Synthesis and Anti-microbial Activity of Novel Pyrrolidine Containing Chalconesand 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-ulcer[10] and lipid lowering agents.[11]

Chalcones on reaction with hydrazine hydrate forms pyrazolines, a five membered nitrogen containing heterocyles. 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-inflammatory[16]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]antitumar, [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 pyrazolinederivatives. 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. H^1 NMR spectra were recorded on Mercury Plus Varian in DMSO d_6 at 400 MHz using TMS as an internal standard. Mass spectra were recorded on Micromass Quattro II using electronspray 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)-1*H*-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 *Candilaalbicans.*,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 37^0C 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.Thestructure of compounds was confirmed by spectral analysis.

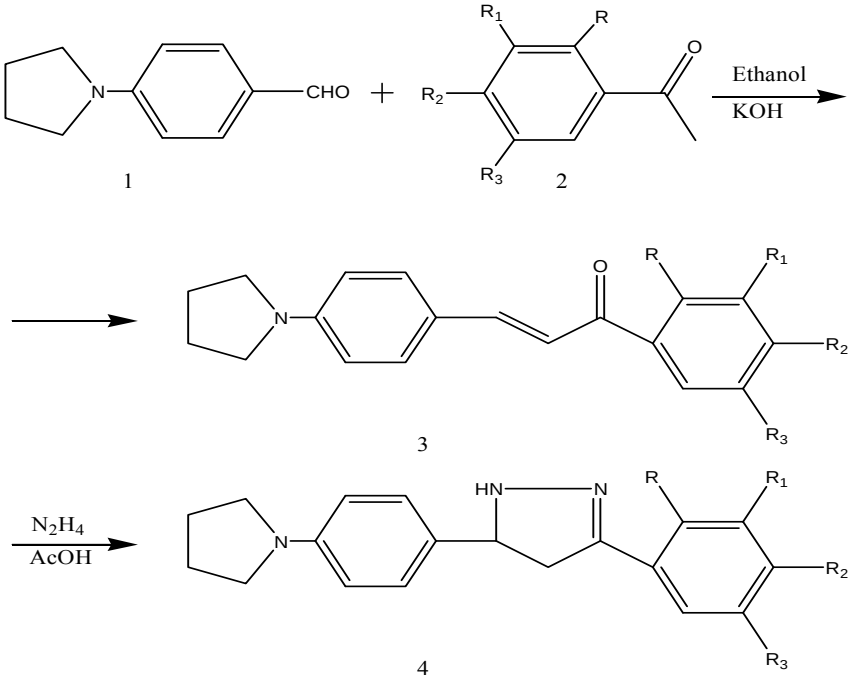
The H^1 NMR of 3-(4-methoxyphenyl)-4,5-dihydro-5-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazole (4a) shows 4.82 δ (dd, J 10.5 and 8.0 Hz, 1H) for pyrazoline CH proton, 3.40 δ (dd, J 16.3 and 10.5 Hz, 1H), 3.05 δ (dd, J 16.3 and 8.0 Hz, 1H) for pyrazoline CH_2, 3.85 δ (s, 3H) for OCH_3.

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

Spectral Data for 3e

H^1 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

H^1 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, OCH_3), 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, 3.33-3.24 δ (m, 4H, pyrrolidine N-CH_2), 2.06-1.94 δ (m, 4H, Pyrrolidine CH_2).

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 ^0C
					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	*Pseudomonas aeruginosa*(ATCC27853)	*Staphylococcus aureus*(ATCC25923)	*E. Coli* (ATCC25922)	*Candilaalbicans*
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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References

[1] D. Lee, K. H. Kim, S. W. Moon, H. Lee, K. S. Kang, J.W. Lee, " Synthesis and biological evaluation of chalcone analogues as protective agents against cisplatin-induced cytotoxicity in kidney cells", Bioorganic and Medicinal Chemistry Letters, 25, 1929-1932, 2015.

[2] D. S. Gond, R. J. Meshram, S. G. Jadhav, G. Wadhwa, R. N. Gacche, " In silico screening of chalcone derivatives as potential inhibitore of dihydrofolatereductase: Assessment using molecular docking, paired potential and molecular hydrophobic potential studies", Drug Invention Today, 5, 182-191, 2013.

[3] Z. Chen, P. Li, D. Hu, L. Dong, J. Pan, L. Luo, W. Zhang, W. Xue, L. Jin, B. Song, "Synthesis, Antiviral Activity, and 3D-QSAR Study of Novel Chalcone Derivatives Containing Malonate and Pyridine Moieties", Arabian Journal of Chemistry , In press (2015), doi: http://dx.doi.org/10.1016/j.arabjc.2015.05.003.

[4] Z. N. Siddiqui, T. N. M. Musthafa, A. Ahmad, A. U. Khan, " Thermal solvent-free synthesis of novel pyrazolylchalconesandpyrazolines as potential antimicrobial agents", Bioorganic and Medicinal Chemistry Letters, 21, 2860-2865, 2011.

[5] Y. L. Hsu, P. L. Kuo, W. S. Tzeng, C. C. Lin, "Chalcone inhibits the proliferation of human breast cancer cell by blocking cell cycle progression and including apoptosis", Food and Chemical Toxicology, 44, 704-713, 2006.

[6] G. Wang, C. Li, L. He, K. Lei, F. Wang, Y. Pu, Z. Yang, D. Cao, L. Ma, J. Chen, Y. Sang, X. Liang, M. Xiang, A. Peng, Y. Wei, L. Chen, " Design, synthesis and biological evaluation of a series of pyranochalcone derivatives containing indole moiety as novel anti-tubulin agents", Bioorganic and Medicinal Chemistry, 22, 2060-2079, 2014.

