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SYNTHESIS AND EVALUATION OF SOME NEW 6-FLURO-QUINOLIN-4 (1*H*)-ONE DERIVATVES FOR THEIR ANTI-MICROBIAL ACTIVITIES

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ABSTRACT
The present work is a bonafide and novel for the synthesis of 6-fluro-quinolin-4(1*H*)-one derivatives. Around 30 new derivatives were synthesized, with the standard chemicals and well established procedures. The synthesized compounds were tested for their preliminary tests, physical constants, TLC, solubility, etc. IR, ^{1}H-NMR Spectra and CHN analysis confirmed the structures of the final compounds. The proposed compounds were screened for their antimicrobial, antifungal, antitubercular and anti-inflammatory activities with the standard drugs in the well-equipped microbiology and pharmacology lab by using standard methods.
Key Words. Antibacterial, Antifungal**,** 6-fluro-quinolin-4 (1*H*)-one derivatives

INTRODUCTION

The need of new anti-microbial agents is justified because more microorganisms are being resistance to the present drugs available in the market. Word wide researchers are trying to synthesize new drugs with better pharmacokinetic and dynamic properties with less adverse effects. The literature survey suggests that the 6-fluro-quinolin-4(1*H*)-one have proved to be good bioactive molecules. They have shown diverse biological activities like anti-bacterial, anti-fungal, anti-inflammatory, anti-tubercular, anticonvulsant, anti-HIV, cardiac stimulant, diuretic and anticancer etc. Therefore in view of above facts it was thought of interest to synthesize some 6-fluro-quinolin-4 (1*H*)-one Derivatives. IR, ^{1}H-NMR Spectra and CHN analysis confirmed the structures of the final compounds. The proposed compounds were screened for their antimicrobial, antifungal, antitubercular and anti-inflammatory activities with the standard drugs in the well-equipped microbiology and pharmacology lab by using standard methods

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MARERIALS AND METHODS:

EXPERIMENTAL:

Melting points were determined in open capillary method and are uncorrected. Purity of the compound was checked on Silica gel TLC plates. IR spectra were recorded on Thermo Nicolate IR 200 spectrophotometer using KBr disc method. 1HNMR spectra were recorded on Bruker AMX-400, DMSO d6 as internal standard. Combustion analyses were found to be within the limits of permissible errors.

A] Preparation of diethyl 2-((3-chloro-4-fluorophenylamino) methylene) malonate (I_1). [5]

A mixture of 3-chloro-4-fluro-aniline (0.01mol) and Diethyl ethoxy methylene malonate (0.01mol) was heated at 120-130^{0}C for two hours the resulting ethanol was evaporated off. The crude solid was filtered, dried and recrystallized from n-hexane. M.P. 54-55^{0}C.

B] Preparation of ethyl 7-chloro-6-fluoro-4-oxo-1, 4-dihydroquinoline-3-carboxylate (I_2) [6].

Diphenyl ether was heated under stirring at 240^{0}C. 0.158 mol of ethyl anilinomethylene malonate was added slowly to the boiling diphenyl ether for about 15 minutes after adding the mixture

was refluxed in oil bath for two hours. The mixture was cooled, filtered and washed twice with 200 ml pet ether. The crude solid obtained was dried and purified by recrystallization twice from DMF.M.P. 270^0C.

C] Preparation of 7-chloro-6-fluro-4-oxo-1,4-dihydroquinoline-3-carbohydrazide (I_3). [7]

Ethyl 7-chloro-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate I_2 (0.035 mol) in ethanol (20 ml), DMF (10 ml) was added to 99% hydrazine hydrate (0.035mol) and was refluxed for 12 hours. Excess solvent was removed by distillation and the mixture was poured into crushed ice. The solid separated was filtered, washed with water and dried. The crude solid was purified by recrystallized from ethanol dioxan mixture (1.1) to give whitish-brown solid ;M.P.245-247^{0}C.

D] Preparation of 7-chloro-6-fluro-3-(3-methyl-5-oxo-4, 5 dihydropyrazole-1-carbonyl) quinolin-4(1*H*)-one (I_4). [7]

7-chloro-6-fluro-4-oxo-1, 4-dihydroquinoline-3-carbohydrazide I_3 (0.018 mol) in ethanol (20 ml) was added to ethyl acetoacetate (0.02 mol) and refluxed for 4 hours. To this mixture 2 ml of acetic acid was added and further refluxed for two hours. Excess of solvent was removed and the mixture was poured into ice water. The solid separated was filtered, washed with water and dried. It was purified by recrystallized from ethanol to afford whitish amorphous solid; M. P 218-220^{0}C.

