrazole-4-carbaldehyde(4i)
IR(KBr)(cm^{-1}): 3083.89(Ar-H str), 1681.81(C=O str) 1589.23 (C=N of ring str.), 1474.09 (Ar-C=C str), 1138.07 (C-O-C str), 756.00(C-Cl str). **^{1}H-NMR (400 MHz, ppm):** 9.3(s, 1H, -CHO), 8.0-6.5(m, 8H, Ar-H), 5.3(s, 2H, OCH_2). **MS (m/z):** 392 (M^+); Anal. Calcd (found) for $C_{18}H_{12}Cl_2N_2O_4$, C, 55.24(54.27); H, 3.06(3.02); N, 6.13(6.10)

1-(2-(4-chlorophenoxy)acetyl)-3-(2,4-dichlorophenyl)-1H-pyrazole-4-carbaldehyde(4j)
IR(KBr)(cm^{-1}): 3007.89(Ar-H str), 1686.81(C=O str) 1596.23 (C=N of ring str.), 1485.00 (Ar-C=C str), 1197.07 (C-O-C str), 754.00(C-Cl str). **^{1}H-NMR (400 MHz, ppm):** 9.4(s, 1H, -CHO), 8.0-6.5(m, 8H, Ar-H), 5.2(s, 2H OCH_2). **MS (m/z):** 410 (M^+); Anal. Calcd (found) for $C_{18}H_{11}Cl_3N_2O_3$, C, 52.81(51.79); H, 2.68(2.66); N, 5.86(5.83)

Antimicrobial activity

***In vitro* antibacterial screening**

All the newly synthesized compounds (4a-j) were screened *in vitro* for their antibacterial activity against *Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* by disc diffusion method[14] was performed using Mueller, Hinton agar (Hi-Media) medium. Each compound was tested at a concentration at 40 µg/mL in DMSO. The diameter of zone of inhibition was measured in mm after 24 h incubation at 37^{o}C. The known compound ciprofloxacin was used as standard drug for comparison study. The antibacterial screening data are recorded in Table 2.

***In vitro* antifungal screening**

The compounds (4a-j) were evaluated for their *in vitro* antifungal activity against *Candida albicans* and *Aspergillus nigar* using disc diffusion method[15] with sabouraud's dextrose agar (Hi-Media). Each compound was tested at a concentration of 40 µg/mL in DMSO. The zone of inhibition (mm) was measured. The known compound Amphotericin B was used as standard drug for comparison study. The antifungal screening data are recorded in Table 2.

RESULTS AND DISCUSSION

All the prepared compounds (4a-j) are crystalline solids. All the compounds obtained were having pale yellow to light brown in color and the melting points are reported in Table 1. The compounds (4a-j) are stable at ordinary conditions and are non-hygroscopic. All the compounds are insoluble in water and common organic solvents, but readily soluble in DMF and DMSO.

Synthesis of Pyrazole-4-carbaldehyde derivatives by the above described method resulted in products with good yield. All the reactions were carried out under prescribed laboratory conditions. The solvents and reagents used in synthetic work were of laboratory grade and were purified by distillation. The structures of the newly synthesized compounds were established on the basis of spectral data (IR, ^{1}HNMR and Mass). The newly synthesized pyrazole-4-carbaldehyde with 2,4-dichloro phenyl are tested for antimicrobial activity against *B. subtilis, p. aerugenosa, E. coli, S. aureus, C. albicans* and *A. nigar* showed moderate to significant activity. Compounds 4c and 4f have shown significant antimicrobial activity against all selected bacteria and fungi due to the presence of halogen (bromo and 2, 4, 6-trichloro) attached to the phenoxy moiety. Compounds 4a, 4b, 4d, 4e, 4g, 4h, 4i and 4j having phenyl, -OH, Cl, NO_2, and 4-OCH_3 groups have shown moderate activity against some of the selected bacteria and fungi.

Table 1: Represents physical data of new pyrazol-4-carbaldehyde derivatives

Code	R	Molecular formula	M. W	M. P (^{0}C)	Yield (%)
4a	-H	$C_{18}H_{12}Cl_2N_2O_3$	375	152-156	68
4b	-2-Cl	$C_{18}H_{11}Cl_3N_2O_3$	409	164-166	72
4c	-2,4,6-Cl	$C_{18}H_9Cl_5N_2O_3$	478	172-174	78
4d	-4-OH	$C_{18}H_{12}Cl_2N_2O_4$	391	150-152	70
4e	-4-NO_2	$C_{18}H_{11}Cl_2N_3O_5$	420	148-151	65
4f	-4-Br	$C_{18}H_{11}BrCl_2N_2O_3$	454	127-129	60
4g	-4-OCH_3	$C_{19}H_{14}Cl_2N_2O_4$	405	138-140	55
4h	-2,4-Cl	$C_{18}H_{10}Cl_4N_2O_3$	444	136-138	53
4i	-2-OH	$C_{18}H_{12}Cl_2N_2O_4$	391	174-177	76
4j	-4-Cl	$C_{18}H_{11}Cl_3N_2O_3$	409	186-189	67

Table 2: Shows antimicrobial activity data of pyrazol-4-carbaldehyde derivatives

Code	R	Antibacterial activity Zone of inhibition (in mm)				Antifungal activity Zone of inhibition (in mm)	
		B. subtilis	*P. aerugenosa*	*E. coli*	*S. aureus*	*C. albicans*	*A. nigar*
4a	-H	10	7	12	10	7	12
4b	-2-Cl	10	8	10	7	8	10
4c	-2,4,6-Cl	20	21	22	25	10	12
4d	-4-OH	13	10	12	15	13	12
4e	-4-NO_2	12	11	13	12	13	13
4f	-4-Br	23	20	28	25	12	8
4g	-4-OCH_3	8	11	7	12	10	7
4h	-2,4-Cl	10	9	12	10	10	12
4i	-2-OH	12	10	12	13	10	12
4j	-4-Cl	10	8	7	10	8	7
Ciprofloxacin	---	27	25	27	26	---	---
Amphoterecin B	---	---	---	---	---	27	23

This indicates that the compounds that have chloro and bromo substituents have shown wide spectrum of antimicrobial activity. Ciprofloxacin and Amphoterecin B were used as a standard drug. Minimum inhibitory concentration was carried out for promising compounds such as 4c and 4f have shown activity at 40 µ/mL.

CONCLUSION

Synthesis of the Pyrazole-4-carbaldehyde derivatives bearing 2, 4-dichloro moiety by the above described method resulted in the products with good yield. The structures of the newly synthesized compounds were confirmed on the basis of spectral and elemental analysis data. Pyrazole-4-carbaldehyde derivatives with 2, 4, dichloro moiety are showing moderate to highly significant antimicrobial activity against all tested microorganisms. The chloro and bromo possessing moiety have shown enhanced biological activity stimulated to synthesize more efficient drug against pathogenic microorganisms.

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