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SYNTHESIS OF SOME NOVEL QUINOLINE AND PYRAZOLONE DERIVATIVES VIA KNORR PYRAZOLE AND QUINOLINE SYNTHESIS AND EVALUATION OF THEIR ANTIMICROBIAL ACTIVITIES

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ABSTRACT

Pyrazolones **(5a-l)** were synthesized by the reaction of β-keto ester and hydrazines in the presence of catalytic amount of acetic acid. Formation of 2-quinolones **(6a-l)** took place from β-ketoester and arylamines **(3a-l)** above 100°C. The intermediate anilide undergoes cyclization by dehydration with concentrated sulfuric acid. All the prepared compounds were characterized by their spectral (IR, NMR, Mass) data and screened for their antimicrobial activity. Reaction of hydrazine or substituted hydrazine with 1, 3-dicarbonyl compounds provided the pyrazolone ring system

Key words : Knorr pyrazole synthesis, Knorr quinoline synthesis, 5-Pyrazolone, 2-Quinolone, Antimicrobial activity.

INTRODUCTION

The discovery of pyrazole derivatives as antipyretic agents dates back to 1884, when the German Chemist Ludwig Knorr[1-4] attempted to synthesize quinoline derivatives with antipyretic activity and accidentally obtained antipyrine, which has analgesic, antipyretic and antirheumatic activity. Aminopyrine, a more potent analogue, was synthesized thereafter and these drugs were widely used in market as antipyretics. Pyrazolone and quinolines are important classes of heterocyclic compounds due to their therapeutic importance. In past decades, both the class have been studied for their antipyretic activity and hence, both are considered as milestone of the synthetic antipyretic nuclelus. Quinolines are also the most widely studied nucleus particularly in diseases like antibacterial[5], antifungal[6], antimalarial[7], antitumor[8] and in antiinflammatory[9]. The search

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for synthetic antimalarials other than quinine derivatives was initiated in Germany early in the twentieth century. It was based on the observations of Guttman and Ehrlich[10] made in 1891 that the dye methylene blue had some chemotherapeutic effect on malaria in patients. These observations laid the stone for newer synthetic antimalarials. In 1920's, the first synthetic antimalarial agent pamaquine was synthesized by Schulemann et al.[11], which is 8-aminoquinoline derivative. To get more effective and safe antimalarial compounds, a large series of 4-aminoquinolines was investigated as a part of the extensive cooperative program in the USA during Second World War. In 1943, chloroquine eventually proved most promising drug.

The quinoline nucleus occurs in several natural compounds (cinchona alkaloids) and pharmacologically active substances displaying a broad range of biological activity[12-14]. In addition to the medicinal applications, quinolines have been employed in the study of bioorganic and bioorganometallic processes[15-17].

Inspired from these observations, we planned to synthesize some pyrazolone and quinoline derivatives and evaluate their antimicrobial activity.

The structures of the synthesized compounds were assigned based on elemental analysis, IR, ^{1}H NMR and Mass spectral data. All newly synthesized compounds have been screened for their *in vitro* antimicrobial activity.

EXPERIMENTAL

Melting points were determined in open capillary and are uncorrected. Thin layer chromatography using silica gel G (E. Merck) plates were used to access the reactions and purity of the synthesized compounds. All the products have been characterized by elemental analysis, IR, ^{1}H NMR and mass spectral study. IR spectra were recorded on Shimadzu FTIR-8400 spectrophotometer in KBr disc and noteworthy absorption levels (cm^{-1}) are listed. ^{1}H NMR spectra were recorded on Brucker spectrometer (300 MHz) using TMS as an internal standard and chemical shift are given in δ ppm. Mass spectra were determined using direct inlet probe on a GCMS-QP2010 Mass spectrometer, Elemental analysis were performed on a Carlo Erba EA 1108 elemental analyzer.

General procedure

Procedure for preparation of 4-methyl-3-oxo-N-aryl-pentanamide (3a-l) :

To the mixture of methyl-4-methyl-3-oxo-pentanoate **(1)** (0.01 mol) and aromatic amines **(2a-l)** (0.01 mol) in toluene, few drops of ethylenediamine was added. The solution was refluxed for 12 hrs and methanol was collected using dean and stark. The resulting reaction mass was washed with dilute HCl and finally with water. It was separated out, toluene layer was distilled out under vacuum and oily material was collected, which is sufficiently pure.

