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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME PYRAZOLIDIN-3-ONES DERIVATIVES

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ABSTRACT

Synthesis of 4-benzoyl methyl pyrazolidin–3-one and a series of substituted 4-benzoyl methyl-1-phenyl pyrazolidin–3-one derivatives have been carried out and evaluated for antimicrobial activity.

Key words: Pyrazolidin-3-ones, 2-Methylene aroyl propionic acids, Antimicrobial activity, Friedel-Crafts acylation, Hydrazinolysis

INTRODUCTION

Heterocyclic compounds occur very widely in nature and are essential to life. Nitrogen containing heterocyclic molecules constitute the largest portion of chemical entities, which are parts of many natural products, fine chemicals and biological active pharmaceuticals, vital for enhancing the quality of life[1]. The importance of pyrazolidin containing molecules has significantly raised in the last two decades, because of their multiple pharmacological applications such as antibacterial, antifungal, anticonvulsant, hypotensive, antidepressant, analgesic, anti-inflammatory and neuroprotective activity. Pyrazolidin–3–ones derivatives are also useful for treating diseases of the central nervous system. They had also found a great application in industrial processes[2].

Keeping in the view of significant biological activities exibited by pyrazolidin moiety, in the present work, an attempt is made towards the synthesis of 4-benzoyl methyl pyrazolidin–3-one and a series of substituted 4-benzoyl methyl-1-phenyl pyrazolidin–3-one derivatives. Structure of all the synthesized compounds were then confirmed by spectral analysis. The synthesized compounds were then evaluated for the antibacterial and antifungal activities against *B. subtilis*, *S. aureus*, *E. coli*, *P. aeruginosa* and *Candida albicans* by using modified Kirby Bauer Method[3].

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EXPERIMENTAL

All the chemicals used in the synthesis were of laboratory grade. Melting points were taken in open capillary tubes and are found to be uncorrected. The purity of all compounds was routinely checked by TLC on silica gel-GF 254 (Merck) coated plates.IR spectra were recorded on a FTIR spectrophotometer (Model-84005. Simadzu corporation, Tokyo, Japan) using KBr disk. UV spectra were recorded on UV spectrophotometer (Model No. UV-2401 PC Simadzu Corporation, Tokyo, Japan). ^{1}H NMR spectra were carried out at 300 MH_Z on Bruker DRX-300 spectrometer. Mass spectra were carried out on Mass spectrometer (Jeol SX-102 FAB). The synthesis of new compounds, 4-benzoyl-methyl-pyrazolidin-3-one (**IIa**) and substituted 4-benzoyl-methyl-1-phenyl-pyrazolidin-3-one derivatives (**IIIa-d**) were carried out by using **(Scheme 1).** The intermediate acids (**Ia-d)** were prepared by Friedel-Crafts acylation at room temperature using appropriate hydrocarbon with itaconic anhydride in presence of anhydrous $AlCl_3$ and anhydrous methylene chloride. The titled compounds (**IIa)** and (**IIIa-d)** were prepared from appropriate 2-methylene aroyl propionic acids (**Ia-d**). Hydrazine hydrate is used as a reagent for the syntesis of 4-benzoyl methyl pyrazolidin–3-one (**IIa**) and phenyl hydrazine is used as a reagent for the synthesis of (**IIIa-d**) by refluxing in ethanol containing sodium acetate and acetic acid. The compounds were purified by recrystallization using appropriate solvent.

General procedure for synthesis of methylene aroyl propionic acids (Ia-d) by Friedel-Crafts acylation[4, 5]

Anhydrous aluminium chloride (2.66 g, 0.2 mole), anhydrous itaconic anhydride (1.128g, 0.1 mole) and anhydrous methylene chloride (15 mL) were placed in a three necked flask fitted with separating funnel, mechanical stirrer and reflux condenser. The mixture was stirred well and appropriate hydrocarbon (0.1 mole) was added drop wise with stirring. After stirring for 5 hr. at room temperature, the content of the flask was poured into crushed ice. The excess of methylene chloride were removed by distillation. The resulting mixture was cooled, filtered and crude product was suspended in water, mixed well and sodium carbonate (0.5 g) was added. Then content was added into mixture of water and concentrated hydrochloric acid (pH 2). The product was collected, dried and recrystallized from ethanol.

