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Effect of Naphthoxazole derivatives *i.e.*, 4-(1, 3-benzoxazol-2-yl)-2- phenylnaphtho[1, 2-*d*] [1, 3] oxazole on Salmonella typhoid

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ABSTRACT:

Naphthoxazole derivatives *i.e.*, 3-(1,3-benzoxazol-2-yl) naphthalen-2-ol was synthesized at 130–135^{0}C in the presence of PCl_3 from 3-hydroxynaphthalene-2-carboxylic acid and 2-amino phenol in chlorobenzene. These compounds were characterized by mass spectra, FT-IR and elemental analysis. Antibiotics activity of these compounds was analyzed against Salmonella typhi by using serial dilution method.

Key word: Naphthoxazole, Antibiotic activity, Salmonella typhi, Mass spectra

INTRODUCTION:

At present scenario typhoid fever is important global public health problems, 21.6 million cases and approximately 250,000 deaths annually (J. A. Crump, *et al.,* 2004; A. Kothari, *et al.,* 2008). Typhoid fever is caused by Salmonella typhi. It is estimated that more than 90% of typhoid fever cases were reported in South and Southeast Asian countries (J. A. Crump, *et al.,* 2004;). In many parts of the world, the changing modes of presentation and the development of multidrug resistance have made enteric fever increasingly difficult to diagnose and treat. Multidrug resistant (MDR) occurs against all the three first-line recommended drugs for its treatment that is chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole (S. Kumar, *et al.,* 2008). There had been reports on resistance of Salmoella species against antimicrobial used, beginning with the report of chloramphenicol resistance in 1972 to the report of multidrug resistant strains (C. K. J. Paniker, 1972; M.L. Ackers, 2000).

Due to wide spectrum of biological and photometric activity of naphthoxazole may be used as drug resistant against Salmonella. Naphthoxazoles are important class of heterocyclic compounds because of their wide spectrum of biological and photochromatic activities. 2- Substituted naphthoxazole is a major subunit occurring in a number of biologically active compounds (Devinder K, *et al.,* 2002) and natural products (Sato Y, 1998). They find extensive use as fluorescent probes and as intermediates for dyes (Abbady M A 1966).Ortho substituted naphthoxazole derivatives show promising inhibitory activity for protein tyrosine phosphatase-1B (PTB-1B) and in vivo antidiabetic activity in SLM, STZ-S and db/db mice models. A number of naphthoxazole derivatives possessing antifungal, antiinflammatory, antitumour and antiHIV (Oren, I., 1999) activities have been reported. Some of the phenylaminonaphtho[1,2-d]oxazol-2-yl type compounds were reported as a sensor for water

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in organic solvents by photo-induced electron transfer (PET). There are reports available describing the synthesis and biological activity of naphtho[1,2-d][1,3]oxazole and benzoxazole separately. However, there are no reports available describing synthesis and biological activity of benzoxazole derivatives incorporated with naphthoxazole heterocycles in a single moiety. Therefore, as a part of ongoing research work on synthesis of biologically important fused heterocycles, we report here the synthesis of novel 4-(1,3-benzoxazol-2-yl)-2- phenylnaphtho[1,2-d] (Saitz, C., 2001) oxazole derivatives and their antimicrobial activity study. The synthesized derivatives are the structural analogues of bis (benzoxazole) natural product UK-1, a secondary metabolite with interesting biological activity. This UK-1 was also found to be fluorescent, on excitation at 335 nm, it emits at 530 nm.

It binds to double strand DNA 10 times more tightly in the presence of Mg2+ than in its absence. The decrease in emission intensity is the detection tool for its binding with DNA strand. It is also used as inhibitor of human topoisomerase II. It shows wide spectrum of potential anticancer activity against leukemia, lymphoma, and certain solid tumour derived cell lines. The benzoxazole derivatives are used as fluorescent probes (Dey, J. K,; 1990) and sensors for the detection of different metal ions.

