Synthesis and Antifungal Activity of Some New Quinazoline and Benzoxazinone Derivatives

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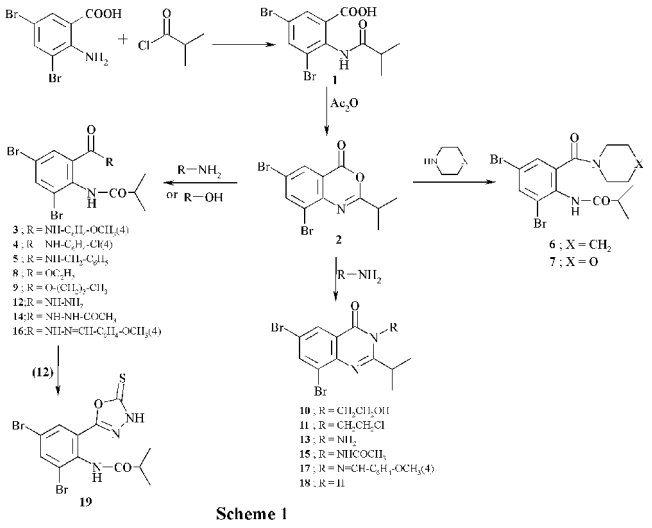
Summary

The hitherto unknown 2-isopropyl-6,8-dibromo-4*H*-3,1-benzoxazin-4-one (**2**) was subjected to condensation with either primary or secondary amines affording the benzamide derivatives (**3–7**), while with alcohols in presence of the base, corresponding esters were obtained (**8** and **9**). Acylation of the hydrazide (**12**) or its cyclized form (**13**) gave (**14–17**). The quinazolinone derivative (**18**) was obtained either when (**12**) was reacted with nitrous acid or via fusion of (**2**) with ammonium acetate. The thione (**20**) which was obtained via reaction of (**18**) with Lawesson's reagent, was subjected to either alkylation yielding (**21–25**) or desulphurization with primary amines affording (**26** and **27**). Treatment of (**18**) as well as (**20**) with a chlorinating agent provided (**29, 30**) and (**28, 29**) mixtures, respectively. Ten of our compounds were examined against *Sclerotium cepivorum* as well as *Botrytis allii* on PDA media. These compounds showed a significant reduction of mycelial growth and scleratia number of these fungi which cause the white rot and neck rot diseases of onion.



Scheme 1

Introduction

The pronounced biological and pharmacological activities of benzoxazinone and quinazolinone derivatives, such as anticonvulsant [1–3], antihistaminic [4], antihypertensive [4,5], analgesic and anti-inflammatory [6,7], antimicrobial [8–11] and antifungal [12], have stimulated these authors to synthesize some new derivatives of these classes of compounds with the hope of obtaining new structures with enhanced potency or of finding new applications.

Also we aimed to incorporate a sterically bulky group such as an isopropyl group in position-2 to detect its role in the nature and ease of reaction of these compounds.

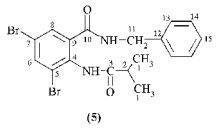
Results and Discussion

Chemistry

The hitherto unknown 6,8-dibromo-2-isopropyl-(4*H*)-3,1-benzoxazin-4-one (**2**) as a key starting compound has been obtained in fairly good yield by cyclization of 3,5-dibromo-2-isobutyroylaminobenzoic acid (**1**) which is obtained by condensation of 3,5-dibromoanthranilic acid with isobutyroyl chloride in pyridine (Scheme 1).

According to Ismail [13] and El-Khamry [8,14] the aminolysis of benzoxazinone (**2**) with primary amines in ethanol provided the expected benzamide derivatives (**3–5**) (Scheme 1). With secondary amines in 1,4-dioxane, benzoxazinone (**2**) yielded the expected products (**6** and **7**). However, when the reaction was carried out in ethanol the unexpected ethyl 3,5-dibromo-2-isobutyroylaminobenzoate (**8**) was obtained as the only product, which means that piperidine or morpholine acts as a base favouring the forma-

Table 1. ^{13}C-NMR of compound (**5**).



(5)

No. of carbon	δ (ppm)	No. of carbon	δ (ppm)
C-1	19.1	C-9	133.8
C-2	33.9	C-10	164.9
C-3	175.2	C-11	42.4
C-4	138.9	C-12	138.9
C-5	119.5	C-13	127.2
C-6	138.8	C-14	128.2
C-7	124.8	C-15	126.7
C-8	130.2		

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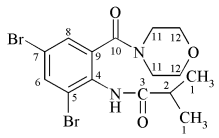
Table 2. ^{13}C-NMR of compound (**7**).



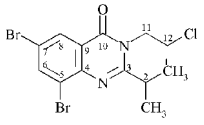
(**7**)

No. of carbon	δ (ppm)	No. of carbon	δ (ppm)
C-1	19.4	C-7	123.4
C-2	35.4	C-8	129.0
C-3	175.9	C-9	132.9
C-4	138.9	C-10	166.2
C-5	119.7	C-11	42.1
C-6	135.9	C-12	66.5

tion of ethoxide ion which promotes ring opening of (**2**) to give the ester (**8**) (Scheme 1). This observation is supported by the reaction of (**2**) with ethanol and/or *n*-butanol in the presence of pyridine as a base to give the esters (**8** and **9**), respectively (Scheme 1). The structures of (**3–9**) have been confirmed by their analytical data as well as spectroscopic data IR, ^{1}H-NMR, MS (Tables 6 and 7) and ^{13}C-NMR data for compounds (**5**) and (**7**) (Tables 1 and 2).

