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SYNTHESIS, CHEMICAL CHARACTERISATION OF SIX MEMBERED HETEROCYCLIC COMPOUND AND IT'S PHARMACOLOGICA; ACTIVITY

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ABSTRACT

Six novel pyrimidinone derivatives (IIIa - IIIf) were synthesized by conventional method. The newly synthesized derivatives were characterized by spectroscopical methods using IR, ^{13}C-NMR spectroscopy and Mass spectrometry. All the synthesized compounds were screened for their antibacterial and antifungal activity bycup-plate-agar-diffusion method. The antibacterial activity screening revels hat the compound IIIb has comparable activity and compound IIIc shows moderate activity as that of standard ampicillin against gram positive and gram-negative bacteria. All synthesized compounds IIIc were found to be active as antifungal against Candida albicans.

KEYWORDS: Pyrimidinone, Antifungal, Antibacterial

INTRODUCTION

Infectious diseases have presented serious threats to human health in recent years. A progressive reduction in susceptibility to the antimicrobial drugs now in use is revealed by this widespread illness [1]. Additionally, the antimicrobial drugs available on the market come with a host of disadvantages, including a limited antimicrobial spectrum, low efficacy, possible toxicity, and the slow development of microbial resistance [2]. Thus, one of the hardest things in the antibacterial sector has always been creating novel chemicals with superior antibacterial activity.

Nitrogen-containing heterocycles are the building blocks of many physiologically active substances and medications and are abundantly present in natural goods, manufactured pharmaceuticals, and functional materials. In the pharmaceutical industry, various synthetic nitrogen-containing heterocyclic compounds have gained popularity as medications in addition to physiologically active natural chemicals. Examples of these include captopril for hypertension, delorazepam for anxiety, isoniazid for tuberculosis, and chlorpromazine for psychosis. At least one nitrogen heterocycle is thought to be present in more than 80% of the top-selling small-molecule medications [3, 4].

Since pyrimidinones are vital components of all cells and organisms, their superior pharmacological capabilities make them one of the most important heterocyclic compounds in the field of nitrogen-containing heterocyclic chemistry, which is both challenging and fruitful in the development of anti-infective medications [5, 6]. Pyrimidinone molecule production and drug screening have attracted a lot of attention. This is due to the fact that compounds' polarity, lipophilicity, and capacity to form hydrogen bonds can all be improved by the distinct chemical structure of the pyrimidinones moiety, which also benefits pharmacokinetics, pharmacology, and toxicity. Consequently, pyrimidinone medications have minimal toxicity, high activity, and favourable pharmacokinetic and pharmacodynamic characteristics [7]. Promising anti-

inflammatory [8], anti-HIV [9], antibacterial [10], antinoceptive [11], and antiviral properties are displayed by hetero-fused pyrimidines [12]. One well-known elegance of aza-bridgehead fused heterocyclic compounds with a variety of medicinal applications is the organisation of pyrido[1,2-a]pyrimidin-4-ones. This kind of structural sample can be found in the antiallergic drug ramastine, the human leukocyte elastase inhibitor ssr69071, the well-known psychiatric medications risperidone and paliperidone, and antioxidants [13]. In neurology, fused pyrimidines are widely employed, particularly in the treatment of neurodegenerative conditions including Parkinson's disease [14], anxiety disorders, and depression [15]. Numerous pyrimidine-primarily based spinoff examples, such as 2-phenyl amino derivatives, 4-phenylaminoderivatives, and 2.4bis(phenyl amino) derivatives, have been studied as potential anticancer drugs [16]. derivatives of 6 bis(phenyl amino) [17], and derivatives of 4 aryl substitutions [18]. In view of these observations and in continuation of our previous work in pyridine pyrimidinones, we have now synthesized some novel heterocyclic compounds containing the pyrimidinone nucleus and tested their antimicrobial activities.

