SYNTHESIS OF SOME NOVEL PYRAZOLINES AS BIOLOGICALLY POTENT AGENTS.

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ABSTRACT : Pyrazolines ***3a-l*** have been synthesised by the cyclocondensation of different chalcones ***2a-l*** with hydrazine hydrate in presence of acetic acid. All the products were screened for their antimicrobial activity against several microbes.

INTRODUCTION

Among the wide variety of heterocycles that have been explored for developing pharmaceutically important molecules, pyrazolines **(1,2)** have played an important role in medicinal chemistry. Some of them have received considerable attention as potential antimicrobial agents **(3,4)**. Moreover, quinazoline derivatives are associated with various biological activities **(5-9)**. These valid observations led us to prepare pyrazoline derivatives bearing quinazoline moiety.

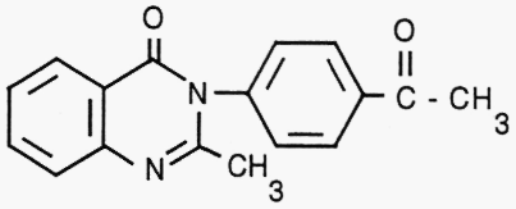
The starting compound 2-methyl-3-(p-acetophenyl)-4(3H) quinazolone ***1*** was condensed with different araldehydes to yield 1-aryl-3-(p-2'-methyl-4 (3H)- quinazolones -3'-yl-phenyl) propenones ***2a-l***. Compounds ***2a-l*** were then reacted with hydrazine hydrate and acetic acid to afford different 1-acetyl-5-aryl-3-(p-2'-methyl-4 (3H)-quinazolon-3'-yl-phenyl) pyrazolines ***3a-l*** (scheme).

The constitution of all the products was established by elemental analyses, IR and PMR spectral study. All the compounds were screened for their antimicrobial activity against different strains of bacteria and fungi.

RESULTS AND DISCUSSION

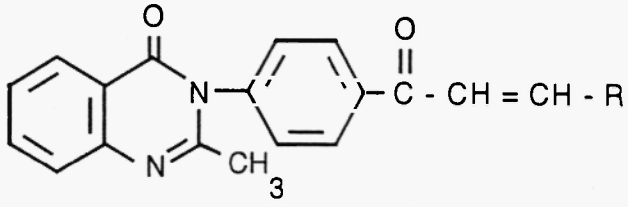
All the compounds reported in Table-2 were tested ***in vitro*** for their antimicrobial activity against various microbes. Under identical condition, the standard antibiotics showed zones of inhibition like Ampicillin 18-29 mm, Chloramphenicol 21-27 mm, Norfloxacin 20-28 mm against bacterial strains and Greseofulvin showed zones of inhibition of 15-25 mm against ***A. awamori***.

SCHEME



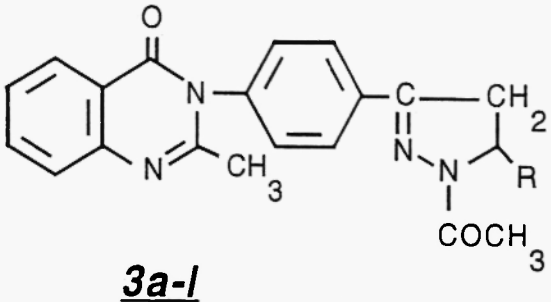
1

R - CHO



2a-l

CH_3COOH $NH_2NH_2H_2O$



3a-l

R = Aryl

It can be concluded from the Table-2 that the compounds ***2e, 2i, 3a, 3i*** were highly active against ***B. megaterium.*** The compounds ***2a, 2c, 2f, 2g, 2j, 3a, 3b, 3c, 3g, 3h,*** and ***3i*** showed significant activity against ***E. coli.*** In case of ***B. Substilis,*** the compounds ***2i, 2h, 3a, 3i*** displayed maximum activity, while the compounds ***2c, 2f, 2h, 3a, 3c*** and ***2h, 2k, 2a, 3a*** exhibited significant activity against ***Ps. fluorescens*** and ***A. awamori*** respectively.

