Synthesis and Antimicrobial Study of Novel Chromones, Pyrazolines And Benzothiazepines Having Thiazole Nucleus

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Abstract:

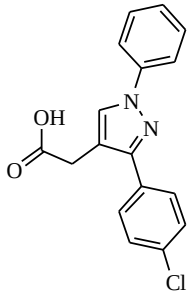
Chalcones study became a part of interest in both educational and industrial world. Chalcones are precursors for flavonoids and other derivatives which can be synthesized in laboratory. A series of some novel Chalcones (2a-e) were synthesized and their derivatives Chromones (3a-e), Pyrazolines (4a-e) and Benzothiazepines (5a-e) were synthesized using DMSO/I_2, hydrazine hydrate/alcohol and 2-aminothiophenol/alcohol respectively and screened them for their antimicrobial activity. Structures of synthesized compounds were confirmed by spectral study.

Keywords: Chalcone, Chromone, Pyrazoline, Benzothiazepine, Antimicrobial activity.

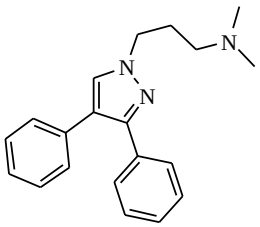
INTRODUCTION

The study of heterocyclic compounds envelops extensive area of chemistry. In recent age, heterocyclic compounds have been given extensive attention due to their importance in pharmacological and agricultural fields. Thiazole bears sulphur and nitrogen which is five member heterocyclic compounds which have the diverse biological properties.

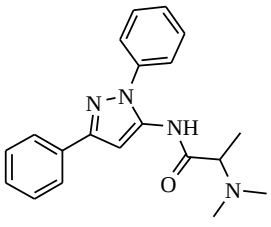
The pyrazole core has chief role in numerous drug structures. Pyrazole compounds are significant class of compounds which be a focused for extreme concentration of chemists due to their pharmacological base[1-4]. Pyrazole derivatives exhibit antimicrobial, anti-inflammatory, antitumor[4], cytotoxic, antiviral, antileishmnial and antioxidant activities. Pyrazole derivatives also possess many applications on crop protection like herbicidal, fungicidal and insecticidal[2] activities. Examples of pyrazole ring containing natural products are (S)-3-pyrazolylalanine, pyrazomycine, and 4,5-dihydro-3-phenyl-6*H*-pyrrolo[1,2-b]pyrazole. Following drugs are examples of biologically active synthetic pyrazole derivatives.



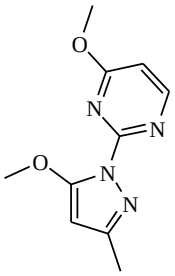
Lonazolac (NSAD)