MATERIALS AND METHODS:

All chemicals were purchased from Merck and Sigma-Aldrich as 'synthesis grade' and used without similarly purification. Melting factors have been determined by way of open tube capillary technique. Purity of the compounds was checked via thin layer chromatography(TLC) on silica gel G plates and the spots were placed beneath extremely violet light. The IR spectra had been measured the use of a Shimadzu FTIR-8400s spectrophotometer.13C- NMR spectra have been recorded on Bruker Avance-300 MHZ in DMSO as an internal standard; chemical shifts (δ) are pronounced in elements in step with million (ppm). Mass spectra have been recorded on a JEOL JMS-D 300 tool.

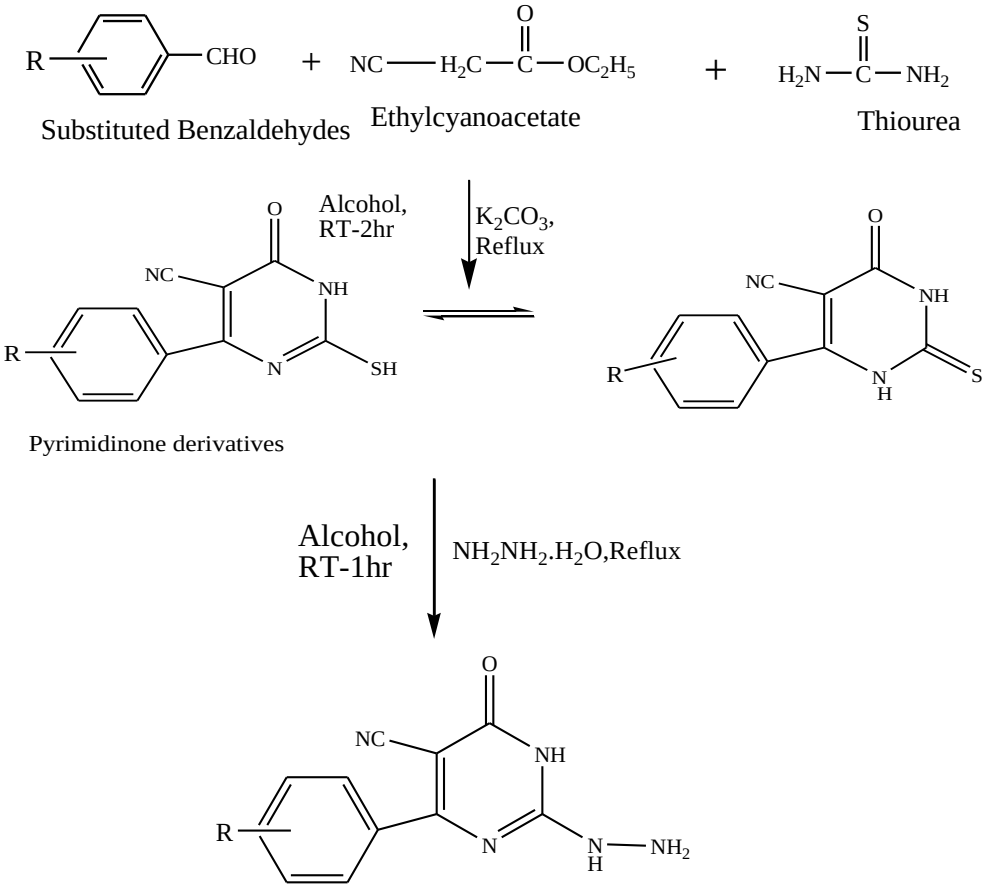
2.1 Experimental: [19]