The compounds ***3h*** and ***2g*** have been selected for their agrochemical and pharmaceutical screening by Du Pont Agricultural Products U S A and MERCK Pharmaceuticals U S A respectively.

IN VITRO EVALUATION OF PHARMACOLOGICAL STUDIES

The antimicrobial activity was assayed by using the cup-plate agar diffusion method (**10**) by measuring the inhibition zones in mm. All the compounds were screened ***in vitro*** for their antimicrobial activity against a variety of bacterial strains such as ***Bacillus megaterium, Escherichia coli, Bacillus subtilis, Pseudomonas flourescens*** and fungi such as ***Aspergillus awamori*** at a concentration of 50 μg. Known antibiotics like Chloramphenicol, Ampicillin, Norfloxacin and Greseofulvin were used for comparison purpose.

EXPERIMENTAL

All the melting points are uncorrected. Infrared Spectra (KBr) were recorded on a Shimadzu-435-IR spectrophotometer and ^{1}H-PMR spectra on Hitachi NMR-1200 using TMS as an internal standard.

Preparation of 1-Aryl-3-(p-2'-methyl-4 (3H)-quinazolon-3'-yl-phenyl) propenones *2a-l.*

To a well stirred solution of 2-methyl-3-(p-acetophenyl-4 (3H)-quinazolone (*1*, 0.01 mol) and araldehyde (0.01 mol) in ethanol (25 ml), 40% NaOH (3 ml) was added. The reaction mixture was heated for 10 min. and left overnight. The contents were poured onto ice water, acidified, filtered and crystallised from ethanol. ***2h***, yield 75%, M.P.. 120^{o}C, Calcd. for $C_{25}H_{20}O_3N_2$: C 75.60 , H 5.01 , N 7.05 %. Found C 75.75 , H 5.05, N, 7.10 % IR υmax (KBr) 1700 (C=O,str. of quinazolone) 1670 (C=O str.), 1590 (C=N str) cm^{-1}. ^{1}H-PMR δ ppm (TFA) : 2.39 (s, 3H, -CH_3), 3.9 (s, 3H, -OCH_3), 7.0-8.1 (m, 12H, Ar-H).

Similarly, other members of ***2*** were prepared. The physical constants are given in Table 1.

Preparation of 1-Acetyl-5-aryl-3-(p-2'-methyl-4 (3H)-quinazolon-3'-yl-phenyl) pyrazolines *3a-l*.

A mixture of chalcone (***2***, 0.01 mol) and hydrazine hydrate (0.01 mol) were condensed in acetic acid (20 ml) for 10 hrs. in oilbath. The contents were cooled, poured onto crushed ice and neutralized with ammonia. The separated solid was filtered, dried and crystallised from ethanol. ***3h***; yield 55%, M.P. 246^{o}C, Calcd. for $C_{27}H_{24}O_3N_4$: C 71.61 , H 5.30 , N 12.38 %. Found C 71.69 , H 5.25, N, 12.45 % IR υmax (KBr) 1700 (C=O, str. quinazolone) 1640 (C=O str.), 1590 (C=N str) cm^{-1}. ^{1}H-PMR δ ppm (TFA) : 2.4 (s, 3H, $-CH_3$), 2.7 (s, 3H, $-COCH_3$), 3.4 (dd, 1H, $-CH_A$), 3.8-4.3 (m, 4H, CH_B + $-OCH_3$), 5.5 (dd,1H,CH_x) , 7.0-8.1 (m, 12H, Ar-H).

Similarly, other members of ***3*** were prepared. The physical constants are given in Table 1.