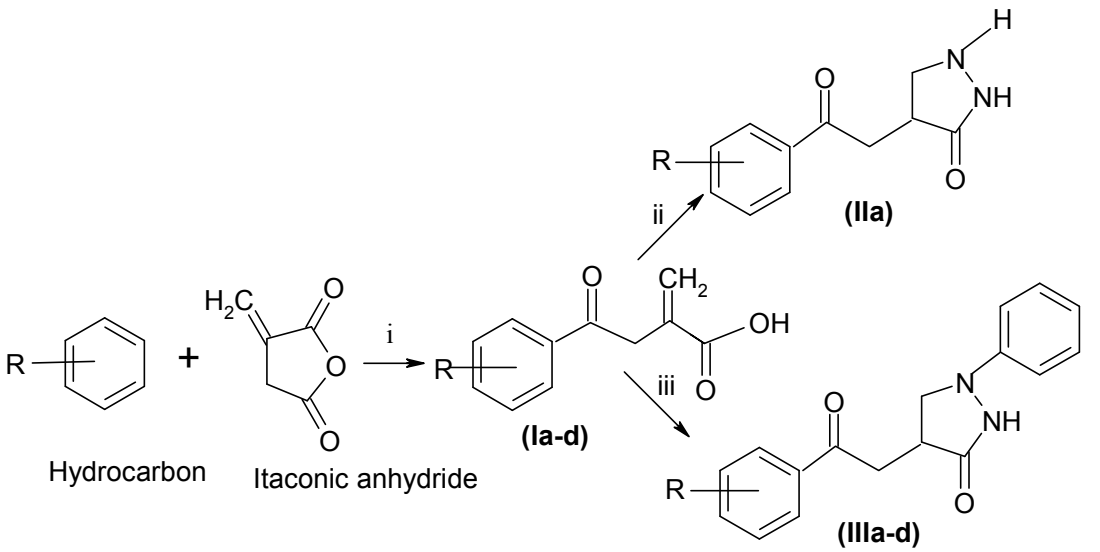
General procedure for synthesis of benzoyl methyl pyrazolidin-3-one (IIa) [6-9]

The appropriate methylene aroyl propionic acid (**Ia)** (0.1 mole) was refluxed for 12 hr. with hydrazine hydrate (0.1 mole) in ethanol (25 mL) containing $NaHCO_3$ (0.5 g) to

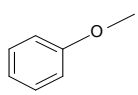
generate free hydrazine. The reaction mixture was concentrated and poured into cold water to obtain the crude product. The crude product was purified by recrystallization from ethanol.

General procedure for synthesis of substituted 4-benzoyl methyl-phenylpyrazolidin-3-ones (IIIa-d) [10-17]

The equimolar mixture of appropriate methylene aroyl propionic acids (**Ia-d**) and phenyl hydrazine was refluxed for 15 hr. in ethanol (10 mL) containing acetic acid and $NaHCO_3$ (0.5 g). The reaction mixture was concentrated and poured into cold water to get crude product. The crude products were purified by recrystallization from ethanol to obtain the titled compounds (**IIIa-d)**.



Scheme 1: Synthesis of 4-benzoyl-methyl-pyrazolidin-3-one (IIa) and substituted 4-benzoyl-methyl-1-phenyl-pyrazolidin-3-ones (IIIa-d).

Where **R** = **IIa:** -H; **IIIa:** -H; **IIIb:** 

IIIc: -OMe

IIId: -2,5-di-Me

Reagents and conditions

(i) $AlCl_3$, CH_2Cl_2, Friedel-Crafts acylaton, reflux 5-6 h at room temp.

(ii) Hydrazine hydrate, reflux 12 h.

(iii) Phenyl hydrazine, reflux 16

4–(2–Oxo–phenyl–ethyl)-pyrazolidin-3-one (IIa)

Practical yield : 73 .81 %

Melting point : 152-156 ^{0}C

R_f value : 0.75 (Toluene: Ethyl formate: Formic acid-5: 4: 1)

λ_{max} : 285 nm

IR (cm^{-1}): 3313.48 (N–H), 3218 (Ar. C–H), 1668.31 (C=O), 1595.88 (Ar.Ring).

^{1}H NMR (δ): 2.303 (1H, m, H-5a), 2.683 (1H, m, H-5b), 2.721 (1H, m, H-6a), 3.177 (1H, sm, H-4), 3.73 (1H, m, H-6b), 7.45 (5H, m, Ar-H), 8.769(1H, s, NH)

Mass spectra (m/z): 204, 197, 173, 159

4–(2–Oxo–phenyl–ethyl)–1–phenyl-pyrazolidin-3-one (IIIa)

Practical yield : 56.52 %

Melting point : 142-145 ^{0}C

R_f value : 0.72 (Toluene: Ethyl formate: Formic acid-5: 4: 1)

λ_{max} : 234.50 nm

IR (cm^{-1}) : 3265.48 (N–H), 3236.33 (Ar. C–H), 1666.38 (C=O), 1598.88 (Ar. Ring).

^{1}H NMR (δ) : 2.063 (2H, m, CH2) 2.721 (1H, m, H-6a), 3.73 (1H, m, H-6b),7.203 (10H, m, Ar-H), 8.769(1H, s, NH)

Mass spectra (m/z) : 280, 263, 244, 235

4–[2–(4–Phenoxy–phenyl)–2–oxo–ethyl]–1-phenyl pyrazolidin-3-one (IIIb):

Practical yield : 42.25 %

Melting point : 135-137 0C

R_f value : 0.77 (Toluene: Ethyl formate: Formic acid-5: 4: 1)

λ_{max} : 283 nm

IR Spectra : 3236 (N–H), 1643.24 (C =O), 1598.88 (Ar. Ring).

