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Journal of Chemical and Pharmaceutical Research

J. Chem. Pharm. Res., 2010, 2(1): 47-52

ISSN No: 0975-7384

Synthesis and study of antibacterial and antifungal activity of novel 2-(5-substituted methylamino-1,3,4-thiadiazol-2yl)phenols

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Abstract

A new series of Anti bacterial and Antifungal agents with 2-(5-amino-1, 3, 4-thiadiazol-2-yl) phenol as the central scaffold unit has been synthesized. The newly synthesized compounds were characterized by IR and ^{1}HNMR spectral methods. The compounds were screened for antibacterial activity against pathogenic microbes Bacillus subtilus, Staphylococcus aureus, E.coli, in comparison with the reference drug Ampicillin, Ciprofloxacin and Doxycycline and antifungal activity against Candida albicans and comparable to that of Fluconazole as a reference drug and in this investigation the significant level of activity was illustrated.

Keywords: Antibacterial, Antifungal

Introduction

The major classes of almost all antibiotics have encountered resistance in clinical applications. The increasing antibiotic resistance of gram positive bacterial is becoming a serious problem for human beings. Apart from this primary and opportunistic fungal infection continue to increase rapidly and as a consequence invasive fungal infection constitutes a major cause of mortality for the patients. Candida albicans is one of the most common opportunistic fungi responsible for these kinds of infections [1]. Several five membered aromatic systems having three hetero atoms at symmetrical position have been studied because of their interesting physiological properties. It is also well established that various derivatives of 1,2,4-triazole, 1,3,4-thiadiazole exhibit broad

spectrum of pharmacological properties such as antibacterial and antifungal activities[2]. Moreover, synthesis of thiadiazoles and triazoles has attracted widespread attention due to their diverse applications as antibacterial [3], antimycobacterial [4], antifungal [5] and antidepressant agents [6].Because of these findings and continuing our work towards synthesis of potentially active new compounds, it seems appropriate to synthesize and study the Anti bacterial and Antifungal activity of new 2,5 disubstituted 1,3,4-thiadiazole.

Experimental Section

Antibacterial activity: [7, 8]

The synthesized compounds were evaluated for the in-vitro antibacterial activity against microorganism strains *Bacillus subtilus* (MTCC-441), *Staphylococcus aureus* (NCTC 6571), *E.coli (*NCTC 10418*)* by Cup-plate agar diffusion method using nutrient agar.

Antifungal activity: [7, 8]

The compounds were also tested for the in-vitro antifungal activity against C*andida albicans* (ATCC10231) by cup plate method at 100 µg/ml concentration of test compounds by Cup-plate agar diffusion method using Sabouraud-Dextrose agar.

Table No. 1: Antibacterial and Antifungal activities of the synthesized compounds

SL. No.	Compd.	Zone of inhibition at 100µg/ml (in mm.)			
		B.subtilus	S.aureus	E.coli	C.albicans
1	4a	22	24	23	23
2	4b	17	16	15	15
3	4c	15	22	22	16
4	4d	14	16	15	13
5	4e	22	23	22	25
Std.	Ciprofloxacin	20	23	25	--
Std.	Ampicillin	15	16	18	--
Std.	Doxycycline	22	35	30	--
Std.	Fluconazole	--	--	--	30

Melting Points were determined in open capillary method and are uncorrected. IR spectra were recorded on Perkinelmer FTIR-spectrophotometer using KBr disc method. The ^{1}H-NMR spectra were recorded on sophisticated multinuclear FT-NMR spectrometer model Avance-II (Bruker) using dimethylsulphoxide-d_6 as solvent and tetramethylsilane as internal standard.

