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Synthesis, Characterization and Biological Evaluation of Some Novel *5-(Benzotriazole 1-Yl-Methyl)-2-Phenyl-1, 3, 4-Oxadiazole* Azo Compounds as a Anti-Microbial Agents

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Abstract: In the present study a series of *5-(benzotriazole 1-yl-methyl)-2-phenyl-1,3,4-oxadiazole* azo derivatives were prepared from benzotriazole and ethyl chloro acetate through an effective synthetic scheme and determined its anti-microbial activity by using disc diffusion method. All the titled compounds were characterized by IR, H-NMR and MASS spectroscopy. Most of the compounds were exhibited excellent anti-microbial activity due to the presence of benztriazole and oxadiazole. The entire titled compounds anti-microbial activities were tested against the standard drug.

Key words: Benzotriazole · Ethyl chloro acetate · Azo dye and anti-microbial activity

INTRODUCTION

Bentriazole nucleus containing molecules are an important class of heterocyclic compound holding three nitrogen atoms are fused with benzene ring is exhibiting a wide pharmacological activities such as anti-bacterial [1-4], anti-tubercular [5], anti-inflammatory, anti-convulsant [6], DNA cleavage [7], herbicidal [8] and anti-viral [9] etc., In addition to that, in the year of 1977 United State environmental protection agency reported that benzotriazole molecules are to be very less toxic, low hazard and safest molecules for human beings. Research on Oxadiazole is says that it is another class of heterocyclic compounds plays an important role in the medicinal chemistry for more than a two decades. It shown a least drug resistant when the nucleus properly substituted at second and fifth position. From the existing literature, we came to know that oxadiazole containing molecules act as an Anti-bacterial [10-15], anti-fungal [16, 17], anti-inflammatory and muscle relaxant activity [18]. So, we decided to combine these heterocyclic nucleuses together to prepare novel heterocyclic compounds and we hope that it would be more biologically active than individual nucleus containing compounds. The entire synthesized compound structures were confirmed by spectral results and biological activities were ascertained by disc diffusion method against the standard drugs.

MATERIAL AND METHODS

The chemicals and reagents used in this project were of LR and analytical grade. We were bought it from varies company like Merk, Sigma and Ranboxy and Alrich. All the synthesized compounds sharp melting points were identified by open capillary tube method. In this project each intermediates as well as final product purity were ascertained by TLC using silica gel as a stationary phase and mobile phase consist of a mixture of n-hexane and ethyl acetate. IR of synthesized compounds was done with FT-IR spectrophotometer in the range of 400 to 4000 cm^{-1}. ^{1}H-NMR was recorded on NMR spectrometer and chemical shift (δ) was found in parts per million. Mass spectra were recorded on Shimadzu mass spectrometer. All those apparatus which is used in this project were in excellent condition before starts our work.

