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Synthesis And Antimicrobial Activities of Some New Heterocyclic Compounds Based On 3-Aryl-1-Phenylpyrazol-4-Carboxaldehyde

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Abstract
In the present investigation, the synthesis and antimicrobial evaluation of heterocyclic fused ring system via Claisen-Schmidt condensation using Vilsmeier-Haack reagent. The heterocyclic substrate is prepared by treatment of acetophenone with phenylhydrazine. The phenylhydrazone derivatives upon treatment with DMF-$POCl_3$ afforded 3-aryl-1-phenylpyrazol-4-carboxaldehyde. Subsequently the Claisen-Schmidt condensation of 3-aryl-1-phenylpyrazol-4-carboxaldehyde with 3-acetylpyridine in methanolic NaOH afforded the corresponding aldehyde. The structures of these newly synthesized compounds were characterized by ^{1}H NMR spectroscopic studies. All the synthesized compounds were screened for their antimicrobial evaluation. Some of the compounds exhibited promising antimicrobial activity. From the present study it may be concluded that synthesized compounds are fruitful in terms of their structural novelty and marked biological activities.

Keywords: Claisen-Schmidt condensation, Vilsmeier-Haack reagent, Heterocyclic, 3-aryl-1-phenylpyrazol-4-carboxaldehyde, Antimicrobial

1. Introduction
Chalcone scaffolds are privileged chemical structures in the medicinal chemistry sector [1-3]. They are secondary metabolites of plants and found in α,β-unsaturated forms, which have a more thermodynamically stable *trans*-conformation between two aryl groups [4-5]. Chemically chalcones are easily prepared using various reaction procedures and strategies. For instance, the named reaction Claisen-Schmidt condensation is one common methodology to prepare the title compound through carbonyl derivative condensation in the presence of base [6-8]. Chalcone scaffolds are privileged chemical structures in the medicinal chemistry sector. They are secondary metabolites of plants and found in α,β-unsaturated forms, which have a more thermodynamically stable *trans*-conformation between two aryl groups [9-10]. Chalcone and its derivatives are the cores of various biologically interesting compounds, and frequently they have been isolated from different medicinal plants such as *Dracaena cinnabari*, *Medicago sativa*, and *Angelica keiskei*. Chemically chalcones are easily prepared using various reaction procedures and strategies [11-12]. For instance, the named reaction Claisen-Schmidt condensation is one common methodology to prepare the title compound through carbonyl derivative condensation in the presence of base. Additionally, the carbonylative Heck coupling reaction, the Sonogashira isomerization coupling reaction, the continuous flow deuteration reaction, the Suzuki–Miyaura coupling reaction, and solid acid catalyst-mediated reactions are known [13-14]. The precursors of the flavonoids and isoflavones, chalcones serve as promising template scaffolds for synthesizing and developing pharmacologically active compounds in conjugation with other heterocyclic moieties which have a large role in the sector of medicine to prepare potential drug discovery and improve pharmaceuticals. Chalcone derivatives incorporating heterocyclic scaffolds are become promising candidates as future drug sources owing to their similar or superior activities compared to those of the standard derivatives [15]. To date, the basic chemical structure of chalcone serves as potential source of much research for planning to design and develop various drugs. Chalcones with an *N*-heterocyclic moiety such as pyrrole, imidazole, thiazole, pyrazole, oxazole, isooxazole, pyridine, pyrazoline, indole, benzothiazole, benzimidazole, and quinoline scaffolds play a significant role in the area of medicine. Pyrazoles with their

distinctive scaffold possess wide range of anticancer bioactivities. Though more widely known for their use in analgesic, antipyretic and anti-inflammatory actions, pyrazoles can also have antileukemic, antitumor and anti-proliferative.

2. Materials and Methods

All chemicals and solvents were purchased from commercial sources (Merk) used without further purification. All compounds were characterized by spectroscopic data and compared with the data available in the literature. The NMR spectra were recorded in DMSO-d_6. ^{1}H NMR spectra were obtained on a Bruker Advance 3400 and deuterated DMSO was used as solvent. The reactions were monitored by Thin Layer Chromatography (TLC) using silica gel. The melting points were determined on a melting point apparatus. All other reagents were of analytical grade.

