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SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL (E)1-[4-((6-CHLORO-PYRIDAZINE-3-YL)AMINO)-PHENYL]-3-PHENYL-PROPENONE DERIVATIVES

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ABSTRACT

Some new chalcone enabled pyridazine analogues were synthesized via reaction between substituted aromatic aldehyde and 3, 6-disubstituted pyridazine ring. The final compounds were screened for antimicrobial activities by in vitro method. Prepared novel series of pyridazine derivatives showed promising and encouraging results in view of antimicrobial studies with *E.Coli, S.Aureus, A.Niger and B. Albicans.*

Keywords: Pyridazine, Chalcone, Aldehyde, Antimicrobial, Claisen Schmidt condensation

1. INTRODUCTION

Polyfunctional heterocycles have their own place in development of the synthetic chemistry owing to their manifold applicability [1]. Among heterocycles, organic stuffs containing pyridazine nucleus has numerous pharmacological effects such as anxiolytic [2], anti-inflammatory [3, 4], antihypertensive [5], and antimicrobial [6, 7], antituberculosis [8-10], anticancer [11], Antidiabetic [12] Antifeedant [13] antiplatelet activities [14, 15] antifungal [16] Scaffold for Nucleophilic Catalysis [17] Neuromuscular Blocking Activity [18]. Pyridazine derivatives which are a rarity in nature [19, 20] and being pharmacologically active nucleus, our research group had synthesized the novel heterocycles containing pyidazine and chalcone motifs [21]. Present work is the extended work of our team expecting augmented effect in antimicrobial results and attempted to synthesize the polyfunctional heterocycles coined with pyridazine and chalcone groups.

2. MATERIAL AND METHODS

2.1. Materials

All the reagents and solvents used for the synthesis were purchased from Sigma Aldrich, Spectrochem and were used as such without further purification.

2.2. Physical measurement

All melting points are uncorrected and were determined on Gallenkamp electric melting point apparatus.

IR spectra were recorded on a Bruker Germany make, 3000 Hyperion microscope with Vertex 80 FTIR system. 1H NMR spectra were recorded on a varian-600 ($CDCl_3$) solution. Chemicals shifts are reported as δ values relative to tetramethylsilane (TMS) as internal reference. Thin layer chromatography was performed on silica gel coated plates for monitoring the reactions. The spots could be visualized easily under UV light and in iodine vapours.

2.3. Antibacterial and Antifungal Activity

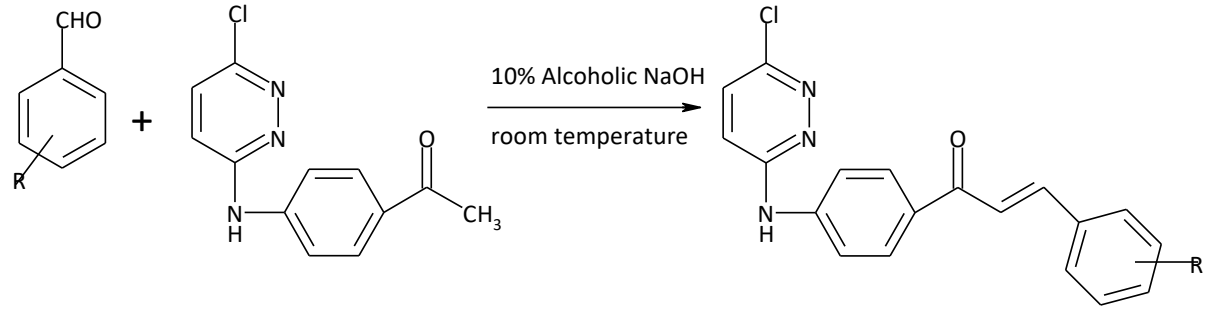
Compounds of the scheme were screened for antimicrobial studies using antibiotic assay of cup-plate agar diffusion method [22, 23]. For antibacterial testing, both gram +ve bacteria (*Escherichia coli*) and gram –ve bacteria (*Staphylococcus aureus*) were randomly selected. To study antifungal activity, *Aspergillus niger* and *Candida albicans* were randomly employed. Penicillin and Griesofulvin were used as standard. Predetermined concentration of sample i.e. 20mg/ml was used in DMSO as a solvent. The cultures were maintained on agar medium inoculated with 72 hr. About 20 ml of the inoculated medium was evenly smeared in a petridish (13 cm diameter) and allowed to set for 2 hr. The cups (10 mm in diameter) were punched in petridish and loaded with predetermined concentration of sample in DMSO. The petridishes were incubated at 30-35°C for two days. After the 24-26 hr zone of inhibition was observed in the plates. After the completion of incubation, zone of

