umkristallisieren. Ausb. 0,3 g (44,6 % d.Th.); Schmp. 128° (Ether). – IR (KBr): 2950 (CH), 2238 (CN), 1722 cm^{-1} (CO). – ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.63–2.13 (m,4H,CH_2), 2.63–3.23 (m,4H,CH_2), 4.03 (s,6H,OCH_3). – MS (80 eV): m/e = 274 (31 %, M^+), 158 (100 %). – $C_{14}H_{14}N_2O_4$ (274.28). Ber. C 61.3 H 5.14 N 10.2 Gef. C 61.1 H 5.15 N 10.3.

Die als Nebenprodukt bei der Umsetzung von **1** mit **2b** nach chromatographischer Aufarbeitung mit Benzol/Essigester (92.5:7.5) in 4 % Ausbeute erhaltenen Kristalle erwiesen sich in allen spektroskopischen und analytischen Daten als identisch mit **10**.

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4 Dc ließen sich im Reaktionsgemisch nur Verbindungen der Konstitution **3** nachweisen.

[Ph 486]

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Synthesis of New 2,3-Disubstituted 4 (3*H*)-Quinazolones and Related Products as Potential Antiviral Agents

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Sixteen new 2,3-disubstituted 4 (3*H*)quinazolone derivatives were synthesized and evaluated for their antiviral activities against Gomphrena mosaic and Sunnhemp rosette virus. Most compounds show antiviral activity against Gomphrena mosaic virus.

Synthese einiger 2,3-disubstituierter neuer 4(3*H*)-Chinazolone und verwandter Verbindungen als potentiell antivirale Verbindungen

Sechzehn neue 2,3-disubstituierte 4(3*H*)-Chinazolon-Derivate wurden synthetisiert und ihre antivirale Wirkung gegen Gomphrena Mosaik und Sunnhemp Rosette Virus geprüft. Die meisten dieser Verbindungen zeigen antivirale Wirksamkeit gegen Gomphrena Mosaik Virus.

Importance of 4(3*H*)-quinazolones as antimalarial[1] hypnotic[2], anticonvulsant[3] and antiviral[4] agents has been reported earlier. In view of broad spectrum biological activities associated with various 4(3*H*)-quinazolones, it was considered of interest to synthesize some new 2,3-disubstituted 4(3*H*)-quinazolones and to test them for their virus inhibiting effect. The results are reported in the present communication.

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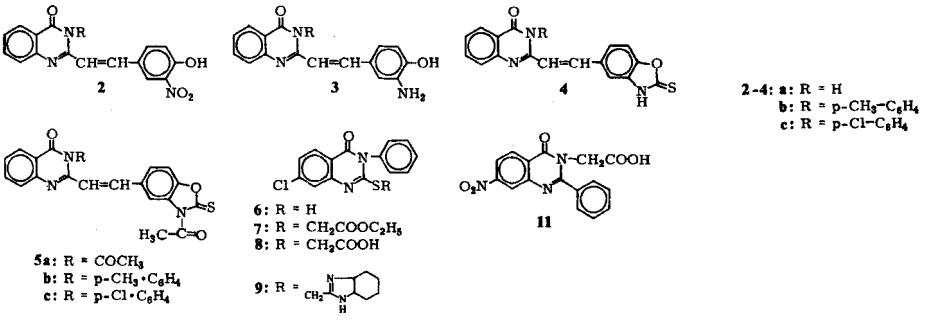
Condensation of 2-methyl-3-(4'-methylphenyl)-4(3*H*)-quinazolinone **(1b)** with 3-nitro-4-hydroxybenzaldehyde in acetic acid furnished **2b**. Reduction of the nitro group in **2b** with hydrazine hydrate/Raney Ni formed **3b** which was cyclised with CS_2 to yield **4b**. **4b** was characterised by preparing its acetyl derivative **5b**.

7-Chloro-2-mercapto-3-phenyl-4(3*H*)-quinazolinone **(6)** on treatment with ethylchloroacetate yielded **7** which was hydrolysed to the corresponding carboxylic acid **8**. Refluxing **6** with 2-chloromethyl benzimidazole has yielded **9**. 7-nitro-2-phenyl-3-carboxymethyl-4(3*H*)-quinazolinone **(11)** was synthesised by treatment of 7-nitro-2-phenyl-1,3-benzoxazin-4-one with glycine.



Results and Discussions

Results of antiviral activity (Tab. 2) have clearly indicated that most of the compounds significantly inhibited GMV when mixed with it before inoculation (in vitro) or applied 24 h prior to virus challenge (in vivo). High degree of inhibitory response was observed with **3b** while **3a** was least inhibitory.