2.1 Experimental Section

Synthesis of 3-(4-Chlorophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde

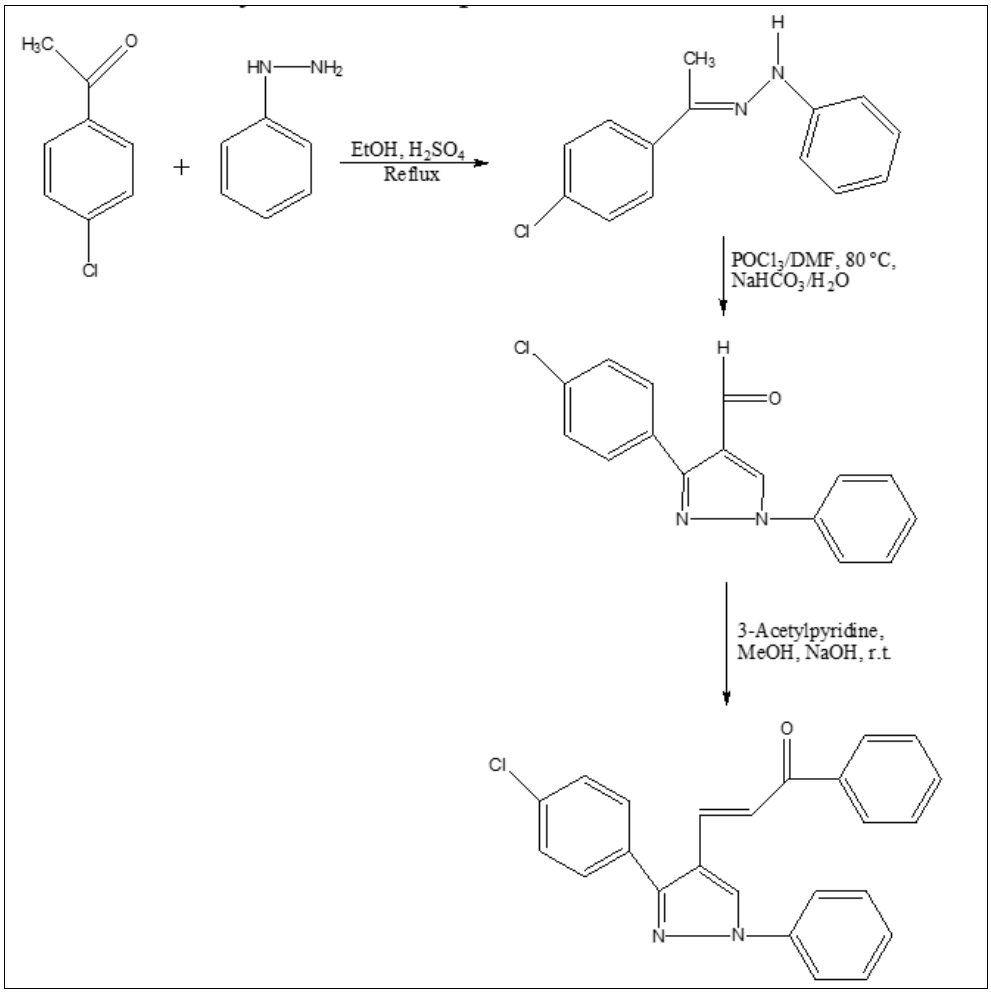
To a solution of acetophenones (10 mmol) and phenylhydrazine (10 mmol) in EtOH (10 mL) was added a drop of concentrated H_2SO_4 and the resultant solution was refluxed for 2 h. On cooling, precipitates were filtered, washed with cold EtOH and dried, provided sufficiently pure (by TLC) hydrazone, which were immediately used for the next step. $POCl_3$ (15 mmol) was added drop wise to dry DMF (15 mmol) in round bottom flask at 0°C and the resultant mixture was stirred for 30 minutes until the formation of Vilsmeier-Haack reagent appeared. The corresponding solution of phenylhydrazones (5 mmol) in minimum amount of dry DMF were added dropwise to the Vilsmeier-Haack reagent, which were warmed at r.t. and heated at 70- 80 °C for 5 h. The cool reaction mixture was poured into crushed ice and neutralized with a cool saturated K_2CO_3 solution. The precipitates were filtered, strongly washed with water and crystallized from ethanol, affording pure compound**.**

2.2 Synthesis of (E)-3-(3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(pyridin-3-yl) prop-2-en-1-one

A mixture of 3-aryl-1-phenylpyrazol-4-carboxaldehydes (10 mmol) and 3-acetyl pyridine (10 mmol) were stirred in methanolic sodium hydroxide solution for 24 h at room temperature. Upon completion, the precipitates formed were filtered off, washed with water and dried. The compounds were crystallized from ethanol.