General procedure for preparation of 4-isopropyl-5, 6, 7, 8-substituted quinoline-2(1H)-ones (6a-l) :

A mixture of 4-methyl-3-oxo-N-aryl-pentanamide (0.01mol) and concentrated sulphuric acid was heated to 60-70^{O}C for 5 hrs. The reaction mixture was cooled and slowly poured into the crushed ice. The product was extracted with dichloromethane. The dichloromethane was distilled out and the resulting residue was purified in ethyl acetate.

General procedure for preparation of 5-isopropyl-2-substituted-2, 3-dihydropyrazole-3(1H)-ones (5a-j) :

To a mixture of methyl-4-methyl-3-oxo-pentanoate **(1)** (0.01 mol) and hydrazines **(4a-j)** (0.01mol) in methanol, 2-5 drops of glacial acetic acid was added. The mixture was heated at reflux temperature for 1 hr. It was cooled and poured into the ice. Resulting solid was filtered and washed with water, dried and purified by isopropyl alcohol.

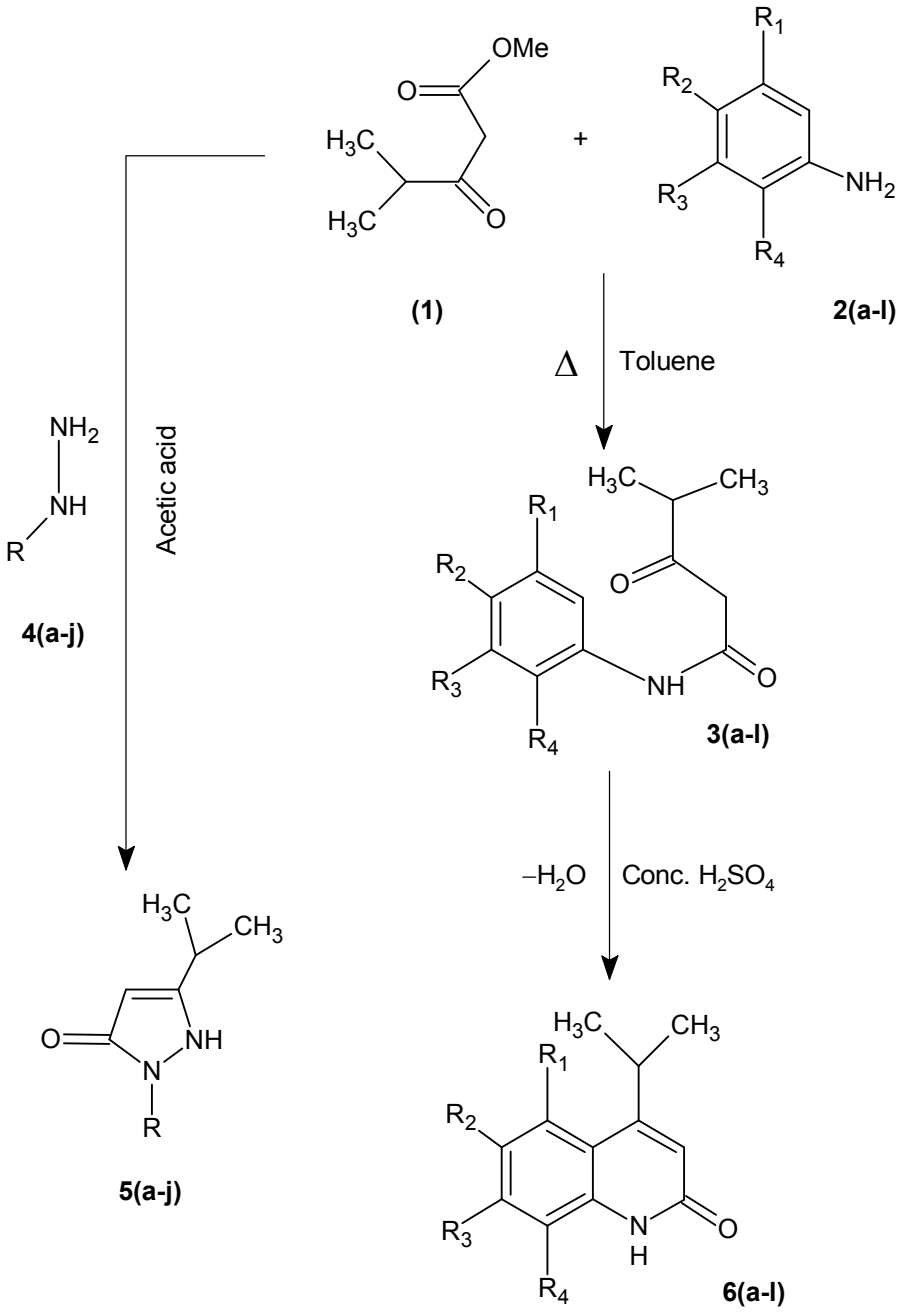
Spectroscopic data

IR spectrum (KBr) cm^{-1} of **(5b)** showed absorption frequencies (in cm^{-1}) at : 1392 (isopropyl), 3393 (N-H pyrazolone), 1702 (C=O)

IR spectrum (KBr) cm^{-1} of **(6a)** showed absorption frequencies (in cm^{-1}) at : 1381 (isopropyl), 3268 (N-H), 1651 (C=O), 1286 (C-N).

Mass spectrum of the compound **(5b)** recorded its molecular ion at m/z 202 and others at 187, 173, 160, 145, 132, 120, 91, 77, 69, 51 and 41

Mass spectrum of the compound **(6a)** recorded its molecular ion at m/z 187 and others at 172, 170 and 128.


OMe
O
H3C
H3C
O
+
R1
R2
R3
R4
NH2
(1)
2(a-l)
Δ
Toluene
NH2
NH
R
4(a-j)
Acetic acid
H3C
CH3
R1
R2
R3
R4
O
NH
O
3(a-l)
–H2O
Conc. H2SO4
H3C
CH3
O
NH
N
R
5(a-j)
H3C
CH3
R1
R2
R3
R4
N
H
O
6(a-l)

Scheme

^{1}H NMR **(5b)** (DMSO-d_6) δppm : 1.17 (d, 6H)-CH-($\underline{C}H_3$)$_2$, 2.71 (m, 1H) -$\underline{C}$H-(CH_3)$_2$, 5.38 (s, 1H)-CH-Pyrazolone, 7.15 (m, 5H) -Aromatic, 11.42 (s, 1H)-NH