[7] R. Raj, A. Saini, J. Gut, P. Rosenthal, V. Kumar, " Synthesis and in vitro antiplasmodial evaluation of 7-chloroquinoline-chalcone and 7-chloroquinoline-ferrocenylchalcone conjugates", European Journal of Medicinal Chemistry, 95, 230-239, 2015.

[8] K. V. Sashidhara, K. B. Rao, V. Kushwaha, R. K. Modukuri, R. Verma, P. K. Murthy, " Synthesis and antifilarial activity of chalcone-thiazole derivatives against a human lymphatic filarial parasite, *Brugiamalayi*", European Journal of Medicinal Chemistry, 81, 473-480. 2014.

[9] K. V. Sashidhara, S. R. Avula, V. Mishra, G. R. Palnati, L. R. Singh, N. Singh, Y. Chhonker, P. Swami, R. S. Bhatta, G. Palit, " Indentification of quinoline-chalcone hybrids as potential antiulcer agents". European Journal of Medicinal Chemistry, 89, 638-653, 2015.

[10] K. V. Sashidhara, R. P. Dodda, R. Sonkar, G. R. Palnati, G. Bhatia, " Design and synthesis of novel indole-chalcone fibrates as lipid liowering agents", European Journal of Medicinal Chemistry, 81, 499-509, 2014.

[11] M. Yusuf, P. Jain, " Synthesis and biological studies of pyrazolines and related compounds", Arabian Journal of chemistry, 7, 553-596, 2014.

[12] M. Rani, M. Yusuf, S. A. Khan, P. P. Sahota, G. Pandove, " Synthesis, studies and in-vitro antibacterial activity of N-substituted 5-(furan-2-yl)-phenyl Pyrazolines", Arabian Journal of Chemistry, 8, 174-180, 2015.

[13] S. N. Shelke, G. R. Mhaske, V. D. B. Bonifacio, M. B. Gawande, " Green synthesis and anti-infective activities of fluorinated pyrazoline derivatives", Bioorganic and Medicinal Chemistry Letters, 22, 5727-5730, 2012.

[14] A.Kumar, B. G. Varadaraj, R. K. Singla, " Synthesis and evaluation of antioxidant activity of novel 3,5-disubstituted-2-pyrazolines", Bulletin of Faculty of Pharmacy, Cairo University, 51, 167-173, 2013.

[15] R. S. Joshi, P. G. Mandhane, S. D. Diwakar, S. K. Dabhade, C. H. Gill, " Synthesis, analgesic and anti-inflammatory activities of some novel pyrazolines derivatives", Bioorganic and Medicinal Chemistry Letters, 20, 3721-3725, 2010.

[16] S. Bano, K. Javed, S. Ahmad, I. G. Rathish, S. Singh, M. S. Alam, " Synthesis and biological evaluation of some new 2-pyrazolines bearing benzene sulfonamide moiety as potential anti-inflammatory and anti-cancer agents", European Journal of Medicinal Chemistry, 46, 5763-5768

[17] G. Lu, H. Chu, M. Chen, C. Yang, " Synthesis and bioactivity of derivatives novel strobilurin derivatives containing the pyrrolidine-2,4-dione moiety", Chinese Chemical Letters, 25, 61-64, 2014.

[18] K. Lv, M. Liu, L. Feng, L. Sun, Y. Sun, Z. Wei, h. Guo, " Synthesis and antibacterial activity of naphthyrione derivatives containing mono/difluoro-methyloximepyrrolidine scaffolds", European Journal of Medicinal Chemistry, 47, 619-625, 2012.

[19] S. Malik, P. Ahuja, K. Sahu, S. A. Khan, "Design and synthesis of new of 3-(benzo[d]isoxazole-3-yl)-1-substituted pyrrolidine-2,5-dione derivatives as anticonvulsants", European Journal of Medicinal Chemistry, 84, 42-50, 2014.

[20] X. Li, Y. Li, W. Xu, " Design, synthesis and evaluation of novel galloylpyrrolidine derivatives as potential anti-tumor agents", Bioorganic and Medicinal Chemistry, 14, 1287-1293,2006.

[21] T. Yavuz, O. Uzun, A. Macit, C. Comunoglu, O. Yavuz, C. Silan, H. Yuksel, H. A. Yildirim, " Pyrrolidinedithiocarbamate attenuates the development of monocrotaline-induced pulmonary arterial hypertension", Pathology-Research and Practice, 209, 302-308, 2013.

[22] M. Seki, O. Tsuruta, R. Tatsumi, A. Soejima, " Synthesis and biological evaluation of pyrrolidine derivatives as novel and potent sodium channel blockers for the treatment of ischemic stroke", Bioorganic and Medicinal Chemistry Letters, 23, 4230-4234, 2013.

[23] S. D. Pardeshi, J. P. Sonar, S. A. Dokhe, S. N. Thore, " Synthesis and antimicrobial evaluation of novel N-(4-(pyrrolidin-1yl)benzylidene)-arylamine and diethyl(arylamino)(4-pyrrolidin-1-yl)phenyl)methyl)phosphonate", Heterocyclic Letters, 5,1,97-104,2015.

[24] S. D. Pardeshi, J. P. Sonar, S. A. Dokhe, A. M. Zine, S. N. Thore, " Synthesis and antimicrobial screening of novel 3-aryl-2(4-(pyrrolidin-1-yl)phenyl)thiazolidin-4-ones", Indian Journal of Heterocyclic Chemistry, 24, 3, 329-332, 2015.