

SYNTHESIS AND ANTIMICROBIAL EVALUATION OF 1H-BENZOTRIAZOL-1-YL{2-HYDROXY-5-[(E) PHENYLDIAZENYL]PHENYL}METHANONE DERIVATIVE

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ABSTRACT

Objective: The objective of the present study was to synthesize newer antimicrobial 2,3-dihydro-1H-benzotriazol-1-yl{2-hydroxy-5-[(E)-phenyldiazenyl]phenyl}methanone derivatives.

Methods: The 2-hydroxy benzoyl chloride was substituted on Benzotriazole to form the intermediate 1H-benzotriazol-1-yl(2-hydroxyphenyl)methanone. Thus formed intermediate 1H-benzotriazol-1-yl(2-hydroxyphenyl)methanone synthesized was coupled with various aromatic diazonium salts forming Benzotriazole derivatives. The synthesized derivatives were characterized by Physical, Chemical properties, IR, NMR, Mass spectra. The five derivatives (Ic to Vc) were screened for antibacterial and antifungal activity.

Results: The derivatives IIIc and IVc showed highest antimicrobial activities when compared to standard. The Ic, IIc and IVc derivatives showed good antifungal activities. Rest of the derivatives showed medium antibacterial and antifungal activities.

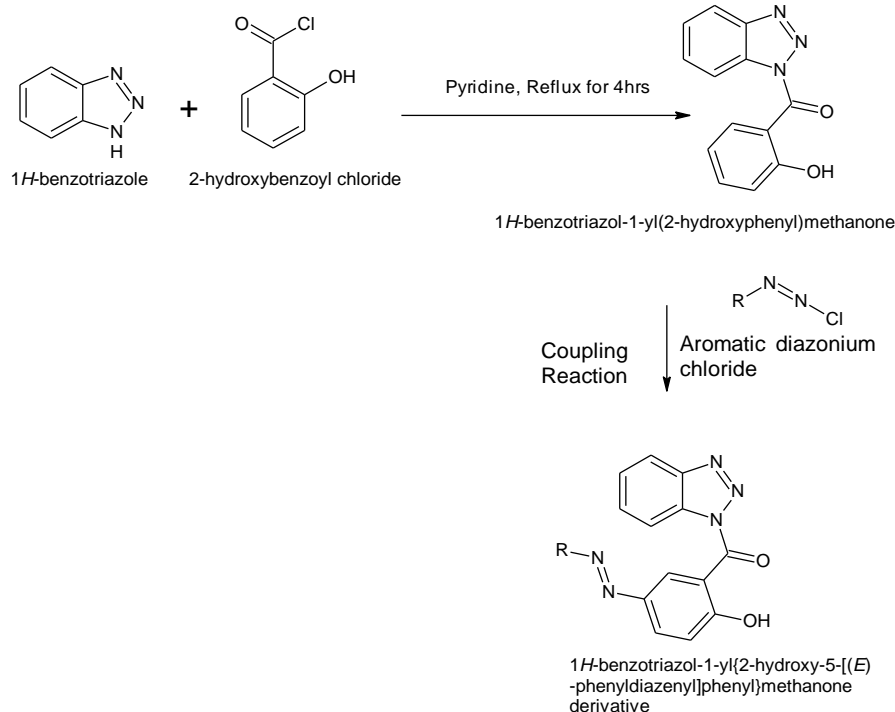
Conclusion: The synthesized derivatives showed good antibacterial and antifungal activity.

Keywords: Antibacterials, Anti fungals, Benzotriazole derivatives, Diazonium coupling.

