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AN EASY, EFFICIENT SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 5-ARYL-1'-PHENYL-3'-(PYRIDIN-3-YL)-3,4-DIHYDRO-1'H, 2H-3,4'-BIPYRAZOLES

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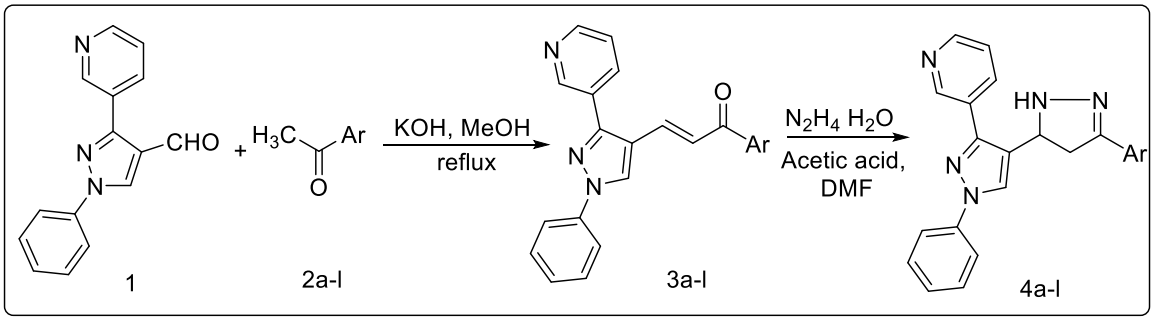
ABSTRACT: A novel series of pyridinyl-bipyrazole derivatives were prepared from corresponding chalcone derivatives and hydrazine hydrate using Michael addition reaction in the presence of acetic acid as catalyst. The method proved to an easy, simple and high yielding with short reaction time. The compounds structures established on the basis of various spectral data and the screening result of antimicrobial activity of the title compounds showed moderate to good results compared to their standards.

KEYWORD: Pyridine, pyrazole aldehyde, pyrazoline, chalcone and antimicrobial activity.

INTRODUCTION: Heterocyclic derivatives are pivotal core of many biologically and pharmacologically interesting compounds. A vast number of nitrogen containing heterocyclic building blocks have application in pharmaceutical and agrochemical research and drug discovery[i]. Heterocyclic compounds containing nitrogen have been considered as a source of potential interest in natural product research and they are frequently used in generating newer therapeutic compounds for therapeutic uses[ii]. In addition, the pyrazole core embedded in several natural products and drugs[iii]. Among this prolific family of heterocycles 1,3-diaryl pyrazoles attract great interest in owing to their wide range of applications in the medicinal chemistry. Pyrazole derivatives have been reported in the literature to exhibit various pharmacological activities such as anti-microbial[iv], anti-inflammatory[v], antitubercular[vi], antitumor[vii], antiangiogenesis[viii], antiparasitic[ix], antiviral[x], and also possess analgesic and anxiolytic activity[xi]. Furthermore, Pyrazolines derivatives have been found in natural products in the form of vitamins, alkaloids and pigments. In the last decades, great attention has been paid on the pyrazoline derivatives due to their unique molecular structure with simplicity of preparation and their wide applications in the pharmaceutical field[xii]. Most of the members of this family have wide range of spectrum of biological activities such as antibacterial[xiii], analgesic[xiv], anti-inflammatory[xv], antiviral[xvi], antifungal[xvii], antiarthritic[xviii], cerebroprotective effect[xix] and antidepressant[xx] activities. There are several substituted pyrazolines having bleaching property and also act as luminescent, fluorescent agents[xxi] and they are also used in the synthesis of biodegradable agrochemicals[xxii]. In view of advantage of nitrogen heterocyclic derivatives, we made considerable efforts to design and synthesis novel nitrogen heterocyclic

derivatives. In continuation of our research program we taken up synthesis of pyridinyl-bipyrazole derivatives and evaluated for their antimicrobial activity.



Experimental: All the chemicals were purchased from commercial sources and were used without purifications. All the solvents were dried and distilled prior to their usage. ^{1}H NMR (400 MHz) and ^{13}C NMR (101MHz) spectra of the intermediates and the final compounds were recorded using a Bruker BiospinAvance-III spectrometers with chemical shift values (δ) given in part per million (ppm) relative to TMS and using $CDCl_3$ as solvent. Column chromatography was conducted using silica gel of 60-120 mesh (Merck). The reaction progress was monitored by using TLC with silica gel 60-F254 plates and visualizing under UV light. Mass spectra of the final and the intermediate compounds were recorded in the ESI (ES^+) mode.

