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Research Article

Synthesis, Characterization and antimicrobial activity of azole-pyrazolidin-3-one derivatives

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Abstract

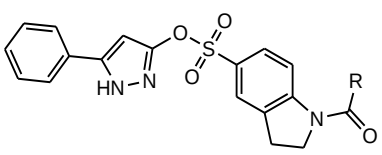
Pyrazole derivatives have attracted considerable attention in last decade in view of diverse chemotherapeutic potential including anti-cancer. In the present research work some derivatives of pyrazole, 4-(1H-imidazol-1-yl)-5-phenylpyrazolidin-3-one **(4a-g)**, were synthesized by treating the corresponding hydrazones with base in moderate yields. The synthesized derivatives were characterized by FT-IR, ^{1}H NMR and Mass spectroscopy and screened for *in vitro* antimicrobial activity. The compounds **4c, 4f** and **4g** showed significant antimicrobial activities.

Keywords: Imidazole, cyclization, base, antimicrobial activity

1. Introduction

Nitrogen, heterocyclic compounds are of great importance in medicinal chemistry because of diverse chemotherapeutic potential and component of many natural products. Imidazole nucleus appears in number of natural products like amino acids, histidine, purines and biotin. It possesses a broad spectrum of properties as antimicrobial [1], analgesic, anti-inflammatory [2], anti tubercular [3], anti-parkinson and monoamine oxidant (MAO) inhibitory activities [4,5]. Azoles are widely used for the treatment of local and systemic fungal infections and known as antimicrobial agent due to their safety profile and high therapeutic index [6].

Literature survey revealed that pyrazole and its derivatives have diverse chemotherapeutic potential[7], many of useful compounds such as Celecobix Phenylbutazone belongs to pyrazoles, and shows anticancer activities [8,9]. Pyrazolone associated with diverse biological activities as antimicrobial [10,11], anticonvulsant [12], analgesic [13], antidepressant [14], anti-inflammatory [15], lipid peroxidation and anticancer [16]. It was recently found that the new compounds **1** and **2** were found to have good cytotoxicity activity against human renal, colon, breast, lung, stomach and prostate cell lines *in vitro* [17]. (Figure1). Figure 1. Representative Pyrazoles and pyrazolidinones derivatives



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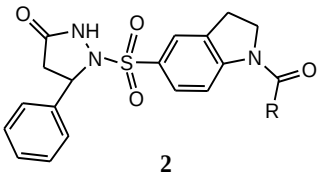

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2. Experimental

All chemicals used are of analytical grade and solvent were distilled prior to use. Melting points were determined by open capillary method and are uncorrected. The progress of reaction was monitored by thin layer chromatography. FTIR spectra were recorded on Shimadzu 8400 IR Spectrometer. ^{1}H NMR recorded on Bruker 300 MHz, NMR spectrometer while Mass spectra were obtained with LC-MS, Shimadzu 2020 Spectrometer.

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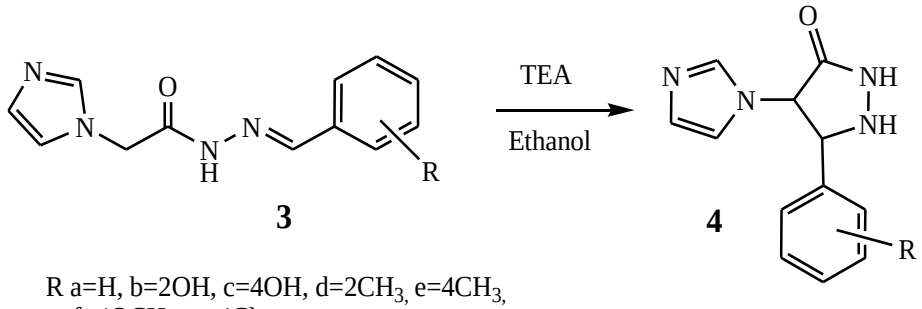
2.1 Material and Methods

2.2 General procedure for synthesis of hydrazones

The various N'-benzylidene-2-(1H-imidazol-1-yl) acetohydrazide were synthesized as per reported procedure in our earlier work [18].

