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Journal of Chemical and Pharmaceutical Research

ISSN No: 0975-7384
CODEN(USA): JCPRC5

J. Chem. Pharm. Res., 2011, 3(3):83-86

Antifungal activity studies of some quinazolinone derivatives

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ABSTRACT

*3-Aryl-2-methyl-quinazolin-4-ones **1** were treated with nitrofurfural diacetate **2** in presence of piperidine and drops of concentrated sulphuric acid to obtain 3-aryl-2-[(5-nitro-2-furfuryl)vinyl]quinazolin-4-ones **3** in fairly good yields. The structures of these compounds were confirmed on the basis of elemental analyses, IR, NMR and mass spectral data. These compounds were also tested for their antifungal activities.*

Key words: quinazolinones, nitrofurans, antifungal activity, synthesis.

INTRODUCTION

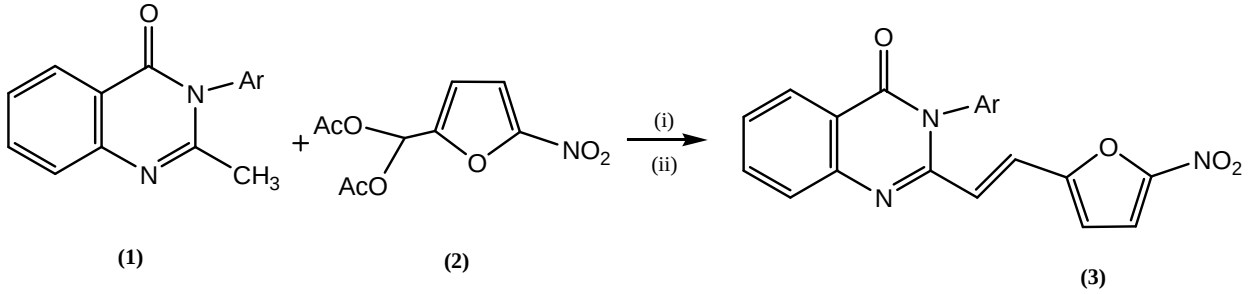
Substituted-quinazolin-4(3H)-ones have been reported to possess a broad spectrum of biological activities[1-6]. Some of them are used as hypnotic, sedative and anticonvulsive drugs[7]. Further, many nitrofuran derivatives find their use as potential chemotherapeutic agents[8-9].

Keeping in view of these findings and in continuation of our studies on 4(3H)-quinazolinones of biological and pharmacological significance[10-11], it was decided to synthesize a series of quinazolinones carrying nitrofuran moiety and to study their antifungal properties.

EXPERIMENTAL SECTION

In this paper, we wish to report the antifungal activities of vinylquinazolinones. For the present investigation, various substituted anilines were condensed with 2-methyl-3,1-benzoxazin-4-one in the presence of phosphorus oxychloride in toluene medium to obtain 3-aryl-2-methyl-quinazolin-4-ones **1** in 60-70% yield. 2-Methyl-3,1-benzoxazin-4-one was in turn prepared by the cyclization of anthranilic acid with acetic anhydride. 3-Aryl-2-methyl-quinazolin-4-ones **1**

were then condensed with nitrofurfural diacetate **2** in the presence of piperidine and drops of concentrated sulphuric acid to afford vinylquinazolinones **3** (**Scheme-1**). Nitrofurfural diacetate **2** required for this reaction, was obtained by the literature method[12]. The characterization data of these compounds **3** are given in Table-I.



(1) **(2)** **(3)**

Reagents: (i) Conc. H_2SO_4 (ii) Piperidine

Scheme I

Method for antifungal activity

All the synthesized compounds were screened for their antifungal activity against *C.albicans* according to disc-diffusion method[13]. Furacin and Fluconazole were employed as standard drugs for comparison. Their diameters of zone of inhibition (in mm) were measured at 5 µg/ml concentration. Control test with solvents was performed for every assay, but did not show any inhibition of the fungal growth. The results are given in Table 2.

All the synthesized compounds were purified by recrystallization using suitable solvents. The purity of all the synthesized compounds were checked by TLC. Detection was done by exposure to iodine vapours. Their melting points were determined in open capillaries and were uncorrected. The structures of synthesized compounds were characterized by their IR spectra which were recorded on a Shimadzu FT-IR 157 infrared spectrophotometer. KBr disc method was used to record IR spectra. The structures of synthesized compounds were characterized and confirmed by recording their ^{1}H NMR spectra in DMSO-d_6 on a 90 MHz Perkin-Elmer R-32 NMR spectrometer. Tetramethyl silane was used as the reference standard and chemical shift values were given in δ, ppm. The structures of some of the synthesized compounds were also confirmed by Mass spectral analysis carried out on a Jeol JMS-D mass spectrometer.