^{1}H NMR Spectra : 2.063 (2H, m, CH_2) 2.721 (1H, m, H-6a), 3.73 (1H, m, H-6b), 7.257 (5H, m, Ar-H), 7.65 (10H, m, Ar-H), 8.790 (1H, s, NH)

Mass spectra (m/z) : 372, 355, 341, 327

4–[2–(4–Methoxy–phenyl)–2–oxo– ethyl]–1–phenyl pyrazolidin-3-one (IIIc):

Practical yield : 63 .12 %

Melting point : 159-163 ^{0}C

R_f value : 0.80 (Toluene: Ethyl formate: Formic acid-5: 4: 1)

λ_{max} : 241 nm

IR (cm^{-1}) : 3281.56 (N–H), 3245.37 (Ar. C–H), 1600.81(C=O), 1499.66 (Ar. Ring).

^{1}H NMR (δ) : 2.72 (1H, m, H-6a), 3.75 (1H, m, H-6b), 3.875 (3H, s, OCH_3), 7.380 (10H, m, Ar-H)), 9.969(1H, s, NH)

Mass spectra (m/z) : 310, 296, 279, 265

4–[2–(2, 5–Dimehyl-phenyl)–2–oxo–ethyl]-1–phenyl-pyrazolidin-3-one (IIId):

Practical yield : 46 %

Melting point : 132-136 ^{0}C

R_f value : 0.43 (Toluene: Ethyl formate: Formic acid-5: 4: 1)

λ_{max} : 281.50 nm

IR (cm^{-1}) : 3286.48 (N-H str.), 3219.13 (Ar. C-H), 1666.38 (C=O), 1548.13 (Ar. ring).

^1H NMR (δ) : 2.020 (1H, m, 6a), 3.24 (1H, m, 6b), 7.734 (10H, m, Ar-H), 8.87 (1H, br, s, NH)

Mass spectra (m/z) : m/z 309, 291, 279, 263

Antimicrobial activity

The synthesized compounds were screened *in vitro* for antibacterial and antifungal activity. The antibacterial activity was carried out against four bacterial species *B. subtilis, S. aureus, E. coli and P. aeruginosa* and antifungal activity was carried out against *C. albicans* species. The activity studies were carried out by Disc diffusion technique according to modified Kirby Bauer Method[3].

Table 1: Results of Antimicrobial activity by using disc diffusion method

Name of the compound	Diameter of zone of inhibition (mm)				
	S. aerus	***B. subtilis***	***P. aeruginosa***	***E. coli***	***C. albicans***
IIa	17	12	11	10	17
IIIa	22	13	14	-	19
IIIb	23	13	12	11	19
IIIc	21	14	13	12	18
IIId	22	14	12	-	18
Benzyl Penicillin	25	15	17	16	-
Fluconazole	-	-	-	-	20
DMF	-	-	-	-	-

(-) indicates no inhibition zone (no activity)

Benzyl penicillin and fluconazole were used as standards against bacterial and

fungal strains respectively at conc. of 50 μg/mL. Nutrient broth and sabourds agar were used as a medium for antibacterial and antifungal activity. Dimethyl formamide (DMF) was used as a solvent control. The synthesized compounds have shown significant activity against *B. subtilis and S. aureus*, which are gram positive bacteria and moderate activity against *E. coli and P. aeruginosa*, which are gram negative bacteria when compared with standard drug benzyl penicillin. The compounds have also shown significant inhibition of growth against *Candida albicans*. Screening data of antibacterial and antifungal activity revealed that the synthesized compounds are found to be active. The results of biological activity are shown in Table 1**.**

RESULTS AND DISCUSSION

The synthesis of new compounds, 4-benzoyl-methyl-pyrazolidin-3-one (**IIa**) and a series of substituted 4-benzoyl-methyl-1-phenyl-pyrazolidin-3-one (**IIIa-d**) were carried out using **Scheme 1**. The intermediate 2-methylene aroyl propionic acids (**Ia-d)** were prepared by Friedel-Crafts acylation at room temperature using appropriate hydrocarbons with itaconic anhydride in presence of anhydrous $AlCl_3$ and anhydrous methylene chloride. The titled compounds (**IIa)** and (**IIIa-d)** were prepared from appropriate 2-methylene aroyl propionic acids (**Ia-d**) by hydrazinolysis using hydrazine hydrate for (**IIa**) and phenyl hydrazine for (**IIIa-d**) by refluxing in ethanol containing sodium acetate and acetic acid. The compounds were obtained in good yield and purified by recrystallization using appropriate solvent. The structures of all the newly synthesized compounds were then confirmed by spectral studies. Finally the compounds are subjected to antibacterial studies. The results of biological activities are shown in Table 1**.** The compounds were synthesized effectively in a very good yield and the structures were confirmed by spectral analysis. The newly synthesized compounds showed significant antibacterial activity against gram positive bacteria in comparison to that of standard drug benzyl penicillin. The compounds showed potent antifungal activity in comparision to that of standard drug fluconazole. The compounds if pass the clinical trials can prove to be potent antibacterial and atifungal agents.

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