inhibition was measured in mm. Solvent DMSO was also employed as control in entire study.

2.4. General procedure for synthesis of chalcone

Aromatic aldehyde **1** (1mmol) and ketone **2** (1mmol) were mixed in 10 cm^3 of ethanol in 100 cm^3 round bottom flask in an ice-bath. 2 cm^3 of 20% NaOH solution was added dropwise. Subsequently reaction was allowed to stir overnight at room temperature. Completion of reaction was confirmed by TLC method. After completion, contents of the flask were poured over crushed ice and slight acidic pH was maintained using dilute HCl. Solid obtained were filtered, dried and purified by percolating through silica gel (mesh size 60-120).

The physical data values and yield are shown in table 1. The identification of listed chalcone (3) was attempted by spectral techniques such as IR, NMR.



(1) **(2)** **(3)**

3. RESULTS AND DISCUSSION

3.1. Spectral data of (E)-1-(4-((6-chloropyridazin-3-yl)amino)phenyl)-3-phenyl prop-2-en-1-one [3a]

Molecular Composition (%) calculated: C = 67.96, H = 4.20, Cl = 10.56, N = 12.51, O = 4.76 Found C = 67.90, H = 4.22, Cl = 10.52, N = 12.55, O = 4.73, ***^{1}HNMR ($CDCl_3$, ppm)***: 6.88 (s, 1H), 7.19 (d, J =9.2 Hz 1H), 7.37 (d, J =9.2 Hz, 1H)), 7.42-7.44 (m, 3H), 7.57 (d, J =15.7 Hz, 1H), 7.55 (d,8.7, 2H), 7.65-7.67 (m,2H), 7.84 (d, J =15.7Hz, 1H),8.08 (d, J=8.7,2H). ***IR (KBr, cm^{-1})***: 3307, 3115, 1680, 1567, 1392, 968, 740, 692.

3.2. Spectral data of (E)-1-(4-((6-chloropyridazin-3-yl)amino)phenyl)-3-(-4-nitrophenyl)prop-2-en-1-one [3b]

Molecular Composition (%) calculated: C = 59.93, H = 3.44, Cl = 9.31, N = 14.71, O = 12.60 Found: C = 59.85, H = 3.55, Cl = 9.28, N = 14.81, O = 12.55 ***^{1}HNMR ($CDCl_3$, ppm)***: 7.00 (s, 1H), 7.15 (d, J = 9.1 Hz, 1H), 7.37 (d, J = 9.1Hz, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 15.6Hz, 1H), 7.83 (d, J = 15.6Hz, 1H), 7.90 (d, 7.3 Hz,2H), 8.10(d, J= 8.5Hz, 2H), 8.22 (d,7.7 Hz, 2H). ***IR (KBr, cm^{-1}):*** 3310, 3122, 1655, 1577, 1527, 953, 835.

3.3. Spectral data of (E)-1-(4-((6-chloropyridazin-3-yl)amino)phenyl)-3-(-3-nitrophenyl)prop-2-en-1-one [3c]

Molecular Composition (%) calculated: C = 59.93, H = 3.44, Cl = 9.31, N = 14.71, O = 12.60 Found: C = 59.65, H = 3.58, Cl = 9.25, N = 14.59, O = 12.76. ***^{1}HNMR ($CDCl_3$, ppm)***: 7.09 (s, 1H), 7.18 (d, J = 9.1 Hz, 1H), 7.39 (d, J = 9.1Hz, 1H), 7.60 (d, J = 8.5 Hz, 2H), 7.63 (m, 1H), 7.75 (d, J = 15Hz, 1H), 7.85 (d, J = 15Hz, 1H), 7.93 (d, 7.3 Hz,1H), 8.11(d, J= 8.5Hz, 2H), 8.27 (d,7.7 Hz, 1H), 8.53 (s, 1H). ***IR (KBr, cm^{-1})***: 3314, 3125, 1660, 1580, 1525, 1378, 898, 850, 625.