General procedure for synthesis of (E)-1-Aryl-3-(1-phenyl-3-(pyridin-3-yl)-1H-pyrazol-4-yl)prop-2-en-1-ones (3a-l): A mixture of 1-Phenyl-3-(pyridin-3-yl)-1H-pyrazole-4-carbaldehyde **(1)** (1 mmol), aryl methyl ketones **(2a-l)** (1 mmol) and KOH (1 mmol) in methanol (10 ml) was refluxed for 4 hrs. The reaction mixture was monitored by TLC. After completion of the reaction, the mixture was poured into ice cold water, extracted with EtOAc and dried over Na_2SO_4. The solvent was evaporated and residue was purified by column chromatography to afford pure corresponding (E)-1-Aryl-3-(1-phenyl-3-(pyridin-3-yl)-1H-pyrazol-4-yl)prop-2-en-1-ones **(3a-l)**.

General procedure for 5-Aryl-1'-phenyl-3'-(pyridin-3-yl)-3,4-dihydro-1'H,2H-3,4'-bipyrazoles (4a-l): A solution of (E)-1-Aryl-3-(1-phenyl-3-(pyridin-3-yl)-1H-pyrazol-4-yl)prop-2-en-1-ones **(3a-l)** (1 mmol) and hydrazine hydrate (1.5 mmol) in ethanol (10 ml) was refluxed for 4-6 hrs in the presence of glacial acetic acid. The reaction mixture was monitored by TLC after completion of the reaction. The reaction mixture was cooled to room temperature then poured into ice cold water. The precipitated material was filtered washed with ice water, dried and purified by column chromatography to afford pure corresponding 5-Aryl-1'-phenyl-3'-(pyridin-3-yl)-3,4-dihydro-1'H,2H-3,4'-bipyrazoles **(4a-l)**.

1',5-diphenyl-3'-(pyridin-3-yl)-3,4-dihydro-1'H,2H-3,4'-bipyrazole (4a): IR (KBr): 1594 and 3243 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.99-3.06 (dd, 1H, CH), 3.45-3.51 (dd, 1H, CH), 5.11-5.16 (dd, 1H, CH), 7.29-7.34 (m, 2H, ArH), 7.39-7.54 (m, 5H, ArH), 7.71-7.73 (m, 4H, ArH), 8.06-8.08 (m, 2H, ArH), 8.63-8.64 (d,1H, ArH), 8.95 (s, 1H, pyrazole ring proton); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 40.8, 53.9, 119.0, 119.4, 123.1, 123.3, 126.3, 126.9, 127.1, 129.5, 131.5, 133.4, 135.7, 135.9, 135.5, 139.6, 147.7, 148.7, 149.1, 150.8; ESI-MS: m/z=366 $[M+H]^+$.

1'-phenyl-3'-(pyridin-3-yl)-5-(p-tolyl)-3,4-dihydro-1'H,2H-3,4'-bipyrazole (4b): IR (KBr): 1598 and 3233 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 3H, CH_3), 3.14-3.20 (dd, 1H, CH), 3.72-3.80 (dd, 1H, CH), 5.75-5.79 (dd, 1H, CH), 7.21-7.23 (d, 2H, ArH), 7.29-7.31 (m, 1H, ArH), 7.41-7.45 (m, 3H, ArH), 7.56-7.58 (d, 2H, ArH), 7.67-7.69 (d, 2H, ArH), 7.86 (s, 1H, pyH), 8.16-8.18 (d, 1H, ArH), 8.98 (s, 1H, pyrazole ring proton); ^{13}C NMR ($CDCl_3$, 100

MHz): δ 21.5, 42.6, 51.0, 119.0, 119.1, 122.0, 126.0, 126.2, 126.6, 126.9, 127.8, 129.3, 129.4, 129.5, 135.8, 139.5, 141.3, 147.1, 149.2, 156.0, ; ESI-MS: m/z=380 $[M+H]^+$.

5-(4-methoxyphenyl)-1'-phenyl-3'-(pyridin-3-yl)-3,4-dihydro-1'H,2H-3,4'-bipyrazole (4c): IR (KBr): 1593 and 3239 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.61-3.06 (dd, 1H, CH), 3.84 (s, 3H, OCH_3), 3.95 (dd, 1H, CH), 5.17-5.19 (dd, 1H, CH), 7.39-7.44 (m, 2H, ArH), 7.49-7.64 (m, 5H, ArH), 7.71-7.73 (d, 4H, ArH), 8.06-8.08 (m, 2H, ArH), 8.63-8.64 (d,1H, ArH), 8.95 (s, 1H, pyrazole ring proton); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 41.2, 51.9, 55.4, 119.1, 123.4, 123.5, 126.7, 126.7, 127.4, 129.2, 131.9, 135.2, 135.1, 135.4, 139.3, 146.7, 148.1, 149.2, 150.1; ESI-MS: m/z=396 $[M+H]^+$.

