

Synthesis and Anti-microbial Activity of Novel Pyrrolidine Containing Chalcones and Pyrazolines

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Abstract

4-(pyrrolidin-1-yl)benzaldehyde(1) was condensed with acetophenone to give chalcones (3a-3i) which are further cyclized with hydrazine hydrate to afford pyrazolines (4a-4i) by conventional and non-conventional route. The synthesized compounds were evaluated for antifungal and antibacterial activities.

Keywords: Chalcones, Pyrazolines, Ultrasound

Introduction

Heterocyclic compounds are gain much more importance in the field of pharmaceuticals, most biologically important compounds used currently contains heterocyclic ring as a backbone of their structure. 1,3-Diarylprop-2-en-1-ones, generally called as chalcones are important role in the organic chemistry, they act as synthones for many important heterocycles. Chalcones act as precursor for flavonoids and isoflavonoids in plants.^{1, 2} The derivatives of chalcones are reported to possess many important pharmacological activities like antiviral,³ antibacterial,⁴ antifungal,⁵ anticancer,^{6,7} antiplasmodial,⁸ antifilarial.⁹ The chalcone derivatives are also reported as anti-ulcer¹⁰ and lipid lowering agents.¹¹

Chalcones on reaction with hydrazine hydrate forms pyrazolines, a five membered nitrogen containing heterocycles. Various pyrazoline and derivatives of pyrazolines were reported for important pharmaceutical and biological activities.¹² Pyrazolines were reported as antibacterial,¹³ antifungal, anti-tubercular,¹⁴ antioxidant,¹⁵ analgesic, anti-inflammatory¹⁶ and anticancer agents.¹⁷

Pyrrolidine, a five membered saturated nitrogen containing heterocyclic ring, had an important role in the structural backbone of many biologically important compounds. Pyrrolidine derivatives were reported in the literature as antifungal,¹⁸ antibacterial,¹⁹ anticonvulsant,²⁰ antitumor,²¹ antihypertensive,²² and sodium channel blocker agents.²³ These finding promotes us to synthesis the pyrrolidine incorporated novel chalcones and pyrazolines derivatives. The literature survey shows that there was no such report for the pyrrolidine incorporated chalcone and pyrazoline derivatives. In continuation of our research work to synthesis pyrrolidine containing heterocycles^{24,25} we report the synthesis of pyrrolidine containing chalcones and pyrazolines.

Experimental

All the chemical were purchased from sigma-aldrich, used without further purification. The melting points were recorded by open capillary method and are uncorrected. H¹ NMR spectra were recorded on Mercury Plus Varian in DMSO d₆ at 400 MHz using TMS as an internal standard. Mass spectra were recorded on Micromass Quattro II using electrospray ionization technique. The progress of

reaction was monitored by TLC (silica, 80:20 hexane/ ethyl acetate). Biotechnics(35 kHz) ultrasonic bath was used for ultrasonic irradiation.

General procedure for synthesis of (E) -1-aryl-3-(4-(pyrrolidin-1-yl)phenyl)prop-2-en-1-one(3a-3i)

Conventional Method

To a solution of 4-(pyrrolidin-1-yl)benzaldehyde(1) (0.010mole) in 50mL ethanol, various acetophenone (2) (0.010mole) was added, to this solution KOH (0.020mole) was added. The resultant reaction mixture was stirred overnight, after completion of reaction (monitored by TLC, hexane: ethyl acetate, 80:20), the reaction was poured over crushed ice and made acidic with dilute HCl, resultant crude product was filtered and recrystallized from ethanol to give compound 3a-3i

Ultra sonication Method

To a solution of 4-(pyrrolidin-1-yl)benzaldehyde(1) (0.010mole) in 50mL ethanol, various acetophenone (2) (0.010mole) was added, to this solution KOH (0.020mole) was added. The resultant reaction mixture was irradiated in ultrasonic bath for 2Hrs, after completion of reaction (monitored by TLC, hexane: ethyl acetate, 80:20), the reaction was poured over crushed ice and made acidic with dilute HCl, resultant crude product was filtered and recrystallized from ethanol to give compound 3a-3i

General procedure for synthesis of 3-(aryl)-4,5-dihydro-5-(4-(pyrrolidin-1yl)phenyl)-1H-pyrazole (4a-4i)

