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Synthesis, Characterization & Pharmacological Activities Of Substituted-2-Methyl-7-Amino -4-Quinolones

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Abstract: The synthesis and pharmacological activities of substituted -2-Methyl-7-substituted-sulphonomides-4-quinolones (2a-m), substituted -2-Methyl-7-substituted- azo -4-quinolones (3a- m), substituted -2-Methyl-7-substituted-Schiff bases -4-quinolones (4a-m), substituted -2-Methyl-7-substituted- N-phenylthiourea -4-quinolones (5a-m) respectively from substituted 2-Methyl-7-amino-4-quinolones (1a-m) is reported in this paper. The structures of synthesized products have been characterized on the basis of FT-IR, ^{1}HNMR, FAB-MS and elemental analysis. The title compounds are found to have antibacterial and antifungal activities.

Keywords: Quinolones, Schiff bases, sulphonomides, Ethyl aceto acetate, Anilines, etc.

I. INTRODUCTION

Quinolones and their derivatives occur in excellent anti-bacterial agents[1, 2], broad spectrum antimicrobial activity and are very active against aerobic Gram-negative microorganisms but less active against Gram-positive microorganisms[3, 6]. They are extremely useful for the treatment of a variety of infectious diseases[6, 7] and also introduced as antitumor agents[8]. The coordination of these molecules with metal ions is of considerable interest from biological and pharmaceutical point of view. Quinolones exhibit potent in vitro and in vivo antimycobacterial activity[9]. Among the fluoroquinolones, norfloxacin is a synthetic, broad-spectrum antibacterial agent for oral administration. Furthermore, there was little cross-resistance between norfloxacin and agents of other antibiotic. The action mechanism of norfloxacin involves inhibition of bacterial DNA gyrase, which is essential for DNA replication[10-15]. Recently some Schiff's base found to possess anticancer activity. Schiff's bases derivatives possess wide range of pharmacological activities like antioxidant, antiinvasive, antiviral, antipyretic, anti-inflammatory, antidepressant, and blood pressure lowering etc. Azo compounds have been found to possess wide spectrum of biodynamic properties. Many of them have been reported as antibacterial[16], antimicrobial[17], diagnostic aid[18], antineoplastic[19], urinary antiseptic[20] and topical dermatologic activities. Sulphonamides have a broad spectrum of bacteriostatic activity, affecting gram positive, gram negative and many protozoan organisms. They are known to exhibit a wide variety of biological activities such as antiviral, antibacterial, antifungal[21], antitubercular, herbicidal, insecticidal[22], and to act as chelating agents[23], in catalysis[24], in anion recognition[25] and to play a role in some epoxy resin curing agents containing amino functional groups.

Result and discussion

In view of these observations, it was thought worthwhile to synthesize several compounds in which substituted -2-Methyl-7-substituted- sulphonomides-4-quinolones , substituted -2-Methyl-7-substituted- azo -4-quinolones, substituted -2-Methyl-7-substituted-Schiff bases -4-quinolones, substituted -2-Methyl-7-substituted- N-phenylthiourea -4-quinolones have been linked with new moiety

The reaction sequence leading to the formation of desired heterocyclic compounds are outlined in Scheme-I. The starting material substituted 2-Methyl-7-amino-4-quinolones (1a-m) was prepared by the reaction of substituted anilines with ethyl aceto acetate in presence of con. H_2SO_4. Synthesis of substituted -2-Methyl-7-substituted- sulphonomides-4-quinolones (2a-m) by reaction of substituted 2-Methyl-7-amino-4-quinolones (1a-m) with different sulphonil chlorides in presence of ethanol. The compound 1(a-m) which on coupling with different aromatic hydroxyl compounds in presence of $NaNO_2$ and HCl at 0-5^{0}C yielded substituted -2-Methyl-7-substituted- azo -4-quinolones (3a- m).The substituted -2-Methyl-7-substituted-Schiff bases -4-quinolones (4a-m) was prepared by condensation of material substituted 2-Methyl-7-amino-4-quinolones (1a-m) with different aldehydes. Synthesis of substituted -2-Methyl-7-substituted- N-phenylthiourea -4-quinolones (5a-m) by the reaction of phenyl thio-cyanide with substituted 2-Methyl-7-amino-4-quinolones (1a-m). The UV-Vis-spectra of the substituted -2-Methyl-7-substituted- azo -4-quinolones (3a- m) were recorded and the values of absorptions (max) and fastness properties are shown in Table –I. It is apparent that the wavelength of maximum absorptions azo compound was observed at 200-500nm in EtOH solutions. Variation in max is being attributed to structural variation of electron–rich aromatic compounds with N=N linkage used for the preparation of these azo compounds.