E] Preparation of 6-fluro-3- (3-methyl-5-oxo-4, 5-dihydro- *H*-pyrazole-1-carbonyl)-7-(substituted) quinolin-4 (1*H*)-one (V_1-V_5). [8]

The mixture of 7-chloro-6-fluro-3- (3-methyl-5-oxo-4, 5 dihydropyrazole-1-carbonyl) quinolin-4(I*H*)-one (0.005 mole), Piperazine (0.01 mole), Pyridine (10 ml) and Triethyl amine (3 ml) was stirred at 120-130^{0}C for 10 hours. After completion of the reaction, the reaction mixture was cooled to room temperature. The mixture was poured into crushed ice and neutralized with dilute HCl. The solid product was filtered dried and recrystallized from DMF and Ethanol (2.1). Similarly V_2, V_3, V_4 and V_5 were prepared by using Morpholin, Imidazole, Piperadine and Pyrollidine. Analytical data's were given in the table.

F] Preparation of 7-chloro-6-fluro-3-(5-substituted-1, 3, 4-oxadiazole-2-yl) quinolin-4(1*H*)-one (P_1-P_7). [8,9]

A mixture of an equimolar quantity of 7-chloro-6-fluro-4-oxo-1, 4-dihydroquinoline-3-carbohydrazide I_3 (0.006mol) and substituted aromatic acids (0.006) in 15 ml of phosphorus oxychloride was refluxed for 8 hours. The progress of the reaction was monitored by TLC using ethyl acetate. acetone (9.1) as eluent. The reaction mixture was cooled and poured carefully on to crushed ice (200g) with constant stirring and neutralized with sodium bicarbonate solution (10%w/v). The resulting solid thus obtained was collected by filtration, washed well with cold water, dried and recrystallized from ethanol. DMF (2.1) to give (P_1-P_7). Analytical data was given in the table1.

ANTIBACTERIAL ACTIVITY. [1, 2]

The compounds were tested in-vitro for their antibacterial activity against two microorganisms viz. *Escherichia coli* (NCTC 10418), and *Staphylococcus aureus* (NCTC 6571) which are pathogenic in human beings.

Method. Disc Agar diffusion method using Mueller-Hinton agar using E.coli, S. *aureus*

ANTIFUNGAL ACTIVITY. [3,4]

The compounds were tested in-vitro for their antifungal activity against *Candida albicans* (ATCC 10231) and *Aspergillus niger* (ATCC 16).

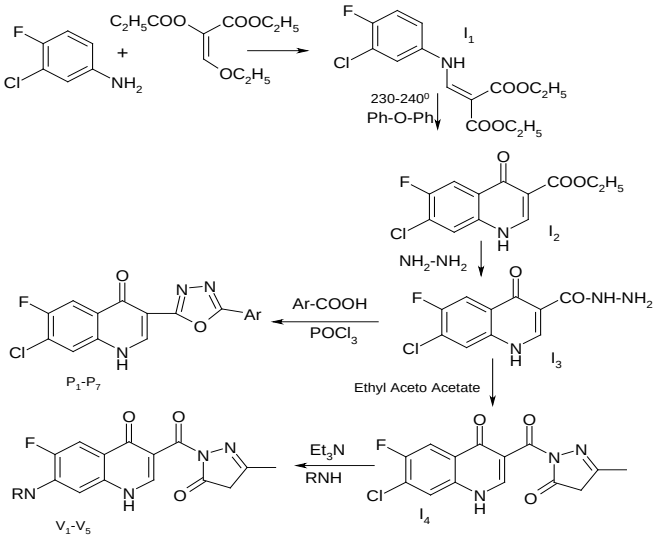
Method. Cup-Plate agar diffusion method using Sabouraud-dextrose agar using *C.albicans* & *A. Niger.*

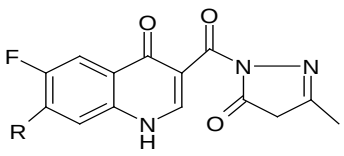
RESULT AND DISCUSSION:

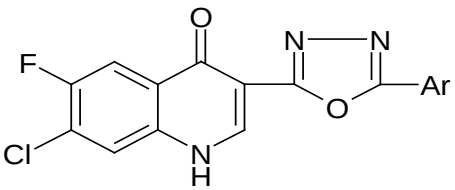
In the present research work, we have synthesized 13 new 6-fluro-Quinolinones as explained in the scheme. The purity of the compounds was checked by TLC and melting point. Structures of these compounds were confirmed by IR, ^{1}HNMR and elemental analysis. Possible QSAR studies are carried out. The synthesized compounds were subjected to anti bacterial and anti fungal activities by Disc diffusion method against the standard strains of *E.coli* (NCTC-10418), *S.aureus* (NCTC-6571) and for anti fungal activities, *C.albicans* (ATCC-1023),*A.niger* (ATCC-16) by cup plate method.

