Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Issue 3, 2013

Research Article

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

***C. M. JAMKHANDI, JOHN INTRU DISOUZA**

Department of Pharmacy JJT University Jhunjhunu, Rajasthan India, Tatyasaheb Kore College of Pharmacy Warananagar, Dist: Kolhapur, 416113, Maharashtra, India. Email: cmjamakhandi@gmail.com

Received: 24 Feb 2013, Revised and Accepted: 31 Mar 2013

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-hudroxy 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, I R, NMR, Mass spectra. The five derivatives(Ic to Vc) were screened for antibacterial and antifungal activity.

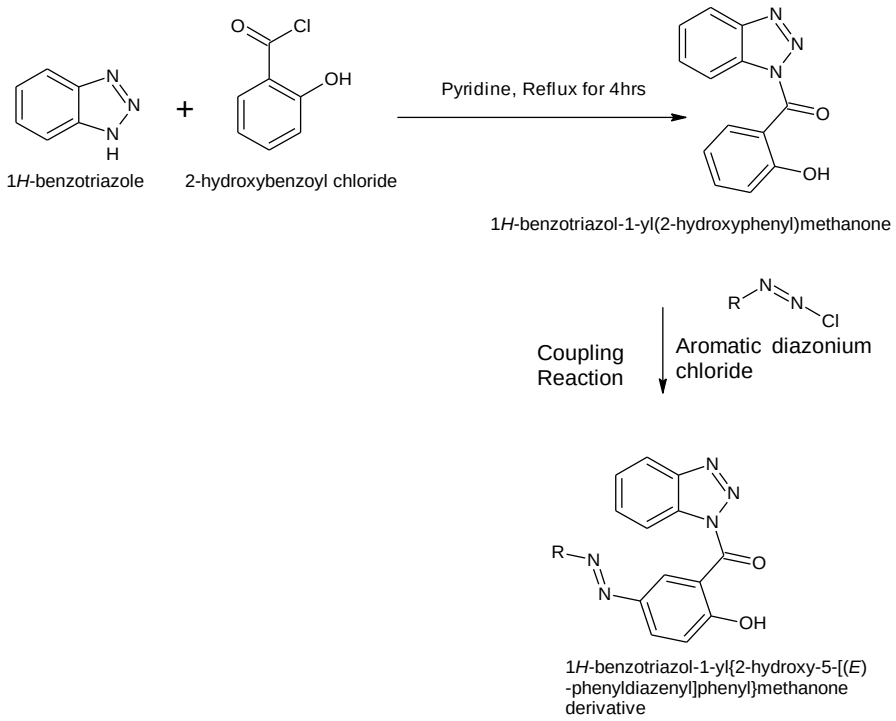
Results: The derivatives IIIc and IVc showed highest antimicrobial activities when compared to standard. The Ic, IIc and IVc derivatives showed good antifungal activities. Rest of the derivatives showed medium antibacterial and antifungal activities.

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 benzotraizole 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 $CHCl_3$, and dried in a vacuum desiccators for 15 hr to give 5.12 g (90%) of as a white powder.

Synthesis of 1*H*-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 1*H*-benzotriazol-1-yl{2-hydroxy-5-[(*E*)-phenyldiazenyl]phenyl}methanone (Ic): the aniline (0.1M) was converted to dizoniun 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-(1*H*-benzotriazol-1-ylcarbonyl)-4-hydroxyphenyl]diazenyl}benzoic acid (IIc): the p-amino benzoic acid was converted to dizoniun 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 1*H*-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 1*H*-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*, NH_2). 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.

