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Synthesis of 2-Methyl/phenyl-3-[(4-substituted-benzylidene) Amino-phenyl]-6 & 8-disubstituted-1,3-quinazolin-4-ones as Potential Anthelmintic Agents

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Thirty 2-Methyl/phenyl-3-[(4-substituted-benzylidene) amino-phenyl]-6 &8-disubstituted-quinazoline-4-ones were synthesised and screened for their anthelmintic activity aganist *Hymenolepis nana* infection in mice and *Nippostrangylus brasilliensis* infection in rat. Some of the compounds were also tested for their antiviral and antibacterial activity.

INTRODUCTION

Quinazolin and their derivatives have been shown to possess a wide spectrum of biological activities. The most notable being the CNS depressant[1] and anthelmintic properties[2,3]. This observation have led us to synthesize the structurally related compounds.

Condensation of 4-amino acetanilide with substituted aldehyde yielded the corresponding schiff's bases (I) which were hydrolysed to form 4-(substituted-benzylidene) amino-aniline (II). The second intermediate 2-methyl/phenyl 6 & 8-disubstituted-benzoxazine-4-ones (IV) were prepared from 3 & 5-disubstituted anthranilic acid[4] (III) by successive reaction with acetic anhydride and benzoyl chloride[5,6]. Reaction of compound (II) with (IV) in dry pyridine gave the final products 2-methyl/phenyl-3-[(4-substituted-benzylidene) amino-phenyl]-6 & 8-disubstituted, 1,3-quinazolin-4-ones (V) (5-34), (scheme-1).

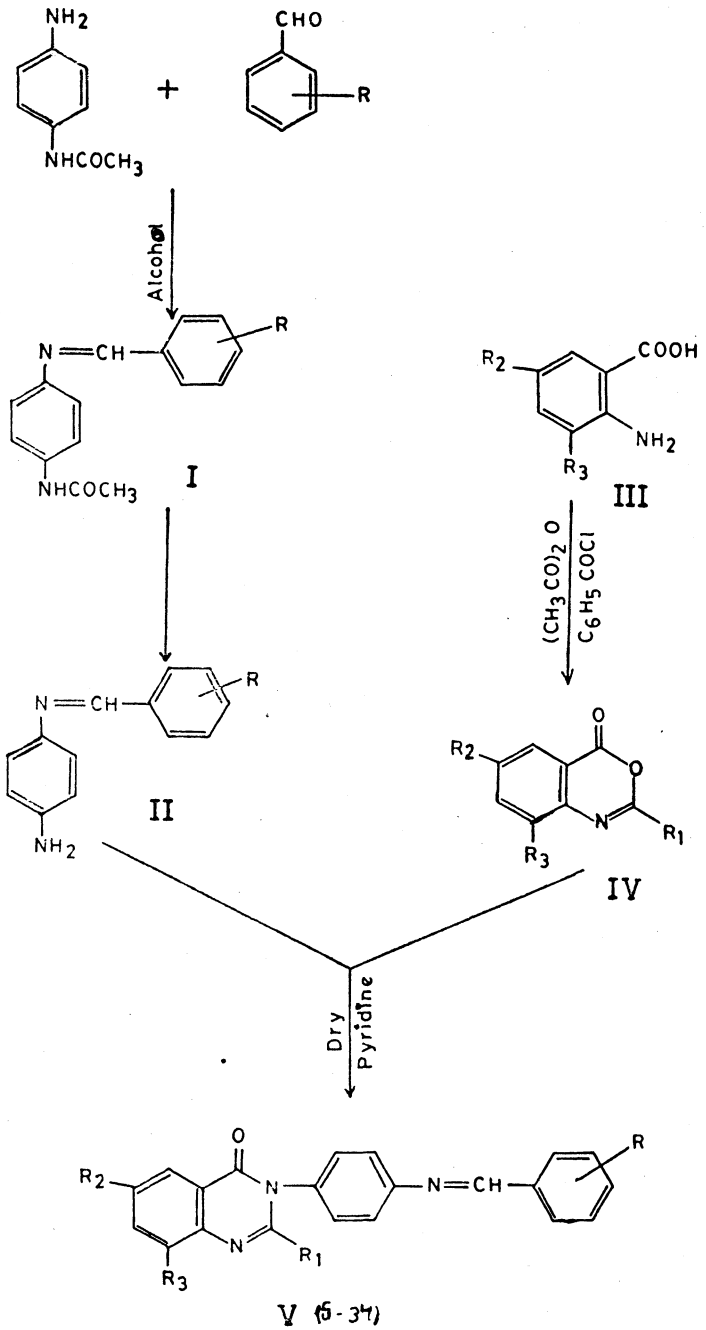
EXPERIMENTAL

Melting points were determined in sulphuric acid bath and are uncorrected. The structures of all the compounds were firmly established by their IR and PMR spectra recorded on Perkin-Elmer 157 infrared (ν_{max} in cm^{-1}) and Perkin-Elmer R–32 instrument, chemical shifts in δ-scale downfield from internal TMS reference. The purity of all the compounds was checked by TLC on silica gel G plates using iodine vapours and $KMnO_4$ spray as visualising reagents.