On condensation of **2** with ethanolamine at elevated temperature (*ca.* 170 °C), the expected aminolysis is favoured over ester formation, giving the quinazoline derivative (**10**) which is converted into the corresponding chloro derivative (**11**) by treatment with thionyl chloride (Scheme 1). The structures of (**10**) and (**11**) were established by elemental analysis, IR, ^{1}H-NMR, and MS spectra (Tables 6 and 7), and ^{13}C-NMR data for compound (**11**) (Table 3).

Table 3. ^{13}C-NMR of compound (**11**).

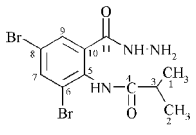


(**11**)

No. of carbon	δ (ppm)	No. of carbon	δ (ppm)
C-1	21.2	C-7	123.9
C-2	32.6	C-8	129.9
C-3	160.9	C-9	128.7
C-4	143.9	C-10	162.3
C-5	119.4	C-11	41.6
C-6	140.9	C-12	45.5

On the other hand, treatment of (**2**) with hydrazine hydrate in ethanolic solution either at room temperature or at 0 °C afforded a mixture of the hydrazide derivative (**12**) and 3-aminoquinazolinone derivative (**13**), while in boiling ethanol or heating both without solvent at *ca.* 170 °C, the cyclized form (**13**) was obtained as a sole product in good yield (Scheme 1).

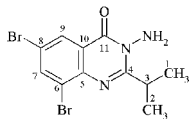
Table 4. ^{13}C-NMR of compound (**12**).



(**12**)

No. of carbon	δ (ppm)	No. of carbon	δ (ppm)
C-1	20.2	C-7	140.8
C-2	20.4	C-8	124.3
C-3	31.6	C-9	128.8
C-4	163.1	C-10	132.9
C-5	138.9	C-11	160.6
C-6	119.6		

Table 5. ^{13}C-NMR of Compound (**13**).



(**13**)

No. of carbon	δ (ppm)	No. of carbon	δ (ppm)
C-1	20.1	C-7	140.2
C-2	21.3	C-8	124.1
C-3	31.5	C-9	128.4
C-4	160.9	C-10	128.9
C-5	143.7	C-11	159.1
C-6	119.1		

Furthermore, boiling of (**12**) in *n*-butanol gave (**13**) in quantitative yield. The structures of (**12**) and (**13**) were confirmed by elemental analysis and spectral data; IR, ^{1}H-NMR, and MS spectra (Tables 6 and 7), beside ^{13}C-NMR for compounds (**12**) and (**13**), (Tables 4 and 5).

The structures of (**12**) and (**13**) were further supported by the following chemical proofs:

- Acetylation of (**12**) and or (**13**) with acetyl chloride gave the corresponding acetyl derivatives (**14**) and (**15**), respectively, in fairly good yield. Also, cyclization of (**14**) by heating at its melting point and/or refluxing with phosphorus oxychloride afforded (**15**) in quantitative yield (Scheme 1).
- Condensation of (**12**) and/or (**13**) with *p*-anisaldehyde yielded the corresponding Schiff's bases (**16**) and (**17**), respectively. Cyclization of (**16**) gave (**17**) quantitatively (Scheme 1).
- Nitrosation [15] of (**12**) and/or (**13**) with nitrous acid at 0 °C afforded the same product 6,8-dibromo-2-isopropylquinazolin-4-one (**18**) (Scheme 1).
- Addition of (**12**) to carbon disulphide in alkaline medium yielded oxadiazole derivative (**19**) (Scheme 1).

Table 6. Characterization data of compounds prepared [a].

