Synthesis and Antifungal Activities of 5-(*o*-Hydroxy phenyl)-2-[4'-aryl-3' chloro-2'-azetidinon-1-yl]-1,3,4-thiadiazole

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Abstract: New series of 5-(*o*-hydroxy phenyl)-2-[4'-aryl-3'-chloro-2'-azetidinon-1-yl]-1,3,4-thiadiazole have been synthesized and the structures of the new compounds were established on the basis of IR, ¹H NMR spectral data. *In vitro* antifungal activity (MIC activity) was evaluated and compared with standard drugs of ketoconazole. Compounds **3c** in the series has shown interesting antifungal activity against both *C. albicans* and *A. niger* fungus. In the gratifying result, most of the compounds were found to have moderate antifungal activity.

Keywords: Synthesis, Antifungal activity, Thiadiazole, Ketoconazole.

Introduction

Microbial diseases are very common all over the world. Currently, used anti microbial agents are not effective due to development of the resistance against them and therefore, it is an ongoing efforts for the synthesis of the new antimicrobial agents. Antimicrobial agents reduces or completely block the growth and multiplication of bacteria and are helpful in the treatment of various infectious diseases like meningitis, malaria, Tuberculosis, pneumonia, AIDS, etc.

1, 3, 4 Thiadiazole and its derivatives represents one of the most biological active classes of compound possessing a wide spectrum of activities. Literature survey shows that the 1,3,4 thiadiazole nucleus is associated with diverse pharmacological activities such as antifungal¹, antibacterial^{2,3}, anti-inflammatory^{4,5,6}, anticancer^{7,8}, antitubercular^{9,10}, antiviral^{11,12} and antiparkinsonism^{13,14}.

The scientific literature also states that antiviral and antibacterial of the thio urea derivatives are due to the presence of - NH - C(S) - NH function in the molecule and the change in the activity depends on the nature of the substituent¹⁵. These observations prompted us to synthesize some new thiadiazole and to investigate their antifungal activity.

Experimental

All the solvent were used are of LR grade and were obtained from Merck, CDH and S. d. fine chemicals. Melting points were recorded by open capillary method and were uncorrected, Thin Layer Chromatography was performed on Silica gel G and R_f value was calculated. ^1H NMR spectra was recorded on a Bruker model DPX 300 FT-NMR Spectrometer in CDCl_3 using TMS as internal standard.

Synthesis Activity

Preparation of 2-amino-5-(o-hydroxy phenyl)-1,3,4 thiadiazole (1)

An ethanolic solution of salicylic acid was mixed with aqueous solution of thiosemicarbazide with continuous stirring. Then few drops of concentrated sulphuric acid were added and the solution was refluxed for 2 h. The crude product was obtained on cooling which was then further washed with cold water and recrystallized with ethanol.

Preparation of 5-(o-hydroxy phenyl)-2-(benzylidin-amine)-1,3,4 thiadiazole (2a-f)

A mixture of compound **1** with different aryl aldehydes in ethanol in presence of concentrated sulphuric acid was refluxed for 4-6 h. The crude product was obtained on cooling and was washed with cold water and recrystallized with ethanol.

Preparation of 5-(o-hydroxy phenyl)- 2-(4' aryl-3'chloro-2'azeetidino-1-yl)amino-1,3,4 thiadiazole (3a-f)

Ethanolic solution of compound **2** and triethylamine in dioxane was mixed with constant stirring. The mixture was cooled below 0°C using salt and ice. Then few drops of chloroacetyl chloride was added and solution was stirred for 5 h and filtered. The filtrate was then refluxed for 5 h and cooled to obtain the crude product. The product was then washed with cold water and recrystallized by ethanol. The physical and analytical data of the products are given in Table 1.

Table 1. Physical and analytical data of compound synthesized

Compound	Ar	Mol. Formula	Melting Point, $^\circ\text{C}$	% Yield	R_f Value
3a	$\text{C}_7\text{H}_7\text{O}_2^-$	$\text{C}_{18}\text{H}_{10}\text{ClN}_3\text{O}_4\text{S}$	240	52	0.591
3b	$\text{C}_4\text{H}_3\text{O}^-$	$\text{C}_{15}\text{H}_8\text{ClN}_3\text{O}_2\text{S}$	260	56	0.591
3c	C_8H_7^-	$\text{C}_{19}\text{H}_{12}\text{ClN}_3\text{O}_2\text{S}$	220	58.2	0.591
3d	$\text{C}_8\text{H}_9\text{O}_2^-$	$\text{C}_{19}\text{H}_{14}\text{ClN}_3\text{O}_4\text{S}$	250	52.5	0.591
3e	$\text{C}_6\text{H}_5\text{O}_2^-$	$\text{C}_{17}\text{H}_{10}\text{ClN}_3\text{O}_3\text{S}$	230	49.9	0.591
3f	$\text{C}_6\text{H}_4\text{Cl}^-$	$\text{C}_{17}\text{H}_9\text{Cl}_2\text{N}_3\text{O}_2\text{S}$	245	51.2	0.591