Synthesis of 2-Methyl-3-(4-dimethylamino-benzylidene) amino-Phenyl quinazolin-4-one(8)

A mixture of 4-(dimethyl-amino-benzylidene) amino-aniline (2.4 gm, 0.01 mol) and 2-methyl-benzoxazine-4-one (1.6 gm, 0.01 mol) in dry pyridine (30 ml) was refluxed on sand bath at room temperature for 12 hrs. The resulting mixture, poured on crushed ice, the solid mass separated,

Scheme—I



V (5-34)

was filtered, wash with water and crystallized from chloroform, yield : 2.5 gm (62 %), m.pt. 158°C.

(Found, % C, 75; H, 5.5; N, 14.0; $C_{24}H_{22}N_4O$)

(Requires, % C, 75.3; H, 5.7; N, 14.6).

IR(KBr): 1670 cm^{-1} (N—CO), 1630 cm^{-1} (N=C), 1600 cm^{-1} (C=Phenyl) 1375 cm^{-1} (—CH_3).

PMR ($CDCl_3$): 1.5 [s, 9*H*, CH_3, $N(CH_3)_2$]

6.80–7.40 (m, 13*H*, Ar—*H*, N=C*H*)

Similarly other compounds of the series were prepared and the results are summarized in Table–1.

Biological Assay

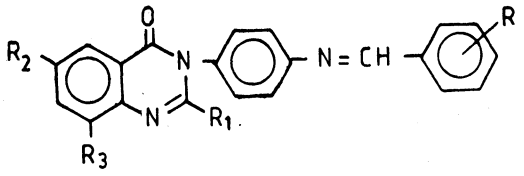
(*i*) *Anthelmintic activity*—Some of the compounds of this series were tested for their cestodicidal activity against *H. nana* infection in mice using the technique of Steward[7]. The oral dose was 250 mg/kg daily given for three days. Niclosamise was used as the standard drug which cleared 100% of the above infection.

The best compound of the series was (30) which caused 100% elimination of H. nana infection in mice at the oral dose of 250 mg/kg.

Some of the compounds were also screened for their anti-hookworm activity against *N. brasiliensis* infection in rats by standard methods[8] at the oral dose of 250 mg/kg. Thiabendazole was used as the standard drug which cleared the infection at a dose of 50 mg/kg daily given for 3 days. The results are summarized in Table–2.

(*ii*) *Antimicrobial activity*—Some of the compounds belonging to this series have also been tested for their *in vitro* and *in vivo* growth inhibitory activity against plant viruses, using the standard method[9]. The solution of test compounds were prepared by dissolving 5 mg in 1 ml distilled water. These solution were termed "Test solutions". The percent inhibition was expressed as % inhibition $= \frac{C-T}{C} \times 100$ where C = number of lesions on control leaves and T = number lesion on treated leaves. The host plants used were *Nicotinia Glutinosa* (NG) for *Tobacco mosaic virus* (TMV). The antibacterial screening was carried out against *Bacillus subtilis* and *staphylococcus aureus* by agar plate diffusion[10]. In this method a standard 5 mm diameter sterilised filter paper disc impregnated with the compound (10 mg/ml) was placed on a agar plate, seeded plates were incubated for 24 hour at 37°C and then observed for zone of inhibition of bacterial growth around the disc. In each case three replications were performed. The results are reported in Table–3.

TABLE 1
CHARACTERIZATION DATA OF COMPOUNDS (5-34)