2.3 General procedure for synthesis of 5-(substituted phenyl)-4-(1H-imidazol-1-yl) pyrazolidin-3-one

To a stirred solution of hydrazones (0.01 mol) in dry ethanol (20ml), TEA (1.68 ml, 0.012 mol) was added dropwise. The reaction mixture was stirred for 20 minute at rt. and then refluxed for 4-6 hr. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured on crush ice and acidified by dil. HCl, extracted with ethylacetate (20 ml x 3). The combined organic layer were washed with water and dried over anhydrous Na_2SO_4. The solid obtained was crystallized from aq. Ethanol. The synthetic route is given in Scheme 1. **Scheme 1. Synthesis of pyrazolidin-3-one derivatives**



R a=H, b=2OH, c=4OH, d=2CH_3, e=4CH_3, f=4OCH_3, g=4Cl

2.3.1 4-(1H-imidazol-1-yl)-5-phenylpyrazolidin-3-one

Yield (%) 59, MP. 186-188 (^{0}C), IR (KBr): cm^{-1}, 3267 (NH), 3049, 2926, 1674 (CONH), 752, 695 (monosub ring).^{1}H NMR (300 MHz, $CDCl_3$): δ ppm, 8.41 (s, 1H, NH), 7.54-6.92 (m, 8H, Ar-H), 4.74 (d, 1H, CH), 3.92 ((d, 1H, CH). MS: m/z, 228 [M^+].

2.3.1 5-(2-hydroxyphenyl)-4-(1H-imidazol-1-yl) pyrazolidin-3-one

Yield (%) 55, MP. 204-206 (^{0}C), IR (KBr): cm^{-1}, 3317 (OH), 3037, 2810, 1679 (CONH), 756 (ortho disub). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm, 9.21 (s, 1H, NH), 7.38-6.90 (m, 7H, Ar-H), 5.12 (br, 1H, OH), 4.86 (d, 1H, CH), 3.14 (d, 1H, CH). MS: m/z, 243 [M^+-1].

2.3.1 5-(4-hydroxyphenyl)-4-(1H-imidazol-1-yl) pyrazolidin-3-one

Yield (%) 60, MP.220-222 (^{0}C), IR (KBr): cm^{-1}, 3312, 3254 (OH, NH), 3010, 2913, 1672 (CONH), 814(para disub). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm, 9.81(s, 1H, NH), 7.63-7.10 (m, 7H, Ar-H), 4.72 (br, 1H, OH), 3.43 (d, 1H, CH).

2.3.1 5-(2-methylphenyl)-4-(1H-imidazol-1-yl) pyrazolidin-3-one

Yield (%) 58, MP. 153-155(^{0}C), IR (KBr): cm^{-1}, 3374 (NH), 3086, 2940, 2706, 1680 (CONH), 759 (ortho disub). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm, 8.72 (s, 1H, NH), 7.42-6.91 (m, 7H, Ar-H), 3.22 (d, 1H, 1H), 2.47 (s, 3H, Ar-CH_3). (MS: m/z, 242.10 [M^+].

2.3.1 5-(4-methylphenyl)-4-(1H-imidazol-1-yl) pyrazolidin-3-one

Yield (%) 52, MP. 174-176 (^{0}C), IR (KBr): cm^{-1}, 3410 (NH), 3070, 2932, 2816, 1665(CONH), 822 (para disub). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm, 8.80 (s, 1H, NH), 7.24-6.73 (m, 7H, Ar-H), 4.12 (d, 1H, CH), 2.35 (s, 3H, Ar-CH_3).

2.3.1 5-(4-methoxyphenyl)-4-(1H-imidazol-1-yl) pyrazolidin-3-one

Yield (%) 50, MP. 168-170 (^{0}C), IR (KBr): cm^{-1}, 3381 (NH), 3045, 2953, 2723, 1642 (CONH), 1216, 805 (para disub). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm, 8.92 (s, 1H, NH), 7. 46-6.81 (m, 7H, Ar-H), 4.32 (d, 1H, CH), 3.64 (s, 3H, OCH_3). MS: m/z, 258 [M^+].

