Available online at www.elixirpublishers.com (Elixir International Journal)

Applied Chemistry

Elixir Appl. Chem. 69 (2014) 22830-22833

ISSN: 2229-712X

Synthesis and Study of Some New Substituted Quinazolinone Derivatives as Fungicides

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ARTICLE INFO

Article history:
Received: 8 October 2013;
Received in revised form:
19 March 2014;
Accepted: 29 March 2014;

Keywords
Quinazolinone,
Fungicidal,
Oryzae.

ABSTRACT

A number of 5-Phenyl-1,2,4-triazolo[4,3-a]-quinazolin-6-ones(3), 3-(2,4-dichlorophenoxymethyl)-1,2,4-triazolo-[4,3-a]-quinazolin-6-ones(4) and 5-phenyl-3-mercapto - 1,2,4-triazolo-[4,3-a] -quinazolin-6-ones (5). These title compounds have been prepared by reaction of 2-hydrazino-3-phenyl-4-quinazolone (2) with formic acid, methoxy phenyl acetic acids and carbon disulphide respectively. These compounds have been evaluated for their fungicidal activity against Pyricularia oryzae, Pseudopernospora cubensis, Sphaeotheca fuliginea and Phytopthora infestans at 500 and 100 ppm.

Introduction

Quinazolone and its derivatives have been associated with diverse biological activities like hypnotic[1], anticonvulsant[2], CNS depresent[3], pesticidal[4] and antibacterial[5,6]. The activity is due to presence of a pyrimidine ring[7,8] and a cyclic >C=O function in nitrogen containing heterocycles[9]. Likewise various 1, 2, 4-triazole derivatives have showed varied biocidal activities [10-20]. The aryloxy methyl moiety at 3 position is an important structural feature for biological activities[21-24].

Since SH function is an important toxophore like phenol function and as it is placed adjacent to N-atom, so it will work as ligand to chelate with essential metal which fungus needs in its metabolism results in the destruction of the fungus[25].

Therefore it is thought of interest to combine either two or three of the above mentioned biolabile rings together in a molecular framework to see the additive effect of these rings towards the biological activities. The investigation was found to be of further interest because of compactness and planarity of such ring systems may be an additive factor for enhancing activities as it does with pesticidal, herbicidal, fungicidal, nematicidal, rodenticidal and inflammation inhibitory activities.

The required quinazolones (1) and (2) were prepared following the literature method[26,27]. Compounds (3) ,(4) and (5) were prepared by the reaction *of 2-hydrazino-3-phenyl-4-quinazolone (2) with formic acid, methoxy phenyl acetic acids and carbon disulphide respectively*. The details of different compounds (3), (4) and (5) were given in Scheme-I and Table-I.

Materials and method-

Procedure for one typical case for each step has been discussed. Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded in KBr on a Perkin – Elmer 881 Spectrophotometer (ν_{max} in cm^{-1}), ^1H NMR spectra in DMSO-d6 on a Perkin-Elmer R-32(400 MHz) Spectrophotometer using TMS as internal reference (chemical shifts in δ, ppm).

2-Mercapto-3-phenyl-4-quinazolone (1a) –

This compound was prepared according to the reported method[19] by refluxing a mixture of anthranilic acid (0.01M) and phenyl isocynate (0.01 M) in methanol for 5 hours. The solvent was removed and reaction mixture was poured into ice cold water. The solid mass thus precipitated was filtered, washed, dried and re-crystallized from aqueous ethanol, mp 183^0C, yield 74%.

Other compounds of this type were prepared similarly and their melting points were recorded (R=H, 183^0C; 3, 5-Br_2, 199^0C; 2, 4-Cl_2, 207^0C)

2-Hydrazino-3-phenyl-4-quinazolone (2a) –

This compound was prepared according to the reported method[20]. A mixture of 2-mercapto-3-phenyl-4-quinazolone (1a) (0.01 M), and hydrazine hydrate (0.01M) in methanol (100 ml) was refluxed for 4 hours. The solvent was removed and reaction mixture was poured into water. The solid thus obtained was filtered, washed, dried and re-crystallized from aqueous ethanol. mp 113^0C, yield 66%.

Other compounds of this type were prepared similarly and their melting points were recorded (R=H, 113^0C; 3, 5-Br_2, 141^0C; 2, 4-Cl_2, 129^0C)

5-Phenyl-1,2,4-triazolo[4,3-a] quinazolin-6-ones (3a)-

A mixture of 2a (0.01M) and formic acid (0.015M) was refluxed in benzene for 4 hours. The reaction mixture was cooled to obtain the desired product which was dried and re-crystallized from aqueous ethanol.

mp 214^0C, yield 62%.

Analysis: $C_{15}H_{10}N_4O$

Calcd: C 68.99; H 3.52; N 20.99 %.

Found: C 68.70; H 3.82; N 21.37%.