Scheme

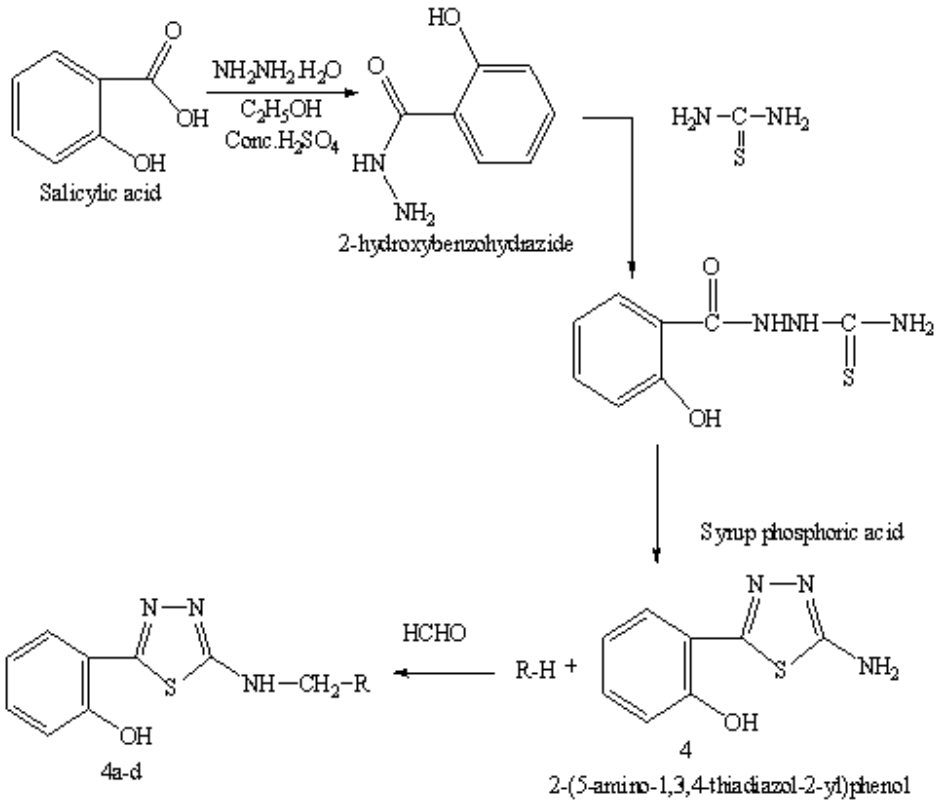
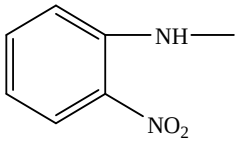
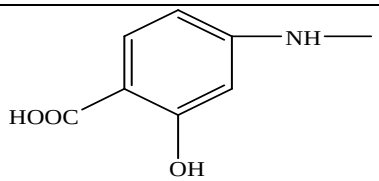
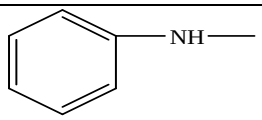
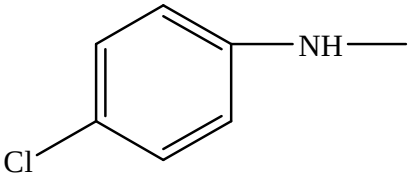
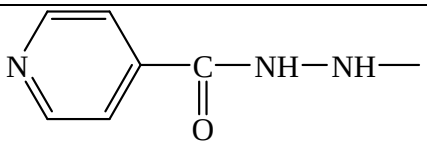


Table No.2: Physical Constants of Different Synthesized Compounds

Compounds	R	Meltng point(°C)	% Yield	Molecular Formula
4a		116-117	75	$C_{15}H_{13}N_5O_3S$
4b		180-181	65	$C_{16}H_{10}N_4O_4S$
4c		120-121	62	$C_{15}H_{14}N_4OS$

4d		148-150	72	$C_{15}H_{13}ClN_4OS$
4e		165-166	62	$C_{15}H_{14}N_6O_2S$

Procedure for synthesis: [9, 10]

General procedure for hydrazination of Salicylic acid and reaction with thiourea to form thiosemicarbazide (3)

To a cleaned and dried round bottom flask added, accurately weighed 13.8g of salicylic acid and dissolved it into 46ml of ethanol. After it, added 5ml of hydrazine hydrate and shaked well for uniform distribution and finally 10 drops of conc. sulphuric acid. Further reflux the mixture for 6-7 hours. After completion of the reaction the reaction mixture was poured on crushed ice where white crystals separated out which were filtered with cold water. The crystals were recrystallized with ethanol. Finally needle shaped whitish crystals appeared which were dried and collected. To a pre dried and cleaned round bottom flask poured accurately weighed 1.52g of hydrazine derivative and dissolved it completely into 44ml of ethanol and then added accurately weighed 7.6g of thiourea. Refluxed the reaction mixture for 12 hours, after completion of the reaction, the reaction mixture was poured into a beaker and kept into cold condition for over night. Cream coloured needled shaped crystals appeared which were kept at a temperature of 0^0C-1^0C.

General procedure for synthesis of 2-(5-amino-1, 3, 4- thiadiazol-2-yl) phenol (4)

To a cleaned and dried iodine flask, 4.58 g of thiosemicarbazide derivative was gradually added to 20ml of 85% syrupy phosphoric acid at a temperature of 120^{o}C for 20 minutes. The reaction mixture was heated under stirring at this temperature for further 30 minutes and then poured into 500ml of crushed ice water and left overnight. The precipitated solid was filtered off, washed with water and crystallized from ethanol to afford the final product 2-(5-amino-1, 3, 4-thiadiazol-2-yl) phenol. Yield 69%, m.p. 135-136^{0}C.

Procedure for the synthesis of 2-(5-substituted Methylamino-1, 3, 4-thiadiazol-2yl) phenols (4a-d)

To a mixture of 2-(5-amino-1, 3, 4- thiadiazol-2-yl) phenol (2.22g, 0.01mol) and appropriate amine (a-d) (1.38g, 0.01mol) and formaldehyde (2ml) were taken in a beaker. The mixture was irradiated in a microwave oven for 3 min with 40% power, at interval of 30 seconds. After the completion of the reaction, ice-cold water was added to the reaction mixture and solid thus separated was filtered and dried to afford 4a-d and recrystallized from ethanol. The yield and m.p. are listed in the table 1.

