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Synthesis and biological evaluation of azetidinone derivatives with pyrazolone moiety

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A Schiff base has been prepared by the reaction of 4-acetyl-5-methyl-2-(4-methylphenyl)-2,4-dihydro-3*H*-pyrazole-3-one with different substituted amines. Treatment of this Schiff base with chlorobactyl chloride affords the corresponding azetidinone in good yield. All the new compounds have been characterized by IR, ^{1}H NMR, GC-MS and elemental analysis. The antibacterial activity of these compounds has been determined with the reference of standard drug.

Keywords: 2-Azetidinone, pyrazolone, Schiff base, antimicrobial activity

The synthesis of heterocyclic compound has always drawn the attention of chemist over the years mainly. Because of their important biological activities[1]. Pyrazolones is a five-member heterocyclic compound containing one ketonic group and two nitrogen atoms adjacent to each other. Pyrazolone derivatives play an important role in heterocyclic compound history and possess considerable biological activities, thus making it an important pharmacophore for carrying out further drug research[2]. One such heterocyclic, 2-azetidinone, a very well-known compound for the medicinal chemistry, since it forms a part of antibiotic molecules[3]. They are carbonyl derivatives of azetidinone containing carbonyl group at position- 2. These are known as 2-azetidinone[4]. The 2- azetidinone ring system, a common structural features of a number of wide spectrum β-lactam antibiotics, including penicinils, cephalosporin, carbapenems, nocardiacins and monobactams, which have been widely use as chemotherapic agent to treat bacterial infections and microbial diseases[5]. The utility of azetidinone as synthon for various biological active compounds as well their recognitions as antibacterial[6], anticonvulsant[7], antimicrobial[8], antitubercular[9], anti-inflammatory[10], anthelmintic[11], anesthetic[12], antioxidant[13]. They also function as enzyme inhibitors[14] and are effective on the CNS[15]. Cycloaddition of monochloroacetylchloride with imines (Schiff base) result in formation of 2- azetidinone(β-lactam). The reaction involves direct acylation of Schiff base with monochloroacetylchloride. The reaction is carried out with base as triethylamine gives β- lactam.