It is evident that compounds **2b** and **2c** with p-methyl or chloro substitution at position 3 of the quinazolone moiety significantly inhibited infection of GMV. **3b** having a free amino group exhibited maximum protection against GMV whereas, loss in the inhibitory action was noticed when it was cyclized with CS_2 to **4b**. Marked reduction in virus infectivity was also observed with **5a**.

The considerable inhibition was observed with **9** in vivo as well as in vitro. However, **7** and **8** with the -COOH group and its ester were reduced the virus multiplication rate as well.

In general, virus inhibitory action of these compounds might be associated with the NH_2 group likewise the benzimidazolyl moiety also increased the inhibitory response.

The degree of inhibition of two unrelated and morphologically different RNA viruses (GMV-spherical; SRV-tubular) was variable from compound to compound. All the derivatives have exhibited antiviral activity against infection of GMV but had no effect against SRV. This variation might be due to the morphological variation in virus particles and also the quantity of protein in virions.

We wish to thank the head, Department of Chemistry for providing necessary research facilities, Dr. *H.N. Verma*, head of Plant Virus Laboratory, for antiviral testing, and the Director, Central Drug Research Institute, Lucknow, for spectral and elementary analysis.

Experimental

Melting points: open capillaries (uncorr.); *IR spectra:* Perkin Elmer 177 in KBr. *^{1}H-NMR-spectrum:* in $CDCl_3$ at 100 Mhz. Spectrophotometer. 2-Chloromethyl benzimidazole[6], 3-nitro-4-hydroxybenzaldehyde[7], 7-Chloro-3-aryl-2-mercapto-4(3*H*)-quinazolone **6**[8] and 7-Nitro-2-phenyl-1,3-benzoxazin-4- one **(10)**[9] were prepared following the reported methods.

2-Methyl-3-(4'-methylphenyl)-4(3H)-quinazolone **(1b)**

1a–c were prepared adopting the reported methods[5].

2-(4'-Hydroxy-3'-nitrostyryl)-3-(4'-methylphenyl)-4(3H)-quinazolinone **(2b)**

0.01 mole solution of **1b** in 15 ml of glacial acetic acid and 0.01 mole 4-hydroxy-3-nitro-benzaldehyde were refluxed for 10 h. The reaction mixture was cooled, the solid separated was recrystallised from acetic acid. The physical data of **2a–c** are recorded in Tab. 1.

2-(4'-Hydroxy-3'-aminostyryl)-3-(4'-methylphenyl)4(3H)-quinazolinone **(3b)**

1 g **2b** in 30 ml absol. ethanol was refluxed with addition of 1 ml 99 % hydrazine hydrate, in parts, presence of Raney Ni in traces. The amine was isolated by distilling off the excess of ethanol and triturating the sticky mass with petroleum ether (b.p. 40–60°). **3a–c** thus synthesised are recorded in Tab. 1.

2-(Benzoxazolin-2'-thion-3'-yl-5'-vinyl)-3-(4'-methylphenyl)-4(3H)-quinazolinone **(4b)**

0.003 mole of **3b**, 0.2 g KOH and 0.003 mole (0.22 ml) carbon disulphide in 30 ml ethanol was heated under reflux for 3 h. The filtrate was warmed to 60–70 °C for 30 min and diluted with 30 ml of warm water (60–70°). After treatment with 5 ml of 1:1 (v/v) acetic acid with stirring the product separated as glistening crystals was recrystallised from DMF/methanol. **4a–c** thus synthesised are recorded in Tab. 1.

2-[Benzoxazolin-2'-thion-3'-acetyl-5'-vinyl]-3-(4'-methylphenyl)-4(3H)-quinazolinone **(5b)**

1 g **4b** was refluxed in 10 ml of acetic anhydride with a drop of pyridine for 1 h. It was then cooled and poured slowly on ice cold water with stirring. The white solid obtained, was recrystallised from DMF/methanol. **5a–c** thus prepared are recorded in Tab. 1.

7-Chloro-3-phenyl-2-carbethoxymethylthio-4(3H)-quinazolinone **(7)**

0.01 mole (2.88 g) **6**, 0.01 mole (1.48 g) ethyl chloroacetate and 0.01 mole (1.4 g) anhydrous potassium carbonate in dry acetone was refluxed for 18 h and filtered hot. The solid mass which separated out on cooling was dried and recrystallised from isopropanol.