Fezolamin



Difenamizole



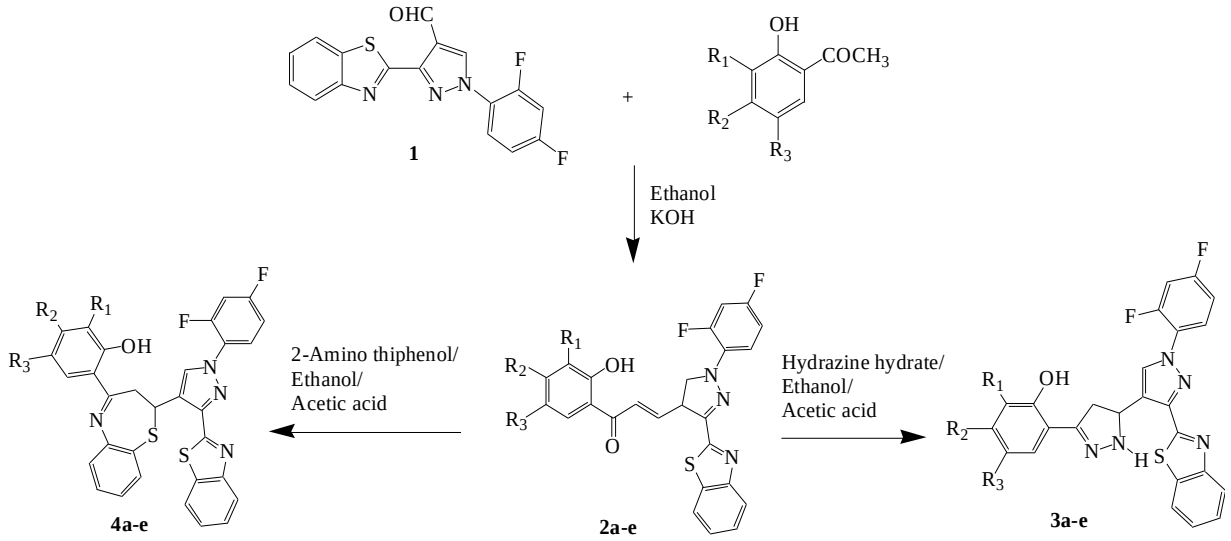
Mepirizole

Chalcones are the intermediates in the synthesis of flavones, biosynthesis of flavonoids, which are substances widespread in plants and with a broad range of biological activities[5-8]. Chalcones form the basic nucleus for a variety of important biologically active compounds like flavones, pyrazolines, and benzothiazepines. 1,4-Benzothiazepine derivatives are of considerable interest because of their biological activity[9-12] as inhibitors of HIV-1 integrase, intitumor, antibiotics, enzyme inhibitors, muscle relaxant and anticonvulsant, sedatives and hypnotics. Taking into consideration the importance of these heterocyclic compounds along with fluorine we intend to synthesize bioactive novel chromones, pyrazolines and benzothiazepines from intermediate like called chalcone.

EXPERIMENTAL WORK

The melting points of all the synthesized compounds were studied in open capillary tubes and are uncorrected. Purity of all compounds was determined by TLC and column chromatography. TLC was performed on precoated silica-gel plates, which was observed under UV light. IR (KBr) spectra were recorded on a Perkin-Elmer (spectrum on a FT-IR) spectrophotometer. The ^{1}H NMR were recorded on a Bruker Avance II 400 MHz NMR spectrometer in $CDCl_3$ and DMSO as a solvent, chemical shift (δ) are expressed in ppm downfield from TMS and coupling constant (J) are expressed in hertz(Hz). Mass spectra were recorded on Waters, Q-TOF MICROMASS (LC-MS).

Scheme



MATERIALS AND METHOD

Synthesis of the compounds was done by conventional method.

Synthesis of 2a-e

A mixture of acetophenone (0.002 mol) and aldehyde **1** (0.002 mol) was dissolved in 30mL of ethanol and 10 mL of 40% KOH was added in 100 mL capacity con. flask. The reaction mixture was stirred at room temperature for 48 hours. Then reaction mixture was poured over a crushed ice and content were

acidified with conc. HCl. The yellow solid thus obtained was filtered and crystallized from acetic acid to afford the pure compound **2a-e**. The same experimental procedure was followed to prepare other analogs of this series **Table**.

2a: IR: (KBr) (cm^{-1}): 3384 (-OH stretching), 3062-2920(trans >C=C< stretching), 1632(C=O stretching), 1526(-C=C- & -C=N- stretching), 976 (Ar-Cl stretching); ^{1}H NMR: δ 2.32 (s, 3H), 7.04 (s, 1H), 7.4-7.6 (m, 2H), 7.43 (d, 1H, J=2.5 Hz), 7.62-7.70 δ (m, 2H), 7.92-8.04 (m, 3H), 8.13 (m, 1H) 8.25 (s, 1H), 9.16 (s, 1H), 12.62 (s, 1H); Mass: m/z 510.5(M^+).

Synthesis of 3a-g

2a-e (0.0002 mol) was dissolved in 5mL ethanol. To this mixture 0.2 mL hydrazine hydrate was added. The reaction mixture was refluxed for 3 hr. The reaction content was then acidified with 2mL of acetic acid and heating was continued for next 3 hours. The reaction mixture was quenched onto crushed ice. The solid thus obtained was filtered off and crystallized from alcohol to afford pure compound **3a-e**. The same experimental procedure was followed to prepare other analogs of this series. Characterization data listed in **Table**.

(3a): IR: (KBr) (cm^{-1}): 3080 (-OH stretching), 3340 (N-H stretching), 1594-1489 (-C=C- & -C=N- stretching). 1HNMR: 2.26 δ (3H, s), 3.18 δ (1H, dd), 3.64 δ (1H, dd), 4.96 δ (1H, dd), 6.22 δ (1H, broad s), 7.06 δ (2H, m), 7.28 δ (2H, m), 7.76 δ (2H, m), 7.92 δ (m, 2H), 8.72 δ (1H, d), 10.85 δ (1H, s), 11.20 δ (1H, s). MASS: (m/z): 522.10 (M^+).

