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Synthesis of some novel benzoxazole derivatives and their antimicrobial activity

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ABSTRACT

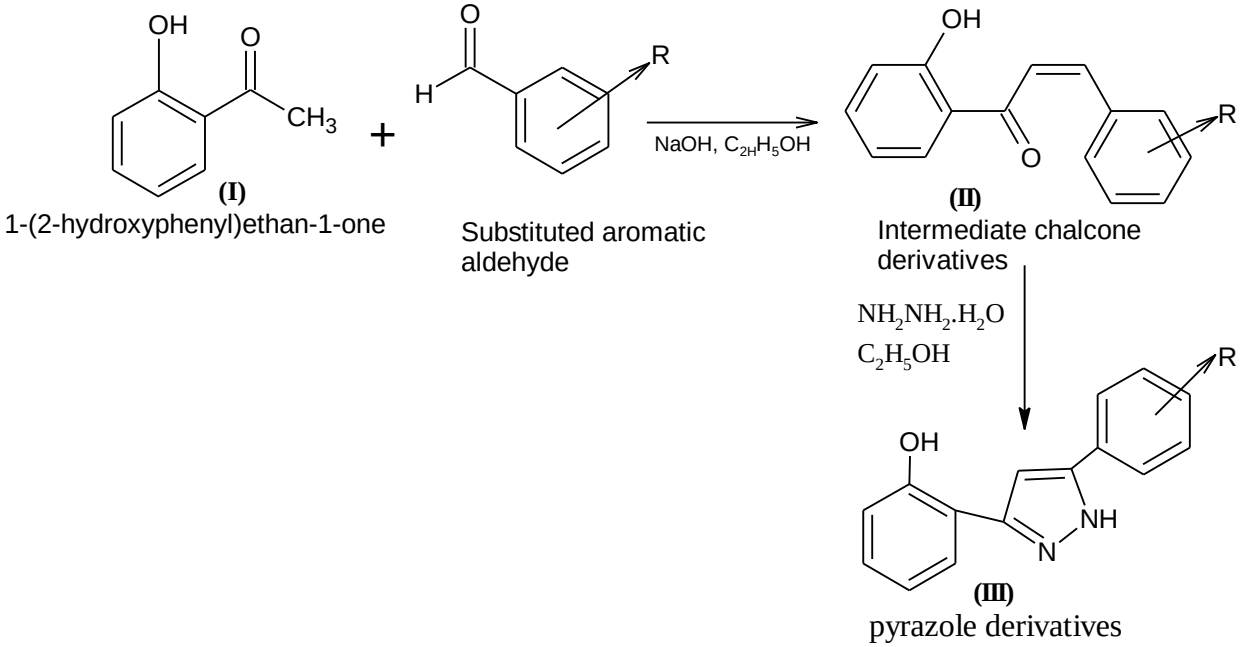
The conventional methodology was adopted to synthesize the novel substituted pyrazole derivatives from substituted chalcone derivatives as starting material. The intermediate chalcone derivatives(II) were prepared from reaction between equimolar quantities of substituted Aromatic aldehydes (0.01mol) and acetophenone(I) (0.01mol) in the presence of sodium hydroxide solution(0.02mol) using ethanol as solvent. The novel pyrazole derivatives were synthesized by means of cyclization reaction between equimolar quantities of substituted chalcone intermediates (0.02 mol) and hydrazine hydrate (0.02 mol) using sodium acetate in ethanol as solvent. All the synthesized derivatives were characterized by Infrared pectroscopy(IR), Mass spectroscopy(MS) and proton nuclear magnetic resonance(1H NMR). All the pyrazole derivatives were screened for anti bacterial activity by disc diffusion method against the organisms, S.aureus and E.coli. The derivatives are also screened for Antifungal activity using Candida albicans by double dilution method on nutrient agar media. The standard drug used was Ampicillin for anti-bacterial and Ketoconazole for anti-fungal activity.

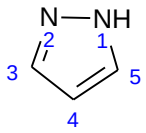
Keywords: Pyrazoles, acetophenone , aromatic aldehydes, chalcones, antimicrobial activity,

INTRODUCTION

Pyrazoles are interesting class of organic compounds, composed of three carbon atoms and two nitrogen atoms present at adjacent position (Fig 1)[1]. Pyrazoles continue to occupy a prime place in heterocyclic chemistry due to their presence in various bioactive heterocyclic molecules of pharmaceutical and agrochemical importance [1]. Number of compounds containing pyrazole have been successfully commercialized, such as Celecoxib, Rimonabant, Sulfaphenazole and Penthiopyrad [2, 3]. The reviews clearly emphasize the importance of pyrazoles in naturally occurring as well as synthetic agents and does an important class itself possess diversified pharmacological actions such as anticancer agents [4,5],antimicrobial [5,12], enzyme inhibitor agents[13], anti corrosionagents [14], catecholase activity [15], and extractive activity [16,17]. This

point encouraged further investigation in the field. The present work was formulated, bearing in mind that the biological activities of known moieties and attempting certain structural modification or adaptation in light of the recent trends in drug research incorporating newly emerged pharmacophores on existing moiety. Hence in the present study we synthesized some novel pure pyrazole derivatives and screened for anti microbial activity.