Synthesis of 3-aryl-2-[(5-nitro-2-furyl)vinyl]quinazolin-4-ones 3

An equimolecular mixture of suitably substituted quinazolinone **1** (0.01 mol) and 5-nitro-2-furfuraldehyde diacetate (2.43g, 0.01 mol) in absolute ethanol (20 ml) was treated with concentrated sulphuric acid (20 ml) followed by the addition of piperidine (10 ml). The resulting solution mixture was heated under reflux for 1-2 hours. The solid that separated out on cooling the reaction mixture was filtered, washed and recrystallized from dimethylformamide. The characterization data of these compounds **3** are given in Table 1.

RESULTS AND DISCUSSION

The IR spectrum of compound **3c** showed an absorption band at 1680 cm^{-1} which is characteristic of tertiary amide carbonyl group. The asymmetric and symmetric stretching frequencies of the nitro group were observed at 1540 cm^{-1} and 1340 cm^{-1} respectively. Similarly, IR spectra of compounds **3b** and **3d** showed similar absorption bands. The structures of these compounds were further confirmed by NMR spectral data. In the NMR spectrum of compound **3c**, the methyl protons of p-tolyl moiety resonated as singlet at δ, 2.5 integrating for three

protons. The physical characterization data of all the compounds has been summarized in Table 1.

Table 1: Physical characterization data of compounds

Compd	Ar	Yield (%)	M.P. (^{0}C)	Mol formula	Elemental Analysis Found(Calcd.)		
					%C	%H	%N
3a	Ph	80	254-256	$C_{20}H_{13}N_3O_3$	69.91 (69.97)	3.75 (3.79)	12.19 (12.24)
3b	p-BrC_6H_4	81	229-231	$C_{20}H_{12}BrN_3O_3$	56.81 (56.87)	2.80 (2.84)	9.91 (9.95)
3c	p-Me C_6H_4	78	213-215	$C_{21}H_{15}N_3O_3$	70.52 (70.59)	4.16 (4.20)	11.71 (11.76)
3d	m-Cl C_6H_4	57	231-233	$C_{20}H_{12}ClN_3O_3$	63.52 (63.58)	3.13 (3.18)	11.14 (11.13)
3e	m-Cl-p-F C_6H_3	81	196-198	$C_{20}H_{11}ClFN_3$	60.62 (60.68)	2.73 (2.78)	10.58 (10.62)
3f	o-MeO C_6H_4	51	191-193	$C_{21}H_{15}N_3O_4$	67.49 (67.56)	4.01 (4.02)	11.21 (11.26)
3g	m-Me C_6H_4	68	197-199	$C_{21}H_{15}N_3O_3$	70.51 (70.59)	4.21 (4.20)	11.72 (11.76)
3h	p-NO_2 C_6H_4	50	242-244	$C_{20}H_{12}N_4O_5$	61.81 (61.86)	3.02 (3.09)	14.39 (14.43)
3i	2,5-Cl_2 C_6H_3	53	226-228	$C_{20}H_{11}Cl_2N_3O_3$	58.21 (58.25)	2.63 (2.67)	10.13 (10.19)

Table 2: Infrared/H^{1}NMR/MS data of synthesized compounds

Compd	IR wave numbers cm^{-1}	NMR protons(δ ppm)	m/z
3b	1675(C=O),1600 (C=C), 1550 & 1340(NO_2 asym & sym)	--	422(M^+), 342(M-Br)
3c	1680(C=O),1600 (C=C), 1540 & 1340(NO_2 asym & sym)	2.5(s,3H,p-tolyl-H), 6.5-6.7(d,2H,vinyl-H),7.1-7.4(m,8H,Ar-H),7.7-7.9(d,2H,furyl-H)	359(M^+), 313(M-NO_2)
3e	1681(C=O),1600 (C=C), 1545 & 1340(NO_2 asym & sym)	--	396(M^+), 360(M-Cl)

Table 3: Antifungal activity data of compounds 3

Compound	Zone of inhibition in (mm) at 5 µg/ml concn. (*C. albicans)*
3a	18
3b	13
3c	12
3d	--
3e	12
3f	14
3g	10
3h	15
3i	09
Furacin (Standard)	18
Fluconazole (Standard)	17

The signal at δ, 2.4 for the methyl group at position-3 of quinazolinone ring disappeared and the signal due to –CH=CH- protons appeared at δ, 6.5-6.7. This confirmed the involvement of the

methyl protons in the condensation reaction. The aromatic protons were seen as a multiplet at δ, 7.7-8.0. The furyl protons were seen as two doublets at δ, 7.7-7.9.

The mass spectrum of compound **3a** was fully consistent with the assigned structure. The molecular ion peak appeared at m/z 359 corresponding to the molecular formula $C_{20}H_{13}N_3O_3$. A peak appeared at m/z 313 due to the loss of NO_2 radical from the molecular ion.

The screening data indicate that among the compounds tested, the antifungal activity of compound **3a** carrying phenyl group was comparable to that of Furacin and Fluconazole. Compound **3h** carrying p-nitrophenyl group showed moderate antifungal activity compared to the standard drugs. However, the remaining compounds possessed lesser degree of activity compared to the standard drugs. The results are given in Table 3.

Acknowledgement
The authors are thankful to Head, RSIC, CDRI Lucknow and Director, SIF, IISc Bangalore for providing nitrogen analysis, mass and nmr spectral data.

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