Conventional Method

To a solution of (E) -1-aryl-3-(4-(pyrrolidin-1-yl)phenyl)prop-2-en-1-one (3a-3) (0.005mole) in 20mL ethanol, hydrazine hydrate (0.005mole) was added, the resulting reaction mixture was refluxed for 3Hrs, the reaction mixture was made acidic with one drop of glacial acetic acid and further refluxed for 3Hrs, after completion of reaction (monitored by TLC, hexane: ethyl acetate, 80:20), the reaction mixture was poured over crushed ice, product was filtered and purified by column chromatography over silica (120mesh) to give compound 4a-4i

Ultra sonication Method

To a solution of (E) -1-aryl-3-(4-(pyrrolidin-1-yl)phenyl)prop-2-en-1-one (3a-3) (0.005mole) in 20mL ethanol, hydrazine hydrate (0.005mole) was added, the resulting reaction mixture was made acidic with one drop of glacial acetic acid and irradiated in ultrasonic bath for 3Hrs, after completion of reaction (monitored by TLC, hexane: ethyl acetate, 80:20), the reaction mixture was poured over crushed ice, product was filtered and purified by column chromatography over silica (120mesh) to give compound 4a-4i

Antimicrobial activity

The synthesized compounds were screened for antimicrobial activity against *Pseudomonas aeruginosa* (ATCC27853), *Staphylococcus aureus* (ATCC 25923), *E. Coli*(ATCC 25922)and *Candidaalbicans*.,by disc diffusion method. Solution of 10mg/mL concentration was prepared in DMSO Whatmann filter paper no41disc (6mm) were placed on the surface of inoculated agar plate and 10µL of each dissolved compoundwas loaded on disc. DMSO was usedas control. The petri dishes were incubated at 37°C for 24 Hrs. Bioactivity was determined bymeasuring diameter of inhibition zone in mm.

Result and Discussion

4-(pyrrolidin-1-yl)benzaldehyde(1) on reaction with acetophenone gives (*E*) -1-aryl-3-(4-(pyrrolidin-1-yl)phenyl)prop-2-en-1-one (3a-3). As compare to conventional method, the non-conventional route (use of ultra-sonic irradiation) has advantages with respect to time consumption and yield of product. The time consumption was reduced from overnight to 2Hrs with the increase in product yield from 60-70% to 75-80%.

3-(aryl)-4,5-dihydro-5-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazole (4a-4) was prepared by reacting (*E*)-1-aryl-3-(4-(pyrrolidin-1-yl)phenyl)prop-2-en-1-one (3a-3) with hydrazine hydrate under conventional or non-conventional condition, the time consumption was reduced from 6Hrs to 3Hrs with increase in product yield. The structure of compounds was confirmed by spectral analysis.

The ^1H NMR of 3-(4-methoxyphenyl)-4,5-dihydro-5-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazole (4a) shows 4.82 δ (dd, J 10.5 and 8.0 Hz, 1H) for pyrazoline CH proton, 3.40 δ (dd, J 16.3 and 10.5 Hz, 1H), 3.05 δ (dd, J 16.3 and 8.0 Hz, 1H) for pyrazoline CH_2 , 3.85 δ (s, 3H) for OCH_3 .

Antimicrobial study show that the compound 3g shows moderate activity against *Candida albicans*, while compound 3e, 4a, 3h shows moderate antibacterial activities, the other compounds shows moderate to minimum activity.

