SCREENING OF POTENTIAL ANTIMALARIALS AGAINST *P. GALLINACEUM* IN CHICKS : PART IX[1]—SOME DERIVATIVES OF 4-AMINOQUINAZOLINE, 4 (3)-QUINAZOLONE, 4-AMINO-BENZ (h) QUINALDINE, BIGUANIDES AND CERTAIN INDIGENOUS DRUGS.[2]

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One hundred and sixteen potential antimalarial compounds belonging to the substituted 4-alkyl-amino-quinazolines, 2-styryl-3-aryl-4-(3)-quinazolones, 3-p-(N-aryl)-sulphonamido-phenyl-4-(3)-quinazolones, 4-aryl-amino-benz (h) quinaldines and N^1-aryl-N^5-(4′-quinazolyl) biguanides and indigenous drugs have been screened against blood induced *Plasmodium gallinaceum* infection in 7 days old chicks. None of the compounds tested showed any antimalarial activity at 1 and 4 times the MED of quinine.

In the previous communications (Basu *et al.*, 1962; Jaswant Singh *et al.*, 1954; Misra *et al.*, 1955 and Sen Gupta *et al.*, 1959), the results of screening of 373 potential antimalarials belonging to diverse chemical groups which included substituted biguanides, sulpha-biguanides, 1 : 2-dihydro-s-triazines, thioureas, sulphides, thiopegans, 4 (3)-quinazolones, 4 (3)-sulphaquinazolones and 4-amino-quinolines were reported. These studies were extended to the screening of a further series of 116 compounds which included 4-alkyl-amino-quinazolines, 2-styryl-4 (3)-quinazolones, 3-p-(N-aryl) sulphonamido-phenyl-4 (3)-quinazolones, 4-aryl-amino-benz (h) quinaldines, N^1-aryl-N^5-(4′-quinazolyl) biguanides and indigenous drugs, and the results are reported in this paper.

METHODS

The compounds received from various sources were given the Malaria Institute (now National Institute of Communicable Diseases) survey numbers

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1. Parts I to IV and VI have been published in Indian J. Malariology, **6** (1952), 145; **7** (1953), 117; **7** (1953), 311; **8** (1954), 1 and **10** (1956), 299; and Parts V, VII and VIII in J, Sci. Industr. Res., **14C** (1955), 173; **18C** (1959), 28; and **21C** (1962), 245, respectively.
2. This work was done in continuation of the C.S.I.R. Scheme "Screening of antimalarials" after the screening set up was taken over by the Institute.
3. Formerly Malaria Institute of India.

(MIS) and were made into solutions or suspensions in terms of base content equivalent to one fourth, one and four times, the minimum effective dose (MED) of quinine. They were screened against *Plasmodium gallinaceum* infection in seven days old chicks according to the standard technique (Jaswant Singh *et al.*, 1952 and 1953). Seventy five per cent or more reduction in the parasite count in the treated group as compared to the control group denoted antimalarial activity, Any mortality which could not be attributed to the parasitaemia following the administration of the drug, indicated some toxicity of the dosage tried.

RESULTS AND DISCUSSION

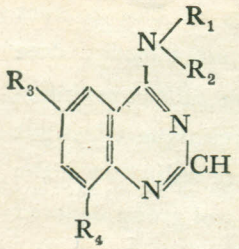
The results of screening of different compounds against *P. gallinaceum* in chicks are recorded in Table I.

4-Amino-quinazoline derivatives.—Nineteen 6 : 8-dihalo-4-mono or di-(β-hydroxy ethyl) amino-quinazoline hydrochlorides (I) were tested and found inactive at ¼, 1 or 4Q dosages (Table 1). Most of the compounds were found to be toxic at Q and 4Q dosages.