Synthesis of 4a-e

A mixture of **3a-e** (0.0002 mol) and 2-amino thiophenol (0.0002 mol) in absolute ethanol (5mL) was refluxed for 4 hours. After 4 hours few drops of glacial acetic acid was added and the reaction mixture was refluxed for further 4 hours. The reaction mixture was cooled and poured onto crushed ice and solid product separated out was filtered off, washed with water, dried and purified from alcohol **4a-e**. The same experimental procedure was followed to prepare other analogs of this series. Characterization data listed in **Table**.

(4c): IR: **(KBr) (cm^{-1}):** 3433 (-OH stretching), 3085 (Aromatic C-H stretching), 1594-1458 (-C=C- & -C=N ring stretching), 1556 (-C=N Stretch of thiazepine), 650 (-C-S stretch of thiazepines); ^{1}H NMR: 2.92 δ (dd, 1H, J=10 & 13 Hz), 3.35 δ (dd, 1H J= 13&5Hz), 5.46 δ (dd, 1H J= 10 & 5 Hz), 6.95-7.03 δ (m, 2H), 7.21 (dd, 1H J= 3.6 & 5.02 Hz), 7.27-7.34 δ (m, 3H), 7.4- 7.45 δ (m, 2H), 4.48 δ (d, 1H J=2.5 Hz), 7.51- 7.55 δ (m, 1H), 7.69 δ (dd, 1H J= 7.7 & 1.3 Hz), 7.83- 7.93 δ (m, 1H), 7.97 δ (d, 1H J= 2.5 Hz), 15.02 δ (bs 1H).

MASS: (m/z): 583.02 (M^+).

RESULT AND DISCUSSION

Synthesis of compounds **2a-e** was done by known literature scheme as shown in **scheme** and employed as starting material for intended compounds. The IR spectrum of compound **2a** showed the bands at 1632 and 1526 cm^{-1} for conjugated C=O and C=C bonds respectively. The ^{1}H NMR spectrum of

this compound showed a singlet at δ 12.62 which shows the presence of O-H proton. Compounds **2a-e** on refluxing with hydrazine hydrate was converted into pyrazolines **3a-e**. The IR spectrum of compound **3a** exhibited a bands at 3080 and 3340 cm^{-1} corresponding to O-H and –N-H respectively. Presence of downfield broad signal for two protons at 10.85-11.20 also depicted the presence of O-H and N-H protons. Compounds **2a-e** on refluxing with 2-amino thiophenol and acetic acid was converted into benzothiazepines **4a-e.** IR spectrum of 4c showed bands at 3433 for –OH stretching 1556 cm^{-1} for thiazepine –C=N. ^{1}H NMR 2.92 and 3.35 for thiazepine ring where as broad peak for O-H proton appeared at 15.02. The formation of the novel synthesized compounds also confirmed by mass spectrometry.

Table. Characterization data of the synthesized compounds

Sr. No.	R_1	R_2	R_3	M.P. °C	Yield%
2a	H	Me	Cl	172	67
2b	H	H	Cl	196-199	64
2c	Cl	H	Cl	208	58
2d	H	H	Br	278	62
2e	H	H	Me	162	55
3a	H	Me	Cl	185	63
3b	H	H	Cl	225	54
3c	Cl	H	Cl	243	46
3d	H	H	Br	252	44
3e	H	H	Me	203	56
4a	H	Me	Cl	186	83
4b	H	H	Cl	212	92
4c	Cl	H	Cl	211	85
4d	H	H	Br	194	83
4e	H	H	Me	203	76

Biological Activity

The synthesized compounds were tested for their antibacterial activity.

Antibacterial activity

Inoculation of *E.coli* was carried out in 50µl sterile nutrient broth and test samples were added at various concentrations. Tubes were incubated at 37°C for 24 hours. Turbidity was taken as an indication of bacterial growth. Minimum Concentration showing no turbidity was recorded and reported as MIC. Compounds **2a, 2d, 3a** and **4d** showed moderate antimicrobial activity and rest of remain like untreated.

Antioxidant activity

Estimation of GSH

A total of 7×10^5 cells were plated per well in 6-well plates with 2ml culture medium for 18h and exposed to test samples at given concentrations for 30 min before exposure to 2mM H_2O_2 for 3h. The cells were washed and harvested in 0.5 ml of PBS with 0.1% of Triton X - 100. After 10 min of incubation, the mixture was centrifuged (3000 g, 10 min, 4°C) and 0.3 ml of the supernatant was mixed with 1.0 ml of Tris-base (0.8 mol/l)-EDTA (0.02 mol/l) buffer, pH 8.9. Following the addition of 0.1 ml of DTNB (0.01 mol/L) in methanol. The content of reduced GSH in the cells was measured at 412 nm and expressed as percentage of untreated control.

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