5-(3-methoxyphenyl)-1'-phenyl-3'-(pyridin-3-yl)-3,4-dihydro-1'H,2H-3,4'-bipyrazole (4d): IR (KBr): 1598 and 3233 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.18(s, 3H, OCH_3), 2.78-3.01 (dd, 1H, CH), 3.25-3.41 (dd, 1H, CH), 5.10-5.12 (dd, 1H, CH), 7.37-7.39 (m, 2H, ArH), 7.41-7.54 (m, 5H, ArH), 7.72-7.78 (m, 4H, ArH), 8.01-8.04 (m, 2H, ArH), 8.59-8.60 (d,1H, ArH), 8.85 (s, 1H, pyrazole ring proton); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 41.8, 51.8, 55.7, 119.2, 119.3, 123.8, 124.3, 126.7, 126.9, 127.2, 128.3, 132.0, 133.7, 134.9, 135.0, 135.3, 137.7, 138.2, 148.1, 148.6, 148.2, 150.2; ESI-MS: m/z=396 $[M+H]^+$.

5-(4-fluorophenyl)-1'-phenyl-3'-(pyridin-3-yl)-3,4-dihydro-1'H,2H-3,4'-bipyrazole (4e): IR (KBr): 1598 and 3233 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.91-3.00 (dd, 1H, CH), 3.42-3.49 (dd, 1H, CH), 5.13-5.16 (dd, 1H, CH), 7.19-7.24 (m, 2H, ArH), 7.21-7.24 (m, 8H, ArH), 7.62-7.71 (d, 2H, ArH), 8.03-8.04 (m, 2H, ArH), 8.64-8.66 (d,1H, ArH), 8.91 (s, 1H, pyrazole ring proton); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 39.8, 51.9, 118.1, 120.4, 122.8, 123.7, 125.2, 126.7, 127.6, 128.2, 130.2, 132.8, 134.0, 136.6, 138.1, 145.2, 143.7, 146.8, 151.8, 156.2; ESI-MS: m/z=384 $[M+H]^+$.

5-(4-chlorophenyl)-1'-phenyl-3'-(pyridin-3-yl)-3,4-dihydro-1'H,2H-3,4'-bipyrazole (4f): IR (KBr): 1598 and 3233 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.69-2.98 (dd, 1H, CH), 3.35-3.42 (dd, 1H, CH), 5.10-5.15 (dd, 1H, CH), 7.15-7.20 (m, 3H, ArH), 7.29-7.36 (m, 5H, ArH), 7.42-7.45 (d, 2H, ArH), 8.02-8.05 (m, 2H, ArH), 8.61-8.63 (d,1H, ArH), 8.79 (s, 1H, pyrazole ring proton); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 41.6, 51.9, 118.6, 119.0, 122.5, 128.3, 128.9, 126.8, 127.7, 128.5, 130.5, 133.7, 135.1, 135.6, 138.2, 144.7, 145.7, 147.0, 150.1; ESI-MS: m/z=400 $[M+H]^+$.

5-(4-bromophenyl)-1'-phenyl-3'-(pyridin-3-yl)-3,4-dihydro-1'H,2H-3,4'-bipyrazole (4g)

IR (KBr): 1588 and 3243 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.91-3.01 (dd, 1H, CH), 3.25-3.29 (dd, 1H, CH), 5.01-5.10 (dd, 1H, CH), 7.22-7.38 (m, 3H, ArH), 7.39-7.44 (m, 5H, ArH), 7.69-7.72 (d, 2H, ArH), 8.05-8.06 (m, 2H, ArH), 8.60-8.62 (d,1H, ArH), 8.78 (s, 1H, pyrazole ring proton); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 41.1, 52.1, 119.5, 119.9, 122.2, 122.5, 127.1, 127.8, 128.9, 129.4, 132.9, 136.1, 136.8, 138.4, 139.8, 145.9, 148.1, 149.3, 150.2; ESI-MS: m/z=444 $[M+H]^+$.