4-(3)-Quinazolone derivatives.—All the sixtynine 2-p-substituted styryl-3-aryl-6-alkyl/(H or halo -4 (3)-quinazolones (II) (Dhatt, 1963) tested, were found to be inactive at Q and 4Q dosages (Table I). Previously some 2-alkyl-3-aryl-6 alkyl/(H or halo)-4 (3)-quinazolones, (Bami and Dhatt, 1957, Coatney *et al.*, 1953, Jain and Narang, 1953, Jaswant Singh *et al.*, 1954, and SenGupta *et al.*, 1959) based on the 4 (3)-quinazolone structure of highly active but toxic febrifugine alkaloid(Baker *et al.*,1953 and Hewitt *et al.*, 1952)were reported to have limited antimalarial activity. These studies showed that the introduction of a 2-styryl (p-methoxy or dimethyl amino) group into the 3-aryl-4 (3)-quinazolones, completely destroyed the antimalarial activity.

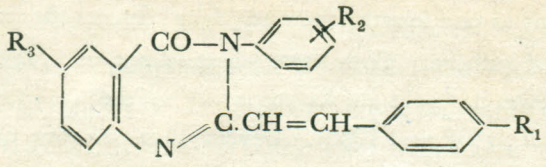
Six 2-alkyl-3-p-(N-aryl) sulphonamido-phenyl-4 (3)-quinazolone derivatives (III) (Dhatt, 1964) were tested and found to be inactive at Q and 4Q dosages (Table I). These results were in conformity with the previous findings (Basu *et al.*, 1962 and Dhatt and Bami, 1959).

4-amino-benz (h)-quinaldine derivativee.—All the eight 4-aryl-amino-benz (h)-quinaldine derivatives (IV) tested, were found to be inactive at Q and 4Q dosages (Table I).



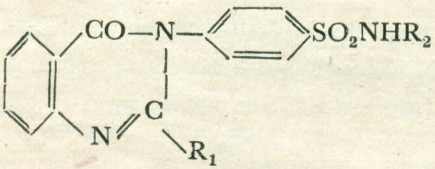
(I)

R_1 = H or β—hydroxy ethyl
R_2 = β—hydroxy ethyl
R_3 = Cl, Br. 1.
R_4 = H, Cl, Br, 1.



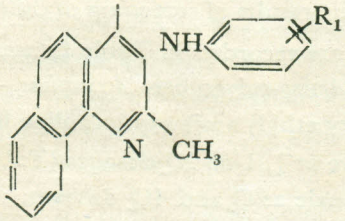
(II)

R_1 = H, OCH_3, N $(CH_3)_2$
R_2 = H, CH_3, OCH_3, Cl, Br. etc.
R_3 = H, CH_3 Cl, Br.



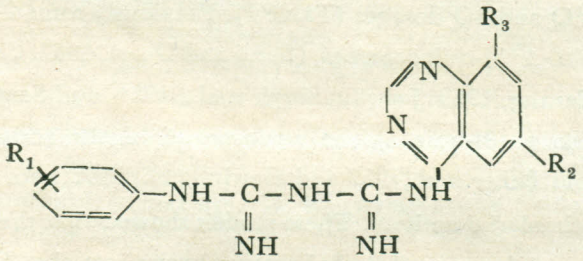
(III)

R_1 = CH_3, C_2H_5
R_2 = aryl



(IV)

R_1 = H, CH_3, OCH_3, Cl, Br, 1, etc.



(V)

R_1 = Cl, OCH_3, OC_2H_5 etc.
R_2 = Cl, Br, 1.
R_3 = H, Cl, Br, 1.