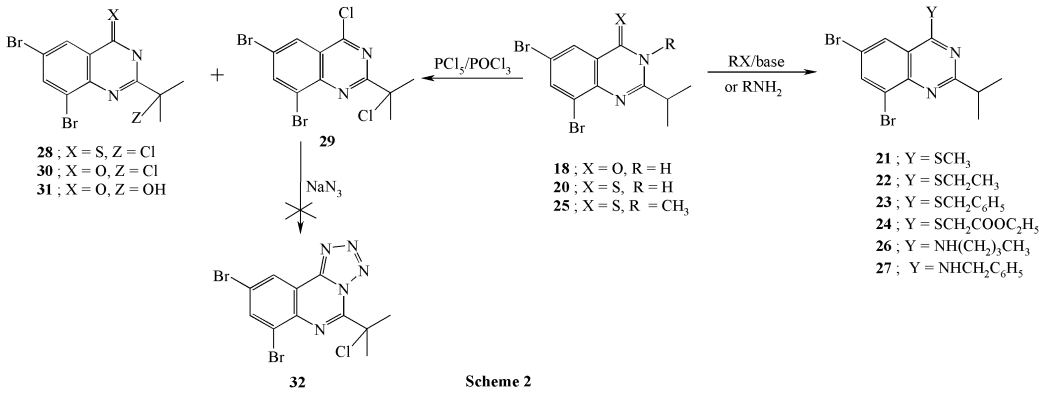
Compd. No.	Mp °C (colour)	Yield % (solvent)	Molecular Formula (M.Wt)	IR cm^{-1} $\nu_{NH,OH}$	$\nu_{C=O}$	$\nu_{C=S}$
1	198–200	85	$C_{11}H_{11}Br_2NO_3$			
	colourless	(E)	(365.02)	3280	1710,1660	–
2	60–62	78				
	pale yellow	(Pa)	$C_{11}H_9Br_2NO_2$ (347.01)	–	1773	–
3	277–278	60	$C_{18}H_{18}Br_2N_2O_3$	3282	1650	–
	colourless	(T)	(470.16)			
4	289–290	76	$C_{17}H_{15}Br_2ClN_2O_2$	3210,3160	1660	–
	colourless	(T+E)	(474.58)			
5	249–250	94	$C_{18}H_{18}Br_2N_2O_2$	3280	1660	–
	colourless	(M)	(454.16)			
6	205–207	82	$C_{16}H_{20}Br_2N_2O_2$	3210,3180	1690	–
	colourless	(Pb)	(432.15)			
7	198–200	85	$C_{15}H_{18}Br_2N_2O_3$	3210,3160	1670	–
	colourless	(Pb)	(434.13)			
8	130–132	75	$C_{13}H_{15}Br_2NO_3$	3220	1720	–
	colourless	(Pc)	(393.07)			
9	98–100	78	$C_{15}H_{19}Br_2NO_3$	3275	1725	–
	colourless	(Pb)	(421.13)			
10	139–140	60	$C_{13}H_{14}Br_2N_2O_2$	3470	1660	–
	colourless	(Pc)	(390.07)			
11	115–117	70	$C_{13}H_{13}Br_2ClN_2O$	–	1650	–
	yellow	(Pb)	(408.52)			
12	160–162	65	$C_{11}H_{13}Br_2N_3O_2$	3320,3280	1665	–
	colourless	(Pb)	(379.05)			
13	139–140	25	$C_{11}H_{11}Br_2N_3O$	3330,3280	1660	–
	pale yellow	(Pa)	(361.04)			
14	259–260	80	$C_{13}H_{15}Br_2N_3O_3$	3220,3180	1660	–
	colourless	(T+E)	(421.09)			
15	198–200	65	$C_{13}H_{13}Br_2N_3O_2$	3470,3210	1680,1660	–
	colourless	(Pb)	(403.07)			
16	280–282	70	$C_{19}H_{19}Br_2N_3O_3$	3250,3180	1670	–
	colourless	(T+M)	(497.18)			
17	160–162	75	$C_{19}H_{17}Br_2N_3O_2$	–	1670	–
	pale yellow	(T+E)	(479.17)			
18	268–270	90	$C_{11}H_{10}Br_2N_2O$	3160	1680	–
	colourless	(E)	(346.02)			
19	238–240	75	$C_{12}H_{11}Br_2N_3O_2S$	3260,3110	1665	1230
	colourless	(T+E)	(421.11)			
20	218–220	92	$C_{11}H_{10}Br_2N_2S$	3170	–	1230
	yellow	(Pb)	(362.08)			
22	60–62	72	$C_{13}H_{14}Br_2N_2S$	–	–	–
	colourless	(Pa)	(390.14)			
23	90–92	63	$C_{18}H_{16}Br_2N_2S$	–	–	–
	colourless	(Pa)	(452.21)			
24	80–82	54	$C_{15}H_{16}Br_2N_2O_2S$	–	1725	–
	colourless	(Pa)	(448.17)			
26	190–192	60	$C_{15}H_{19}Br_2N_3$	3210	–	–
	pale yellow	(T)	(401.14)			
27	170–172	65	$C_{18}H_{17}Br_2N_3$	3160	–	–
	pale yellow	(T)	(435.16)			
28	180–182	45	$C_{11}H_9Br_2ClN_2S$	3120	–	1220
	yellow	(Pb)	(396.53)			
29	150–152	52	$C_{11}H_8Br_2Cl_2N_2$	–	–	–
	pale yellow	(T)	(398.91)			
30	255–257	65	$C_{11}H_9Br_2ClN_2O$	3220	1670	–
	pale yellow	(Pb)	(380.47)			
31	210–212	80	$C_{11}H_{10}Br_2N_2O_2$	br.3350–3300,3210	1670	–
	colourless	(Pb+T)	(362.02)			

E = Ethanol, T = Toluene, M = Methanol, Pa = Petroleum ether 40–60 °C, Pb = Petroleum ether 80–100°C, Pc = pet-ether 60–80 °C.
[a] Elemental analyses were correct to within ±0.4%.

Table 7. ^{1}H-NMR and MS data of prepared compounds.