Result and Discussion

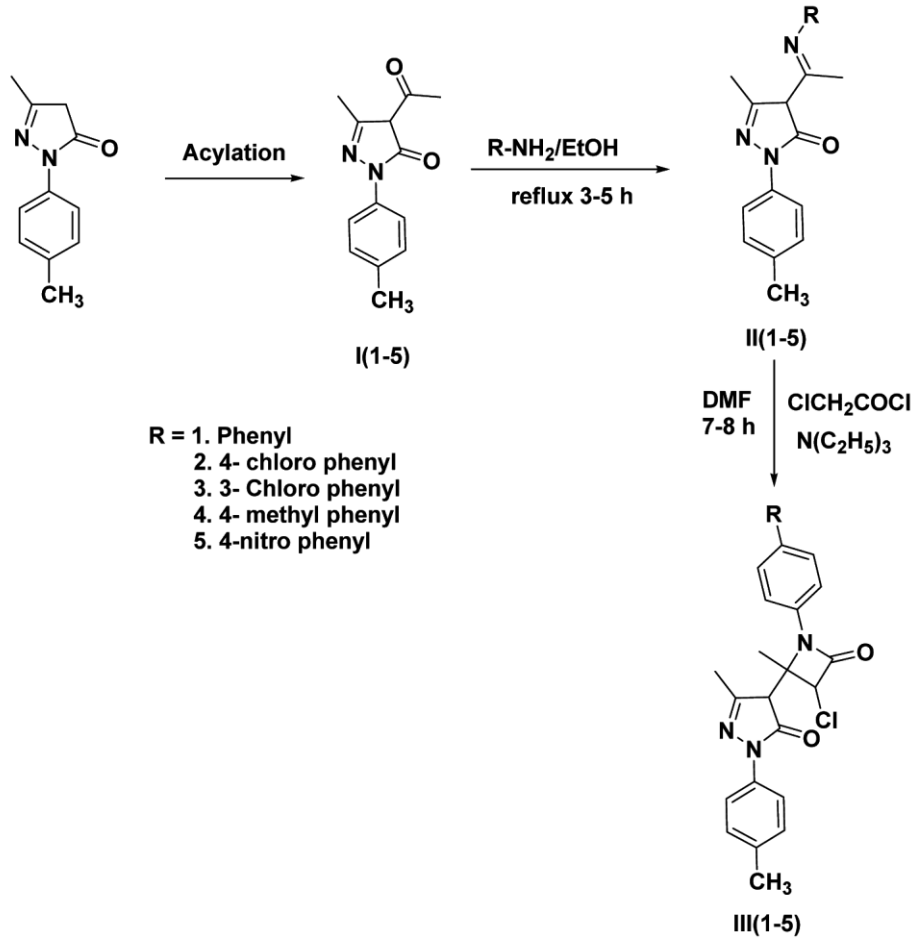
Chemistry

Azetidinone derivatives III1-5 were prepared using the method summarized in Scheme I. First, 3-methyl-1-(4-methylphenyl)-2-pyrazolineon acylation gives 4-acetyl-5-methyl-2-(4-methyl- phenyl)-2,4-dihydro-3H-pyrazole-3-one derivatives I(1-5). Compounds I(1-5) on reaction with substituted amines afforded Schiff base derivatives II(1-5). Finally the Schiff bases upon reaction with chloroacetyl chloride in the presence of triethylamine afforded azetidinone derivatives III(1-5).

The structure of compounds was assigned on the basis of spectral data. In the IR spectra of azetidinone derivatives the carbonyl group of the β-lactam ring appeared as a characteristic absorption band in the IR range 1660-1675 cm^{-1}.The IR absorption bands and 1H NMR signal characteristic of azomethine group disappeared from the spectra of azetidinone derivatives which conforms that the cyclization reaction with chloroacetyl chloride took place. The 1H NMR spectra of III(1-5) showed signals, which are characteristic for CH-Cl that appears in the range of 5.2-5.9. Synthetic route is given as below.

Experimental Section

Melting points were recorded in open capillary tube and are uncorrected. The IR spectra were recorded on a Perkin–Elmer 37 spectrophotometer and ^{1}H NMR spectra were recorded in DMSO-d_6 with TMS as internal standard on Bruker AM 400



Scheme I

instrument (at 400 MHz). Mass spectra were recorded on MS route JMS 600-H. All the synthesized compounds were purified by recrystalization. All the chemicals and solvents were AR grade and were used without further purification.

General procedure

Step-1: Synthesis of 4-acetyl-5-methyl-2-(4-methylphenyl)-2, 4-dihydro-3*H*-pyrazole-3-one

3-Methyl-1-(4-methylphenyl)-2-pyrazoline-one in solution of dioxane and acetyl chloride was refluxed for 2h in oil bath with calcium hydroxide and cooled to RT. The resulting reaction mass is added to dil. HCL, the crude product (I1-5) was collected by filtration and washed several time with water and then dried in air.

Step- 2: Synthesis of Schiff base

4-Acetyl-5-methyl-2-(4-methylphenyl)-2, 4-dihydro-3*H*-pyrazole-3-one (0.01mol) is treated with substituted amine in ethanol reflux for 3-5 h. Then mixture is cooled. Solid yellow product (II1-5) filtered and washed with methanol or ethanol.

Step-3: Synthesis of 2-azetidinone derivatives

Schiff bases obtained in step-2 (0.01mol) in DMF on further treatment with base triethylamine (0.01 mol) and acylated with chloroacetyl chloride (0.01mol) as cyclic agent. The reaction mixture was stirred for 5-7 hrs. The product (III1-5) was isolated and purified by recrystallization from ethanol.

III1.4-(3-Chloro-2-methyl-4-oxo-1-phenyl-azetidin-2-yl)-5-methyl-2-p-tolyl-2,4-dihydro-pyrazol-3-one

m.p.141-143°C (uncorrected). Yield: 65%. IR: 2893 Aromatic C-H stretching, 1669 C=O, 1605, C=N, 1537, C=C Ar., 759 cm^{-1} C-Cl; ^1H NMR: δ 6.98-7.63 (8H, m, Ar-H), 3.1 (1H, s, Pyrazolone), 5.04 (1H, s, CH), 1.96 (3H, s, CH_3), 2.34 (3H, s, CH_3), 1.56 (3H, s, CH_3). Anal. Calcd for $C_{20}H_{20}ClN_3O_2$: C, 66.05; H, 5.28; N, 11.0. Found: C, 66.03; H, 5.30; N, 11.04%.