3.4. Spectral data of (E)-1-(4-((6-chloropyridazin-3-yl)amino)phenyl)-3-(-4-fluorophenyl)prop-2-en-1-one [3d]

Molecular Composition (%) calculated: C = 64.51, H = 3.70, Cl = 10.02, F = 5.37, N = 11.88, O = 4.52, Found: C = 64.32, H = 3.55, Cl = 9.92, F = 5.57, N = 11.73, O = 4.41, ***^{1}HNMR ($CDCl_3$, ppm)***: 6.86 (s, 1H), 7.18 (d, J = 9.2 Hz, 1H), 7.38 (d, J =9.2Hz, 1H), 7.48 (d, J = 15.6 Hz, 1H), 7.49(d, J = 8.8 Hz, 2H) 7.55 (d, J = 6.8&1.8Hz, 2H), 7.80 (d, J = 15.6Hz, 1H), 7.98 (d, J = 8.8Hz 2H), 8.08(dd, J= 6.5&1.8Hz, 2H). ***IR (KBr, cm^{-1})***: 3305, 3112, 1695, 1398, 818, 712.

3.5. Spectral data of (E)-4-(3-(4-((6-chloropyrida-zin-3-yl)amino)phenyl)-3-oxoprop-1-en-1-yl)benzonitrile [3e]

Molecular Composition (%) calculated: C = 66.58, H = 3.63, Cl = 9.83, N = 15.53, O = 4.43
Found: C = 66.51, H = 3.54, Cl = 9.89, N = 15.59, O = 4.49, ***^{1}HNMR ($CDCl_3$, ppm):*** 6.87 (s, 1H), 7.19 (d, J = 9.2 Hz, 1H), 7.38 (d, J =9.2Hz, 1H), 7.42-7.44 (m, 2H), 7.55 (d, J = 8.7Hz, 2H), 7.57 (d, J = 15.6Hz, 1H), 7.66 (m, 2H) 7.83 (d, J = 15.6Hz, 1H), 8.08(d, J= 8.7Hz, 2H). ***IR (KBr, cm^{-1}):*** 3312, 3112, 2229, 1645, 845, 812, 712.

3.6. Spectral data of (E)-1-(4-((6-chloropyridazin-3-yl)amino)phenyl)-3-(-4-(diamethylmino) phenyl)prop-2-en-1-one [3g]

Molecular Composition (%) calculated: C = 66.58, H = 5.05, Cl = 9.36, N = 14.79, O = 4.22, Found: C = 66.56, H = 5.69, Cl = 10.18, N = 13.97, O = 4.41, ***^{1}HNMR ($CDCl_3$, ppm):*** 3.0(s,6H),6.88 (s, 1H),6.98 (d,J=8.5,2H), 7.18 (d, J = 9.2 Hz, 1H), 7.37 (d, J =9.2Hz, 1H), 7.55 (d, J = 8.7Hz, 2H), 7.47 (d, J = 15.6Hz, 1H), 7.66 (d,J=8.5, 2H) 7.73 (d, J = 15.6Hz, 1H), 8.08(d, J= 8.7Hz, 2H). ***IR (KBr, cm^{-1}):*** 3308, 3110, 1660, 1590, 1335, 837, 745.