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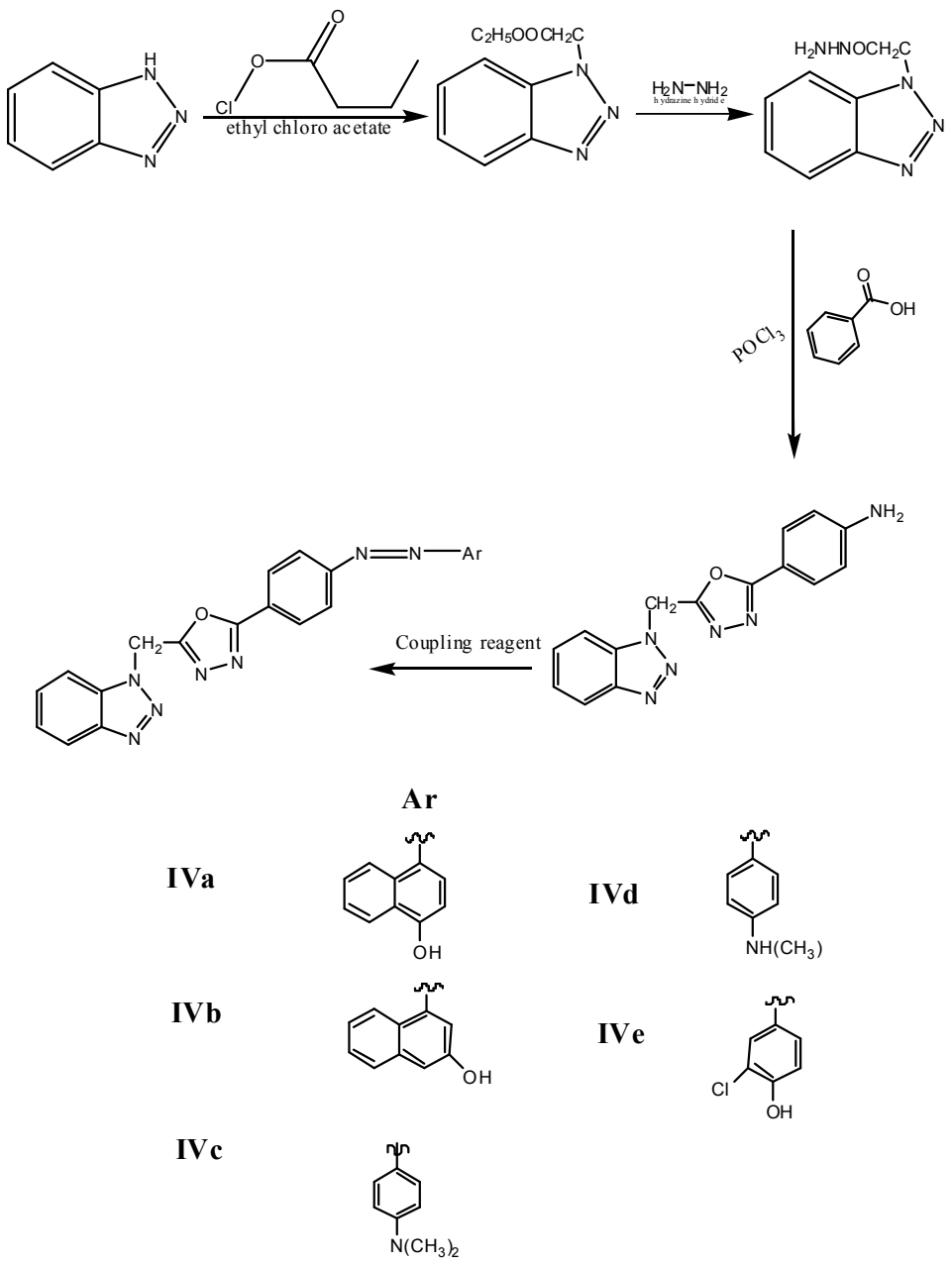
Scheme of Synthesis



Step-1

Synthesis of (ethyl 2-(1h benzo [1,2,3] triazole-1-yl)acetate: A mixture of benzotriazole (0.01 mole), ethyl chloro acetate (0.01 mole) and potassium carbonate 3g were taken in a beaker contained 60ml of acetone and stirred forcefully for 6 hours. The solid mass was obtained as a needle shaped brown crystals.

Step-2

Synthesis of (2h benzo [1,2,3] triazole-1-yl aceto hydrazine): Ethanolic solution of ethyl 2-(1h benzo [1,2,3] triazole-1-yl)acetate (step-I) was taken in a round bottom flask and add hydrazine hydrate 20ml into the flask and then refluxed on water bath for 3 hours. The excess solvent removed by distillation. The solid crystals was obtained, filtered and re-crystallized from ethanol.

Step-3

Synthesis of 5-(benzotriazole 1-yl-methyl)-1,3,4-oxadiazole-2yl)benzenamine: 2H benzo [1, 2, 3] triazole-1-yl aceto hydrazine (step-II) was refluxed with p-amino benzoic acid in the presence of phosphorous oxy chloride (10ml) for 6 hours. The content was then poured into ice-cold water and basified with sodium bi carbonate solution. The product was separated out as a solid.

Step-4

General Method of Preparation of Azodyes: 5-(benzotriazole 1-yl-methyl)-1,3,4-oxadiazole-2yl)benzenamine was treated with sodium nitrite and hydrochloric acid at 0-5°C, the unstable diazonium salt is stabilized by reacting with suitable coupling reagents.