N^1-Aryl-N^5-(6′ : 8′-dihalo-4′-quinazolyl)-biguanide—All the twelve N^1-aryl-N^5-(6′ : 8′-dihalo-4′-quinazolyl)-biguanide hydrochlorides (V) tested were found to be inactive at $\frac{1}{4}$Q to Q dosages showing that the replacement of N^5-dialkyl group in case of highly active N^1-aryl-N^5-dialkyl biguanides with (6 : 8-dihalo)-4 quinazolyl grouping had resulted in complete loss of antimalarial activity (Table I). These results were in conformity with the previous

TABLE I

Screening tests for antimalarials against P. Gallinaceum in chicks

MIS no. of compound	Compounds	Dosage in multiples/ fractions of MED. of quinine(Q)	Activity
	Hydrochlorides of 4-Amino-quinazolines[1]		
360	6:8-Dibromo-4-β-hydroxy-ethyl-	1	Inactive
		$\frac{1}{4}$	,,
361	6-Iodo-4-β-hydroxy-ethyl-	1	Toxic
		$\frac{1}{4}$	Inactive
362	6:8-Di-iodo-4-β-hydroxy-ethyl-	4	Toxic
		1	,,
		$\frac{1}{4}$	Inactive
		$\frac{1}{16}$	,,
363	6-Chloro-8-bromo-4-β-hydroxy-ethyl-	4	Toxic
		1	Inactive
364	6-Chloro-8-iodo-4-β-hydroxy-ethyl-	1	Toxic
		$\frac{1}{4}$	Inactive
365	6-Bromo-8-chloro-4-β-hydroxy-ethyl-	1	,,
		$\frac{1}{4}$	,,
366	6-Bromo 8-iodo-4 β hydroxy-ethyl-	4	,,
		1	,,
367	6-Iodo-8-chloro-4-β-hydroxy-ethyl-	1	Toxic
		$\frac{1}{4}$	Inactive
368	6 Iodo-8-bromo-4-β-hydroxy-ethyl-	1	Toxic
		$\frac{1}{4}$	Inactive
369	6-Chloro-4-di-(β-hydroxy-ethyl)	1	Toxic
		$\frac{1}{4}$	Inactive
370	6:8-Dichloro-4-di-(β-hydroxy-ethyl-	1	Toxic
		$\frac{1}{4}$	Inactive
371	6-Bromo-4-di-(β-hydroxy-ethyl-	1	Toxic
		$\frac{1}{4}$	Inactive
372	6-Iodo-4-di-(β-hydroxy-ethyl)-	1	Toxic
		$\frac{1}{4}$	Inactive
373	6:8-Di-iodo-4-di-(β-hydroxy-ethyl)	1	Toxic
		$\frac{1}{4}$	Inactive
374	6-Chloro-8-bromo-4-di-(β-hydroxy-ethyl)-	1	Toxic
		$\frac{1}{4}$	Inactive
375	6-Chloro-8-iodo-4-di-(β-hydroxy-ethyl)-	1	Toxic
		$\frac{1}{4}$	Inactive
376	6-Bromo-8-chloro-4-di(-β-hydroxy-ethyl)-	1	,,
		$\frac{1}{4}$	,,
377	6-Iodo-8-chloro-4-di-(β-hydroxy-ethyl)-	1	,,
		$\frac{1}{4}$	,,
378	6-Iodo-8-bromo-4-di-(β-hydroxy-ethyl)-	1	,,
		$\frac{1}{4}$	,,

1. All the 4-amino-quinazoline derivatives were supplied by the Chemistry Department, Lucknow University, Lucknow.

Hydrochlorides of Biguanide Derivatives[1]