5-(3,4-dimethoxyphenyl)-1'-phenyl-3'-(pyridin-3-yl)-3,4-dihydro-1'H,2H-3,4'-bipyrazole (4h): IR (KBr): 1592 and 3235 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.56(s, 3H,OCH_3), 2.89(s, 3H, OCH_3), 2.93-3.02 (dd, 1H, CH), 3.21-3.30 (dd, 1H, CH), 5.12-5.18 (dd, 1H, CH), 7.39-7.41 (m, 3H, ArH), 7.49-7.52 (m, 5H, ArH), 7.64-7.68 (d, 2H, ArH), 8.01-8.03 (m, 2H, ArH), 8.65-8.68 (d,1H, ArH), 8.90 (s, 1H, pyrazole ring proton); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 39.5, 44.3, 52.0, 55.6, 118.6, 119.4, 122.8, 123.9, 126.7, 126.9, 127.6, 128.0, 130.9, 135.1, 135.9, 137.5, 138.9, 144.9, 145.3, 147.1,148.2, 148.7, 150.3; ESI-MS: m/z=426 $[M+H]^+$.

5-(2,4-dichlorophenyl)-1'-phenyl-3'-(pyridin-3-yl)-3,4-dihydro-1'H,2H-3,4'-bipyrazole (4i): IR (KBr): 1595 and 3234 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.90-3.06 (dd, 1H, CH), 3.41-3.45 (dd, 1H, CH), 5.10-5.13 (dd, 1H, CH), 7.12-7.18 (m, 2H, ArH), 7.45-7.54 (m, 5H, ArH), 7.72-7.78 (d, 3H, ArH), 7.99-8.01 (m, 2H, ArH), 8.60-8.64 (d,1H, ArH), 8.91 (s, 1H, pyrazole ring proton); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 38.9, 54.7, 117.8, 119.6, 122.5, 124.3,

125.7, 126.1, 127.0, 129.1, 132.3, 132.7, 135.0, 135.7, 138.1, 143.9, 146.2, 147.5, 150.1; ESI-MS: m/z=434 $[M+H]^+$.

4-(1'-phenyl-3'-(pyridin-3-yl)-3,4-dihydro-1'H,2H-[3,4'-bipyrazol]-5-yl)phenol (4j): IR (KBr): 1587 and 3231 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.95-3.02 (dd, 1H, CH), 3.25-3.31 (dd, 1H, CH), 5.16-5.19 (dd, 1H, CH), 7.02-7.09(s, 1H, ArH), 7.15-7.18(d, 1H, ArH), 7.21-7.25 (m, 2H, ArH), 7.29-7.36 (m, 5H, ArH), 7.65-7.69 (d, 2H, ArH), 8.02-8.05 (m, 2H, ArH), 8.59-8.60 (d,1H, ArH), 8.93 (s, 1H, pyrazole ring proton); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 39.1, 55.0, 117.2, 118.9, 122.8, 123.8, 125.1, 126.0, 128.2, 133.5, 134.4, 135.8, 137.1, 139.2, 145.3, 148.2, 149.0, 150.7; ESI-MS: m/z=382 $[M+H]^+$.

1'-phenyl-3'-(pyridin-3-yl)-5-(m-tolyl)-3,4-dihydro-1'H,2H-3,4'-bipyrazole (4k): IR (KBr): 1591 and 3236 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.54 (s, 3H, CH_3), 2.78-3.01 (dd, 1H, CH), 3.25-3.41 (dd, 1H, CH), 5.10-5.12 (dd, 1H, CH), 7.38-7.45 (m, 2H, ArH), 7.46-7.58 (m, 5H, ArH), 7.72-7.78 (m, 4H, ArH), 8.00-8.05 (m, 2H, ArH), 8.19-8.20 (d,1H, ArH), 8.85 (s, 1H, pyrazole ring proton); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.7, 42.3, 51.2, 119.1, 119.6, 121.5, 125.8, 126.3, 126.7, 127.0, 127.6, 129.3, 129.5, 130.1, 135.8, 139.0, 142.0, 146.7, 149.0, 154.3; ESI-MS: m/z=380 $[M+H]^+$.

5-(2-bromo-4-nitrophenyl)-1'-phenyl-3'-(pyridin-3-yl)-3,4-dihydro-1'H,2H-3,4'-bipyrazole (4l): IR (KBr): 1590 and 3242 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.02-3.08 (dd, 1H, CH), 3.44-3.48 (dd, 1H, CH), 5.12-5.7 (dd, 1H, CH), 7.42-7.80 (m, 8H, ArH), 7.92-7.96 (m, 2H, ArH), 8.42-8.44 (d,1H, ArH), 8.89 (s, 1H, pyrazole ring proton); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 39.6, 55.3, 119.6, 122.5, 125.1, 125.8, 126.1, 127.0, 127.4, 128.3, 129.1, 132.3, 132.7, 135.0, 136.0, 138.1, 144.0, 144.7, 146.2, 147.6,150.2, 155.2; ESI-MS: m/z=490 $[M+H]^+$.