INTRODUCTION

Benzotriazole derivatives reported to have various activities such as antifilarial[1], anticonvulsant and anti-inflammatory[2], antitumor[3] activities; literature study reveals the antiviral activity[4]. Some Benzotriazole derivatives were also reported to be effective as antimicrobials [5]. Continuing the search for antimicrobial agents the present study focused on synthesis and screening of 2,3-dihydro-1H-benzotriazol-1-yl{2-hydroxy-5-[(E)-phenyldiazenyl]phenyl}methanone derivatives for antibacterial

and antifungal activity. The methods of synthesis of Benzotriazole derivatives with different techniques have been reported [6]. Synthesis of some azobenzoyl benzotriazoles were reported [7], diazonium coupling reactions was used to modify the silk fibroin [8]. Antibacterial activities of some benzotriazole derivatives were reported [9-11]. For some benzotriazole derivatives antioxidant activity was reported [12]. Under present study newer Benzotriazole derivatives were synthesized with diazonium coupling reaction and following published chemical procedures [13-15].



Scheme 1: Synthetic pathway of 2,3-dihydro-1H-benzotriazol-1-yl{2-hydroxy-5-[(E)-phenyldiazenyl]phenyl}methanone derivatives.

METHODS

Procedure of Synthesis

Synthesis of Benzotriazole (a): 10.8 gm of *O*-phenylenediamine was added to mixture of 12g (11.5 ml) of glacial acetic acid and 30 ml of water, which was cooled to 15°C, stir. Then solution of 7.5g of sodium nitrite in 15 ml water was added in portion. The temperature increased slowly to 85°C and then cools slowly. When temperature was 45°C the mixture was chilled at ice bath for 30 min. Pale brown solid separated by the filtration. The recrystallization was done using benzene as solvent.

Synthesis of 2-hydroxybenzoyl chloride (b): A mixture of Methyl salicylate (0.1M), thionyl chloride (0.1M) and chloride and 1 drop of dimethylformamide (DMF) were added, followed by heating the mixture at 68°C for 3 hr. After the initial suspension turns into a yellow solution, the heating source was removed and the acid chloride precipitates as a pale red solid. After cooling the reaction mixture to 25°C, the solid was collected via filtration using a Buchner funnel, washed with CHCl₃, and dried in a vacuum desiccators for 15 hr to give 5.12 g (90%) of as a white powder.

Synthesis of 1H-benzotriazol-1-yl(2-hydroxyphenyl) methanone(c): The compound (a) in equimolar was refluxed with compound (b) of equimolar concentration in benzene solvent for 4hrs and then neutralized with sodium carbonate solution produces a Pale yellow color creamy compound. On recrystallization produces pale yellow compound

Synthesis of 1H-benzotriazol-1-yl{2-hydroxy-5-[(E)-phenyldiazenyl]phenyl}methanone (Ic): the aniline (0.1M) was converted to dizonium salt and treated with compound (c) at temperature below 5°C. Spectral data FTIR (KBr cm⁻¹): 2932.22 (HC Aromatic), 1567.21 (-N=N str), 1705.55(-C=O). 1H-NMR (DMSO 1δ ppm): 7.4-7.8 (12H, m,Ar), 12.9 (1H,s,-OH). m/z of m⁺ ion is 343.

Synthesis of 4-[(E)-[3-(1H-benzotriazol-1-ylcarbonyl)-4-hydroxyphenyl]diazenyl]benzoic acid (IIc): the p-amino benzoic acid was converted to dizonium salt and treated with compound (c) at temperature below 5°C. Spectral data FTIR (KBr cm⁻¹): 2964.92 (HC Aromatic), 1598.59 (-N=N str), 1753.15 (-C=O). 1H-NMR (DMSO 1δ ppm): 7.3-7.9 (12H, m,Ar). m/z of m⁺ ion is 387.

Synthesis of 1H-benzotriazol-1-yl {5-[(E)-(4-chlorophenyl) diazenyl]-2-hydroxyphenyl} methanone (IIIc): The compound (c)

was treated with equimolar 4-Chlorophenol and refluxed for 4 hrs in benzene solvent. Spectral data FTIR (KBr cm⁻¹): 2894.33 (HC Aromatic), 1721.03 (-C=O str), 1416.50 (-C-N str), 3337.73 (-NH-str). 1H-NMR (DMSO 1δ ppm): 7.32-7.9 (12 H, m,Ar). 12.91 (1H, s, OH), m/z of m⁺ ion is 377.