379	N^1-p-Chloro-phenyl-N^5-(6′-bromo-4′-quinazolyl)-	1	Inactive
		$\frac{1}{4}$	,,
380	N^1-p-Chloro-phenyl-N^5-(6′:8′-dibromo-4′-quinazolyl)-	1	,,
		$\frac{1}{4}$	,,
381	N^1-p-Chloro-phenyl-N^5-(6′-iodo-4′-quinazolyl)-	1	,,
		$\frac{1}{4}$	,,
382	N^1-p-Chloro-phenyl-N^5-(6′:8′-di-iodo-4′-quinazolyl)-	1	,,
		$\frac{1}{4}$	,,
383	N^1-p-Chloro-phenyl-N^5-(6′-chloro-8′-bromo-$4^{4'}$-quinazolyl)-	1	,,
		$\frac{1}{4}$	,,
384	N^1-p-Chloro-phenyl-N^5-(6′-chloro-8′-iodo-4′-quinazolyl)-	1	,,
		$\frac{1}{4}$	,,
385	N^1-p-Chloro-phenyl-N-^{5}-(6′-bromo-8′-iodo-4′-quinazolyl)-	1	,,
		$\frac{1}{4}$	,,
386	N^1-p-Chloro-phenyl-N^5-(6′-iodo-8′-chloro-4′-quinazolyl)-	1	,,
		$\frac{1}{4}$	,,
387	N^1-p-Methoxy-phenyl-N^5-(6′-chloro-8′-bromo-4′-quinazolyl)-	1	,,
		$\frac{1}{4}$	,,
388	N^1-p-Methoxy-phenyl-N^5-(6′-bromo-8′-chloro-4′-quinazolyl)-	1	,,
		$\frac{1}{4}$	,,
389	N^1-p-Ethoxy-phenyl-N^5-(6′-bromo-8′-chloro-4′-quinazolyl,-	1	,,
		$\frac{1}{4}$	,,
390	N^1-p-Ethoxy-phenyl-N^5-(6′:8′-dibromo-4′-quinazolyl)-	1	,,
		$\frac{1}{4}$	,,

4-Amino-Benz (h) Quinaldine Derivatives[2]

391	Hydrochloride of 4-p-chloro-phenyl-	4	Inactive
		1	,,
392	Hydrochloride of 4-m-chloro-phenyl-	1	,,
		$\frac{1}{4}$	,,
393	4-p-Bromo-phenyl-	4	,,
		1	,,
394	4-p-Iodo-phenyl-	4	,,
		1	,,
395	4-m-Iodo-phenyl-	4	,,
		1	,,

1 All the hydrochlorides of biguanide derivatives were supplied by the Chemistry Department, Lucknow University, Lucknow.

2 All the 4-amino-benz (h)-quinaldine derivatives were supplied by the Armed Forces Medical College, Poona.

396	4-p-Tolyl-	4	Inactive
		1	,,
397	4-Phenyl-	4	,,
		1	,,
398	4-p-Anisyl-	4	,,
		1	,,

4(3)-Quinazolone Derivatives[1]

399	2-p-Dimethyl amino-styryl-3-p-tolyl-	4	Inactive
		1	,,
400	2-p-Dimethyl amino-styryl-3-phenyl-	4	,,
		1	,,
401	2-p-Dimethyl amino-styryl-3-o-tolyl-	4	,,
		1	,,
402	2-p-Dimethyl amino-styryl-3-o-anisyl-	4	,,
		1	,,
403	2-p-Dimethyl amino-styryl-3-o-chloro-	4	,,
	phenyl-	1	,,
404	2-p-Dimethyl amino-styryl-3-p-anisyl-	4	,,
		1	,,
405	2-p-Dimethyl amino-styryl-3-p-chloro-	4	,,
	phenyl-	1	,,
406	2-p-Dimethyl amino-styryl-3-m-tolyl-	4	,,
		1	,,
407	2-p Dimethyl amino-styryl-3-phenyl-6-	4	,,
	bromo-	1	,,
408	2 p-Dimethyl amino-styryl-3-o-tolyl-	4	,,
	6-bromo-	1	,,
409	2-p-Dimethyl amino-styryl-3-p-tolyl-6-	4	,,
	bromo-	1	,,
410	2-p-Dimethyl amino-styryl-3 o-anisyl-	4	,,
	6-bromo-	1	,,
411	2-p-Dimethyl amino-styryl-3-p-anisyl	4	,,
	6-bromo-	1	,,
412	2-p-Dimethyl amino-styryl-3-o-chloro-	4	,,
	phenyl-6-bromo-	1	,,
413	2-p-Dimethyl amino-styryl-3-p-chloro-	4	,,
	phenyl-6-bromo-	1	,,

1 All the 4(3)-quinazolone derivatives were supplied by the Chemistry Department, National Institute for Communicable Diseases (Formerly Malaria Institute of India), Delhi-6.