3.7. Spectral data of (E)-1-(4-((6-chloropyridazin-3-yl)amino)phenyl)-3-(2,4-dimethoxy phenyl)prop-2-en-1-one [3h]

Molecular Composition (%) calculated: C = 63.72, H = 4.58, Cl = 8.96, N = 10.62, O = 12.13, Found: C = 63.81, H = 4.46, Cl = 8.82, N = 10.73, O = 12.18, ***^{1}HNMR ($CDCl_3$, ppm):*** 3.73(s,6H),6.85 (s, 1H),6.89(s,1H),6.98 (d,J=8.5,1H), 7.17 (d, J = 9.2 Hz, 1H), 7.38 (d, J =9.2Hz, 1H), 7.55 (d, J = 8.7Hz, 2H), 7.52 (d, J = 15.6Hz, 1H), 7.62 (d,J=8.5, 1H) 7.78 (d, J =15.6Hz, 1H), 8.08(d, J= 8.7Hz, 2H). ***IR (KBr, cm^{-1}):*** 3312, 3105, 1658, 1567, 1322, 833, 752, 678.

3.8. Spectral data of (E)-3-(4-Chlorophenyl)-1-(4-((6-chloropyridazine-3-yl)amino)phenyl) prop-2-en-1-one [3i]

Molecular Composition (%) calculated: C = 61.64, H = 3.54, Cl = 19.15, N = 11.35, O = 4.32 Found: C = 61.51, H = 3.48, Cl = 19.28, N = 11.22, O = 4.21, ***^{1}HNMR ($CDCl_3$, ppm):*** 6.88 (s, 1H), 7.12 (d, J = 9.2 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 7.48 (d, J =15.6Hz, 1H), 7.49 (d, J = 8.5Hz, 2H), 7.55 (d, J = 6.8Hz, 2H), 7.66 (d, J = 8.5Hz, 2H), 7.80 (d,J=15.6,1H)8.07(d, J= 6.8Hz, 2H). ***IR (KBr, cm^{-1}):*** 3305, 3142, 1680, 1540, 1282, 812, 730.

3.9. Spectral data of (E)-3-(3-Chlorophenyl)-1-(4-((6-chloropyridazine-3-yl)amino)phenyl) prop-2-en-1-one [3j]

Molecular Composition (%) calculated: C= 61.64, H = 3.54, Cl = 19.15, N = 11.35, O = 4.32 Found: C= 61.72, H = 3.39, Cl = 19.01, N = 11.49, O = 4.45, ***^{1}HNMR ($CDCl_3$, ppm):*** 6.88 (s, 1H), 7.12 (d, J = 9.2 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 7.40 (m, 1H), 7.48 (d, J =15.6Hz, 1H), 7.50 (s, J=8.3,1H), 7.55 (dd, J = 6.8 &1.8Hz, 2H), 7.63 (d, J = 8.5Hz, 1H),7.71 (s,1H), 7.80 (d,J=15.6,1H),8.07(dd, J= 6.8&1.2Hz, 2H). ***IR (KBr, cm^{-1}):*** 3309, 3140, 1678, 1535, 1305, 805, 702.

3.10. Spectral data of (E)-3-(2-chlorophenyl)-1-(4-((6-chloropyridazin-3-yl)amino)phenyl) prop-2-en-1-one [3k]

Molecular Composition (%) calculated: C= 61.64, H = 3.54, Cl = 19.15, N = 11.35, O = 4.32 Found: C= 61.71, H = 3.44, Cl = 19.08, N = 11.24, O = 4.48, ***^{1}HNMR ($CDCl_3$, ppm):*** 6.84 (s, 1H), 7.17 (d, J = 9.2 Hz, 1H), 7.39 (d, J = 9.2 Hz, 1H), 7.38-7.40 (m, 1H), 7.46 (d, J =15.6Hz, 1H), 7.47-7.48 (m,1H), 7.56 (dd, J = 6.8 &1.8Hz, 2H), 7.63 (d, J = 8.5Hz, 1H),7.71 (d, J=8.5,1H), 7.78 (d,J=15.6,1H),8.09(dd, J= 6.8&1.2Hz, 2H). ***IR (KBr, cm^{-1}):*** 3312, 3135, 1680, 1538, 1320, 745, 727.