III2. 4-[3-Chloro-1-(4-chloro-phenyl)-2-methyl-4-oxo-azetidin-2-yl]-5-methyl-2-p-tolyl-2,4-dihydro-pyrazol-3-one

m.p.156-157°C (uncorrected). Yield: 68%. IR: 2896 Aromatic C-H stretching, 1665 C=O, 1602, C=N, 1542, C=C Ar., 762 cm^{-1} C-Cl; ^{1}H NMR: δ 7.0-8.09 (8H, m, Ar-H), 3.0 (1H, s, Pyrazolone), 5.04 (1H, s, CH), 1.93 (3H, s, CH_3), 2.33 (3H, s, CH_3), 1.53 (3H, s, CH_3). Anal. Calcd for $C_{20}H_{19}Cl_2N_3O_2$: C, 60.57; H, 4.65; N, 10.1. Found: C, 60.59; H, 4.60; N, 10.09%.

III3. 4-[3-Chloro-1-(3-chloro-phenyl)-2-methyl-4-oxo-azetidin-2-yl]-5-methyl-2-p-tolyl-2,4-dihydro-pyrazol-3-one

m.p.147-148°C (uncorrected). Yield: 67%. IR: 2899 Aromatic C-H stretching, 1668 C=O, 1609, C=N, 1540, C=C Ar., 763 cm^{-1} C-Cl; ^{1}H NMR: δ 7.0-8.09 (8H, m, Ar-H), 3.1 (1H, s, Pyrazolone), 5.06 (1H, s, CH), 1.93 (3H, s, CH_3), 2.34 (3H, s, CH_3), 1.52 (3H, s, CH_3). Anal. Calcd for $C_{20}H_{19}Cl_2N_3O_2$: C, 60.59; H, 4.60; N, 10.9. Found: C, 60.6; H, 4.61; N, 10.07%.

III4. 4-(3-Chloro-2-methyl-4-oxo-1-p-tolyl-azetidin-2-yl)-5-methyl-2-p-tolyl-2,4-dihydro-pyrazol-3-one

m.p.154-155°C (uncorrected). Yield: 70%; IR: 2896 Aromatic C-H stretching, 1662 C=O, 1610, C=N, 1535, C=C Ar., 757 cm^{-1} C-Cl; ^{1}H NMR: δ 6.99-7.86 (8H, m, Ar-H), 3.04 (1H, s, Pyrazolone), 5.02 (1H, s, CH), 1.96 (3H, s, CH_3), 2.33 (3H, s, CH_3), 1.52 (3H, s, CH_3). Anal. Calcd for $C_{22}H_{22}ClN_3O_2$: C, 66.75; H, 5.60; N, 10.61. Found: C, 66.8; H, 5.59; N, 10.62%.

III5. 4-[3-Chloro-2-methyl-1-(4-nitro-phenyl)-4-oxo-azetidin-2-yl]-5-methyl-2-p-tolyl-2,4-dihydro-pyrazol-3-one

m.p.154-155°C (uncorrected). Yield: 70%. IR: 2902 Aromatic C-H stretching, 1670 C=O, 1608, C=N, 1534, C=C Ar., 756 cm^{-1} C-Cl; ^{1}H NMR: δ 7.0-8.86 (8H, m, Ar-H), 3.2 (1H, s, Pyrazolone), 5.09 (1H, s, CH), 1.96 (3H, s, CH_3), 2.35 (3H, s, CH_3), 1.55 (3H, s, CH_3). Anal. Calcd for $C_{21}H_{19}ClN_4O_4$: C, 59.09; H, 4.49; N, 1.13. Found: C, 59.11; H, 4.48; N, 13.1%.

Biological Study

Antibacterial activity

We have used the Agar cup Method to evaluate the antibacterial activity. It is one of the non automated *in vitro* bacterial susceptibility tests. This classic method yields a zone of inhibition in mm result for the amount of antimicrobial agents that is needed to inhibit growth of specific microorganisms (Figure 1). It is carried out in Petri plates. Antibacterial activity of compounds is shown in Table I.

Antifungal activity

Antifungal activity of compounds (III 1-5) is shown in Table II and Figure 2.