IR(KBr):1695(>C=O);1665,1646(>C=N);
1554,1540,1482(Aromatic ring); 1147,1080 (C-N-C)

^{1}HNMR: 7.4-8.0(m, 9H, ArH+1H at C_3).

Other compounds of this type were prepared similarly and recorded in Table-1

3-(2,4-Dichlorophenoxymethyl)-1,2,4-triazolo[4,3-a]quinazolin-6-ones(4a)-

A mixture of 2a (0.01M) and 2,4-dichlorophenoxy acetic acid (0.01M) was refluxed in methanol for 3 hours. The solvent was removed and reaction mixture was poured into water. The solid thus obtained was filtered, washed, dried and re-crystallized from aqueous ethanol.

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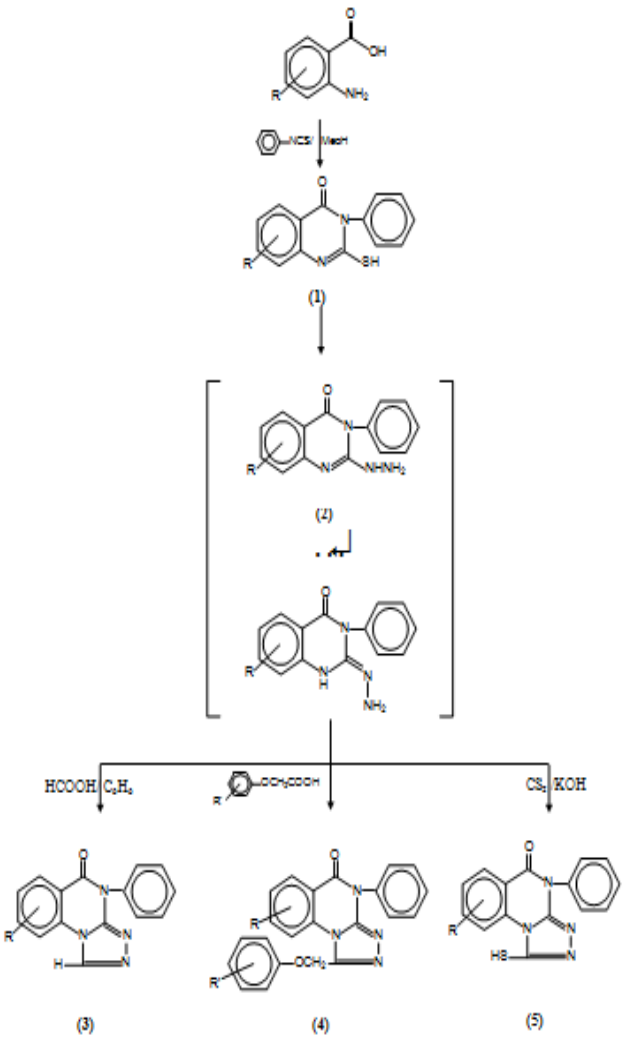
mp187^{0}C, yield 72%.
Analysis: $C_{22}H_{14}N_4O_2Cl_2$
Calcd: C 60.42; H 2.98; N 12.52 %.
Found: C 60.55; H 3.21; N 12.84%.
IR(KBr):1692(>C=O); 1653 (>C=N); 1531,1488,1407(Aromatic ring); 1197 (C-N-C);790,760 (C-Cl)
^{1}HNMR: 4.3 (s, 2H, CH_2) ;7.5-8.2(m, 12H, ArH).
Other compounds of this type were prepared similarly and recorded in Table-1

5-Phenyl-3-mercapto-1,2,4-triazolo[4,3-a] quinazolin-6-ones (5a)-

A mixture of 2a (0.01M), carbon disulphide(0.01M) and potassium hydroxide(0.02M) was refluxed in methanol for 4 hours. The solvent was removed and reaction mixture was cooled, water was added to the residue and acidified with dil HCl to precipitate the solid mass which was filtered, washed, dried and re-crystallized from aqueous ethanol.
mp183^{0}C, yield 70%.
Analysis: $C_{15}H_{10}N_3OS$
Calcd: C 60.97; H 3.09; N 8.86 %.
Found: C 61.22; H 3.04; N 19.05%.
R(KBr):1695(>C=O);1622(>C=N);1552,1498,1477(Aromatic ring);1213(>C=S); 1164 (C-N-C)
^{1}HNMR:7.5-8.1(m, 10H, ArH +SH).
Other compounds of this type were prepared similarly and recorded in Table-1

Scheme 1



Evaluation of fungicidal activity-

The anti fungal activity was evaluated by agar plate technique against *Pyricularia oryzae, Pseudopernospora cubensis, Sphaeotheca fuliginea* and *Phytopthora infestans* at concentrations 500 ppm and 100 ppm. The replications in each case was three. On the basis of growth recorded on 7th day of incubation the fungicidal activity of test compounds was calculated in terms of present inhibition of mycelial growth using the following formula.

$$\text{Present inhibition of mycelial growth} = \frac{dc - dt}{dc} \times 100$$

Where dc = Average diameter growth of the colony in control sets on 7th day of incubation.
dt = Average diameter growth of the colony in treatment set on 7th day of incubation.
Diameter growth=apparent diameter of the colony–diameter of colony of the inoculums

Results and discussion

It is evident from the activity data that the all of the tested compounds have significant fungitoxicity at 500 ppm against all the fungi but their toxicity decreased considerably at lower concentration, although compounds having serial number 3b, 3c, 4a, 4b, 4c,, 4e, 4f, 5a, 5b, 5c, 5d, 5e and 5f show greater anti fungal activity against all the organisms but the result are very spectacular except for compounds 4f.