Step-1: Synthesis of Pyrimidinone derivatives: After numerous substituted benzaldehyde (1 mmol), ethylcyano acetate (1 mmol), and thiourea (1 mmol) were dissolved in an alcohol, the mixture was refluxed for two hours with the addition of 3 mmol of potassium carbonate. The solvent was then concentrated and added to ice-bloodless water while being stirred. The solution was neutralised with glacial acetic acid, which led to the separation of different pyrimidinone compounds that were filtered, rinsed with water, and recrystallized from methanol.Yield: 90%; MP 138-40 °C; R_f 0.67; IR (cm^{-1}): 3267 (–NH of amide), 3232 (–NH), 2342 (C,N), 1683 (C,O), 1159(C,S); 1H NMR (d, ppm): 3.76 (s, 3H, OCH_3), 6.75 (d, 2H,J= 8.5 Hz, H-3, 4, Phenyl), 7.21 (d, 2H, J= 8.4 Hz, H-2,6,Phenyl), 9.32 (s, 1H, NH), 12.65 (br s, 1H, NH–C,O).

Step-2: Synthesis of Pyrimidinone Hydrazides: The aforementioned compounds (1 mmol) were heated to a boil and refluxed for one hour in an ethanol, hydrazine hydrate (99%; 4 mmol).Strong separation occurred as a result of allowing the reaction aggregate to cool. The product that was triggered was filtered and then given a water wash. With ethanol, it recrystallized. Yield: 82%; mp 179–80 0C; Rf 0.2; IR (cm-1): 3285(–NH of amide), 3218 (–NHNH2), 2210 (C,„N), 1680(C,O), 1065 (C–O–C); 1H NMR (d, ppm): 3.84 (s, 3H, OCH3), 3.97

(br s, 3H, NHNH2), 6.93 (d, 2H, J =8.4 Hz,H-3,5, phenyl), 7.77 (d, 2H, J= 8.4 Hz, H-2,6, phenyl),11.71 (br s, 1H, NH–C,O).

Step-3: Synthesis of Pyrimidinone containing Schiff base derivatives: The pyrimidinone hydrazide compounds (1 mmol) dissolve in an 9:1 solution of pure alcohol and glacial acetic acid. Pyridine-4-carbaldehyde (1.1 mmol) alcoholic solution was added to this mixture and refluxed for two to three hours. After being concentrated to half its original amount, the solvent was added to freezing water. The resultant material was filtered, rinsed with water, and then crystallised again from methanol. **IIIa)**Yield: 63.03%; MP 206-207°C; R_f 0.59; IR (cm^{-1}):665.04 (C-Cl),1696 (C=O), 3373 (–NH of amide),1457 (C=N),2863 (C-N),3104 (Ar-CH); 13C NMR (d, ppm): 88.43 (s,1C,-CH), 116.12 (s,1C,-CN), 119.65-159.68 (m,13C , Ar-C), 177.32 (s, 1C, -HC=O). **IIIb)**Yield: 54.5%; MP 215 -218°C; R_f 0.6; IR (cm^{-1}):3372 (C-OH),1621 (C=O), 3364 (–NH of amide),1414 (C=N),2401 (C-N),3211 (Ar-CH); 13C NMR (d, ppm): 88.43 (s,1C,-CH), 116.12 (s,1C,-CN), 119.65-159.68 (m,13C , Ar-C), 177.32 (s, 1C, -HC=O). **IIIc)**Yield: 75.05%; MP 215-216 °C; R_f 0.64; IR (cm^{-1}):719.567 (C-Br),1645.75 (C=O), 3376.12 (–NH of amide),1412.10 (C=N),2153.65 (C-N),3163 (Ar-CH); 13C NMR (d, ppm): 88.43 (s,1C,-CH), 116.12 (s,1C,-CN), 119.65-159.68 (m,13C , Ar-C), 177.32 (s, 1C, -HC=O).**IIId)**Yield: 91.06%; MP 200-203°C; R_f 0.87; IR (cm^{-1}): 1069 (C–O–C),3298.62 (–NH of amide),1500 (C=N),2254 (C-N),3107 (Ar-CH); 13C NMR (d, ppm): 88.43 (s,1C,-CH), 116.12 (s,1C,-CN), 119.65-159.68 (m,13C , Ar-C), 177.32 (s, 1C, -HC=O).**IIIe)**Yield: 70.79%; MP 201-203°C; R_f 0.65; IR (cm^{-1}):2638.62(C-N),1604.77(C=O), 3371.57(–NH of amide),1404.98(C=N),2854.65(C-N),3100(Ar-CH); 13C NMR (d, ppm): 88.43 (s,1C,-CH), 116.12 (s,1C,-CN), 119.65-159.68 (m,13C , Ar-C), 177.32 (s, 1C, -HC=O). **IIIf)**Yield: 68.04%; mp 204-206°C; R_f 0.68; IR (cm^{-1}):1654.78(C=O), 3342.54 (–NH of amide),1403.56 (C=N),2664.04(C-N),3102 (Ar-CH); 13C NMR (d, ppm): 88.43 (s,1C,-CH), 116.12 (s,1C,-CN), 119.65-159.68 (m,13C , Ar-C), 177.32 (s, 1C, -HC=O).