7-Chloro-3-phenyl-2-carboxymethylthio-4(3H)-quinazolinone **(8)**

It was prepared by refluxing 1.08 g **7** in 5 ml of methanol and 15 ml of 10 % NaOH for 1 h. Excess of methanol was distilled off and the remainder was neutralized with acetic acid. The solid mass thus obtained was dried and recrystallised from acetic acid/methanol. Constants are given in Tab. 1.

7-Chloro-3-phenyl-2[benzimidazolylmethylthio]4(3H)-quinazolinone **(9)**

1.44 g **6**, 0.88 g 2-chloromethyl-benzimidazole and 0.7 g anhydrous K_2CO_3 was refluxed in 25 ml dry acetone for 4 h. Excess of acetone was distilled off, and the pale coloured solid, thus separated on cooling, was dried and recrystallised from methanol.

Tab. 1: *2,3-Disubstituted 4(3H)-quinazolones*

Compound No.	Yield %	m.p. °C	Molecular formula	Calcd. %		Found %	
				C	H	C	H
2a	55	274	$C_{16}H_{11}N_3O_4$	62.1	3.5	62.1	3.1
2b	60	223–225	$C_{23}H_{17}N_3O_4$	69.2	4.2	69.2	4.4
2c	62	235	$C_{22}H_{14}N_3O_4Cl$	62.9	3.3	62.5	3.6
3a	60	182–183	$C_{16}H_{13}N_3O_2$	68.8	4.6	68.5	4.5
3b	65	194–196	$C_{23}H_{19}N_3O_2$	71.7	4.9	71.4	5.2
3c	59	205	$C_{22}H_{16}N_3O_2Cl$	67.7	4.1	68.0	4.2
4a	60	280	$C_{17}H_{11}N_3O_2S$	63.5	3.4	63.9	3.4
4b	70	263–265	$C_{24}H_{17}N_3O_2S$	70.0	4.1	70.0	4.1
4c	65	280	$C_{23}H_{14}N_3O_2ClS$	63.9	3.2	63.7	3.4
5a	70	259	$C_{21}H_{15}N_3O_4S$	62.2	3.7	62.1	3.6
5b	72	280	$C_{26}H_{19}N_3O_3S$	68.9	4.1	68.7	4.1
5c	68	152	$C_{25}H_{16}N_3O_3ClS$	63.2	3.3	63.1	3.6
7	63	119–120	$C_{18}H_{15}N_2O_3Cl$	57.6	3.9	57.5	3.7
8	71	275	$C_{16}H_{11}N_2O_3ClS$	55.4	3.2	55.3	3.2
9	75	250–251	$C_{22}H_{15}N_4OClS$	63.1	3 5	63.0	3.4
11	80	250–251	$C_{16}H_{11}N_3O_5$	59.0	3.3	59.2	3.7

IR(KBr) **3b:** 3100 (NH), 1650 cm^{-1} (C=O); **4b:** 1655 (C=O), 1100 cm^{-1} (C=S); **5b:** 1670 (C=O), 1105 cm^{-1} (C=S); **8:** 1710 (C=O, ester), 1660 cm^{-1} (C=O ring); **10:** 3300 (NH), 1685 cm^{-1} (C=O); **12:** 2900 (OH, carboxylic), 1700 (C=O carboxylic), 1620 cm^{-1} (C=O, ring).

^{1}HNMR ($CDCl_3$): δ (ppm) = **4b:** 5.3 (Hump; J=7Hz, NH), 6.22 (d; J=15Hz, Ph-C<u>H</u>=), 7.27 (d; J=15Hz, N=C(N) C<u>H</u>=) 7.21–8.50 (m, H aromat).

5b: 2.1 (s; J=7Hz, CH_3), 6.3 (d; J=15Hz, PhC<u>H</u>=), 7.29 (d; J=15Hz, N=C(N)-CH=), 7.20–8.6 (m; H aromat.).

7-Nitro-2-phenyl-3-carboxymethyl-4(3H)-quinazolinone **(11)**

0.005 mole (1.34 g) 7-Nitro-2-phenyl-1,3-benzoxazin-4-one and 0.006 mole (0.45 g) glycine was refluxed in 10 ml of pyridine containing 5 ml of water for 5 h. The major portion of pyridine and water was distilled off. The residue was digested with 100 ml 1N-HCl for 2 h on a steambath. The solid thus separated was recrystallised from methanol.

Antiviral activity

Antiviral activity of the 4(3H)-quinazolone derivatives were evaluated, both in vitro as well as in vivo, against Gomphrena mosaic virus (GMV) and Sunnhemp rosette virus (SRV) in C. amaranticolor plants.