RESULT AND DISCUSSION

4-(5((1h-benzo[d][1,2,3]triazol-1-yl)methyl)-1,3,4-oxadiazol-2yl)-N-phenzyl)diazenyl)naphthalen-1-ol(IVa): Yield 65%, M.P- 123°C; IR (KBr): 3024 (Ar-H str), 1220 (Ar-H, ben), 1627 (C=N), 1245 (C-N), 3238 (Ar-OH, Str), 1256(Ar-OH, ben); NMR ($CDCl_3$)- δ6.80 – 7.10(S,4H,Ar-H), δ7.23 - 7.36(d,3H,Ar-H), δ7.46 – 7.72(t,2H,Ar-H), δ7.81 – 7.98(d,3H,Ar-H), δ8.07 – 8.38(m,2H,Ar-H), δ4.8-4.9(S,3H,CH_2-H and OH-H); Mass(m/z)-447(M^+).

4-(5((1h-benzo[d][1,2,3]triazol-1-yl)methyl)-1,3,4-oxadiazol-2yl)-N-phenzyl)diazenyl)naphthalen-2-ol(IVb): Yield 74%, M.P- 126°C; IR (KBr): 3070 (Ar-H str), 1245 (Ar-H, ben), 1600 (C=N), 1214 (C-N), 3456 (Ar-OH, Str), 1175 (Ar-OH, ben); NMR ($CDCl_3$)- δ6.82 – 7.15(d,4H,Ar-H), δ7.24 - 7.46(m,3H,Ar-H), δ7.51 – 7.80(m,2H,Ar-H), δ7.85 – 7.91(d,3H,Ar-H), δ8.12 – 8.45(m,2H,Ar-H), 5.10-5.16(S,3H,CH_2-H and OH-H), Mass(m/z)-447(M^+).

4-(5((1h-benzo[d][1,2,3]triazol-1-yl)methyl)-1,3,4-oxadiazol-2yl)-n-phenzyl)diazenyl)n,n-dimethylbenzenamine (IVc): Yield 65%, M.P- 91°C; IR (KBr): 3033 (Aromatic proton streaching), 1210 (Aromatic proton bending), 1676 (C=N), 1275 (C-N); NMR ($CDCl_3$)- δ6.85-6.90 (d,2H,Ar-H), δ7.15 –7.48(m,2H,Ar-H), δ7.57 –7.61(d,4H,Ar-H), δ7.69-7.87(d,2H,Ar-H), δ7.91-8.09 (m,2H,Ar-H), δ5.06-5.09(S,2H,CH_2-H), δ2.84-2.92 (S,6H,CH_3-H); Mass(m/z)-424(M^+).

4-(5((1h-benzo[d][1,2,3]triazol-1-yl)methyl)-1,3,4-oxadiazol-2yl)-N-phenzyl)diazenyl)N-methylbenzenamine (Ivd): Yield 65%, M.P- 186°C; IR (Kbr): 3087 (Aromatic proton streaching), 1214 (Aromatic proton bending), 1610 (C=N), 1365 (C-N); NMR ($CDCl_3$)- δ6.86-6.94(d,3H,Ar-H), δ7.12 –7.49(m,2H,Ar-H), δ7.53 –7.67(m,5H,Ar-H), δ7.81-8.04(m,2H,Ar-H), δ5.02-5.05(S,2H,CH_2-H), δ4.22-4.26(S,1H,NH-H), δ2.87-2.95 (S,3H,CH_3-H); Mass(m/z)-410(M^+).

4-(5((1h-benzo[d][1,2,3]triazol-1-yl)methyl)-1,3,4-oxadiazol-2yl)-N-phenzyl)diazenyl)2-chlorophenol (IVe) Yield 65%, M.P- 104°C; IR (KBr): 3005 (Ar-H str), 1143 (Ar-H, ben), 1613 (C=N), 1265 (C-N), 3560 (Ar-OH, Str), 1145 (Ar-OH, ben), 774 (chlorine); NMR ($CDCl_3$)- δ6.51 – 6.55(d,2H,Ar-H), δ6.74 - 6.86(m,2H,Ar-H), δ7.01 – 7.23(m,3H,Ar-H), δ7.45 – 7.57(S,1H,Ar-H), δ7.72 – 7.82(m,3H,Ar-H), 5.10- 5.16(S,3H,CH_2-H and OH-H); Mass(m/z)-431(M^+).