3.11. IR spectral data

Peaks in the range of 1650-1700 and 1450-1600 cm^{-1} in IR absorption spectra was indicative of characteristic carbonyl >C=O and C=C functionalities respectively. The strong band at 3305-3315 cm^{-1} was found due to characteristic of secondary N-H stretching bond. The band at 720-730 cm^{-1} shows halide C-Cl stretch.

3.12. ^{1}HNMR spectra

The ^{1}H NMR spectra of chalcones displayed peak at 7.1 ppm which was assigned for N-H and vinylic protons (Hα and Hβ) of chalcone group showed peak at 7.75 ppm and 7.85 ppm for respectively with doublets having coupling constant 15.6. The coupling constant suggested chalcone may be in the form of s-trans.

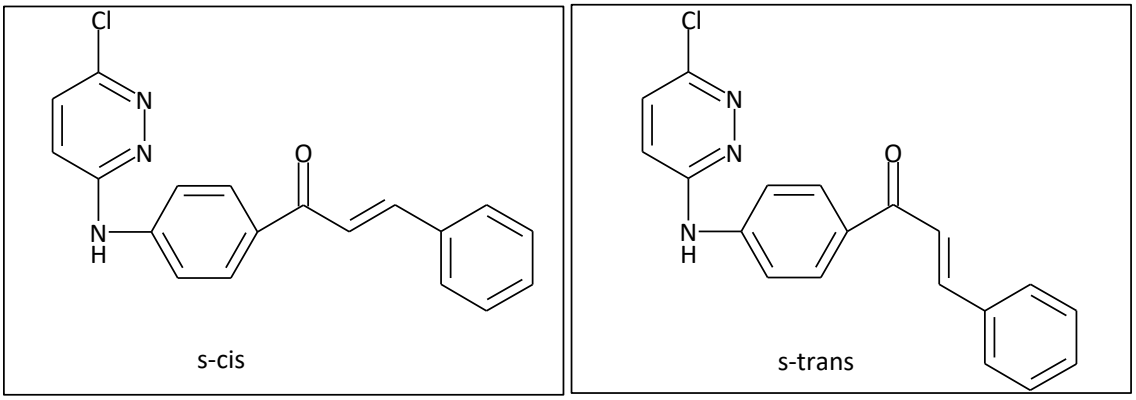


Table 1: Synthesis of some new chalcones using substituted aromatic aldehyde and 2, 6 disubstituted pyridazine ring.

Compound	R	M.P. (°C)	Yield (%)
3a	H	184	79
3b	*p*-NO_2	230	85
3c	*m*-NO_2	242	78
3d	*p*-F	252	80
3e	*p*-CN	272	82
3f	*p*-OCH_3	226	88
3g	$N(Me)_2$	188	75
3h	*m*-OMe & *p*-OMe	208	78
3i	*p*-Cl	212	80
3j	*m*-Cl	220	82
3k	*o*-Cl	225	85

Table: 2: Biological Activity for antibacterial and antifungal study of synthesized chalcone derivative of pyridazines

Compound Code	Zone of Inhibition (mm)			
	E. coli	*S. aureus*	*A. niger*	*B. albicans*
3a	16	18	12	15
3b	19	22	--	16
3c	20	21	15	15
3d	22	26	16	24
3e	21	25	18	16
3f	12	13	19	20
3g	15	15	--	21
3h	14	18	17	16
3i	20	23	--	15
3j	19	22	18	20
3k	15	19	18	15
Penicillin	28	32	--	--
Griesofulvin	--	--	25	28

3.13. Antimicrobial activity

Compound 3d (fluorine substituted) was found more active than other derivatives of pyridazine ring, although zone of inhibition had suggested that it is not more potent than the standards. It was found that compound 3e and 3j were also moderately active against the pathogens.

4. CONCLUSION

It was found that pyridazine nucleus is not naturally distributed in nature, hence it was worthwhile to track synthetic route to access its pharmacological efficacies. Synthesized novel compound 3 will be an addition to the wide library of chalcones which are an important synthons for the preparation of five and six membered heterocycles. In our consideration compounds like 3d, 3e and 3j were found to be satisfactory with microbial studies but its performance in other activities can be studied.

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