Table I- UV-VIS Section of substituted -2-Methyl-7-substituted- azo -4-quinolones (3a- m) and colour fastness properties.

Code	Colour	max	Fastness properties			
			Silk		Wool	
			Light[a]	wash[b]	Light[a]	Wash[b]
3a	Red	470	2	3	2-3	3-4
3b	Red	476	3-4	2-3	3-4	2
3c	Red	472	2	4	2	3
3d	Red	461	2-3	3-4	2-3	2- 3
3e	Red	462	4	2-3	3	3-4
3f	Orange	444	2-3	3-4	2-3	2- 3
3g	Red	430	3-4	2-3	3-4	2
3h	Red	447	2	4	3	2-3
3i	Red	471	3	2-3	3-4	3
3j	Orange	427	3-4	3	2-3	2- 3
3k	Red	422	2	3	4	2-3
3l	Red	437	3-4	2-3	3-4	2
3m	Purple	482	4	3-4	2-3	3

- IN EtOH solution **(3a-m)**
- [a]Light-fastness: 1-minimum, 2-poor, 3-moderate, 4-fairly good, 5-good. 6-very good.
- [b]wash-fastness: 1-poor, 2-fair, 3-good, 4-very good and 5-excellent.

BIOLOGICAL ACTIVITIES

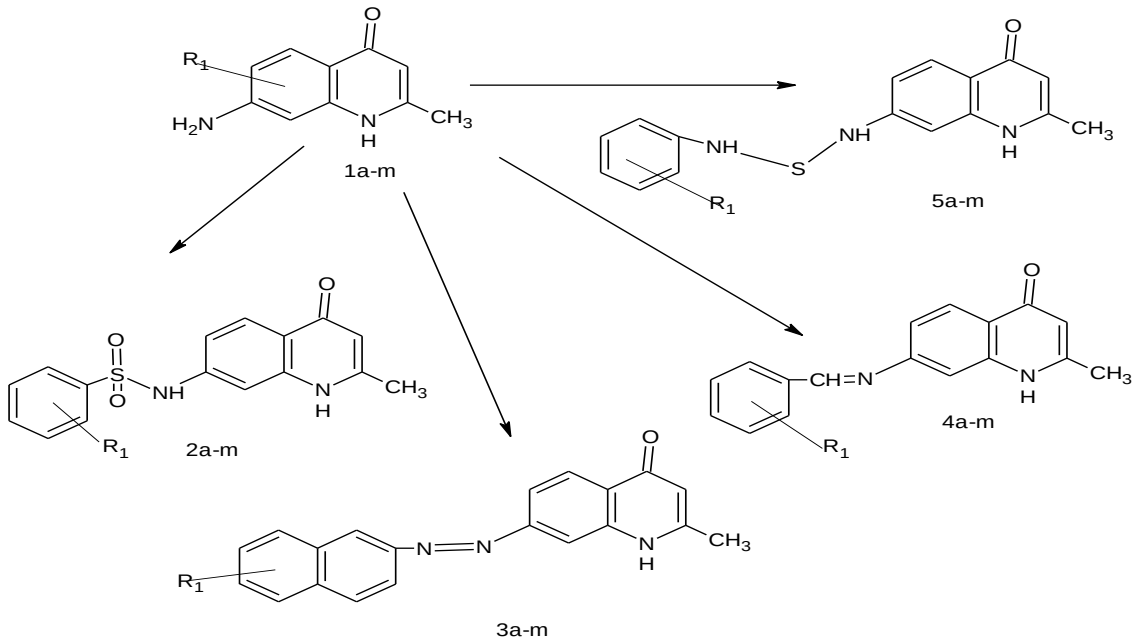
Comparative study of substituted -2-Methyl-7-substituted- sulphonomides-4-quinolones **(2a-m)**, substituted -2-Methyl-7-substituted-Schiff bases -4-quinolones **(4a-m)**, substituted -2-Methyl-7-substituted- N-phenylthiourea -4-quinolones **(5a-m)** respectively from substituted 2-Methyl-7-amino-4-quinolones **(1a-m)** have been observed by using Norfloxacine and Griseofulvine as standards. The enhancement in biological activity of compound as compared with the newly synthesized has been observed. The synthesized compounds were tested at 100□g/ml concentration against *Escherichia coli*, *Staphylococcus aureus*, *Ps. acruginosa*, *P.vulgaris*, *A. niger* and *C. albicans* for its antibacterial and antifungal screening as shown in **Table-II**.