Compd. no.	^{1}H-NMR (δ in ppm)	MS (*m/z* %)
1[a]	1.22 [d (*J* = 7), 6H], ≈ at 2.65 (m,1H), 7.88 [d (*J* = 2), 1H], 7.97 [d(*J* = 2), 1H] and 9.08 (s, 1H).	–
2[a]	1.32 [d(*J* = 7), 6H], ≈ at 2.91 (m,1H), 8.10 [d(*J* = 2),1H]] and 8.10 [d(*J* = 2), 1H]	–
5[b]	1.1 [d(*J* = 7), 6H], 2.58 (m, 1H), 4.38 (d,2H), 7.29 (m,5H), 7.65 [d(*J* = 2), 1H], 8.05 [d(*J* = 2),1H], 8.80 (t,1H) and 9.55 (s,1H).	[M–H_2O] (436,9.62%), 421 (7.82%), 393 (2.11%), 345 (16.45%), 91 (100%).
7[a]	1.22 [d(*J* = 7), 6H], 2.61 [m, 1H], 3.52 (m, 4H), 3.82 (m, 4H), 7.27 [d(*J* = 2), 1H], 7.68 [d(*J* = 2), 1H] and 8.28 (s_{br}., 1H).	$[M+2]^+$ (434,23%), 348 (83.71%), 277 (33.68%), 87 (100%)
8[a]	1.20 [d(*J* = 7), 6H], 1.45 [t (*J* = 7), 3H], 2.61 [m, 1H], 4.35 [q(*J* = 7), 2H], 7.86 [d(*J* = 2), 1H], 7.93 [d(*J* = 2), 1H] and 8.31 (s_{br}. 1H)	–
9[a]	0.97 [t(*J* = 7), 3H], 1.22 [d(*J* = 7), 6H], 1.45 (m, 2H), 1.77 (m, 2H), 2.61 (m, 1H), 4.27 [t(*J* = 7), 2H], 7.88 [d(*J* = 2), 1H], 7.93 [d(*J* = 2), 1H] and 8.33 (s_{br}., 1H).	–
10[a]	1.40 [d(*J* = 7), 6H], 2.25 ($s_{br.}$, 1H), 3.38 (m,1H), 3.96 [t(*J* = 5.4), 2H], 4.36 [t(*J* = 5.4), 2H], 8.09 [d(*J* = 2), 1H] and 8.31 [d(*J* = 2), 1H].	$[M]^{\cdot+}$ (390,18%), 347 (100%), 331 (37.67%).
11[a]	1.40 [d(*J* = 2.6), 6H], 3.27 (m, 1H), 3.85 [t(*J* = 2.6), 2H], 4.48 [t(*J* = 2.4), 2H], 8.10 [d(*J* = 1), 1H] and 8.31 [d(*J* = 1), 1H].	$[M]^{\cdot+}$ (408,10%), 373 (100%), 331 (20%).
12[a]	1.39 [d(*J* = 2.8), 6H], 3.72 (m, 1H), 4.85 (s, 2H), 8.10 [d(*J* = 2), 1H], 8.25 (s, 1H), 8.36 [d(*J* = 2), 1H].	–
13[a]	1.36 [d(*J* = 2.8), 6H], 2.30 (s, 2H), 3.18 (m, 1H), 8.12 [d(*J* = 2), 1H], 8.38 [d(*J* = 2), 1H].	$[M]^{\cdot+}$ (361,25%), 346 (35%), 333 (100%).
14[b]	1.11 [d(*J* = 8.6), 6H], 1.91 (s, 3H), 2.65 [m, 1H], 7.67 [d(*J* = 2), 1H], 8.10 [d(*J* = 2), 1H] and at 9.50, 9.97 and 10.08 (3NH).	–
17[a]	1.36 [d(*J* = 7.4), 6H], 3.45 [m, 1H], 3.90 (s, 3H), 7.01 [d(*J* = 8), 2H], 7.86 [d(*J* = 8), 2H], 8.10 [d(*J* = 2), 1H], 8.40 [d(*J* = 2)] and 8.74 (s, 1H).	$[M]^{\cdot+}$ (479,3%), 346 (39.06 %), 331 (100%).
18[a]	1.45 [d(*J* = 7), 6H], 3.05 [m, 1H], 8.15 [d(*J* = 2), 1H], 8.35 [d(*J* = 2), 1H] and 11.75 (s_{br}. 1H).	$M^{\cdot+}$ (346, 40%), 331 (100%), 316 (15%).
19[b]	1.12 [d(*J* = 7), 6H], 2.65 [m, 1H], 7.98 [d(*J* = 2, 1H), 8.25 [d(*J* = 2), 1H] and 9.95 (s, 1H).	$M^{\cdot+}$ (421,13%), 350(52%), 320 (24%), 277(56%), 101 (13%), 71 (100%).
20[a]	1.45 [d(*J* = 7), 6H], 3.05 [m, 1H], 8.16 [d(*J* = 1.2), 1H], 8.77 [d(*J* = 1.2), 1H] and 11.37 (s_{br}., 1H).	$[M+2]^+$ (364,32%), 362(32%), 347(100%), 319(4.1%).
21[a]	–	$[M]^{\cdot+}$ (376,56%), 361(100%).
22[a]	1.8 (m, 9H), 3.8 [m, (1H, 2H) and 8.2 (dd, 2H)	–
23[a]	1.46 [d(*J* = 7), 6H], 3.35 [m, 1H], 4.65 (s, 2H), ≈ at 7.38 (m, 5H) and 7.14 (dd, 2H).	–
24[a]	1.7 (m, 9H), 3.35 [m, 1H], 4.20 (s, 2H), 4.40 (q, 2H) and 8.20 (dd, 2H)	–
25	–	$[M]^{\cdot+}$ (376,0.4%), 361 (11%), 345 (100%).
26[a]	0.98 [t(*J* = 7), 3H], 1.44 (m, 8H), 1.66 (m, 2H), 3.13 [m, 1H], 3.69 [q(*J* = 7), 2H], 5.62 (s_{br}., 1H), 7.76 (d(*J* = 2), 1H), 8.07 [d(*J* = 2), 1H].	$[M+2]^+$ (403,19%), $[M]^{\cdot+}$ (401, 36%), 386(100%), 330(66%)
27[a]	1.36 [d(*J* = 7), 6H], 3.17 [m, 1H], 4.88 (d, 2H), 5.87 ($s_{br.}$, 1H), 7.37 (m, 5H), 7.76 [d(*J* = 2), 1H] and 8.09 [d(*J* = 2), 1H].	$[M+2]^+$ (437,15.7%), $[M]^{\cdot+}$ (45.7%), 329(2.4%), 106 (46.6%), 91(100%).
28[a]	2.06 (s, 6H), 8.16 [d(*J* = 2), 1H], 8.76 [d(*J* = 2), 1H] and 11.01 ($s_{br.}$, 1H).	–
29[a]	2.17 (s, 6H), 8.3 [d(*J* = 2), 1H], 8.35 [d(*J* = 2), 1H]	$[M]^{\cdot+}$ (399,11%), 364 (4.5%), 333 (100%).
30[b]	2.02 (s, 6H), 8.18 [d(*J* = 2), 1H], 8.35 [d(*J* = 2), 1H] and 12.77 ($s_{br.}$, 1H).	$[M]^{\cdot+}$ (380, 12%), 345 (100%), 316 (17.4%).
31[b]	1.48 (s, 6H), 8.14 [d(*J* = 2), 1H], 8.21 [d(*J* = 2), 1H]. The signals of NH and OH are interacted with the solvent.	$[M]^{\cdot+}$ (362, 39%), 344 (100%), 277 (69.6%).