Antimicrobial activity

The antimicrobial activities of the synthesised compounds were screened by using cup-plate agar diffusion method in DMF, using standard Co-Trimazin 25 µg/ml against gram positive and gram negative bacteria such as E. *coli*, S. *typhi*, S. *abony*, P. *aeruginosa*, and B. *subtilis*. The antimicrobial activities of all the synthesized compounds are shown in table 1.



Scheme 1: Synthesis of Pyrazolic chalcone

2.3 Structure characterization by NMR

3-(4-Chlorophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde

Light brown solid; Yield: 84%; mp 140-142 °C; IR (neat, νmax cm-1): 3127, 1672, 1603, 1523; 1H NMR (CDCl3): δ 10.03 (s, 1H), 8.52 (s, 1H), 7.37-7.84 (m, 9H); 13C NMR (CDCl3): 184.33, 153.14, 138.93, 135.44, 132.03, 130.18, 129.89, 129.71, 128.91, 128.08, 122.56, 119.73; Anal. Calcd. for C16H11ClN2O: C, 67.97; H, 3.92; N, 9.91. Found: C, 67.94; H, 3.89; N, 9.96.

3-(3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(pyridin-3-yl) prop-2-en-1-one

Yellow solid; Yield: 64%; mp 162-164 °C; IR (neat, νmax cm-1): 3134, 1665, 1583, 1501, 1404; 1H NMR (CDCl3): δ 9.16 (s, 1H), 8.76 (d, *J* = 4.4 Hz, 1H), 8.37 (s, 1H), 8.21 (d, *J* = 8 Hz, 1H), 7.85 (d, *J* = 15.2 Hz, 1H), 7.76 (d, *J* = 8 Hz, 2H), 7.61 (d, *J* =8.4 Hz, 2H), 7.29-7.50 (m, 7H); 13C NMR (CDCl3): δ 188.83, 153.16, 152.80, 149.62, 139.21, 136.05, 135.76, 134.99, 133.45, 130.65, 130.00, 129.68, 129.08, 127.56, 127.15, 123.73, 120.84, 119.42, 117.96; Anal. Calcd. for C23H16ClN3O: C, 71.59; H, 4.18; N, 10.89. Found: C, 71.65; H, 4.16; N, 10.85

2.4 Structure characterization by FTIR Spectroscopy

Peak area at 3330 cm^{-1} aromatic C-H stretch, The peak area at 2900 $cm^{-1,}$ 2919 $cm^{-1,}$ 2910 cm^{-1}, 2923 cm^{-1}, 2932 cm^{-1}, 2922 cm^{-1}, 2917 cm^{-1} and 2916 cm^{-1} vibration -C-H ring stretching. A strong stretching vibration at 1615 cm^{-1}, 1613 cm^{-1}, 1614 cm^{-1}, 1656 cm^{-1}, 1657 cm^{-1}, 1655 $cm^{-1}$and 1638 cm^{-1} shows the presence of carbonyl(C=O) groups. The –NH bending peak shows at 1459 cm^{-1}, 1403 cm^{-1}, 1400 cm^{-1}, 1410 cm^{-1}, 1404 cm^{-1} and 1407 cm^{-1}. The peak at 1001 cm^{-1}, 1006 cm^{-1}, 1011 cm^{-1}, 1015 cm^{-1} and 1045 cm^{-1} shows C-N stretching.

Table 1: Antimicrobial Activity against pathogens

Sr. No.	Compound	Zone of inhibition in mm				
		Bacteria				
		E. coli	*S. abony*	*P. aeruginosa*	*S. typhi*	*B. subtilis*
1	3-(4-Chlorophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde	12±0.2	11±0.2	10±0.2	12±0.2	13±0.2
2	3-(3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(pyridin-3-yl) prop-2-en-1-one	13±0.2	12±0.2	13±0.2	10±0.2	12±0.2

3. Conclusions

As a part of our research work focused on the development of pyrazole tethered antimicrobial heterocyclic compounds. The synthesis, characterization and *in vitro* cytotoxicity evaluation of the pyrazolic chalcones have been performed. The compounds displayed moderate to good antimicrobial effects against the pathogens. The antimicrobial evaluation data revealed that among the synthesized compounds studied, 3-(3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(pyridin-3-yl) prop-2-en-1-one showed significant antimicrobial activity. The present study offers preliminary pointers which broadening the research scopes for further design, modify and investigate the structure of these molecules to expand the utility of such novel compounds as potential antimicrobial agents.

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