Table – II – Data for in vitro antibacterial and anti Fungal activities (in mm) (NA=not active**, --=**no inhibition of growth **)**

Comp.	Minimum inhibitory concentration's □ g/ml					
	E. *Coli*	S. *aurous*	Ps. *aeruginoa*	P. *Vulgaris*	A.*niger*	C. *albicans*
1a	14	12	9	17	22	14
1b	11	15	10	12	22	12
1c	16	10	11	13	19	NA
1d	13	9	10	15	17	NA
1e	14	12	13	-	12	22
1f	11	15	10	12	22	12
1g	11	9	15	12	22	12
1h	14	10	9	8	NA	11
1i	12	9	NA	10	18	NA
1j	11	12	10	12	22	12
1k	11	9	10	12	22	12
1l	16	10	11	13	19	NA
1m	13	9	10	11	17	NA
2a	14	12	13	-	12	22
2b	15	11	-	9	14	21
2c	11	9	10	12	22	12
2d	NA	10	5	8	NA	11
2e	12	15	NA	10	18	NA

2f	17	7	12	14	12	-
2g	15	10	15	14	16	15
2h	11	15	10	12	22	12
2i	16	10	11	13	19	NA
2j	13	9	10	11	17	NA
2k	14	12	13	-	12	22
2l	11	9	10	12	22	12
2m	11	12	10	12	22	12
4a	NA	10	5	12	NA	11
4b	12	9	NA	10	18	NA
4c	17	7	-	14	12	10
4d	11	13	10	12	22	12
4e	11	9	10	12	22	12
4f	16	10	11	13	19	NA
4g	13	9	10	11	17	NA
4h	14	12	13	-	12	22
4i	15	11	10	9	-	21
4j	11	9	10	12	22	12
4k	NA	10	5	8	NA	11
4l	12	9	NA	10	18	NA
4m	15	10	10	9	10	21
5a	12	9	NA	10	18	NA
5b	17	7	-	14	12	-
5c	-	10	15	14	16	15
5d	11	17	10	12	22	12
5e	16	10	11	13	19	NA
5f	13	9	10	11	17	NA
5g	14	12	13	-	12	22
5h	15	11	13	9	7	21

5i	11	9	10	12	22	12
5j	NA	10	5	8	NA	11
5k	11	9	22	12	22	12
5l	10	10	5	8	NA	11
5m	11	15	22	12	20	12



Where,

	R_1
a	H
b	2-OH
c	3-OH
d	4-OH
e	2-NO_2
f	3-NO_2
g	4-NO_2
h	2-CL
i	3--CL
j	3-OCH_3
k	4-OCH_3
l	3, 4, 5-$(OCH_3)_3$
m	-$N(CH_3)_2$

CONCLUSION

A series of substituted -2-Methyl-7-substituted- sulphonomides-4-quinolones (2a-m), substituted -2-Methyl-7-substituted- azo -4-quinolones (3a- m), substituted -2-Methyl-7-substituted-Schiff bases -4-quinolones (4a-m), substituted -2-Methyl-7-substituted- N-phenylthiourea -4-quinolones (5a-m) respectively from substituted 2-Methyl-7-amino-4-quinolones (1a-m). These compounds were screened for their antibacterial activity against *S. aureus* and *E. coli* as well as for their antifungal activity against *C. albicans* and *A. niger* Showing good result.

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