a = $CDCl_3$, b = DMSO-d_6



Scheme 2

The structures of (**14–19**) were confirmed by correct elemental analysis and spectroscopic data (Tables 6 and 7).

Furthermore, fusion of (**2**) with ammonium acetate (at *ca.* 170 °C) gave the quinazolinone derivative (**18**) (Scheme 1).

The structure of (**18**) was confirmed, beside the microanalysis and spectral data, by the following chemical proofs:

– Treatment of (**18**) with Lawesson's reagent gave [16] the corresponding 6,8-dibromo-2-isopropylquinazoline-4-thione (**20**), which reacted with alkyl halides in the presence of base to give *S*-alkyl derivatives (**21–24**) rather than *N*-alkyl derivatives. Only in the case of methyl iodide was a mixture of *S*-alkyl (**21**) and *N*-alkyl derivatives (**25**) (2:1 ratio) formed (Scheme 2). The constitution of the mixture has been detected from the ^{1}H-NMR data which exhibit signals for two isopropyl methyl groups at δ 1.41 (d) and δ 1.42 (d), two isopropyl CH protons at δ 3.25 (m) and δ 3.32 (m), for S-CH_3 at δ 2.72 (s), for N-CH_3 at δ 3.66(s) and for different four aromatic protons at δ 8.09 (d), δ 8.14 (d), δ 8.18 (d) and δ 8.33 (d), respectively.

Furthermore, desulphurization of (**20**) with primary amines such as *n*-butylamine and benzylamine afforded the corresponding 4-*N*-butyl or benzylamino quinazoline derivatives (**26** and **27**), respectively (Scheme 2).

On the other hand, chlorination of the thione (**20**) with a mixture of $POCl_3$/PCl_5 afforded a mixture of 2-(2′-chloro-2′-propyl)-6,8-dibromoquinazoline-4-thione (**28**) and 4-chloro-2(2′-chloro-2′-propyl)-6,8-dibromoquinazoline (**29**) (Scheme 2).

Chlorination of quinazolinone (**18**) with $POCl_3$/PCl_5 in a molar ratio of 1:1 yielded only the monochloro derivative (**30**) (Scheme 2), while, when the reaction was carried out in an excess of $POCl_3$/PCl_5, the dichloro derivative (**29**) was obtained as sole product (Scheme 2).

The structures of (**20–30**) were confirmed by correct elemental analysis as well as IR, ^{1}H-NMR, and MS (Tables 1 and 2). The structure of both the monochloro derivative (**30**) and the dichloro derivative (**29**) were further supported by the following sequence of chemical proofs:

– Reaction of (**30**) with excess $POCl_3$/PCl_5 mixture afforded the dichloro derivative (**29**) (Scheme 2).

– Hydrolysis of (**30**) with boiling dilute Na_2CO_3 solution yielded the corresponding tertiary alcohol (**31**) (Scheme 2).

– Reaction of (**29**) with NaN_3 in acetic acid gave the unexpected monochloroquinazolinone (**30**) instead of the tetrazoloquinazoline (**32**) (Scheme 2). The reaction probably proceeds by replacement of chlorine atom at C_4 by an azido group which can be replaced as a good leaving group [17] by a hydroxyl group during work-up of the reaction.