3a: IR (cm^{-1}); 2936 (C-H, Aryl), 1741 (C=O), 1472 (C - N), 771 (C-Cl) & 671 (C-S-C). ^1H NMR; 8.9-7.15(Ar), 4.67 (H, OH), 3.87 (OCH_3), 3.83 (H, OH); **3b:** IR (cm^{-1}); 3442 (NH), 2936 (C-H, Aryl), 1744 (C=O), 1472 (C-N), 766 (C-Cl) & 698 (C-S-C). ^1H NMR; 7.71-7.2(Ar), 3.8 (H, OH), 6.8-7.0 (Furan); **3c:** IR (cm^{-1}); 3215 (NH), 2883 (C-H, Aryl), 1778 (C=O), 1454 (C - N), 787 (C-Cl) & 698 (C-S-C). ^1H NMR; 7.44-7.76(Ar), 3.12(H, OH), 2.45(C=C), 7.4(Ar'); **3d:** IR (cm^{-1}); 3215 (NH), 2883 (C-H, Aryl), 1778 (C=O), 1454 (C-N), 787 (C-Cl) & 698 (C-S-C). ^1H NMR; 7.75-7.43, 6.61(Ar), 3.66 (OCH_3), 3.77 (OCH_3), 7.06 (Ar').

Reaction Scheme

3e: IR (cm^{-1}); 3433 (NH), 2933 (C – H, Aryl), 1672 (C = O), 1487 (C - N), 753 (C-Cl) & 673 (C-S-C). ^1H NMR; 7.63, 7.08, 6.86(Ar), 3.34(H, OH), 7.33, 7.45 (Ar'), 3.39 (H, OH); **3f**: IR (cm^{-1}); 3495 (NH), 3022 (C-H, Aryl), 1662 (C=O), 1442 (NH), 758 (C-Cl) & 694 (C-S-C). ^1H NMR; 7.8, 7.48, 6.8(Ar), 3.79(H, OH), 7.3, 7.75, 7.20(Ar').

Biological evaluation

The cup plate method was performed using nutrient agar broth. These agar media was incubated with 0.5 mL of 24 h liquid culture containing 10^7 micro organisms /mL. Plate disc was saturated with solution of each compound (100 mcg/mL in DMF) placed on indicated agar medium. The incubation time was 48 h at 30 °C for *Candida albicans* and *Aspergillus niger* species. Inhibitory activity was measured in mm as the diameter of the observed inhibitory zones. The tests were repeated to confirm the finding and the average of the reading were taken into consideration.

Anti fungal activity

The cup plate method was employed for the *in-vitro* study of antifungal effect against *A. niger* and *C. albicans*. The method was based on diffusion of antifungal compound from reservoir nutrient agar medium such that the growth of the organism is inhibited as circular zone around the bore. The inhibitory effect of the compound **(3a-f)** against these organisms is given in the Table 2.

Table 2. Inhibitory effect of the compound (**3a-f**)

Compound	<i>Aspergillus niger</i>	<i>Candida albicans</i>
3a	+	++
3b	-	+
3c	++	+++
3d	-	+
3e	-	+
3f	+	++

Results and Discussion

The screening result shows all the compounds synthesized were found active against *C. albicans* but not all against *A. niger*. Compound **3c** shows good inhibition area for both the fungus while **3b**, **3d** and **3e** have poor for *C. albicans* and no against *A. niger* **3a** and **3f** shows average inhibitory zone against *C. albicans* but poor against *A. niger*.

References

1. Shabban M R, Saleh T S and Farag A M, *Heterocycl.*, 2009, **78(1)**, 151-159.
2. Yadav S L, Mohd Zaidi, H G and Singh N B, *Asian J Chem.*, 2003, **15(3)**, 1805-1807.
3. Demirayak S, Mohsen U A and Karaburun A C, *Eur J Med Chem.*, 2002, **37**, 255.
4. Bishnoi A, Pandey V K, Saxena R, Joshi M N and Bajpai S K, *Indian J Chem.*, 2002, **41(B)**, 1978-1979.
5. Thomasco M L, Godwood C R, Weaver A E, Ochoada M J, Fard W C, Zurenko G E, Hamel C J, Stapert D, Moerman K J, Schadt D R and Yogi H B, *Bio Org Med Chem., Lett.*, 2003, **13(23)**, 4193-4196.
6. Sawhey S N, Gupta A and Sharma P K, *Indian J Heterocycl Chem.*, 1991, **1**, 8-16.
7. Carigo A, Lesueur B W, and Skibo E B, *J Med Chem.*, 1999, **42**, 3324.
8. Pandey V K and Shukla A, *Indian J Chem.*, 1999, **38(B)**, 1381-1383.
9. Mishra P, Jakav V and Kashaw S K, *J Indian Chem Soc.*, 2006, **83(1)**, 1157.
10. Verma K, Jan K, Milan P and Jiri S, *Eur J Med Chem.*, 2002, **37**, 409-418.
11. Joshi S H and Thaker M K, *Indian J Chem*, 2005, **44B**, 410-412
12. Yadav L D S, Singh S and Dubey S, *Indian J Chem*, 2001, **40B**, 674-677.
13. Yadav S D L and Singh S, *Indian J Chem B*, 2001, **40**, 440-442.
14. Katakya J C S and Harzarika J, *Indian J Hetetrocycl Chem.*, 1999, **61**, 293-296.