The culture of Gomphrena mosaic virus was maintained on Gomphrena globosa L. and Sunnhemp rosette virus on Crotalaria juncea by successive inoculations on healthy hosts. The virus inoculum, in each case, was prepared by grinding fresh leaves showing severe disease symptoms in a sterilized pestle and mortar with distilled water (1 ml/g). The pulp was squeezed through two folds of muslin cloth and the juice was centrifuged at 5000 g for 15 min. Supernatant, thus obtained, was diluted to 1:100 with distilled water and used as virus inoculum.

Tab. 2: *Antiviral activity of 2,3-disubstituted-4(3H)-quinazolones*

Compound No.	Antiviral activity: Percent inhibition of virus infection			
	GMV/CA		SRV/CA	
	in-vivo	in-vitro	in-vivo	in-vitro
2a	39	70	6	10
2b	67	51	19	12
2c	63	65	28	2
3a	25	28	36	15
3b	76	82	15	6
3c	26	47	39	37
4a	38	28	5	32
4b	49	42	12	34
4c	48	51	34	6
5a	72	81	39	15
5b	28	31	36	41
5c	35	46	41	23
7	71	49	30	32
8	70	53	32	47
9	73	67	52	45
11	63	65	28	12

GMV = Gomphrena mosaic virus; SRV = Sunnhemp rosette virus; CA = Chenopodium amaranticolor

The solutions of chemical compounds were prepared by dissolving 2.5 mg compound in 1 ml of ethanol, then the total vol. was made up to 10 ml by adding water. The solutions, thus prepared were termed as "Test-solutions".

For in vitro studies, 1 ml of either of test solutions was mixed with 1 ml of virus inoculum, incubated for 10 min at room temp. (27 °C) and then inoculated on the leaves of C. amaranticolor plants. An equal number of leaves in controls were rubbed with a mixture of virus and water instead of test solutions.

In case of in vivo experiments, the test solutions were applied 24 h prior to virus challenge on to the leaves of C. amaranticolor plants. The control plants were inoculated with a mixture of ethanol and water (1:9). At least four plants with four equal sized leaves were used in each experiment.

All the experiments were performed in an insect free glass house at about 25–30°. Phytotoxic symptoms, if any, were observed throughout the experiments. Local lesions were counted 4 d after virus inoculation. The percent inhibition was calculated by the formula $[C\text{-}T/C] \cdot 100$, where C, is the average number of local lesions on control and T on treated leaves.

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Barbitursäurederivate, 30. Mitt.[1]

Synthese racem. und optisch aktiver basisch substituierter Barbitursäuren[+]

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Durch Kondensation von monoalkylierten Malonestern mit N-monosubstituierten Harnstoffen wurden die 5-monoalkylierten Barbitursäuren **1** erhalten, die zu den 5-Brombarbitursäuren **2** umgesetzt wurden. Aus **2** wurden durch nucleophile Substitution mit Stickstoffbasen die basisch substituierten Barbitursäuren **3–5** hergestellt. Von den 27 synthetisierten Racematen konnten 17 mit Camphersulfonsäure in die Enantiomere gespalten werden.

Derivatives of Barbituric Acid, XXX: Synthesis of Racemic and Optically Active Barbituric Acids Carrying Basic Substituents

Monoalkylated malonates were condensed with *N*-monosubstituted ureas to yield the 5-monosubstituted barbituric acids **1**, which were reacted to the 5-bromobarbituric acids **2**. From **2** the barbituric acids **3–5** having basic substituents were obtained by nucleophilic substitution with *N*-bases. From the 27 racemates obtained, 17 were resolved into the enantiomers with camphersulfonic acid.

Im Gegensatz zu den herkömmlichen Barbitursäuren fanden solche mit heterozyklischen Substituenten in 5-Stellung bisher vergleichsweise wenig Interesse. Die Einführung stickstoffhaltiger Substituenten in 5-Position ergab anfangs pharmakologisch unwirksame Verbindungen[2]. Erst die Darstellung von Barbitursäuren, bei denen das N-Atom eines basischen Substituenten direkt mit dem C-5 verknüpft ist, führte zu pharmakologisch wirksamen Produkten. Eine Reihe von Barbitursäuren dieser Art wurde zwischen 1930 und 1960, vor allem von Gebauer[3][4][5] und Goldhahn[6][7], synthetisiert.

[+] Herrn Prof. Dr. *Engelbert Graf* zum 60. Geburtstag gewidmet.

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