Scheme 1: Synthesis of pyrimidinone derivatives

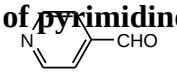
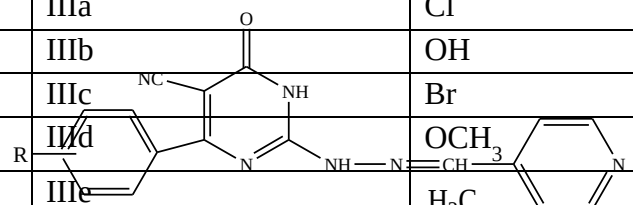


Table 1: Synthesis of compound

S.No.	Derivatives	R
1.	IIIa	Cl
2.	IIIb	OH
3.	IIIc	Br
4.	IIId	OCH_3
5.	IIIe	H_3C, N, H_3C, H
6.	IIIf	



Pyrimidinone containing Schiff bases

2.2 Pharmacological activity: [20-23]

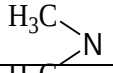
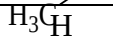
i) Antibacterial activity: Mueller Hinton agar medium tubes were heated to almost 55 degrees Celsius, and 0.5 millilitres of the measured test organism inoculum was added to each tube. After giving the tubes a good shake, the inoculation media were added to the sterilised petridishes and let to settle in a refrigerator that was kept between 4 and 8 degrees Celsius. A DMSO was used to create the test solutions of the synthesised compounds at 40µg/ml and 80µg/ml. Using a sterilised cork borer, cups with a diameter of 7 mm were cut into culture material. Separately, 40µg/ml and 80µg/ml solutions of each test chemical were put to cups. A conventional reference drug, ampicillin, was utilised, with DMSO serving as the control. To allow the solution to diffuse, the petridishes were kept in a refrigerator set at 10 °C for one hour. After that, the petridishes were placed in an incubator that was incubated at 37 °C for a whole day. Using callipers, the zones of inhibition that developed were measured. There was no action in the DMSO control. **Table 2** diameter in millimetres serves as a representation of the test chemicals' activity.

ii) Antifungal activity: Mueller Hinton agar medium tubes were heated to almost 55 degrees Celsius, and 0.5 millilitres of the measured test organism inoculum was added to each tube. After giving the tubes a good shake, the inoculation media were added to the sterilised petridishes and let to settle in a refrigerator that was kept between 4 and 8 degrees Celsius. A DMSO was used to generate test solutions of synthesised compounds at a concentration of 80µg/ml. Using a sterilised cork borer, cups with a diameter of 7 mm were cut into culture material. In cups, the 80µg/ml solutions of each test chemical were added one at a time. DMSO served as the control and griseofulvin as the standard reference medication. To allow the solution to diffuse, the petridishes were kept in a refrigerator set at 10 °C for one hour. After that, the petridishes were placed in an incubator that was kept at 37 degrees Celsius for a full day. Using callipers, the zones of inhibition that developed were measured. There was no action in the DMSO control. Table 3's diameter in millimetres serves as a representation of the test chemicals' activity.