2.3.1 5-(4-chlrophenyl)-4-(1H-imidazol-1-yl) pyrazolidin-3-one

Yield (%) 48, MP.144-146 (^{0}C), IR (KBr): cm^{-1}, 3296 (NH), 30323, 2815, 1687(CONH), 816 (para disub). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm, 8.47 (s, 1H, NH), 7.78-7.05 (m, 7H, ArH), 4. 56 (d, 1H, CH). MS: m/z, 262 [M^+].

2.4 Antimicrobial Activity

The pyrazole derivatives were screened for their *in vitro* antimicrobial activities against bacterial strains *Escherichia coli* and *Staphylococcus aureus* and antifungal strains *Candida albicans* and *Aspergillus niger*. The antimicrobial activity of all synthesized compounds was carried out by Disc diffusion method at the concentration of 100 µg/ml in DMF. The results were compared with respective standard Strptomycin and Amphotericin-B. The zones of inhibition were measured in mm and the data is given Table I.

Table I. Results of antimicrobial activity of compounds 3a-3g

Compound No.	Antimicrobial Activity*			
	E. Coli	***S. aureus***	***C. albicans***	***A. niger***
4a	7.15	9.5	11.3	8.15
4b	10.17	10.35	9.74	7.16
4c	**14.62**	**13.52**	7.57	-
4d	9.8	10.6	10.85	11.25
4e	7.3	-	9.53	10.24
4f	8.2	**13.56**	**12.22**	**13.65**
4g	**12.20**	11.75	**14.53**	**12.8**
Streptomycin	**17.22**	**18.82**	NA	NA
Amphotericin-B	NA	NA	**15.25**	**16.45**

*Zone of inhibition in mm, '-' means no zone of inhibition, NA- Not applicable

All the compounds showed moderate to good activity against the tested strains. The compounds **3c** was found good against bacterial strains while the compounds **3f** and **3g** were good against fungal strains.

3. Results and Discussion

The hydrazones, **3a-g** were prepared by reported method. The compounds 3a-g when treated with triethylamine (TEA) in ethanol afforded the pyrazolone derivatives, **4a-g**. The IR spectrum of compound, **4a** showed peaks at 3267 and 1674 which were due to pyrazolone, NH and carbonyl group respectively. The presence of monosubstituted phenyl ring revealed by peaks at 752 and 695. The ^{1}H NMR spectra displayed sharp signal at δ 8.41, accounting for the NH proton of pyrazolone ring. The signal at δ 4.74 and 3.92 were due to methyne protons of pyrazolone ring. The aromatic proton of imidazole and phenyl ring appears as a multiplate in the region at δ 7.54-6.92. The mass spectra of **4a** showed molecular ion peak at m/z 228, corresponding to molecular formula $C_{12}H_{12}ON_4$.

Similarly the presence of substitution pattern of phenyl ring displayed by peak in respective regions of IR. The broad signal in NMR indicates the presence of hydroxyl group in compound **4c**. In antimicrobial study compound **4f** and **4g** were shown good activity against both the strains.

4. Conclusion

The study reports a simple approach for the synthesis pyrazolone derivatives through cyclization of hydrazones in presence of base. The antimicrobial activity of synthesized compounds showed moderate to good activity *in vivo*. The overall activity of compounds motivates for the future study.

Acknowledgement

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References

[1] Vijesh AM, Isloor AM, Telkar S, Peethambar Sk, Rai S, Isloor N. Synthesis, characterization and antimicrobial studies of some new pyrazole incorporated imidazole derivatives. *Eur J Med Chem* 2011; 46(8): 3531-3536.

[2] Ucucu U, Karaburun NG, Isikdag I. Synthesis and analgesic activity of some 1-benzyl-2-substituted-4, 5-diphenyl-1H-imidazole derivatives. *Farmaco* 2001; 56(4): 285-290.