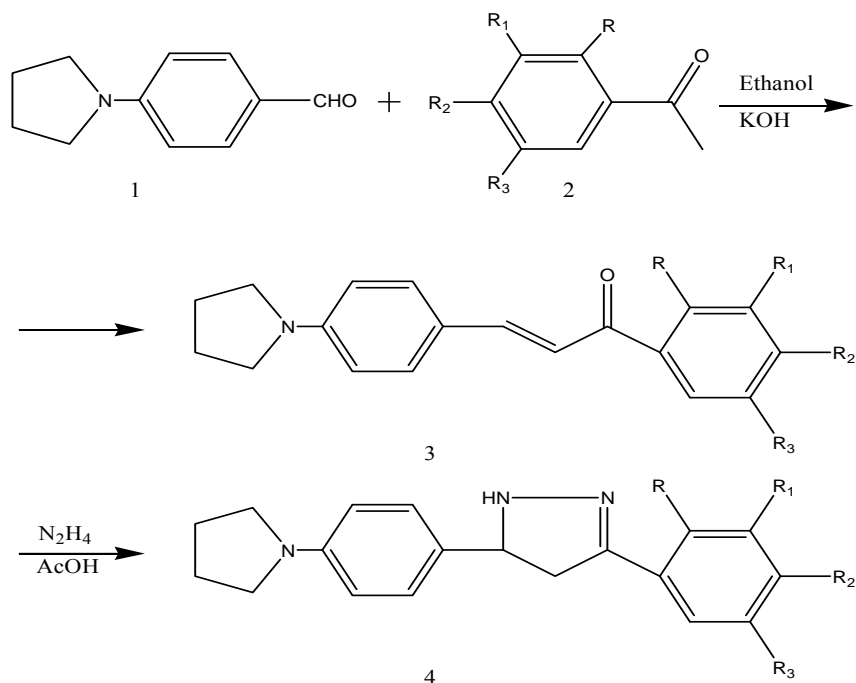
Spectral Data for 3e

^1H NMR 13.25 δ (s, 1H, OH), 8.02-7.27 δ (m, 7H, ArH), 6.92 δ (d, J 15 Hz, 1H, olefinic H), 6.59 δ (d, J 15 Hz, 1H, olefinic H), 3.42 δ (m,m, 4H, pyrrolidine N- CH_2), 2.06 δ (m, 4H, Pyrrolidine CH_2).

Mass (m/z) 372,374 (M+1).

IR (KBr) (cm^{-1}) 3433 (OH), 1635(C=O)

General Scheme



Spectral Data for 4a

^1H NMR 7.68-7.58 δ (m, 2H, ArH), 7.29-7.18 δ (m, 2H, ArH), 6.97-6.88 δ (m, 2H, ArH), 6.59-6.49 δ (m, 2H, ArH), 4.82 δ (dd, J 10.5 and 8.0 Hz, 1H pyrazoline CH), 3.85 δ (s, 3H, OCH₃), 3.40 δ (dd, J 16.3 and 10.5 Hz, 1H), 3.05 δ (dd, J 16.3 and 8.0 Hz, 1H) for pyrazoline CH₂, 3.33-3.24 δ (m, 4H, pyrrolidine N-CH₂), 2.06-1.94 δ (m, 4H, Pyrrolidine CH₂).

Mass (m/z) 322 (M+1).

IR (KBr) (cm⁻¹) 3352 (NH)

Table 1: Physical Data of the Compounds

Compound	R	R ₁	R ₂	R ₃	Yield %		Melting Point °C
					Conventional Method	Ultra sonic Method	
3a	H	H	OCH ₃	H	60	75	110-112
3b	H	H	Br	H	62	78	109-110
3c	H	H	Cl	H	70	80	125-127
3d	OH	H	H	CH ₃	65	77	130-132
3e	OH	H	H	Br	64	76	133-134
3f	OH	H	H	Cl	65	79	118-120
3g	OH	H	CH ₃	Cl	67	80	122-124
3h	OH	H	H	H	68	80	108-110
3i	OH	Cl	H	Cl	66	79	102-103
4a	H	H	OCH ₃	H	59	65	142-144
4b	H	H	Br	H	58	64	140-142
4c	H	H	Cl	H	56	68	170-172
4d	OH	H	H	CH ₃	60	69	175-177
4e	OH	H	H	Br	58	65	180-182
4f	OH	H	H	Cl	54	66	168-170
4g	OH	H	CH ₃	Cl	55	67	145-147
4h	OH	H	H	H	57	63	135-138
4i	OH	Cl	H	Cl	56	65	128-130

Table 2: Antimicrobial activity of the Compounds

Compound	<i>Pseudomonas aeruginosa</i> (ATCC27853)	<i>Staphylococcus aureus</i> (ATCC25923)	<i>E. Coli</i> (ATCC25922)	<i>Candilaalbicans</i>
3a	No zone	No zone	No zone	10mm
3b	No zone	No zone	No zone	No zone
3c	No zone	No zone	No zone	No zone
3d	No zone	11mm	09mm	No zone
3e	No zone	No zone	15mm	11mm
3f	09mm	12mm	10mm	No zone
3g	11mm	10mm	11mm	15mm
3h	10mm	15mm	09mm	10mm
3i	09mm	10mm	10mm	No zone
4a	No zone	No zone	15mm	No zone
4b	No zone	No zone	No zone	No zone
4c	No zone	No zone	No zone	No zone
4d	10mm	No zone	No zone	No zone
4e	12mm	09mm	11mm	10mm
4f	12mm	11mm	12mm	09mm
4g	10mm	No zone	12mm	No zone
4h	12mm	10mm	11mm	No zone
4i	11mm	09mm	12mm	12mm
Gentamicin	21mm	27 mm	24 mm	--
Nastatin	--	--	--	23 mm

Conclusion

Non-conventional method i.e. use of ultrasonic radiation, has improve the yield as well as reduces the time consumption of the synthesis.

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