414	2-Styryl--3-phenyl-6-bromo	4	Inactive
		1	,,
415	2-Styryl-3-o-tolyl-6-bromo-	4	,,
		1	,,
416	2-Styryl-3-p-tolyl-6-bromo-	4	,,
		1	,,
417	2-Styryl-3-m-tolyl-6-bromo-	4	,,
		1	,,
418	2-Styryl-3-p-phenetyl-6-bromo-	4	,,
		1	,,
419	2-Styryl-3-o-anisyl-6-bromo-	4	,,
		1	,,
420	2-Styryl-3-p-anisyl-6-bromo-	4	,,
		1	,,
421	2-Styryl-3-o-chloro-phenyl-6-bromo-	4	,,
		1	,,
422	2-Styryl-3-p-chloro-phenyl-6-bromo-	4	,,
		1	,,
423	2-Styryl-3-p-bromo-phenyl-6-bromo-	4	,,
		1	,,
424	2-p-Methoxy-styryl-3-phenyl-6-bromo-	4	,,
		1	,,
425	2-p-Methoxy-styryl-3-m-tolyl-6-bromo-	4	,,
		1	,,
426	2-p-Methoxy-styryl-3-p-tolyl-6-bromo-	4	,,
		1	,,
427	2-p-Methoxy-styryl-3-o-anisyl-6-bromo-	4	,,
		1	,,
428	2-p-Methoxy-styryl-3-p-phenetyl-6-bromo-	4	,,
		1	,,
429	2-p-Methoxy-styryl-3-p-bromo-phenyl-6-bromo-	4	,,
		1	,,
430	2-Styryl-3-phenyl-6-chloro-	4	,,
		1	,,
431	2-Styryl-3-o-tolyl-6-chloro-	4	,,
		1	,,
432	2-Styryl-3-p-tolyl-6-chloro-	4	,,
		1	,,
433	2-Styryl-3-o-anisyl-6-chloro-	4	,,
		1	,,
434	2-Styryl-3-p-anisyl-6-chloro-	4	,,
		1	,,

435	2-Styryl-3-o-chloro-phenyl-6-chloro-	4	Inactive
		1	,,
436	2-Styryl-3-p-chloro-phenyl-6-chloro-	4	,,
		1	,,
437	2-Styryl-3-p-bromo-phenyl-6-chloro-	4	,,
		1	,,
438	2-p-Methoxy-styryl-3-phenyl-6-chloro-	4	,,
		1	,,
439	2-p-Methoxy-styryl-3-o-tolyl-6-chloro,	4	,,
		1	,,
440	2-p-Methoxy-styryl-3-p-tolyl-6-chloro-	4	,,
		1	,,
441	2-p-Methoxy-styryl-3-o-anisyl-6-chloro-	4	,,
		1	,,
442	2-p-Methoxy-styryl-3-p-anisyl-6-chloro-	4	,,
		1	,,
443	2-p-Methoxy-styryl-3-o-chloro-phenyl-6-chloro-	4	,,
		1	,,
444	2-p-Methoxy-styryl-4-p-chloro-phenyl-6-chloro-	4	,,
		1	,,
445	2-p-Methoxy-styryl-3-p-bromo-phenyl-6-chloro-	4	,,
		1	,,
446	2-Styryl-3-p-bromo-phenyl-	4	,,
		4	,,
447	2-p-Methoxy-styryl-3-p-anisyl-	1	,,
448	2-p-Dimethyl amino-styryl-3-p-bromo-phenyl-6-methyl-	4	,,
		4	,,
449	2-p-Dimethyl amino-styryl-3-p-bromo-phenyl-6-chloro-	1	,,
		1	,,
450	2-p-Dimethyl amino-styryl-3-o-chloro-phenyl-6-chloro·	4	,,
		1	,,
451	2-p-Dimethyl amino-styryl-3-o-anisyl-6-chloro-	4	,,
		1	,,
452	2-p-Dimethyl amino-styryl-3-o-tolyl-6-chloro-	4	,,
		1	,,
453	2-Styryl-3-p-chloro-phenyl-6-methyl-	4	,,
		1	,,
454	2-Styryl-3-o-tolyl-6-methyl-	4	,,
		1	,,
455	2-Styryl-3-p-phenetyl-6-methyl-	4	,,
		1	,,
456	2-p-Dimethyl amino-styryl-3-o-tolyl-6-methyl-	4	,,
		1	,,

