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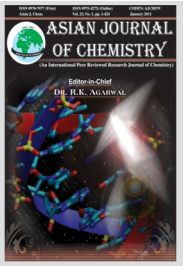

NOTE

N-Aryl-[(2R)-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl]acetamide as Antifungal Agents

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A series of N-aryl-2-[(2R)-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl]acetamide have been synthesized by the condensation of substituted anilines with 3a,4-dihydrofuro[2,3-b]quinoxalin-2(3*H*)-one. The structures of the synthesized compounds have been established on the basis of elemental analysis and spectral data. All the synthesized compounds screened for antifungal activity against *Candida albicans*, *Aspergillus fumigatus*, *Trichophyton rubrum* and *Mirosporum gypsum*.

Key Words: Antifungal, Acetamide, Tetrahydroquinoxalin.

The fungal infection have been increased dramatically in the last few decades. The infection of hairs, nails and outer layer of epidermis are very common in India. The increased intensity of these life threatening fungal infections and the development of the resistance to the currently used antifungal agents warrant the search for novel, alternative chemical moieties[1,2].

A series of N-aryl-2-[(2R)-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl]acetamide have been synthesized by the condensation of substituted anilines with 3a,4-dihydrofuro[2,3-b]quinoxalin-2(3*H*)-one. The structures of the synthesized compounds have been established on the basis of elemental analysis and spectral data. All the synthesized compounds screened for antifungal activity against *Candida albicans*, *Aspergillus fumigatus*, *Trichophyton rubrum* and *Mirosporum gypsum*[3-5].

The melting point was carried out in open capillary tube and was uncorrected. Thin layer chromatography was performed using silical gel coated on a glass plate and spot is visualized by exposure to iodine vapour. IR spectra (KBr) were recorded on a Shimadzu IR spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ + acetone-d_6 on a FX 90Q FT spectrometer using TMS as an internal standard (chemical shift δ).

Synthesis of (2R)-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl-acetic acid (III): To a solution of pure maleic anhydride (4.9 g, 0.05 mol) in ether (20 mL), a solution of *o*-phenylenediamine (4.65 g, 0.05 mol) was added with swirling at room temperature. The warm reaction mixture was cooled. When a brown colour product separates out, it was filtered off, washed with ether and crystalline product was purified by recrystallization from ethanol as colourless needles, Yield 98 %, m.p. 201-202 ºC, found (%) for $C_{10}H_{10}N_2O_3$: C, 54.30; H 5.08; N, 13; IR (KBr, ν_{max}, cm^{-1}): 1660 (NHC=O), 1700 (C=O), 3030 (Ar-C-H), 3450 (NH).

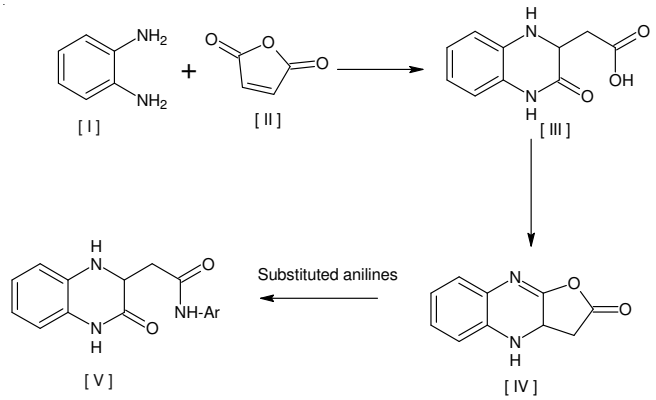
Synthesis of 3a,4-dihydrofuro[2,3-b]quinoxalin-2(3*H*)-one (IV): A mixture of (2R)-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl-acetic acid (**III**) (2.24 g, 0.01 mol) and thionyl chloride (5 mL) in benzene (50 mL) was refluxed for 4 h. The product was isolated and recrystallized from acetone to give (**IV**). Yield 72 %, m.p. 212 ºC, % found (%) for $C_{10}H_6N_2O_2$: C, 60.2; H 3.2; N, 13.2, IR (KBr, ν_{max}, cm^{-1}): 1774 (Lactone C=O).