Biological Activity

Fungicides are still the most effective way to control plant diseases. The search for new chemicals to control onion white rot disease (caused by *S. cepivorum*) and onion neck rot disease (caused by *B. allii*) is one of approaches to control these serious diseases. Therefore, the effect of these new benzoxazinone and quinazolinone derivatives were screened at different concentrations.

Quinazolinone and benzoxazinone derivatives varied greatly in their effect on mycelial growth and sclerotia formation of *S. cepivorum* (Table 8). Derivatives **22** and **9** had the greatest growth reduction effect on *S. cepivorum*, exhibiting 68–88% and 67–77% reduction of fungal growth, respectively, but slightly decreasing the number of sclerotia at 20 ppm concentration. On the other hand, derivatives **17** and **31** were the most inhibitory to sclerotia formation, exhibiting 57–65% and 40–39% reduction in number of sclerotia, respectively, and a moderate reduction on fungus growth. The other examined samples exhibited lower effect on growth and sclerotia formation.

The derivatives generally reduced the growth of *S. cepivorum* more when their concnetration was raised from 10 to 15 ppm, but a non-similar effect was detected when the concentration increased to 20 ppm, which may be due to a stage of toxicity reverse phenomenon that appear in some specific concentrations of fungicides [18]. This phenomenon was detected before with dithiocarbamate and was attributed to inhibition of some biological constituents by fungicide as histidine, cystine, and thiolactic acid [19].

Quinazolinone and benzoxazinone derivatives also reduced the growth of *B. allii* (Table 9). The fungus is greatly affected by derivative **29** followed by derivative **31** exhibiting 50–0% and 41–11% reduction of fungal growth respectively, at 20 ppm concentration. Other derivatives were less effective.

Experimental

Melting points reported are uncorrected. IR spectra were recorded on Pye-Unicam SP 1200 spectrophotometer using the KBr wafer technique. The ^{1}H-NMR were determined on a Varian Gemini 200 MHz, Bruher AC-200

Table 8. Effect of benzoxazinone and quinazolinone derivatives on mycelial growth and number of sclerotia of *S. cepivorum*.

Treatment compound	Mycelial growth (cm) ppm 10	15	20	Means	Number of sclerotia 10	15	20	Means
22	4.5	2.8	2.8	3.3	57.4	82.8	107.5	82.5
7	2.7	3.8	2.9	3.1	87.5	85.3	92.8	62.2
31	5.4	4.8	4.6	4.9	26.3	26.0	85.8	46.0
29	6.2	5.6	5.0	5.6	46.8	38.3	66.0	50.3
9	8.0	7.5	5.2	6.9	62.0	74.1	11.0	49.0
20	8.1	6.3	5.7	6.7	76.4	57.8	73.3	69.1
19	7.3	6.9	7.8	7.3	75.5	47.4	60.5	61.1
23	8.8	8.4	7.5	8.2	76.9	74.9	32.3	61.3
28	7.5	7.3	7.5	7.4	84.4	76.6	49.4	70.1
17	9.0	8.8	8.3	8.7	28.6	26.0	16.1	23.5
Control	9.0	9.0	9.0	9.0	97.3	97.3	97.3	97.3
Means	6.9	6.4	6.0		65.3	62.0	62.9	
L.S.D. 5% Treatment			0.87			7.83		
L.S.D. 5% Concentration			0.45			N.S		
L.S.D. 5% T. x Conc.			N.S.			13.56		

Table 9. Effect of benzoxazinone and quinazolinone derivatives on mycelial growth of *B. allii*.

Treatment compound	Mycelial growth (cm) ppm 10	15	20	Means
29	5.2	5.2	4.5	4.9
31	6.1	6.0	5.3	5.8
20	6.9	5.8	6.0	6.2
9	7.5	6.8	5.8	6.7
28	6.8	7.1	7.1	7.0
19	6.8	7.3	7.1	7.0
22	7.8	7.0	6.8	7.2
23	8.0	7.4	6.8	7.4
7	8.4	7.8	7.1	7.7
17	8.5	7.6	7.2	7.7
Control	9.0	9.0	9.0	9.0
Means	7.2	6.8	6.2	
L.S.D.5% Treatment		0.43		
L.S.D.5% Concentration		0.22		
L.S.D.5% T. x Conc.		0.74		

MHz using TMS as internal standard (chemical shifts in δ-scale). The mass spectra were determined using HP model MS-5988 at electron energy 70 eV.

Synthesis of the Compounds

*3,5-Dibromo-N-isobutyroylanthranilic Acid (**1**)*

To a solution of 3,5-dibromoanthranilic acid (0.01 mol) in anhydrous pyridine (50 mL), isobutyryl chloride (0.02 mol) was added dropwise at room temperature with stirring for 30 min; then the reaction mixture was heated on a water bath for 5 h. After cooling, the reaction mixture was poured on ice cold hydrochloric acid. The produced mass was filtered, washed with water, and crystallized to give (**1**).

*6,8-Dibromo-2-isopropyl-(4H)-3,1-benzoxazin-4-one (**2**)*

A mixture of (**1**) (0.01 mol) and acetic anhydride (50 mL) was heated on a water bath for 5 h. The solid formed after removal of excess acetic anhydride was triturated with petroleum ether 40–60 °C and crystallized to give (**2**).