Synthesis of 1H-benzotriazol-1-yl {2-hydroxy-5-[(E)-(4-nitrophenyl) diazenyl] phenyl} methanone (IVc): the compound (c) was treated with equimolar 4-nitroaniline and refluxed for 4 hrs in benzene solvent. Spectral data FTIR (KBr cm⁻¹): 2922.55 (HC Aromatic), 1704.78 (-C=O), 1H-NMR (DMSO 1δ ppm): 7.1-7.9 (11H, m,Ar). m/z of m⁺ ion is 388.

Synthesis of 4-[(E)-[3-(1H-benzotriazol-1-yl carbonyl)-4-hydroxyphenyl] diazenyl]benzene sulfonamide (Vc): the compound (c) was treated with equimolar 4-benzen sulfonamide and refluxed for 4 hrs in benzene solvent. Spectral data FTIR (KBr cm⁻¹): 2920.00 (HC Aromatic), 1734.78 (-C=O), 1H-NMR (DMSO 1δ ppm): 7.32-7.9 (11H, m,Ar), 12.9(1H, s, -OH), 3.31(2H,s, NH₂). m/z of m⁺ ion is 297.

The melting points of the synthesized derivatives were determined by open capillary (LABHOSP) and were uncorrected. The purity of the compounds was checked using pre coated TLC plates (MERCK, 60F) using Benzene: chloroform: methanol (8:4:2) solvent system. The developed chromatographic plates were visualized under UV at 254nm. IR spectra were recorded using KBr on Shimadzu FTIR model 8400 spectrophotometer and Agilent Technologies CARY 630 FTIR, 1H NMR spectra in DMSO on a BRUKER FT-NMR instrument using TMS as internal standard.

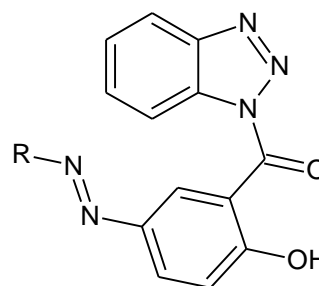
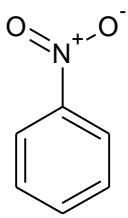
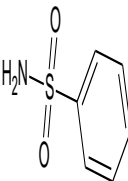


Fig. 1: General structure of 1H-benzotriazol-1-yl {2-hydroxy-5-[(E)-phenyldiazenyl] phenyl} methanone derivatives

Table 1: Physical properties of the Benzotriazole derivatives (Ia to Va)

Derivative	Mol. Formula	Derivative Name	R	%Yield	MP	Mol Weight
Ic	C ₁₉ H ₁₃ N ₅ O ₂	1H-benzotriazol-1-yl{2-hydroxy-5-[(E)-phenyldiazenyl]phenyl}methanone		56	80°C	343.33
IIc	C ₂₀ H ₁₃ N ₅ O ₄	4-[(E)-[3-(1H-benzotriazol-1-ylcarbonyl)-4-hydroxyphenyl]diazenyl]benzoic acid		45	98°C	387.34
IIIc	C ₁₉ H ₁₂ N ₅ O ₂ Cl	1H-benzotriazol-1-yl{5-[(E)-(4-chlorophenyl) diazenyl]-2-hydroxyphenyl}methanone		58	135°C	377.78

IVc	C ₁₉ H ₁₂ N ₆ O ₄	1 <i>H</i> -benzotriazol-1-yl{2-hydroxy-5-[(<i>E</i>)-(4-nitrophenyl)diazenyl]phenyl}methanone		66	120°C	388.33
Vc	C ₁₉ H ₁₄ N ₆ O ₄ S	4-[(<i>E</i>)-[3-(1 <i>H</i> -benzotriazol-1-ylcarbonyl)-4hydroxyphenyl]diazenyl]benzenesulfonamide		45	117°C	422.41

Antimicrobial Activity

The antibacterial activity was screened with two type of bacteria Gram positive and gram negative bacteria. The synthesized compounds were screened for antimicrobial activity (Fig 1 and 2) by adopting cup plate method using Norfloxacin and Ketaconazole as standard drugs in concentration of 1µg/ml. The bacterial strains of *B. subtilis*, *S. aureus*, *E. coli*, and *S. typhi* were

used for antibacterial activity. For antifungal activity *A. niger* and *C. albicans* strains were used. The MICs and MBCs were determined. Agar dilution MICs were determined by using agar plates with an incorporated standard drug dilutions and samples with incubation at 37°C and were defined as the lowest antibiotic concentrations completely inhibiting growth. Broth dilution MICs were determined with overnight broth cultures of the strains to be tested.