1*H*-pyrazole

Fig: Structure of pyrazole

EXPERIMENTAL

Melting points were determined by using Precision melting point apparatus in open capillaries and are uncorrected. The purity of the compounds was checked by TLC on silica gel G plates using n-Hexane, ethyl acetate (6:4) and methanol: chloroform (1:9) solvent system and Ultraviolet lamp and iodine chambers used as a visualizing agent. IR-spectra were recorded using KBr pellets on a SHEMADZU 8000 series spectro-photometer. 1H-NMR spectra on BRUKER 300 MHz Spectrophotometer using Ethanol as solvent and TMS as internal standard (chemical shift values expressed in ppm).

PROCEDURE

General procedure for synthesis of chalcones (Compound-II)

Dissolved equimolar quantities of Aromatic aldehydes (0.01mol) and acetophenone (I) (0.01mol) in sufficient amount of ethanol, added sodium hydroxide solution (0.02mol) slowly and the mixture stirred for 2hr until the entire mixture becomes very cloud. Then the mixture was poured slowly into 400 ml of water with constant stirring and kept in refrigerator for 24 hours. The precipitate obtained was filtered, washed and

recrystallized from ethanol. IR Data: Ar CH = 3088, Ar C=C =1588,C=O= 1634, O-H 3545.

General procedure for synthesis of pyrazole derivatives (Compound III)

A mixture of substituted chalcone (0.02 mol), hydrazine hydrate (0.02 mol) and sodium acetate in ethanol (25 ml) was refluxed for 6hr. The mixture was concentrated by distilling out the solvent under reduced pressure and poured into ice water. The precipitate obtained was filtered, washed and recrystallized. IR Data: Ar CH=3087, Ar C=C = 1587, -C=N 1618, C-N = 1357, N-H = 1280.

Procedure for anti microbial activity [18,22]

Anti bacterial activity

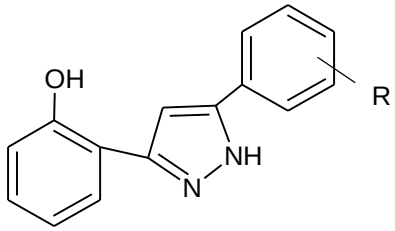
All the compounds synthesized in the present investigation were screened for their anti-bacterial activity by disc-diffusion method. Antibacterial activities were tested on nutrient medium against, Staphylococcus aureus, and Escherchia coli which are representative types of gram positive and gram negative organisms respectively. Nutrient agar medium, test (50 and 100 µg/ml.) and standard Ampicillin (100 µg/ml) were prepared using Dimethyl sulphoxide as solvent. Discs of 6-7 mm in diameter were punched from NO: 1 Whattmann filter paper with sterile cork borer of same size. These discs were sterilized by keeping in oven at 140^0C for 60 minutes. Then standard and test solutions were added to each disc and discs were air-dried. Prepare the strerile petry plates by inoculating the sterile nutrient agar medium with 18-24 hrs old test organisms cultures under aseptic conditions. Then the discs which were previously prepared were carefully kept on the solidified media by using sterilized forceps. These Petri dishes were kept as it is for one-hour diffusion at room temperature and then for incubation at 37^0C for 24 hours in an incubator. The extent diameter of inhibition after 24 hours was measured as the zone of inhibition in millimeters.

Anti-fungal activity

The accurate, precise and quantitative broth double dilution method was used to evaluate the minimal inhibitory concentration (MIC) of synthesized derivatives against C.albicans using Sabourauds Dextrose Broth (SDB) and Malt extract Glucose Yeast extract peptone broth (MGYP) as nutrient medium. Test and standard ketoconazole compounds were dissolved in sterile DMF and DMSO respectively and are serially diluted with Sabourauds Dextrose Broth (SDB) and Malt extract Glucose Yeast extract peptone broth (MGYP) to get required concentration(250 and 500µg/ml). The growth of micro organism in the test compound solutions and control drug was seen after48 hours incubation at 37^0C.

RESULTS AND DISCUSSION

From the literature survey it reveals that the substituted pyrazole moieties are already known for different biological activities. Here we have synthesized some novel pyrazole analogues with different substituted aromatic aldehydes ring system in view to be a good antimicrobial and antifungal agents with less toxic and side effects. Physiochemical properties of pyrazole derivatives are presented in table-1.