*3,5-Dibromo-2-isobutyroylamino-N-arylbenzamides (**3–5**)*

A mixture of (**2**) (0.01 mol) and primary amines, namely *p*-anisidine, *p*-chloroaniline, and benzylamine (0.01 mol), in ethanol (30 mL) was refluxed for 3 h. The solid separated after concentration of ethanol was filtered and crystallized.

*N-[3,5-Dibromo-2-isobutyroylaminobenzoyl]piperidine and Morpholine (**6&7**)*

A mixture of (**2**) (0.01 mol) and secondary amines, namely piperidine and morpholine (0.01 mol), in 1,4-dioxane (30 mL) was refluxed for 12 h. The solid separated after concentration of the solvent was collected and crystallized to give (**6** & **7**).

*Ethyl 3,5-Dibromo-2-isobutyroylaminobenzoate (**8**)*

A mixture of (**2**) (0.01 mol) and secondary amines, namely piperidine and morpholine (0.01 mol), in ethanol (30 mL) was refluxed for 3 h. The solid separated after concentration of ethanol was filtered and crystallized to give the same product (**8**).

*Ethyl 3,5-Dibromo-2-isobutyroylaminobenzoate (**8**) and n-Butyl 3,5-Dibromo-2-isobutyroylaminobenzoate (**9**)*

A mixture of (2) (0.01 mol) and ethyl alcohol or *n*-butyl alcohol (50 mL) in pyridine (1 mL) was refluxed for 3 h, the solid formed after concentration of the solvent was crystallized to give (**8** & **9**) respectively.

*6,8-Dibromo-3-(2′-hydroxyethan-1′-yl)-2-isopropylquinazolin-4-one (**10**)*

A mixture of (**2**) (0.01 mol) and ethanolamine (0.01 mol) was heated for 5 h. After cooling, the solid mass formed was treated with petroleum ether 60–80 °C to give (**10**).

*3-(2′-Chloroethan-1′-yl)-6,8-dibromo-2-isopropylquinazolin-4-one (**11**)*

A mixture of (**10**) (1 g) and thionyl chloride (20 mL) was refluxed on a water bath for 2 h. The solid formed after distillation of excess thionyl chloride was crystallized to give (**11**).

*3,5-Dibromo-2-isobutyroylaminobenzoyl Hydrazine (**12**) and 3-Amino-6,8-dibromo-2-isopropylquinazolin-4-one (**13**)*

A mixture of (**2**) (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (30 mL) was stirred at room temperature for 30 min. The solid formed while stirring was filtered and boiled with pet. ether 40–60 °C to give (**13**) and the

remaining solid was crystallized to give (**12**), which can be cyclized to (**13**) by refluxing in *n*-butanol for 12 h. Also, compound (**13**) can be obtained by fusion of (**2**) with hydrazine hydrate at 160–170 °C for 5 h.

*N-Acetyl-N′-(3,5-dibromo-2-isobutyroylamino)benzoyl Hydrazine (***14***) and 3-Acetylamino-6,8-dibromo-2-isopropylquinazolin-4-one (***15***)*

A mixture of (**12** or **13**) (0.01 mol) and acetyl chloride (20 mL) was refluxed on a water bath for 6 h. The solid formed while heating was collected, washed with petroleum ether 40–60 °C and crystallized to give (**14**) and (**15**) respectively. Compound (**14**) can be cyclized to (**15**) either by heating above its melting point for 2 h. or by refluxing with phosphorus oxychloride (10 mL) on water bath for 24 h.

*N-(3′,5′-Dibromo-2′-isobutyroylamino)benzoyl-4-methoxybenzaldehyde Hydrazone (***16***) and 6,8-Dibromo-3-(4′-methoxybenzyliminio)-2-isopropyl-quinazolin-4-one (***17***)*

A mixture of (**12** or **13**) (0.01 mol) and *p*-anisaldehyde (0.01 mol) in ethanol (50 mL) was refluxed for 6 h. The solid formed while heating was collected and crystallized to give (**16**) and (**17**) respectively. Compound (**16**) can be cyclized to (**17**) either by heating with phosphorus oxychloride (l0 mL) on water bath for 24 h or by fusion at 280 °C for 2 h.

*6,8-Dibromo-2- isopropylquinazolin-4-one (***18***)*
Procedure (A)

A mixture of (**2**) (0.01 mol) and ammonium acetate (0.04 mol) was fused at 160 °C for 6 h. After cooling the solid mass formed was triturated with warm water, filtered, washed with water, and crystallized to give (**18**) in 90% yield.

Procedure (B)

To a solution of (**12** or **13**) (1 g) in concentrated hydrochloric acid (30 mL) at 0 °C, cold sodium nitrite solution (1 g/10 mL of water) was added dropwise within 15 min, with stirring. The reaction mixture was stirred at 0 °C for 3 h. The solid produced was filtered, washed with water, and crystallized to give (**18**) in 80% yield which was identified by comparison of mp, m.mp, TLC, and spectral data with those of a sample prepared by the previous method.