In this study, we have synthesis the noval derivatives of compound Naphthoxazole *i.e.,* 4-(1, 3-benzoxazol-2-yl)-2- phenylnaphtho[1, 2-d][1, 3] oxazole. In addition, we explore its role against the microbe Salmonella typhi that cause typhoid fever in human, we observed this derived compound kill microbe Salmonella typhi, and can be used as drug to against typhoid fever.

Material Methods:

For knowing the effect of Naphthoxazole derivatives *i.e.,* 4 - (1, 3-benzoxazol-2-yl) - 2-phenylnaphtho [1, 2-d] [1, 3] oxazole on Salmonella typhoid. All reagents are used commercial grade. FT-IR spectra were recorded on a Perkin Elmer 257 spectrometer using KBr discs. Mass spectra were recorded on Finnigan Mass spectrometer. The absorption spectra of the compounds were recorded on a Spectronic Genesys 2 UV-Visible spectrophotometer; UV-Visible emission spectra were recorded. Antimicrobial activity was measured by culture.

2.1 Experimental procedure for the synthesis of naphthalen-2-ol :

A mixture of 2-aminophenol 2 (1.09g 0.01 mol) and 3-hydroxynaphthalene-2-carboxylic acid (1.88 g 0.01 mol) was refluxed (133–135^{0}C) in chlorobenzene (10mL) in the presence of PCl_3 (2 g, 1.3mL, 0.01 mol) for 4 h. After completion of reaction, the solid product was precipitated out and was filtered to get crude product 3(yield 80%) which was further recrystalized form ethanol.

2.2 Experimental procedure for the synthesis of 1-amino-3-(1,3-benzoxazol-2-yl) naphthalen-2-ol :

The azo compound 6 (4.45 g 0.010 mol) was heated in water containing NaOH (3.51 g, 0.088) at 50^{0}C and sodium dithionate (3.78 g 0.025 mol) was added at 90^{0}C in portions over period of 1 h. The mixture was heated at 90^{0}C at pH 8–9 until the colour of azo get disappeared (1.5 h). The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mass

was neutralized up to pH 7, filtered and washed well with water 2–3 times and dried well to afford crude 1-amino-3-(1,3-benzoxazol- 2-yl) naphthalen-2-ol 7 in 66% yield. Crude product was recrystalized in ethyl alcohol.

RESULTS AND DISCUSSION:

The synthetic scheme for the preparation of 2-phenylnaphtho [1, 2-d] [1,3]oxazole derivatives is shown. naphthalen-2-ol was prepared by reported procedure from 3-hydroxynaphthalene-2- carboxylic acid 1 and 2-aminophenol 2 in the presence of PCl_3 in chlorobenzene at 130–135^{0}C (Rangnekar D W, 1986). Sulphanilic acid was diazotized to get 4-sulphobenzenediazonium chloride 5, which was further coupled with 3 to get azo compound 6. This azo compound 6 was reduced by using sodium dithionate at pH 8–9 to get 1-amino-3- (1,3-benzoxazol-2-yl)naphthalene-2-ol 7 (NCCLS, 2000) which was confirmed by mass spectral analysis and its M+1 peak was found to be at 277.1. 2-phenylnaphtho [1, 2-d][1,3] oxazole derivatives were synthesized by three different routes from intermediate 1-amino-3- (1,3-benzoxazol-2-yl) naphthalen-2-ol.

PREPARATION OF THE PLATES:

Plates were prepared under aseptic conditions. A sterile 96 well plate was labeled. A volume of 100µL of test material in 10% (v/v) DMSO (usually a stock concentration of 4 mg/ml) was pipette into the first row of the plate. To all other wells 50 µL of nutrient broth was added. Serial dilutions were performed using a multichannel pipette. Tips were discarded after use such that each well had 50 µL of the test material in serially descending concentrations. To each well, 10 µL of resazurin indicator solution was added. Using a pipette 30 µL of 3.3 × strength isosensitized broth added to each well to ensure that the final volume was single strength of the nutrient broth. Finally, 10 µL of bacterial suspension (5 × 106 cfu/ mL) was added to each well to achieve a concentration of 5 × 105 cfu/ mL. Each plate was wrapped loosely with cling film to ensure that bacteria did not become dehydrated. Each plate had a set of controls: a column with a broad-spectrum antibiotic as positive control, a column with all solutions with the exception of the test compound, and a column with all solutions with the exception of the bacterial solution, adding 10 µL of nutrient broth instead. The plates were prepared in triplicate, and placed in an incubator set at 37^{0}C for 18–24 h. The colour change was assessed visually. Any colour changes from purple to pink or colourless were recorded as positive. The lowest concentration at which colour change occurred was taken as the MIC value. The average of three values was calculated and that was the MIC for the test material and bacterial.