^{1}H NMR **(6a)** (DMSO-d_6) δppm : 1.27 (d, 6H) -CH-($\underline{C}H_3$)$_2$, 3.48 (m, 1H) -$\underline{C}$H-(CH_3)$_2$, 6.35 (s, 1H)-CH-Quinoline, 7.15-7.84 (m, 4H)-Aromatic, 11.61 (s, 1H)-NH

Twenty two new compounds were synthesized following this procedure. The physical data, yield details and biological activity of new pyrazolones **(5a-j)** and quinolones **(6a-l)** are presented in Table 1 and Table 2, respectively.

Biological activity

Antibacterial and antifungal activity by cup plate agar diffusion method[18]

All the compounds have been evaluated for their *in vitro* biological assay like antibacterial activity towards Gram positive bacteria viz., *Bacillus coccus, Staphylococcus aureus* and Gram negative bacteria viz., *Pseudomonas aeruginosa, Aerogenes* and antifungal activity towards *Aspergillus niger* at a concentration of 40 μg. The biological activities of synthesized compounds were compared with standard drugs like amoxicillin, benzoyl penicillin, ciprofloxacin, erythromycin and antifungal activity was compared with griseofulvin.

RESULTS AND DISCUSSION

It has been observed from the antimicrobial activity data that all compounds were found to be mild to moderately active against Gram positive and Gram negative bacterial strains. However, the maximum activity was observed in compounds **5f, 5e, 6e** and **6g** substituents against *B. coccus*. The significant activity was observed in compounds **5c, 5e, 6e** and **6l** against *S. aureus.* The compounds **5f, 5i, 6g** and **6k** displayed the maximum activity against *Aerogenes*. In the case of *Pseudomonas aeruginosa*, all the compounds were least active except **5j, 5i, 6c, 6g** and **6k.** The antifungal data revealed that compounds were least toxic to the fungal strain. However, mild activity was shown by the compounds **5e, 5f, 5i, 6e** and **6k** against *A. niger*.