TABLE 2 : Antimicrobial screening results of those compounds which exhibited highest activity (inhibition zone = 17-24 mm at 50 µg concentration)

Standard antibiotics	B.mega	B.subtilis	E.coli	Ps.fluorescens	A.awamori
Chloramphenicol, 21-27 mm Ampicillin 18-29 mm Norfloxacin 20-28 mm Griseofulvin 15-25 mm	2c, 2i, 3a, 3i,	2i, 2h, 3a, 3i	2a, 2c, 2f, 2g, 2j, 3a, 3b, 3c, 3g, 3h, 3i,	2c,2f, 2h, 3c, 3a	2h, 2k, 2a, 3a.

Table - 1 : Physical constants of the compounds *2a-l* and *3a-l*.

compd.	R	Molecular Formula	M.P. (°C)	Yield (%)	%of N Found	%of N Calcd.
2a	C_6H_5-	$C_{24}H_{18}N_2O_2$	133	71	6.61	6.65
2b	2-Cl-C_6H_4-	$C_{24}H_{17}N_2O_2Cl$	122	68	6.85	6.99
2c	4-Cl-C_6H_4-	$C_{24}H_{17}N_2O_2Cl$	135	65	6.90	6.99
2d	2,4-Cl_2-C_6H_3-	$C_{24}H_{16}N_2O_2Cl_2$	160	65	6.48	6.43
2e	3,4-$(OCH_3)_2$-C_6H_3-	$C_{26}H_{22}N_2O_4$	124	59	6.50	6.57
2f	4-N,N-$(CH_3)_2$-C_6H_4-	$C_{26}H_{23}N_3O_2$	138	62	10.20	10.26
2g	C_4H_3O-	$C_{22}H_{16}N_2O_3$	145	58	7.81	7.86
2h	4-OCH_3-C_6H_4-	$C_{25}H_{20}N_2O_3$	120	75	7.01	7.07
2i	2-NO_2-C_6H_4-	$C_{24}H_{17}N_3O_4$	130	70	10.15	10.21
2j	3-NO_2-C_6H_4-	$C_{24}H_{17}N_3O_4$	160	65	10.15	10.21
2k	-CH=CH-C_6H_5	$C_{26}H_{20}N_2O_2$	134	62	7.11	7.14
2l	3,4,5-$(OCH_3)_3$-C_6H_2-	$C_{27}H_{24}N_2O_5$	119	67	6.19	6.14
3a	C_6H_5-	$C_{26}H_{22}N_4O_2$	208	55	13.21	13.27
3b	2-Cl-C_6H_4-	$C_{26}H_{21}N_4O_2Cl$	165	55	12.30	12.26
3c	4-Cl-C_6H_4-	$C_{26}H_{21}N_4O_2Cl$	175	59	12.21	12.26
3d	2,4-$(Cl)_2$-C_6H_3-	$C_{26}H_{20}N_4O_2Cl_2$	182	60	11.35	11.40
3e	3,4-$(OCH_3)_2$-C_6H_3-	$C_{28}H_{26}N_4O_4$	198	58	11.55	11.61
3f	4-N,N-$(CH_3)_2$-C_6H_4-	$C_{28}H_{27}N_5O_2$	215	63	15.01	15.05
3g	C_4H_3O-	$C_{24}H_{20}N_4O_3$	236	53	13.64	13.59
3h	4-OCH_3-C_6H_4-	$C_{27}H_{24}N_4O_3$	246	55	12.42	12.38
3i	2-NO_2-C_6H_4-	$C_{26}H_{21}N_5O_4$	118	59	14.92	14.98
3j	3-NO_2-C_6H_5-	$C_{26}H_{21}N_5O_4$	265	58	14.93	14.98
3k	-CH=CH-C_6H_5-	$C_{28}H_{24}N_4O_2$	164	50	12.55	12.50
3l	3,4,5-$(OCH_3)_3$-C_6H_2-	$C_{29}H_{28}N_4O_5$	178	53	10.90	10.93

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