It is also evident from the fungicidal screening data of the tested compounds showed that compound having 4-Cl chemical species was more effective than other. The most active compounds are 3b, 3c, 4a, 4c, 4e, 5b, 5c, 5d, 5e and 5f (>85%) at 500ppm.

Acknowledgements-

The authors are thankful to Principal, Shibli National College, Azamgarh for providing necessary laboratory facilities and Director RSIC, CDRI, Lucknow for IR and NMR spectral analysis.

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Table 1. Characterization data of the compounds (3), (4) and (5)

Compd	R	R'	Mp ^0C	Yield (%)	Mol. Formula	Analysis					
						Carbon (%)		Hydrogen (%)		Nitrogen (%)	
						Found	Calcd	Found	Calcd	Found	Calcd
3a	H	-	214	62	$C_{15}H_{10}N_4O$	68.99	68.70	3.52	3.82	20.99	21.37
3b	3,5-Br_2	-	237	66	$C_{15}H_8N_4OBr_2$	43.79	42.85	1.92	1.90	13.02	13.34
3c	2,4-Cl_2	-	249	68	$C_{15}H_8N_4OCl_2$	53.99	54.55	2.52	2.42	17.49	16.97
4a	H	H	178	69	$C_{22}H_{16}N_2O_2$	78.10	77.65	4.89	4.71	8.03	8.24
4b	H	4-Cl	181	71	$C_{22}H_{15}N_2O_2Cl$	71.01	70.59	3.78	4.01	7.02	7.49
4c	H	2-CH_3	168	66	$C_{23}H_{18}N_2O_2$	77.52	77.97	5.52	5.08	8.23	7.91
4d	H	4-CH_3	190	71	$C_{23}H_{18}N_2O_2$	78.22	77.97	4.91	5.08	8.13	7.91
4e	3,5-Br_2	H	184	64	$C_{22}H_{18}N_2O_2Br_2$	52.52	52.59	3.52	3.58	5.98	5.58
4f	3,5-Br_2	4-Cl	192	61	$C_{22}H_{17}N_4O_2ClBr_2$	49.78	49.25	3.58	3.17	4.78	5.22
4g	3,5-Br_2	2-CH_3	197	60	$C_{23}H_{20}N_2O_2Br_2$	53.28	53.49	4.28	3.87	5.28	5.43
5a	H	-	183	70	$C_{15}H_{10}N_4OS$	60.97	61.22	3.89	3.40	18.86	19.05
5b	3,5-Br_2	-	195	65	$C_{15}H_8N_4OSBr_2$	40.12	39.82	1.89	1.77	12.27	12.39
5c	4-Cl	-	207	63	$C_{15}H_9N_4OSCl$	55.12	54.88	3.09	2.72	17.03	16.92
5d	5-Cl	-	219	62	$C_{15}H_9N_4OSCl$	55.32	54.88	2.99	2.72	17.15	16.92
5e	4-F	-	223	65	$C_{15}H_9N_4OSF$	58.09	57.88	3.02	2.89	17.89	18.00
5f	4-Br	-	232	62	$C_{15}H_9N_4OSBr$	48.39	48.26	2.53	2.41	15.01	15.19

Table 2. Anti Fungal Activity Data Compounds (3), (4) and (5)

Compd.	Average % inhibition after 7 days							
	Pyricularia oryzae		*Pseudopernospora cubensis*		*Sphaerotheca fuliginea*		*Phytophthora infestans*	
	500 ppm	100 ppm	500 ppm	100 ppm	500 ppm	100 ppm	500 ppm	100 ppm
3a	51	35	51	35	50	34	50	34
3b	87	74	88	75	87	74	87	74
3c	91	78	91	78	90	77	90	77
4a	91	78	91	78	90	77	90	77
4b	80	66	80	66	81	67	81	67
4c	85	73	86	75	85	74	85	74
4d	58	46	62	44	61	43	61	43
4e	87	74	88	75	87	74	87	74
4f	71	55	72	56	72	56	72	56
5a	81	67	81	66	82	66	82	66
5b	93	81	93	81	93	80	93	80
5c	94	81	94	81	94	81	95	83
5d	87	74	88	75	87	74	87	74
5e	91	78	90	77	91	78	90	77
5f	91	78	91	78	90	77	90	77
Carbendazim	100	88	100	89	100	88	100	90

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