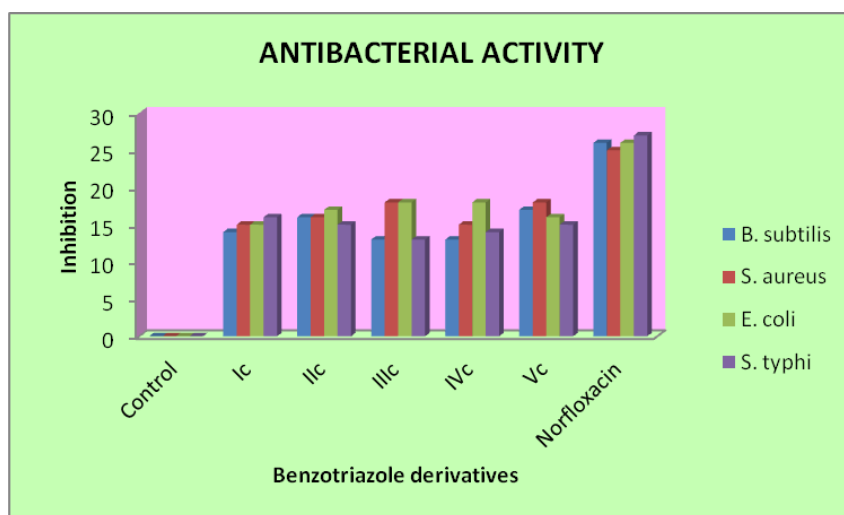


Fig. 2: Graphical representation Antimicrobial activity.

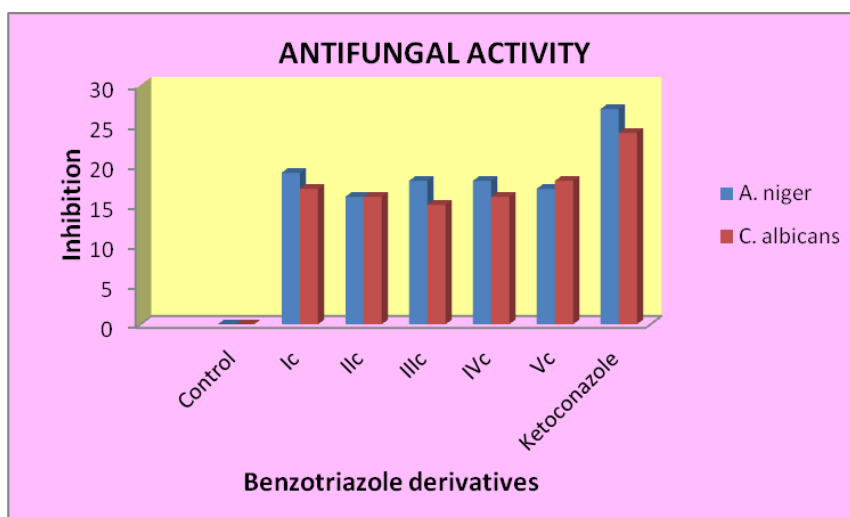


Fig. 3: Graphical representation Antifungal activity

RESULTS AND DISCUSSION

The derivatives synthesized with synthetic scheme (scheme 1 and Figure 1) were characterized by the physical properties (Table 1), chemical properties, and spectral data like IR, NMR and Mass spectra. The derivatives were screened for antibacterial and antifungal activities (Figure 2 and 3).

CONCLUSION

The synthesized derivatives were like I c to Vc showed remarkable Zone of inhibition with standards and have good antibacterial and antifungal activities.

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