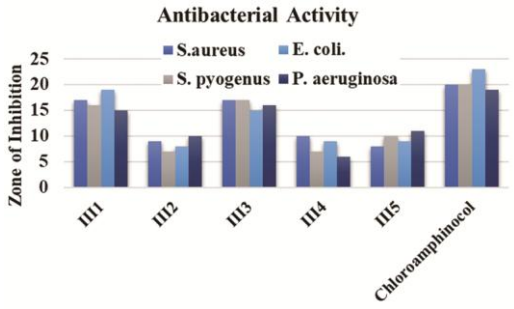


Figure 1 — Graphical representation of antibacterial activity

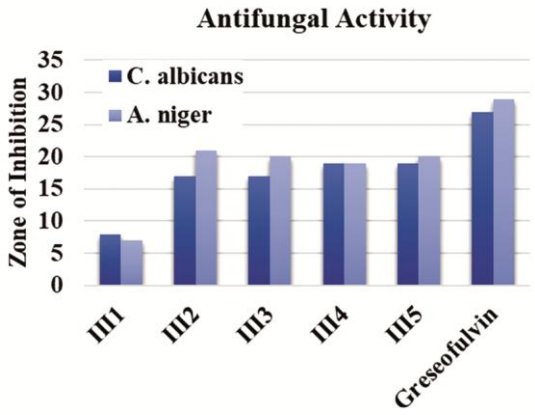


Figure 2 — Graphical representation of antifungal activity

Table I — Antibactarial activity of compounds **III_{1-5}**

Compd	Zone of Inhibition			
	Gram Positive		Gram Negative	
III_1	17	16	19	15
III_2	09	07	08	10
III_3	17	17	15	16
III_4	10	07	09	06
III_5	08	10	09	11
Chloroamphinocol	20	20	23	19

Table II — Antifungal activity of compounds III_{1-5}

Compd	Zone of Inhibition (in mm)	
	C. albicans	*A. niger*
III_1	08	07
III_2	17	21
III_3	17	20
III_4	19	19
III_5	19	20
Greseofulvin	27	29

Compounds III 1-5 showed moderate to good antimicrobial activity against standard drugs.

Conclusion

In this study new 2-azetidionone derivatives have been synthesize from Schiff Bases. The structures of all new compounds were proved using spectral methods. The compounds were evaluated for their antimicrobial. Antimicrobial potential of all compounds was reduced.

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References

1 Gawande S K & Kadsan R E, *Der Pharma Chem*, 6(2) (2014) 70.

2 Rania E S, Parmeshwara R, Babu V H, Rangnatha Y S, Kumar B N & Kumar G A, *IJPSR*, 4 (2012) 424.

3 Bhusari K P, Charbe N B, Mehere A P, Warokar A S, Kakde J W & Mishra A P, *IJRPC*, 1 (2011) 1066.

4 Bagherwal A, Baldi A, Nagar R & Patidar D, *IJCRGG*, 3(1) (2013) 274.

5 Bhutani R, Pathak D P, Husain A, Kapoor G & Ravikant, *IJPSR*, 6(10) (2015) 4113.

6 Dash B, Mahaptra P K, Panda D & Pathak J M, *J Indian Chem Soc*, 61 (1984) 1061.

7 I K Bhat, S K Chaitanya, P D Satynaryana & B J Kalluraya, *Serb Chem Soc*, 72(5) (2007) 437.

8 Chavan A A & Rai N R, *Molecules*, 12 (2007) 2467.

9 Mathew B, Mathew G E, Vijaybaskaram M & Mathew N, *Der Pharma Chem*, 2(6) (2010) 2.

10 Ramlakshmi N, Vijaykumar R, Ilango K, Arunkumar S & Puratchikody A, *Int J Chem Sci*, 6(3) (2008) 1213.

11 Warad D U, Satish C D, Kulkarni V H & Bajgur C S, *Indian J Chem*, 39B (2000) 415.

12 Kumble R R, Taj T, Gireesh T & Badami B V, *J Chem Sci*, 123(5) (2011) 657.

13 Vibhute Y, Chavan S, Zangde S & Vibhute A, *Eur J Chem*, 4(2) (2013) 98.

14 Bhusnure O G, Mokale S S, Nalwar Y S & Vibhute Y B, *JPBMS*, 6(8) (2011) 1.

15 Jauhari S, Surati M & Desai K, *Arch Appl Sci Res*, 4(1) (2012) 645.