Compound	**Zone of Inhibition in mm**							
	S. aureus		***B. subtilis***		***E. coli***		***P. aeruginosa***	
	40 µg/ml	**80 µg/ml**	**40 µg/ml**	**80 µg/ml**	**40 µg/ml**	**80 µg/ml**	**40 µg/ml**	**80 µg/ml**
III a	10	11	12	12	11	12	11	10
III b	14	14	15	17	14	15	15	14
III c	13	14	12	15	11	12	11	12
III d	13	14	11	12	13	12	12	12
III e	12	10	11	10	11	12	08	10
III f	08	09	10	12	10	11	11	12
Ampicillin	19	22	20	23	18	20	17	20

Table 2: Antibacterial activity of pyrimidinone derivatives (III a-h)

Table 3: Antifungal activity ofpyrimidinone derivatives(III a-IIIf)

Compound	**R**	**Zone of Inhibition in mm**
		***C. albicans* (80µg/ml)**
III a	Cl	11
III b	OH	10
III c	Br	15
III d	OCH_3	10
III e		9
III f		8
Griseofulvin	-	20

'-'indicate resistance

RESULTS AND DISCUSSIONS:

Six new compounds (IIIa–IIIf) were synthesized as outlined in Scheme 1. The title compounds pyrimidinone containing Schiffbase derivatives, were synthesized by refluxing step-2 intermediate compound with different substituted aromatic aldehydes in glacial acetic acid and absolute alcohol mixture(9:1).The required step-2 intermediate compound was synthesized from step-1 compound, upon nucleophilic attack by the hydrazine hydrate.

The step-1 compound was synthesized by modified Biginelle condensation method using anisaldehyde, ethyl cyanoacetate and thiourea in the presence of potassium carbonate. In general, the IR spectral data of all the compounds showed characteristic peaks around 3380 $cm^{-1}$for –NH of amide group, 2855 cm^{-1} for C-N and 1683 $cm^{-1}$for C=O indicating the formation of cyanopyrimidine. Similarly, peak around 1404.25 cm^{-1} indicates the formation of Schiff's base.

In 13C-NMR spectral data, all the compounds showed characteristic peak at appropriate d-values. Presence of a singlet around d 115.72 indicates the formation of cyano-pyrimidine ring The structure of the compounds was further supported by mass spectral data. The synthesized compounds gave M+ peak in reasonable intensities. The molecular ion or other related ions produced the appropriate isotopic abundances due to the presence of chlorine and Bromine atom(s). All these newly synthesized compounds (III a-f) were screened for antibacterial and antifungal activities by cup-plate-agar diffusion method.

Antibacterial activity was assayed using the cup-plate-agar-diffusion method using Mueller Hinton agar against Staphylococcus aureus, Bacillus subtilis, Escherichia coli and Pseudomonas aeruginosa using ampicillin as standard. The results of antibacterial studies are given in Table 2. The antibacterial screening data revealed that all the synthesized compounds showed moderate to good bacterial inhibition. It was observed that compounds III b and III c showed good activity against test organisms at 40 and 80µg/ml as compared to standard drug ampicillin. Antifungal activity was assayed using the cup-plate-agar-diffusion method using Sabouraud Dextrose agar against Candida albicans using Griseofulvin as standard. The data of antifungal activity of synthesized compounds (III a-f) are depicted in Table 3.The antifungal screening data revealed that the synthesized compounds were found compound IIIc to good antifungal activity against to Candida albicans.

CONCLUSION

A series of newly compounds IIIa-IIIF were prepared different substituted aromatic aldehydes in glacial acetic acid and absolute alcohol mixture(9:1).The obtained derivatives were screening as antimicrobial and antifungal agents. Two of the synthesized compounds IIIb and IIIc exhibited potent antibacterial and antifungal bioactivity compared with ampicillin and griseofulvin used as reference drugs. The other tested compounds were found to exhibit moderate to low antibacterial activity. Further QSAR studies need to carry out to evaluate the relation between structure and their biological activities by the application of structural modifications as required.

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