COMPOUND-III

Table-1: Physiochemical Properties of pyrazole derivatives

Sample code	R	Mol. Formula	% yield	R_f	m.p.˚C
2a	H	$C_{15}H_{12}O$	74	0.41	134-36
2b	2-OH	$C_{15}H_{12}N_2O_2$	69	0.73	153-55
2c	4-$N(CH_3)_2$	$C_{17}H_{17}N_3O$	81	0.52	167-69
2d	4-Cl	$C_{15}H_{11}ClN_2O$	78	0.59	121-23
2e	4-NO_2	$C_{15}H_{11}N_3O_3$	84	0.47	136-38
2f	2- OCH_3	$C_{16}H_{14}N_2O_2$	87	0.78	140-42
2g	3-NO_2	$C_{15}H_{11}N_3O_3$	79	0.57	149-51
2h	3-OCH_3	$C_{16}H_{14}N_2O_2$	74	0.69	125-27

Spectral data of pyrazole Derivatives

Spectral data of Compound-2a

IR (KBr): 3057(Ar CH), 2955(C=C), 1307(C-N), 3528(O-H), 3258(N-H), 1677(C=N). H^1NMR($CDCl_3$,200MHZ): 7. 84 (1H, d, CH-Ar), 6.8-8.1 (9H, m, Ar-H), 5.04 (1H, s, C-OH). EI ms: m/z: 237 m/e.

Spectral data of Compound-2b

IR (KBr): 3072(Ar CH), 2951(C=C), 1310(C-N), 2937(C-C-), 3537(O-H), 3249(N-H 1675(C=N). H^1NMR($CDCl_3$,200MHZ): 7.74 (1H, d, CH-Ar), 6.8-8.2 (8H, m, Ar-H), 5.07 and6.1(2H, s, C-OH). EI ms: m/z: 253 m/e.

Spectral data of Compound-2c

IR (KBr): 2986(Ar CH), 2960(R CH)2964(C=C), 1684(C=N), 3558(O-H), 3254(N-H) 1257(C-N), 2340(C-N-C), H^1NMR($CDCl_3$,200MHZ): 7.72(s, 1 H, (NH-N) S), 2.708 (6H,s, N-CH_3), 7.74 (1H, d, CH-Ar), 6.8-8.2 (8H, m, Ar-H), 5.07 and 6.1(1H, s, C-OH). EI ms: m/z: 279 m/e.

Spectral data of Compound-2d

IR (KBr): 3082(Ar CH), 2965(C=C), 1327(C-N), 3533(O-H), 3262(N-H), 443(C-Cl), 1701(C=N). H^1NMR($CDCl_3$,200MHZ): 7.67(1H, d, CH-Ar), 6.8-8.1 (8H, m, Ar-H), 5.02 (1H, s, C-OH). EI ms: m/z: 270 m/e.

Spectral data of Compound-2e

IR (KBr): 3075(Ar CH), 2948(C=C), 1320(C-N), 3514(O-H), 3252(N-H), 1538(Ar-NO_2), 1714(C=N). H^1NMR($CDCl_3$,200MHZ): 7.63(1H, d, CH-Ar), 6.8-8.1 (8H, m, Ar-H), 5.09 (1H, s, C-OH). EI ms: m/z: 281 m/e.

Spectral data of Compound-2f

IR (KBr): 2981(Ar CH), 2937(C=C), 1335(C-N), 1737(C=N), 3258(N-H), 1105(C-O-C) H^1NMR($CDCl_3$,200MHZ): 7.66(1H, d, CH-Ar), 6.8-8.1 (8H, m, Ar-H), 5.06(1H, s, C-OH) 3.722 (3H,s, O-CH_3). EI ms: m/z: 267 m/e.

Spectral data of Compound-2g

IR (KBr): 2986(Ar CH), 2934(Ar C=C), 1254(Ar C-N), 2904(C-C), 1382(C-N), 1538(Ar-NO2), 1684(C=N).

Spectral data of Compound-2h

IR (KBr): 2988(Ar CH), 2928(C=C), 1313(C-N), 1737(C=N), 3258(N-H), 1100(C-O-C).

ANTI MICROBIAL ACTIVITY

Anti-bacterial activity

The compounds 2a, 2d, 2e, 2g have shown the poor activity against E. Coli and S.Aureus at 50µg. but the same compounds at 100 µg/ml against same organism have shown moderate activity. The compounds 2b, 2c, 2f, 2h have shown very good activity against S.aureus at 100 µg/ml when compared with the standard drug Amoxicillin.

Anti-fungal activity

The same Compounds also screened for the anti-fungal activity against Candida albicans the compounds 2b, 2c, 2f, and 2h, showed highest degree of inhibition at 250µg/ml and 500µg/ml against C.albicans when compared with the standard drug Ketoconazole. However the activities shown by all the compounds tested were less than that of the standard.

Discussion of Anti-microbial activity

The Discussion part mainly deals with the about the synthesized compounds against the antibacterial and anti-fungal activity. The compounds 2b, 2c, 2f and 2h have shown good anti-bacterial activity due to the presence of electron donating group –OH, OCH_3, and $N(CH_3)2$ group which is attached at second and fourth position of the phenyl ring system and the compounds 2d, 2e, and 2g may be due to the presence of electron withdrawing groups (NO2 and Cl) are attached at the third and fourth position of the phenyl ring system.

CONCLUSION

This present work deals with the preparation of some novel pyrazole derivatives by treating intermediate substituted chalcone compounds with hydrazine hydrate. This method of synthesis is accurate and gives high percent purity with a greater yield. All the derivatives prepared by this method are analyzed by Mass and IR.

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