PHOTOPHYSICAL PROPERTIES:

All synthesized compounds are fluorescent and were studied for their photophysical properties. Their absorption and emission properties were recorded in DMF. All these compounds absorb from 296 to 332 nm and emit from 368 to 404 nm with good Stokes shift ranges from 39 to 108 nm. Out of these compounds, 4-(1,3-Benzoxazol-2-yl)-2-Phenylnaphtho[1,2-d][1,3]oxazole shows good Stokes shift with 108 nm. As compared to 4 - (1,3-Benzoxazol-2-yl)-2-(4-nitrophenyl)naphtho[1,2-d][1,3]oxazole, 4-[4-(1,3-Benzoxazol-2-yl)naphtho [1,2-d][1,3]oxazol-2-yl]phenol shows larger Stokes shift, this property attributed due to electron donating ability of – OH in 4-[4-(1,3-Benzoxazol-2-yl)naphtho[1,2-d][1,3]oxazol-2-yl]phenol for easy

flow of electron from 4-OH phenyl ring to benzoxazole ring via fused naphthoxazole ring system and electron withdrawing ability of – NO_2 in 4-(1,3-Benzoxazol-2-yl)-2-(4-nitrophenyl)naphtho [1,2- d][1,3]oxazole. An effective compound for the biological application should have good fluorescent intensity, high quantum yield and high photo stability. Quantum yield of all compounds were recorded by using tinopal as a reference standard. Absorption and emission characteristics of standard as well as unknown samples were measured at different concentration of unknown samples and standard at (2, 4, 6, 8 and 10 ppm level). Absorbance intensity values were plotted against emission intensity values. A linear plot was obtained. Gradients were calculated for each unknown compound and for standard. All the measurements were done by keeping the parameters such as solvent and slit width constant. Relative quantum yield of all synthesized compounds were calculated by using the formula.

Antimicrobial activity

The novel compounds were evaluated for their in vitro antibacterial activity against *E. coli* and *S. aureus* strains and in vitro antifungal activity against C.albicans and A. niger strains by using serial dilution method. The minimum inhibitory concentration (MIC) was determined for the compounds. The MIC (µg/mL) values recorded in table indicate that most of the tested compounds showed variable inhibitory growth effects against tested bacterial and fungal strains. Antimicrobial data were compared with standard drug Streptomycin and Fluconazole. The MIC values from table reveals that compound 4 - (1,3-Benzoxazol-2-yl)-2-(3-Phenoxyophenyl) naphtho [1,2-d] [1,3] oxazole, 4-[4-(1,3-Benzoxazol-2-yl)naphtho [1, 2-d][1,3]oxazol-2-yl]phenol and 4-(1,3-Benzoxazol-2-yl)-2-methylnaphtho[1,2-d][1,3]oxazole showed good to moderate activity against E. coli and S. aureus. 4-(1,3-Benzoxazol-2-yl) - 2-Phenylnaphtho[1,2-d][1,3]oxazole shows activity against *S. aureus* while 4-(1,3-Benzoxazol-2-yl)-2-(4-nitrophenyl)naphtho[1,2-d][1,3]oxazole showed good activity against *E. coli.* As compared to the antibacterial activity all synthesized compounds showed good antifungal activity against antifungal strains *C. albicans* and *A. niger.* Results mentioned in table showed that compounds showed good inhibition of growth in case of C. albicans as well as *A. niger* while 4-(1,3-Benzoxazol -2-yl)-2-(3-Phenoxyophenyl) naphtho [1,2-d][1,3]oxazole showed moderate activity against both antifungal strain. Electron donating and electron withdrawing groups present on phenyl ring does not affect the growth inhibitory activity against tested bacterial and fungal strains. In general, most of the tested compounds revealed better activity against the antibacterial strain (*E. coli, S. aureus*) and antifungal strain (*C. albicans, A.niger*). Novel compounds are reactive against fungal strain as compared to bacterial strain tested over microorganisms.