*5-(3′,5′-Dibromo-2′-N-isobutyroylamino)phenyl-1,3,4-oxadiazole-2-thione (***19***)*

To a solution of (**12**) (0.01 mol) in ethanol (50 mL) containing KOH (1 g), carbon disulphide (20 mL) was added dropwise at room temperature within 30 min. The reaction mixture was refluxed on a water bath for 10 h. The solvent was removed and the residue was diluted with cold water and neutralized with concentrated hydrochloric acid. The solid separated was filtered washed with water and crystallized to give (**19**).

*6,8-Dibromo-2-isopropylquinazolin-4-thione (***20***)*

A mixture of (**18**) (0.01 mol) and Lawesson's reagent (0.005 mol) in dry toluene (50 mL) was refluxed for 6 h. The solid formed after concentration of the solvent was collected and crystallized to give (**20**).

*6,8-Dibromo-4-S-alkylthia-2-isopropylquinazolines (***21–24***) and 6,8-Dibromo-3-N-methyl-2-isopropylquinazolin-4-thione (***25***)*

To a solution of (**20**) (0.01 mol) in dry acetone (30 mL) in presence of sodium carbonate (1 g), methyl iodide, ethyl bromide, benzyl chloride, or ethyl bromoacetate (0.01 mol) was added, then the reaction mixture was refluxed on a water bath for 12 h. The solid formed after evaporation of the solvent was collected, washed with warm water, dried and crystallized from petroleum ether 40–60 °C to give unseparated mixture of (**21**) and (**25**) as colourless crystals in 55% yield (in case of methyl iodide) and (**22**–**24**).

*4-N-(n-Butylamino)-6,8-dibromo-2-isopropylquinazoline (***26***) and 4-N-(Benzylamino)-6,8-dibromo-2-isopropylquinazoline (***27***)*

A mixture of (**20**) (0.01 mol) and *n*-butylamine or benzylamine (0.01 mol) was heated at 160 °C for 1 h. The solid formed after cooling is treated with toluene to give (**26**) or (**27**).

*2-(2′-Chloro-2′-propyl)-6,8-dibromquinazolin-4-thione (***28***) and 4-Chloro-2-(2′-chloro-2′-propyl)-6,8-dibromoquinazoline (***29***)*

A mixture of (**20**) (1 g), phosphorus oxychloride (20 mL) and phosphorus pentachloride (l g) was heated on a water bath for 24 h. After cooling, the reaction mixture was boiled with petroleum ether 80–100 °C to give (**28**), the remaining residue was crystallized to give (**29**), which can be obtained by heating compound (**18**) with a mixture of phosphorus oxychloride (20 mL) and phosphorus pentachloride (1 g) on a water bath for 24 h. Refluxing compound (**29**) and thiourea in ethanol for 5 h. gave (**28**) in 65% yield.

*2-(2′-Chloro-2′-propyl)-6,8-dibromoquinazolin-4-one (***30***)*

A mixture of (**18**) (0.01 mol), phosphorus oxychloride (0.0l mol), and phosphorus pentachloride (0.01 mol) was heated on a water bath without solvent or refluxed in dry toluene for 24 h. After cooling, the reaction mixture was treated with petroleum ether 80–l00 °C or the solvent (dry toluene) was concentrated and treating the solid mass formed with petroleum ether 80–100 °C to give (**30**).

*2-(2′-Chloro-2′-propyl)-6,8-dibromoquinazolin-4-one (***30***)*

A mixture of (**29**) (0.01 mol) and sodium azide (0.01 mol) in glacial acetic acid (30 mL) was refluxed for 8 h. After cooling the reaction mixture is poured in ice cold water, the solid formed is filtered, washed with water, dried and crystallized from petroleum ether 80–l00 °C to give (**30**) in 80% yield which was identified by comparison of mp, m.mp, TLC, and spectral data with those of a sample prepared by the previous method

*Conversion of (***30***) to (***29***)*

A mixture of (**30**) (1 g) , phosphorus oxychloride (20 mL), and phosphorus pentachloride (1 g) was heated on a water bath for 24 h. After cooling the reaction mixture was boiled with toluene to give (**29**) in 65% yield which was identified by comparison of mp, m.mp, TLC, and spectral data with those of a sample prepared by the previous method.

*6,8-Dibromo-2-(2′-hydroxy-2-propyl)quinazolin-4-one (***31***)*

A mixture of (**30**) (1 g), sodium carbonate (30 mL,10%) was, refluxed for 5 h. The solid formed after neutralization with nitric acid is filtered. washed with water, dried, and crystallized to give (**31**).

Experimental Determination of Biological Activity

Quinazolinone and benzoxazinone derivatives listed in Tables 8 and 9 were added to PDA medium at concentrations 10, 15, 20 ppm and hand shaken before plating. Plates were incubated with 0.5 cm diameter discs of 10 days-old PDA culture of *S. cepivorum*. Plates were incubated at 20 °C till the fungus growth filled up the whole space of the control plates, then diameters of mycelial growth were recorded in the other plates.

Numbers of sclerotia were microscopically counted on 0.5 cm diameter discs of treatment cultures after three weeks incubation. The same technique was applied to determine sensitivity of *B. allii* growth for the above-mentioned treatments.

The experiments were designed complete randomized with factorial arrangement. Data were statistically analyzed by F-test, and LSD used to verify between treatments.

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