No.	R	R_1	R_2	R_3	Yield %	m. pt. °C	Molecular formula	Nitrogen analysis %	
								Found	Calcd.
5	CH_3	3-NO_2	I	H	70	197	$C_{22}H_{15}N_4IO_3$	10.75	10.98
6	C_6H_5	3-NO_2	H	H	60	192	$C_{27}H_{18}N_4O_3$	13.87	12.55
7	C_6H_5	4-OH	H	H	54	220	$C_{27}H_{19}N_3O_2$	9.87	10.07
8	CH_3	4-$N(CH_3)_2$	H	H	62	158	$C_{24}H_{22}N_4O$	14.35	14.66
9	CH_3	2-OH	H	H	60	203	$C_{22}H_{19}N_3O_2$	11.56	11.76
10	CH_3	2-OH	I	H	65	187	$C_{22}H_{16}N_3O_2$	11.66	11.86
11	CH_3	4-$N(CH_3)_2$	I	H	55	166	$C_{24}H_{21}N_4IO_4$	9.88	10.07
12	CH_3	3-NO_2	H	H	65	210	$C_{22}H_{16}N_4IO_3$	10.34	10.63
13	CH_3	4-$N(CH_3)_2$	Br	H	55	144	$C_{24}H_{21}BrN_4O$	12.00	12.25
14	C_6H_5	4-$N(CH_3)_2$	I	H	55	125	$C_{29}H_{23}N_4IO$	9.62	9.83
15	CH_3	4-$N(CH_3)_2$	Br	Br	56	199	$C_{24}H_{20}Br_2N_4O$	10.17	10.37
16	CH_3	2-OH	Br	H	80	178	$C_{22}H_{16}BrN_3O_2$	9.50	9.68
17	CH_3	2-OH	Br	Br	81	136	$C_{22}H_{15}Br_2N_3O_2$	8.01	8.19
18	C_6H_5	2-OH	I	H	65	160	$C_{27}H_{18}N_3IO_2$	7.52	7.73
19	C_6H_5	2-OH	H	H	80	170	$C_{27}H_{19}N_3O_2$	9.17	10.07
20	CH_3	4-Cl	H	H	62	175	$C_{22}H_{16}N_3OCl$	11.00	11.26
21	CH_3	4-Cl	I	H	55	180	$C_{22}H_{15}N_3OICl$	8.21	8.42
22	CH_3	4-Cl	Br	H	55	150	$C_{22}H_{15}BrN_3OCl$	9.91	10.07
23	CH_3	4-OH	Br	Br	68	216	$C_{22}H_{15}Br_2N_3O_2$	8.03	8.19
24	CH_3	4-OH	H	H	60	299	$C_{22}H_{17}N_3O_2$	11.63	11.83
25	CH_3	4-OH	Br	H	62	269	$C_{22}H_{16}BrN_3O_2$	9.42	9.68
26	CH_3	4-OH	I	H	55	175	$C_{22}H_{16}IN_3O_2$	8.53	8.83
27	C_6H_5	4-OH	I	H	62	130	$C_{27}H_{18}N_3IO_2$	7.59	7.73
28	CH_3	3-NO_2	Br	H	50	222	$C_{22}H_{15}BrN_4O_3$	11.13	12.09
29	CH_3	3-NO_2	Br	Br	60	202	$C_{22}H_{14}Br_2N_4O_3$	9.97	10.33
30	C_6H_5	3-NO_2	I	H	55	150	$C_{27}H_{17}N_4IO_3$	7.72	7.89
31	CH_3	4-Cl	Br	Br	53	190	$C_{22}H_{14}Br_2N_3OCl$	7.77	7.99
32	C_6H_5	4-Cl	I	H	50	113	$C_{27}H_{17}N_3OICl$	7.13	7.49
33	C_6H_5	4-Cl	H	H	58	166	$C_{27}H_{18}N_3OCl$	9.51	9.86
34	C_6H_5	4-$N(CH_3)_2$	H	H	60	180	$C_{29}H_{24}N_4O$	12.45	12.81

TABLE 2

Compd. No.	Dose	Anthelmintic Activity % Efficacy	
		H. nana	*N. brasiliensis*
10	250 mg/kg	Inactive	20
11	,,	,,	34
16	,,	,,	36
17	,,	,,	20
18	,,	,,	50
19	,,	,.	10
24	,,	,,	15
27	,,	,,	20
28	,,	,,	26
30	,,	100	55

H. nana=Hymenolepis-nana
N. brasiliensis=Nippostrongylus brasiliensis

TABLE 3

Compd. No.	TMV/NG Reduction in local lesions		Anti bacterial screening	
	in vitro	*in vivo*	*B. Subtilis*	*S. aureus*
10	28[b]	22[b]	−	−
13	37[b]	33[b]	−	−
16	41[b]	39[b]	+	±
17	34[b]	32[b]	±	+
18	41[b]	36[b]	−	±
19	57[a]	50[a]	++	++
21	47[b]	40[b]	+±	+
30	62[a]	54[a]	++	++

TMV−Tobacco Mosaic Virus
NG−Nicotiana Glutinosa (a)=significant at 1% level.
(b)=Significant at 5% level
B. Subtilis=Bacillus subtilis
S. aureus−staphylococcus aureus
(−)=No Inhibition, (+)=15−19 mm, (++)=8—10 mm,
(±)20−25 mm, (±+)=10−14 mm

RESULTS AND DISCUSION

The results in Table-2 showed that the compounds exhibited the activity in the range of (10–55%) against *N. brasilliensis* infection in rat at the oral dose of 250 mg/kg. It is evident from the results given in Table-3 that the compounds exhibited the activity in the range of (28–62%) *in vitro*

and (22–54%) *in vivo* against *Tobacco misaic virus.* The compounds also showed sufficient activity against bacteria used.

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