[3] Alegaon SG, Alagawadi KR, Sonkusare PV, Chaudhary SM, Dadwe DH, Shah AS. Novel Imidazo[2,1-b][1,3,4]thiadiazole carrying rhodanine-3-acetic acid as potential antitubercular agents. *Biorg Med Chem Lett* 2012; 22(5): 1917-1921.

[4] Hadizadeh F, Hosseinzadeh H, Motamed-Shariaty V-S, Seifi M, Kazemi S. Synthesis and antidepressant activity of N-substituted imidazole-5-carboxamides in forced swimming test model. *Iranian J Pham Res* 2008; 7(1): 29-33.

[5] Kalaria PN, Satasia SP, Raval DK. Synthesis, characterization and biological screening of novel 5-imidazo-pyrazole incorporated fused pyran motif under microwave irradiation. *New J Chem* 2014; 38: 1512-1521.

[6] Bektas H, Karaali N, Sachin D, Demirbas A, Karaoglu SA, Demirbas N. Synthesis and antimicrobial activities of some new 1,2,4-triazole derivatives. *Molecules* 2010; 15: 2427-2438.

[7] Amir M, Kumar S. Synthesis and anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation activities of 3, 5-dimethyl pyrazoles, 3-methylpyrazol-5-ones and 3, 5-disubstituted pyrazolines. *Ind J Chem* 2005; 44(B): 2532-2537.

[8] Nitulescu GM, Draghici C, Olaru OT. New potential antitumor pyrazole derivatives: Synthesis and cytotoxic evaluation. *Int J Mol Sci* 2013; 14: 21805-21818.

[9] Kasiotis KM, Tzanetou EN, Haroutounian SA. Pyrazoles as potential anti-angiogenesis agents: A contemporary overview. *Frontier in Chem* 2014; 2(Article 78): 1-7.

[10] Shelke SN, Dalvi NR, Kale SB, More MS, Gill CH, Karale BK. Environmentally benign synthesis of fluorinated pyrazolone derivatives and their antimicrobial activity. *Ind J Chem* 2007; 46(B): 1174-1178.

[11] Bhanat K, Parashar B, Sharma VK. Microwave induced synthesis and antimicrobial activities of various substituted pyrazolidines from chalcones. *Res J Chem Sci* 2014; 4(2): 68-74.

[12] Bhosale SK, Bhosale NS. Synthesis and antimicrobial activity of some pyrazolidin-3-ones derivatives. *Int J Chem Sci* 2008; 6(4): 2256-2263.

[13] Amir M, Kumar H, Khan SA. Synthesis and pharmacological evaluation of pyrazoline derivatives as new anti-inflammatory and analgesic agents. *Bioorg Med Chem Lett* 2008; 18: 918-922.

[14] Aziz MA, Rahma GEAA, Hassan AA. Synthesis of novel pyrazole derivatives and evaluation of their antidepressant and anticonvulsant activities. *Eur J Med Chem* 2009; 44: 3480-3487.

[15] Khode S, Maddi V, Aragade P, Palkar M, Ronad PK, Mamledesai S, Thippeswamy AHM, Satyanarayana D. Synthesis and pharmacological evaluation of novel series of 5- (substituted) aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines as novel anti-inflammatory and analgesic agent. *Eur J Med Chem* 2009; 44: 1682-1688.

[16] Park HJ, Lee K, Park SJ, Ahn B, Lee JC, Cho HY, Lee KI. Identification of antitumor activity of pyrazole oxime ethers. *Bioorg Med Chem Lett* 2005; 15: 3307-3312.

[17] Subramanian S, Sharma VK, Yun J, Jung S-H. Exploration of isosteric replacement of Imidazolidinone motif in 4-phenyl-1-arylsulfonylimidazolidinone with pyrazole and pyrazolidinone for cytotoxicity. *Bull Korean Chem Soc* 2014; 35(10): 2922-2928.