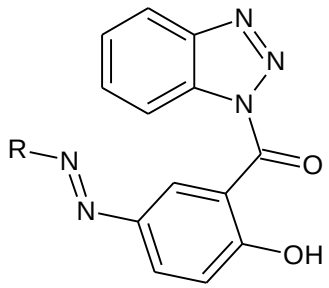
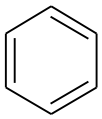
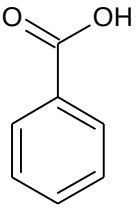
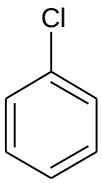
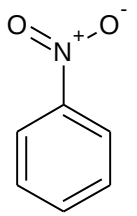
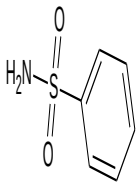


Fig. 1: General structure of 1*H*-benzotriazol-1-yl {2-hydroxy-5-[(*E*)- phenyldiazenyl] phenyl} methanone derivatives

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

Derivative	Mol. Formula	Derivative Name	R	%Yield	MP	Mol Weight
Ic	$C_{19}H_{13}N_5O_2$	1*H*-benzotriazol-1-yl{2-hydroxy-5-[(*E*)-phenyldiazenyl]phenyl}methanone		56	80°C	343.33
IIc	$C_{20}H_{13}N_5O_4$	4-{(*E*)-[3-(1*H*-benzotriazol-1-ylcarbonyl)-4-hydroxyphenyl]diazenyl}benzoic acid		45	98°C	387.34
IIIc	$C_{19}H_{12}N_5O_2Cl$	1*H*-benzotriazol-1-yl{5-[(*E*)-(4-chlorophenyl)diazenyl]-2-hydroxyphenyl}methanone		58	135°C	377.78

IVc	$C_{19}H_{12}N_6O_4$	1*H*-benzotriazol-1-yl{2-hydroxy-5-[(*E*)-(4-nitrophenyl)diazenyl]phenyl}methanone		66	120°C	388.33
Vc	$C_{19}H_{14}N_6O_4S$	4-{(*E*)-[3-(1*H*-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 Norfloxacine 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. albicanus* 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.

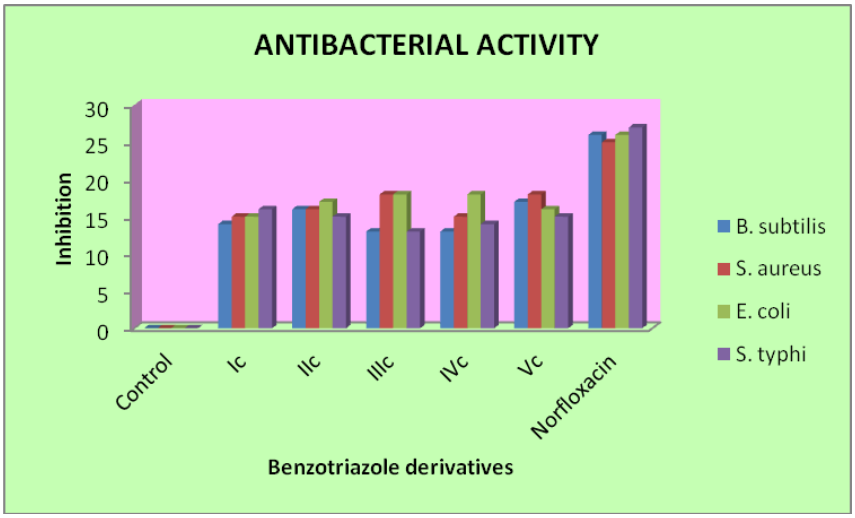


Fig. 2: Graphical representation Antimicrobial activity.

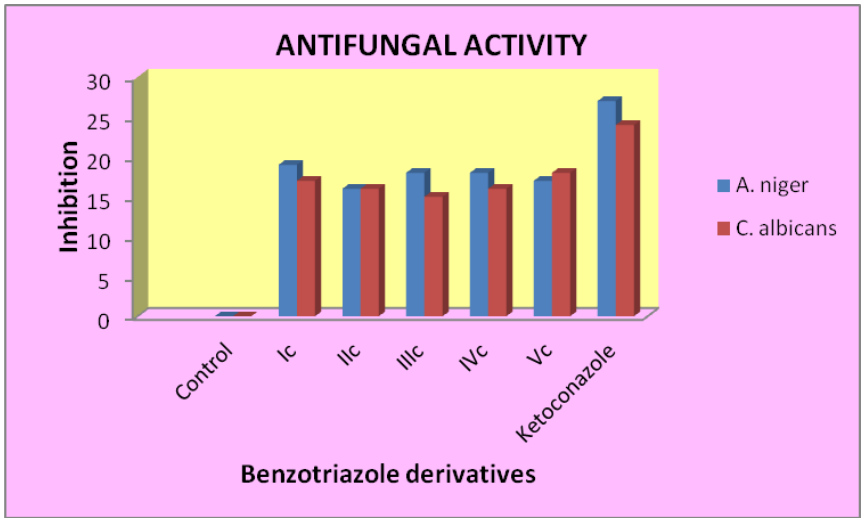


Fig. 3: Graphical representation Antifungal activity

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.