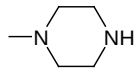
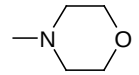
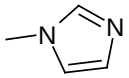
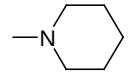
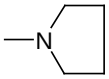
Compound I_4, V_1, V_3, P_1, P_2, P_4, P_5 have shown promising anti bacterial activity against Ciprofloxacin as the standard drug at 100 mcg/ml. Compound I_4, V_2, V_5, P_1, P_4, P_5, P_7 have shown excellent anti fungal activity against Griseofulvin as the standard drug at 100 mcg/ml. With the suitable molecular modification and manipulation with possible SAR studies of these compounds, promising anti microbial agents can be obtained.

SCHEME (P_1-P_7, V_1-V5)







Compound	-R
V_1	
V_2	
V_3	
V_4	
V_5	

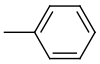
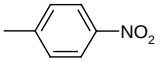
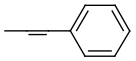
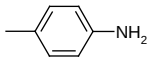
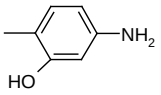
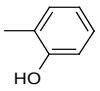
Compound	-Ar
P_1	
P_2	
P_3	
P_4	
P_5	
P_6	
P_7	

Table No. 1. Anti-bacterial and Anti-fungal activity of 6-fluro-quinolin-4(1*H*)-ones compounds.

Compd.	Zone of inhibition at 100µcg/mL (in mm.)			
	E. coli	***S.aureus***	***A. niger***	***C. albicans***
I_4	**23**	**21**	**22**	**21**
V_1	**22**	**23**	16	18
V_2	19	**22**	**23**	**22**
V_3	**24**	12	18	17
V_4	16	17	15	16
V_5	17	18	**22**	**23**
P_1	**24**	**21**	**24**	**25**
P_2	**23**	**24**	17	18
P_3	**24**	**25**	17	19
P_4	**22**	**24**	**22**	**23**
P_5	**22**	**23**	**24**	**25**
P_6	15	16	18	16
P_7	18	17	**25**	**26**
Ciprofloxacin	**24**	**24**	-	-
Griseofulvin	-	-	**25**	**26**

Table No. 2 Analytical data of 6-fluro-quinolin-4(1*H*)-one compounds

Comp.	Mol. Formula	Mol. Wt.	M.P ^{0}C	Yield %	Elemental analyses Calcd. (Found)			LogP	CLogP	CMR
					C	H	N			
I_4	$C_{14}H_9ClFN_3O_3$	322.	218	67	52.27	2.82	13.06	0.65	-0.513	7.810
V_1	$C_{18}H_{18}FN_5O_3$	371	182	78	58.22	4.89	18.86	-0.25	-1.717	9.734
V_2	$C_{18}H_{17}FN_4O_4$	372	270	67	58.06 (58.03)	4.60 (4.57)	15.05 (15,04)	-0.03	-1.703	9.518
V_3	$C_{17}H_{12}FN_5O_3$	353	264	66	57.79	3.42	19.82	-0.71	-1.349	9.048
V_4	$C_{19}H_{19}FN_4O_3$	370	166	75	61.61 (61.54)	5.17 (5.14)	15.13 (15.8)	1.11	-0.321	9.829
V_5	$C_{18}H_{17}FN_4O_3$	356	238	61	60.67 (60.28)	4.81 (4.76)	15.72 (15.58)	0.69	-0.880	9.365
P_1	$C_{17}H_9ClFN_3O_2$	342	106	29	59.75	2.65	12.30	3.08	1.600	8.699
P_2	$C_{17}H_8ClFN_4O_4$	387	183	60	52.80 (52.74)	2.09 (1.92)	14.49 (14.42)	--	1.393	9.311
P_3	$C_{19}H_{11}ClFN_3O_2$	368	94	35	62.05	3.01	11.43	3.87	2.194	9.905
P_4	$C_{17}H_{10}ClFN_4O_2$	357	233	63	57.24	2.83	15.71	2.28	0.643	9.068
P_5	$C_{17}H_{10}ClFN_4O_3$	373	258	44	54.78 (54.66)	2.70 (2.64)	15.03 (14.87)	1.89	-0.037	9.221
P_6	$C_{17}H_9ClFN_3O_3$	358	100	58	57.08	2.54	11.75	2.69	0.919	8.852
P_7	$C_{17}H_{10}ClFN_4O_2$	357	138	38	57.24 (57.18)	2.83 (2.80)	15.71 (15.67)	2.28	0.643	9.068

The combustion analysis of compounds synthesized was found to be within the limits of permissible errors.