IN-VITRO Anti-microbial Result

Paper Disc Diffusion Method: Disc diffusion method [19, 20] was employed to find out the anti-microbial activity of the titled compounds from its zone of inhibition. To find out the anti-microbial activity of the synthesized drugs a sterilized (autoclaved at 120°C for 30 min) culture medium (40-50°C) was prepared and poured in to the Petric plate to give a depth of 3-4 mm and cool it for 15 minutes. The paper impregnated with the titled compounds (IVa-e) (100µg/ml in dimethyl formamide) and standard drugs (100µg/ml in dimethyl formamide) were placed on solidified culture medium and incubated at 37°C for a minimum of 24 hours. *In vitro* anti-microbial activities of IVa-e were found excellent against varies micro organism such as *E coli*, *S.Aureus*, *B.Subtilis*, *P.Vulgaris*, *C.Albicons* and *A.Niger*. Compound IVe shown excellent anti-microbial activities through its zone of inhibition (mm) against *E coli*, *S.Aureus*, *B.Subtilis*, *P.Vulgaris*, *C.Albicons* and *A.Niger* are 18, 21, 18, 14, 14 and 16 respectively, which is very close result with the standard drugs. Some of the synthesized compounds IVa, IVb showed almost moderate anti-microbial activates compare to the standard drug. In this experiment ciprofloxacin (100µg/ml) was using as a standards for anti-bacterial activity and Ketoconazole for anti-fungal activities, respectively. The zones of inhibition of synthesized compounds were depicted in table 1 and Comparisons of anti-microbial activity of all synthesized compounds with the standard drugs were shown in Figure 1 and Figure 2.

Table 1: The Observed Anti-microbial Zone of Inhibition (mm) of Synthesized Compounds (IVa-e)

	Zone of inhibition of anti-bacterial Activity (100 µg/ml)				Zone of inhibition of anti-fungal Activity (100 µg/ml)	
S.NO	E.Coli	S.Aureus	B.Subtilis	P.Vulgaris	C.Albincans	A.Niger
IVa	15	17	16	12	12	13
IVb	13	14	14	11	10	12
IVc	10	13	15	11	12	11
IVd	09	11	14	10	10	10
IVe	18	21	18	14	14	16
Ciprofloxacin	22	24	20	16	-	-
Ketaconazole	-	-	-	-	17	18

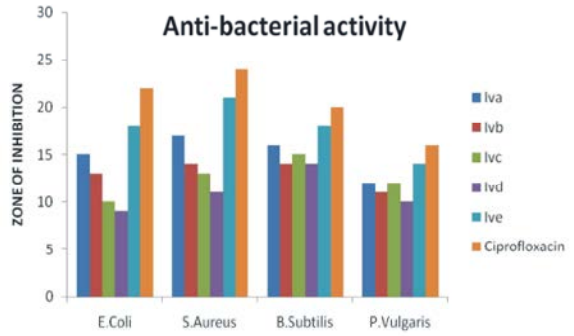


Fig. 1:

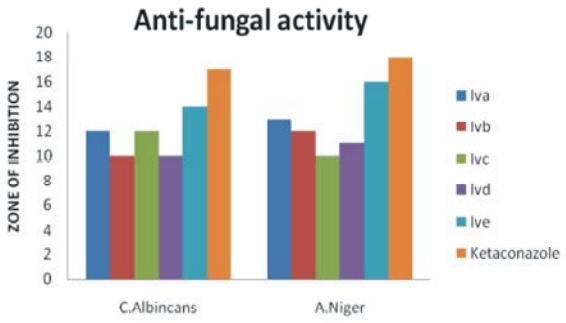


Fig. 2:

CONCLUSIONS

Novel azo derivatives (IVa-e) were synthesized and investigated their anti-microbial activities against standard drugs. Benztriazole and oxadiazole both the nucleus has a unique benefit in therapeutic field more than two decades. In addition to that, due to the existence of azo dye group in titled compounds improves the anti-microbial activity considerably. Among the titled compounds, compound Ive exhibited excellent antimicrobial activity due to the presence of electron withdrawing group as a part of the structure of the molecule. So, compound IVe would be consider as a reference molecule to develop the novel class of anti-microbial agent and it deserves for further investigation.

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