ACKNOWLEDGEMENTS

Authors are thankful to Shri. G. D. Patil Secretary Shree Warana Vibhag Shikshan Mandal Warananagar for providing laboratories facilities. Authors are thankful to Mrs. Dr. U. S. Chougule and Mr Krishnath Paymal, Staff of Organic Chemistry Department IISc Bangalore, CFC and Chemistry Dept of Shivaji University for kind assistance in microbial and spectral data.

REFERENCES

1. MA Rahman. Chalcone: A Valuable Insight into the Recent Advances and Potential Pharmacological Activities. Chem Sci J 2011;29:1-16.
2. KM Dawood, HA Gawad, EA. Rageb, M Ellithey, HA Mohamed. Synthesis, anticonvulsant, and anti-inflammatory evaluation of some new benzotriazole and benzofuran-based heterocycles. Bioorg Med Chem 2006;14 :3672–80.
3. YA Al-Soud, NA Al-Masoudi, ARS Ferwanah. Synthesis and Properties of New Substituted 1,2,4-Triazoles:Potential Antitumor Agents. Bioorg Med Chem 2003;11;1701-08.
4. Bretne Maria et al. Synthesis and biological activity of 1*H*-benzotriazole and 1*H*-benzimidazole analogues – inhibitors of the NTPase/helicase of HCV and of some related *Flaviviridae*. Antiviral Chemistry & Chemotherapy 2005;16:315–26.
5. C. M. Jamkhandi, J. I. Disouza. Benzotriazole Derivatives as Antimicrobial Agents. Asian J Biochem Pharm Res 2012;3 (2):123-130.
6. BV Suma, NN Natesh, V Madhavan. Benzotriazole in medicinal chemistry: An overview. J Chem Pharm Res 2011;3(6):375-81.
7. Katritzaky AR et al. Dye Labeling of Nucleoside. Center for heterocyclic compounds: 396- 402.
8. Murphy AR et al. Modification of silk fibroin using diazonium coupling chemistry and the effects on hMSC proliferation and differentiation. Biomaterials 2008;29:2829–38.
9. C.M. Jamkhandi, J. I. Disouza. Synthesis and Antimicrobial Evaluation of 2-(1H-1,2,3-Benzotriazol-1-yl)-N-Phenylacetamide derivatives. Res J Pharm Tech 2012;5(8): 1072-75..
10. C.M. Jamkhandi, J. I. Disouza. Synthesis and Antimicrobial Evaluation of [(1*H*-benzotriazol-1-ylacetyl) amino] acetic acid Derivatives. Research Res J Pharm Tech 2012;5(9):1197-200.
11. B. V. Suma, N. N. Natesh, CHS Venkatraman, J Jays, V. Madhavan. Synthesis and antibacterial activity of some new 1, 2, 3-Benzotraizole derivatives containing Pyrozolidinedione moieties. Int J Pharm Pharm Sci 2011; 4(1): 169-73.
12. C.M. Jamkhandi, J. I. Disouza. Evaluation of Antioxidant Activity for Some Benzotriazole Substituted with N-Phenylacetamide and acetylcarbamic acid Derivatives. Int J Pharm Pharm Sci 2013;5(2), Article in Press.
13. Vogel's Text Book of Practical Organic chemistry; 4th Edn. Longman Group Ltd 1978; p124.
14. Gerard Vogel H. Drug Discovery and Evaluation. 2nd ed. Springer – Verlag Berlin Heidlbrg New York 2002. p.49.
15. Bansal. RK. Heterocyclic Chemistry, 4th .New Age International Publishers.2005;p 475.