Result and discussion:

The potential activities of the pyridine, pyrazole and pyrazoline derivatives were encouraged to synthesize 5-Aryl-1'-phenyl-3'-(pyridin-3-yl)-3,4-dihydro-1'H,2H-3,4'-bipyrazoles. The compounds were synthesized starting from commercially available 3-acetyl pyridine. The 3-Acetyl pyridine on heated with phenyl hydrazine in the presence of acetic acid to produce 3-(1-(2-Phenylhydrazono)ethyl)pyridine, then it on reaction with DMF & $POCl_3$ to yield 1-Phenyl-3-(pyridin-3-yl)-1H-pyrazole-4-carbaldehyde. The carbaldehyde on reaction with aryl methyl ketone to afford corresponding chalcones, finally the chalcone treated with hydrazine hydrate in the presence of sodium acetate to give require pyrazoline derivates. The synthesised pyrazoline derivative were confirmed by spectral data such as IR, HNMR, CNMR and Mass spectrometry

Table-1: Physical data of 5-Aryl-1'-phenyl-3'-(pyridin-3-yl)-3,4-dihydro-1'H,2H-3,4'-bipyrazoles (4a-l)

S. No	Ar	M. P. (°C)	Reaction time (in hr)	Yield (%)
1	Phenyl	125-128	3	94
2	4-methylphenyl	139-142	3	93
3	4-methoxyphenyl	117-120	2	94
4	3-methoxyphenyl	100-103	2.5	92
5	4-Fluorophenyl	134-136	4	92
6	4-Chlorophenyl	150-153	2	94
7	4-Bromophenyl	134-136	3	93
8	3,4-dimethoxyphenyl	128-131	2.5	92
9	2,4-Dichlorophenyl	118-120	3	91

10	4-hydroxyphenyl	124-126	2	85
11	4-Trifluoromethylphenyl	136-138	3	90
12	2-Bromo-4-nitropenyl	150-152	3	84

Antimicrobial activity:

Antibacterial activity: The synthesized triazoles (**4a-l)** were evaluated for *in vitro* antibacterial activity against four bacterial strains, two Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) and two Gram-negative *(Pseudomonas aeruginosa* and *Escherichia coli)* at a concentration of 100 mg/ mL by paper disc method using Norfloxacin and Ofloxacin as standard drugs for Gram +ve and Gram –ve respectively. The compounds **4a, 4c, 4f, 4g** and **4i** better antibacterial activity against all bacterial stains (**Table-2)**.

Antifungal activity: The synthesized triazoles (**4a-l)** were evaluated for *in vitro* antifungal activity against two fungal strains (*Sclerotium rolfsii* and *Aspergillus niger)* at a concentration of 100 mg/mL by disc diffusion method using Ketoconazole used as the standard drug. Careful observation of the results showed that compounds **4c, 4d, 4g** and **4i** showed better antifungal activity against both organisms (**Table-2)**.

Table-2: Antimicrobial activity of 5-Aryl-1'-phenyl-3'-(pyridin-3-yl)-3,4-dihydro-1'H,2H-3,4'-bipyrazoles (4a-l)

Comp.	*S. aeureus*	*B. subtilis*	*P. aeruginosa*	*E. coli*	*A. Niger*	*S. fsii*
5a	21.0	15.6	22.5	18.9	8.0	11.2
5b	18.9	15.0	21.3	15.3	9.1	11.0
5c	20.1	14.1	23.0	17.0	10.2	13.2
5d	15.6	12.9	20.8	19.1	11.5	14.0
5e	19.5	13.5	19.6	18.0	8.3	11.2
5f	22.0	15.1	19.0	19.6	9.3	10.8
5g	21.4	14.3	21.5	20.0	10.0	9.0
5h	18.6	12.1	21.0	18.8	8.8	8.1
5i	24.1	16.5	19.8	20.1	10.5	12.5
5j	20.0	13.0	22.8	17.9	9.9	12.0
5k	16.3	10.2	15.8	14.2	9.6	10.3
5l	17.8	11.7	12.9	17.5	8.8	11.0
Norfloxacin	26.6	19.8	28.6	25.7	---	---
Ketoconazole	---	---	---	---	11.5	16.6

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