Table No. 3. SPECTRAL DATA

Compound	IR (KBr) (cm^{-1})	^{1}H NMR (DMSO) δ in ppm
V_1	3385 N-H str.3109-C-H Ar., 1697-C=O str. 1550 C-N piperazine 899 C-H def.	6.80-7.10 2H, Ar-CH. 2.86-3.15, 4H piperazine. 2.28-2.48, 2H CH_2 pyrazolones. 1.22-1.27, 3H CH_3.
V_2	3432 N-H str.3057 C-H Ar. 1666-C=O str. 1174.C-O str,morpholine, 798-C-H def., 806 C-F str.	7.00-7.73, 3H, Ar-CH. 3.24-3.31, 4H, morpholine. 2.48-2.59, 2H, CH_2 pyrazole. 1.23- 1.28,3H, CH_3
V_3	3156.-N-H str. 3121 C-H Ar. str. 2988-C-N str. Imidazole 1690 -C=O str, 893-C-H def 844 C-F str.,	7.10-7.30, 2H, Ar-CH. 2.28-2.48, 2H, CH_2 imidazole. 1.20-1.25, 3H, CH_3.
V_4	3106 N-H str.2989 C-H Ar. str. 2857 C-N str. piperidine, 1699-C=O str. 808-C-H def. 787 C-F str.	12.41 1H, N-H. 7.93-7.96 8H, piperidine 6.18-7.10 3H, Ar-CH. 2.4-2.7 2H ,CH_2 pyrazole. 1.23-1.28 3H ,CH_3.
V_5	3284- N-H str.,3049-C-H Ar. Str, 2920 C-N str. Pyrollidine 2852 C-H Alkyl 1678 C=Ostr. 1256 C-N Ar. str.	13.24 1H, N-H. 7.37-7.92 3H Ar-CH. 3.74-3.98 8H, pyrollidine. 1.22-1.27 3H CH_3
P_1	3343 N-H str. 3102 C-H Ar. Str, 2911 C=N Ar str. 1628 C=O str., 1007 C-O ether str.	10.70 1H, NH. 7.80-7.91 1H, quinolone. 7.80-7.90 7H, Ar-CH.
P_2	3123 N-H str,3000 C-H Ar. str, 2918 C=N Ar str. 1696 C=O str. 1539 N=O str 1274 C-F str,	10.91H, NH. 7.87-7.91 3H, quinolone. 6.97-7.37 3H, Ar-CH
P_3	3451 N-H str, 3071 C-H Ar. str, 2866 C=N Ar str.1697 C=O str, 1259 C-F str.	10.80 1H, NH 7.80-7.91 1H, quinolone 7.20-7.37 7H, Ar-CH.
P_4	3422 N-H str.,3310 C-H Ar. str, 2928 C=N Ar str.1585 C=O str. 1240 C-F str.684 C-Cl str.	12.70 1H, N-H 8.10-8.30 1H, quinolone. 6.37-6.54 7H, Ar-CH.
P_5	3437 N-H str, 3387 C=N Ar 3063 C-H Ar. str.-, 3003 OH str, 1586 C=O str 1086 C-O ether str.	13.78 1H, N-H. 8.14-8.17 3H, quinolone. 9.94 1H, OH 6.41-7.12 3H, Ar-CH. 5.03 2H, NH_2
P_6	3304 N-H str, 3113 OH str 3053 C-H Ar. str, 3011 C=N Ar, 1665 C=O str,1138 C-O ether str, 675 C-Cl str.	10.70 1H, NH 9.80 1H OH. 7.80-7.91 1H, quinolone. 7.80-7.90 7H, Ar-CH.
P_7	3427 N-H str,3061 C-H Ar. str, 2925 C=N Ar str. 1703 C=O str 1227 C-O ether str, 758 C-F str. 691 C-H def.	13.86 1H NH. 7.93-8.16 3H,quinolone. 7.35-7.37 4H, Ar-CH. 4.98 2H, NH_2.

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