457	2-p-Dimethyl amino-styryl-3-p-phenetyl-	4	Inactive
	6-methyl-	1	,,
458	2-p-Methoxy-styryl-3-o-tolyl-6-methyl-	4	,,
		1	,,
459	2-p-Methoxy-styryl-3-p-bromo-phenyl-6-	4	,,
	methyl-	1	,,
460	2-p-Methoxy-styryl-3-p-phenetyl-6-methyl-	4	,,
		1	,,
461	2-p-Methoxy-styryl-3-p-chloro-phenyl-6-	4	,,
	methyl-	1	,,
462	2-Styryl-3-p-phenetyl-	4	,,
		1	,,
463	2-Styryl-3-o-chloro-phenyl-	4	,,
		1	,,
464	2-Styryl-3-m-tolyl-	4	,,
		1	,,
465	2-p-Methoxy-styryl-3-phenyl-	4	,,
		1	,,
466	2-p-Methoxy-styryl-3-p-phenetyl-	4	,,
		1	,,
467	2-p-Methoxy-styryl-3-p-bromo-phenyl-	4	,,
		1	,,
468	2-Methyl-3-p-(N-phenyl)-sulphonamido-	4	,,
	phenyl-	1	,,
469	2-Methyl-3-p-(N-o-tolyl)-sulphonamido-	4	,,
	phenyl-	1	,,
470	2-Methyl-3-p-(N-o-chloro-phenyl)-	4	,,
	sulphonamido-phenyl-	1	,,
471	2-Ethyl-3-p-(N-phenyl)-sulphonamido-	4	,,
	phenyl-	1	,,
472	2-Ethyl-3-p-(N-o-tolyl)-sulphonamido-	4	,,
	phenyl-	1	,,
473	2-Ethyl-3-p-(N-o-chloro-phenyl-	4	,,
	sulphonamido-phenyl-	1	,,
	Miscellaneous		
359	Powder of herb *Hul Hul* used in the decoction form as advised by the sender[1]	Inactive even at 48 times the recommended human adult dose.	
424	*Goudanti Hartal* ashes purified (orpiment yellow arsenic) [2]	4	Inactive
		1	,,

1. Supplied by Vaid, G. N. Pant, New Delhi.
2. Supplied by Jagdish Narain, Dhindanewala P.O. Pilani, Rajasthan.

findings where such loss of antimalarial activity was observed when the N^5-dialkyl group was replaced with aryl, substituted sulphonamido phenyl or heterocyclic groupings (Jaswant Singh *et al.*, 1954, Misra *et al.*, 1955 and Sen Gupta *et al.*, 1959).

Indigenous drugs.—Two indigenous drugs were tested : (a) decoction of powder of herb *Hul Hul* at 48 times the recommended human adult dose and (b) purified *Goudanti Hartal* ashes (orpiment yellow arsenic) at 4Q dosage. Both were found to be inactive at these dosages (Table 1).

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