Conclusion:

We have synthesized a novel phenylnaphtho [1,2-d]1,3] oxazole derivatives. The photophysical property study shows that all are fluorescent and absorbs from 296 to 332 nm while emits in the ranges of 368 to 404 nm with excellent quantum yield. These novel compounds were evaluated for in vitro antibacterial activity against *S. typhi* by using serial dilution technique. The synthesized compounds show good antibacterial. We believe

that the insights gained in this study would be useful for the development of potential drug candidates derived from naphtha [1, 2-d] (Devinder K, 2002; Tanaka K, 2001) oxazole derivatives in the development of novel anti infective agents.

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REFERENCES:

1. J. A. Crump, S. P. Luby, and E. D. Mintz, "The global burden of typhoid fever," Bulletin of the World Health Organization, vol. 82, no. 5, pp. 346–353, 2004.

2. A. Kothari, A. Pruthi, and T. D. Chugh, "The burden of enteric fever," Journal of infection in developing countries, vol. 2, no. 4,pp. 253–259, 2008.

3. S. Kumar, M. Rizvi, and N. Berry, "Rising prevalence of enteric fever due to multi drug resistant Salmonella: an epidemiological study," Journal ofMedicalMicrobiology, vol. 57, no. 10, pp. 1247– 1250, 2008.

4. C. K. J. Paniker and K. N. Vimala, "Transferable chloramphenicol resistance in salmonella typhi," Nature, vol. 239, no. 5367, pp. 109–110, 1972.

5. M.L. Ackers, N. D. Puhr, R. V. Tauxe, and E. D. Mintz, "Laboratory-based surveillance of Salmonella serotype typhi infections in the United States: antimicrobial resistance on the rise," Journal of the American Medical Association, vol. 283, no. 20, pp. 2668–2673, 2000.

6. Devinder K, Jacob M R, Reynolds M B and Kerwin S M 2002 Biorg. Med. Chem. 10 3997

7. Sato Y, Yamada M, Yoshida S, Soneda T, Ishikawa M, Nizato T, Suzuki K and Konno F 1998 J. Med. Chem. 41 3015

8. Abbady M A 1966 Preparation and application of some new naphthoxazole dyes. M. Sc. Thesis, Assiut University Assiut, Egypt

9. Chen W, Wright B D and Pang Y 2012 Chem. Commun.48 3824 Experimental procedure for the synthesis of 3-(1,3-benzoxazol-2-yl)naphthalen-2-ol (3) 151

10. Koeth L M, King A, Knight May J, Miller Phillips I and Poupard J A 2000 J. Antimicrob. Chemother. 46 369

11. Kanegae, Y., K. Peariso and S. S. Martinez (1996) Class of photo-stable, highly efficient UV dyes: 2-phenylbenzoxazoles.Appl. Spectrosc.50, 316–19.

12. Dey, J. K. and S. K. Dogra; Absorption andfluorescence characteristics of some 2-alkyl-benzoxazoles 2-aryl-benzoxazoles indifferent solvents and at various acid concentrations.Ind. J. Chem. 1990 (29), 1153–64.

13. Oren, I., O. Temiz, I. Yalcin, E. Sener and N. Altanlar Syn-thesis and antimi-crobial activity of some novel 2,5- and/or 6-substi-tuted benzoxazole and ben-zimidazole derivatives.Eur. J. Pharm. 1999; (7), 153–60.

14. Saitz, C., H. Rodriguez, A. Marquez, A. Canete, C. Jullian and A. Zanocco New synthesis of naphtho- and benzoxazoles: decomposition of naphtho- and benzoxazinones with KOH.Synth.Commun.2001(31), 135–40.

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