Spectral data:

The IR(KBr, cm^{-1}) spectra of compounds 2:1200cm^{-1} (C-O str.), 1606-1460cm^{-1} (C=C str.), 3500-3300 cm^{-1} (N-H str.), 3600 cm^{-1} (O-H str) and 1670-1660 cm^{-1} (C=O str).The ^{1}HNMR(δ, ppm):6.91-7.78(4H,Ar-CH), 5.00(1H,Ar-OH), 8.00(IH, Sec.Amide), 2.0(2H, NH_2).

The IR (KBr, cm^{-1}) spectra of compounds 3: 3200 cm^{-1} (O-H str), 1195 cm^{-1} (C-O str.), 1650-1660 cm^{-1} (C=O str.), 1517 cm^{-1} (N-H bending), 1675 cm^{-1} (C=C str.). The ^{1}HNMR (δ, ppm): 6.91-7.80(4H, Ar-CH), 5.00(1H, Ar-OH), 2.0(2H, NH_2), 8.00(1H, Sec. Amide), 2.00(1H, NH_2).

The IR(KBr, cm^{-1}) spectra of compounds 4:3600 cm^{-1}(O-H str.),3000-3050cm^{-1} (ArC-H str.), 1500-1600 cm^{-1} (ArC=C str.), 700-600 cm^{-1}(C-S str), 1250-1025 cm^{-1}(C-N str),3300-3500 cm^{-1}(N-H str.).The ^{1}HNMR (δ, ppm): 6.79-7.31(4H, Ar-CH), 5.00(1H, Ar-OH), 4.00(2H, NH_2).

The IR(KBr, cm^{-1}) spectra of compounds S_1:3465cm^{-1}(N-H str.), 2365cm^{-1}(ArC-H Str.), 1625cm^{-1}(C-C str.), 1417cm^{-1}(C-N str.), 1515 cm^{-1}(N-O str.), 619 cm^{-1}(C-S str.). The ^{1}HNMR (δ, ppm): 6.79-7.80 (8H, Ar-CH), 5.20(1H, Ar-OH), 4.83(2H, CH_2), 3.94 (1H, NH).

The IR(KBr, cm^{-1}) spectra of compounds S_2:3415cm^{-1}(N-H str.), 2397cm^{-1}(ArC-H Str.), 1618cm^{-1}(C-C str.), 1442cm^{-1}(C-N str.), 1527 cm^{-1}(N-O str.), 620 cm^{-1}(C-S str.). The ^{1}HNMR (δ, ppm): 6.89-7.8.02 (7H, Ar-CH), 6.85(1H, Ar-OH), 4.82(2H, CH_2), 4.2 (1H, NH), 10.85(1H, OH).

The IR(KBr, cm^{-1}) spectra of compounds S_3: 3442cm^{-1}(N-H str.), 2377cm^{-1}(ArC-H Str.), 1640cm^{-1}(ArC-C str.), 1415cm^{-1}(C-N str.), 618 cm^{-1}(C-S str.). The ^{1}HNMR (δ, ppm): 6.84-7.8.02 (8H, Ar-CH), 4.13 (2H, CH_2), 6.55 (1H, NH), 10.05(1H, OH).

The IR(KBr, cm^{-1}) spectra of compounds S_4:3442cm^{-1}(N-H str.), 2367cm^{-1}(ArC-H Str.), 1642cm^{-1}(C-C str.), 1415cm^{-1}(C-N str.), 1564 cm^{-1}(N-O str.), 645 cm^{-1}(C-S str.). The ^{1}HNMR (δ, ppm): 6.37-7.31(8H, Ar-CH), 5.50(1H, Ar-OH), 4.82(2H, CH_2), 4.2 (1H, NH).

The IR(KBr, cm^{-1}) spectra of compounds S_5:3465cm^{-1}(N-H str.), 2365cm^{-1}(ArC-H Str.), 1430cm^{-1}(C-N str.), 611 cm^{-1}(C-S str.). The ^{1}HNMR (δ, ppm): 6.79-7.31 (4H, Ar-CH), 5.50(1H, Ar-OH), 4.42(2H, CH_2), 4.2 (1H, NH), 7.96-9.06 (4H, Pyridine).

Result and Discussion

In this study the structure of the synthesized compounds was elucidated by means of IR, ^{1}HNMR.All the compounds were evaluated for antibacterial and antifungal activity by cup-plate method. As concerns the antibacterial potency of the compounds against B.subtilus, compounds 4a, 4b, 4e were more potent than Ciprofloxacin and Ampicillin and 4a, 4e equipotent to Doxycycline, where as against S.aureus the compounds 4a, 4e were equipotent to Ciprofloxacin, 4a-4e more potent than Ampicillin and less potent than Doxycycline. Against E.coli the compounds were less potent than Ciprofloxacin, Doxycycline and 4a, 4c, 4e were more potent than Ampicillin. The antifungal data reveals that the compounds have shown moderate or weak antifungal activity as compared to Fluconazole.

Acknowledgement

Author thanks to Dr.A.K.Wahi, Dean, Moradabad Educational Trust Group of Institutions, Faculty of Pharmacy, MIT Campus, Moradabad for his immense support in completing our research.

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