The antibacterial activity was compared with standard drugs like amoxicillin, benzoyl penicillin, ciprofloxacin, erythromycin and antifungal activity was compared with standard drug griseofulvin.

Table 1 :

Compounds	Substitution (R)	M. P. (°C)	Yield (%)	Molecular formula	Antimicrobial activity				
					B. coccus	*S. aureus*	*Aerogenes*	*P. aeruginosa*	*A. niger*
5a	H-	89	68	$C_6H_{10}N_2O$	14	10	13	11	17
5b	C_6H_5-	72	62	$C_{12}H_{14}N_2O$	16	12	14	13	14
5c	2, 4-$(Cl)_2$-C_6H_3-	82	55	$C_{12}H_{12}Cl_2N_2O$	17	18	14	16	18
5d	4-COOEt-C_6H_4-	76	66	$C_{15}H_{18}N_2O_3$	12	10	8	9	17
5e	2, 4-$(F)_2$-C_6H_3-	96	59	$C_{12}H_{12}F_2N_2O$	18	16	14	16	19
5f	4-CH_3-C_6H_4-	129	62	$C_{13}H_{16}N_2O$	19	15	18	14	18
5g	4-CH_3-SO_2-C_6H_4--	105	67	$C_{13}H_{16}N_2O_3S$	15	11	10	14	16
5h	4-CH_3-NH-SO_2-CH_2-C_6H_4-	111	59	$C_{14}H_{19}N_3O_3S$	17	18	11	17	15
5i	4-NO_2-C_6H_4-	105	70	$C_{12}H_{13}N_3O_3$	12	10	17	18	19
5j	2, 4-$(NO_2)_2$-C_6H_3-	121	63	$C_{12}H_{12}N_4O_5$	17	14	15	18	12
	Amoxicillin				25	25	20	22	0
	Benzoyl penicillin				18	19	21	21	0
	Ciprofloxacin				20	15	22	16	0
	Erythromycin				22	21	19	23	0
	Griseofulvin				0	0	0	0	26

Table 2:

Compounds	Substitutions				M.P. (°C)	Yield (%)	Molecular formula	Antimicrobial activity				
	R_1	R_2	R_3	R_4				*B. coccus*	*S. aureus*	*Aerogenes*	*P. aeruginosa*	*A. niger*
6a	H	H	H	H	180	30	$C_{12}H_{13}NO$	7	6	8	7	9
6b	H	Br	H	H	219	32	$C_{12}H_{12}NOBr$	10	12	12	13	14
6c	H	Cl	H	H	197	20	$C_{12}H_{12}NOCl$	12	9	11	14	12
6d	H	H	Cl	H	215	29	$C_{12}H_{12}NOCl$	11	10	7	6	11
6e	H	Cl	Cl	H	220	31	$C_{12}H_{11}NO\ C_{l2}$	13	13	11	14	16
6f	H	Cl	H	Cl	235	24	$C_{12}H_{11}NOCl_2$	10	12	11	8	14
6g	H	F	H	H	214	27	$C_{12}H_{12}NOF$	14	10	15	15	13
6h	H	CH_3	H	H	189	35	$C_{13}H_{15}NO$	9	7	10	8	10
6i	H	OCH_3	H	H	181	37	$C_{13}H_{15}NO_2$	9	11	10	12	12
6j	H	H	OCH_3	H	199	36	$C_{13}H_{15}NO_2$	11	12	12	10	14
6k	H	NO_2	H	H	203	28	$C_{12}H_{12}N_2O_3$	12	10	13	14	16
6l	H	H	NO_2	H	210	25	$C_{12}H_{12}N_2O_3$	11	13	10	10	13
					Amoxicillin			25	25	20	22	0
					Benzoyl penicillin			18	19	21	21	0
					Ciprofloxacin			20	15	22	16	0
					Erythromycin			22	21	19	23	0
					Griseofulvin			0	0	0	0	26

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