Synthesis of N-(4-nitrophenyl)-2-[(2R)-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl]acetamide (V): To a mixture of **IV** (2.06 g, 0.01 mol) and 4-nitroaniline (2.76 g, 0.02 mol in benzene (50 mL), a few drops of glacial acetic acid were added and the reaction mixture was refluxed on a steam bath for 4 h. The solvent was distilled off and the residue is filetered and purified by column chromatography on silica gel using benzene-chloroform as eluent (10:90) to give **Va**. Yield 66 %, m.p. 202 ºC. % found C, 55.99, H 3.80, N, 18.32; IR (KBr, ν_{max}, cm^{-1}): 1570 (C-N), 1640 (NHCO), 1662 (C=O), 3030 (ArC-H); ^{1}H NMR (**Vc**) 2.8 (m, 2H, -CH_2CO), 7-7.7 (m, 8H, ArH), 9.6 (s, 1H, NH), 10.3 (s, 1H, NH).

The other compounds **Vb-f** were also prepared in a similar way from **IV** by using different substituted anilines (**Scheme-I**).

TABLE-1
ANTIFUNGAL ACTIVITY OF COMPOUNDS **Va-f**

Compd. (aryl)	*Candida albicans*				*Aspergillus fumigatus,*				*Trichophyton rubrum*				*Mirosporum gypsum*			
	0.25	0.125	0.062	0.031	0.25	0.125	0.062	0.031	0.25	0.125	0.062	0.031	0.25	0.125	0.062	0.031
Va (4-nitrophenyl)	(-)	(-)	(-)	(+)	(-)	(-)	(+)	(+)	(-)	(-)	(-)	(+)	(-)	(-)	(+)	(+)
Vb (3-nitro-phenyl)	(-)	(-)	(-)	(+)	(-)	(-)	(+)	(+)	(-)	(-)	(-)	(+)	(-)	(-)	(+)	(+)
Vc (3-methyl-phenyl)	(-)	(+)	(+)	(+)	(-)	(-)	(+)	(+)	(-)	(-)	(-)	(+)	(-)	(+)	(+)	(+)
Vd (4-methyl-phenyl)	(-)	(-)	(-)	(+)	(-)	(-)	(+)	(+)	(-)	(-)	(-)	(+)	(-)	(-)	(+)	(+)
Ve (3-Chloro-phenyl)	(-)	(-)	(-)	(+)	(-)	(-)	(+)	(+)	(-)	(-)	(-)	(+)	(-)	(-)	(+)	(+)
Vf (4-Chloro-phenyl)	(-)	(-)	(-)	(+)	(-)	(-)	(+)	(+)	(+)	(+)	(+)	(+)	(-)	(-)	(+)	(+)
Ketoconazole	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Blank	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)



Ar = 4-nitrophenyl (**Va**); 3-nitrophenyl (**Vb**); 3-methyl phenyl (**Vc**); 4-methyl phenyl (**Vd**); 3-chloro phenyl (**Ve**); 4-chloro phenyl (**Vf**)

Scheme-I: Synthesis of N-aryl-2-[(2R)-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl]acetamide derivatives

Antifungal activity: The synthesized compounds in the present investigation have been tested against *Candida albicans, Aspergillus fumigatus, Trichophyton rubrum* and *Mirosporum gypsum*. The liquid medium was used for screening the compounds for their antifungal activity[7,8]. The final pH of the media was adjusted to 5.3. Four different concentrations of 0.025, 0.125, 0.062 and 0.031 mm of each compound were used and to each tube was then added 0.1 mL of standardized inoculums of the organism. The tubes were incubated at 28-30 ºC. The presence or absence of growth was observed after 7 days. Ketoconazole was used as standard drug (Table-1).

The structure of the synthesized N-aryl-2-[(2R)-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl]acetamide compounds have been established on the basis of elemental analysis and spectral data. All the synthesized compounds screened for antifungal activity at four different concentrations. The activity of compounds **Va**, **Vb**, **Vd** and **Ve** were found most active against *Candida albicans, Aspergillus fumigatus, Trichophyton rubrum* and *Mirosporum gypsu*m. While the compound **Vf** is least active against used microorganisms.

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