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To Synthesize Naphthalene Derivatives Having Isoxazole Central Core as Anti- Microbial Agents

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Abstract

The presence of heterocycles such as pyrrole, thiazole, oxazole, furane, imidazole, and isoxazole and pyrimidine nucleus as central scaffold is a common feature in the chemical structure of several antimicrobial agents. So the aim has been designed to synthesize the molecule having Naphthalene ring in one of diaryl having isoxazole as pharmacophoric heterocyclic moiety for synthesis of safer anti-microbial agents.

Keywords: Naphthalene, isoxazole, anti-microbial agents.

INTRODUCTION:

A microorganism or microbe is an organism that is microscopic (usually too small to be seen by the naked human eye). Microorganisms are very diverse; they include bacteria, fungi, archaea, and protists; microscopic plants (green algae) and animals such as plankton the planarian and the amoeba. Robert Koch (1843-1910) defined the principles of infectious diseases, namely, that a microbe causing disease in one animal when transferred to another animal produces the same disease (Koch's postulate). Koch also identified *Mycobacterium tuberculosis* and *Vibrio cholera*.[3]

Broadly, all microbes that can grow in the absence of oxygen are called anaerobic bacteria. They include clostridia, a spore-bearing anaerobe, and Gram-negative bacteria like bacteroides and fusobacteria. Microbes that require oxygen to grow are called aerobic bacteria. Those that grow in the presence of some oxygen (but not a lot) are called microaerophilic; they include *Escherichia coli, Neisseria, haemophilus* and others. Gram (1853-1938) classified all bacteria by the colour they take with the Gram's stain. Those that take a blue colour (Gentian violet) are called Gram-positive, and those that take the red stain (eosin) are called Gram-negative.[4]

MATERIALS AND METHODS:

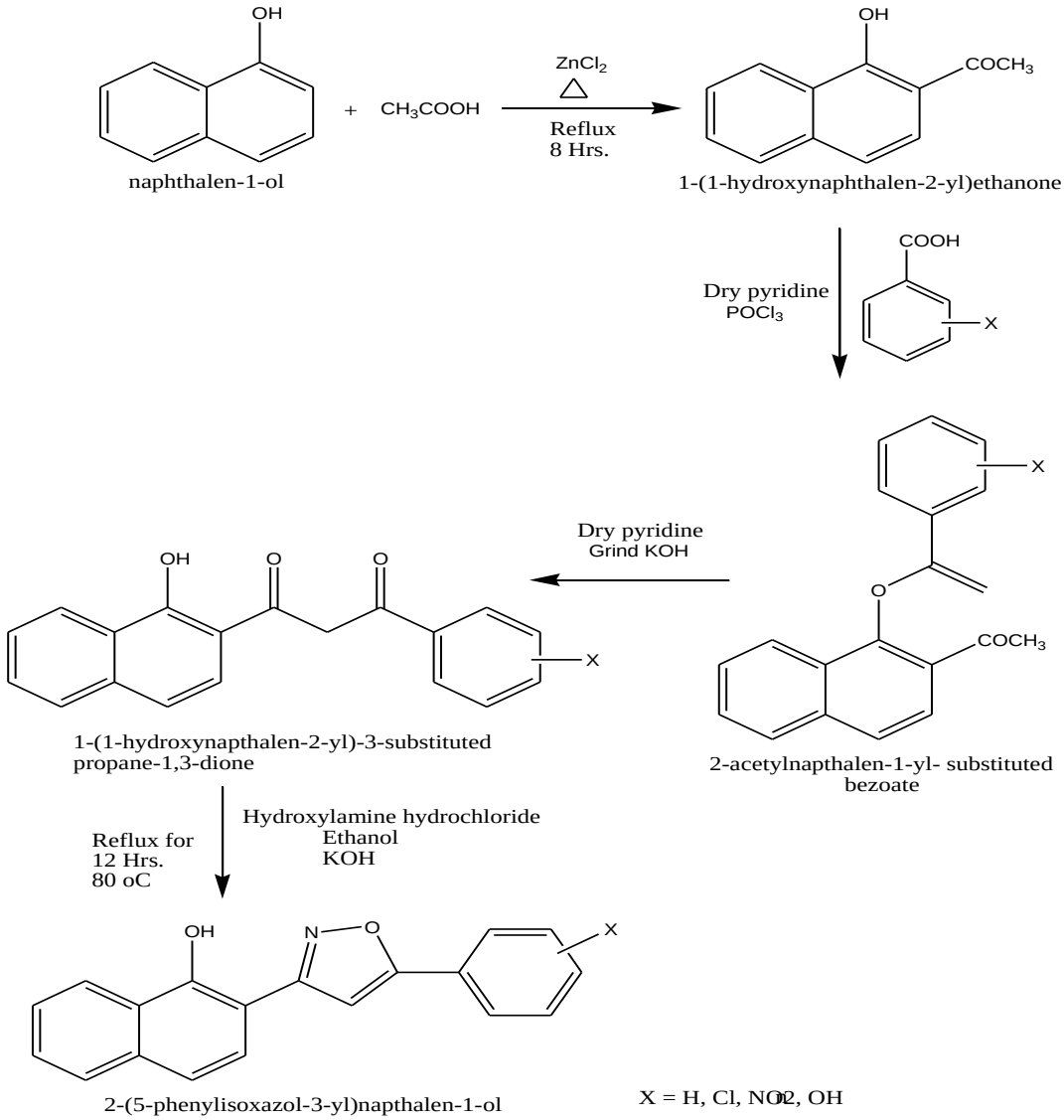
Chemicals:

The chemicals employed in the synthetic work were provided by our college.

Methods:

The identification and characterization of the compound were carried out by the following procedure to ascertain that all prepared compounds were of different chemical nature, than the respective parent compound. Physicochemical parameters have been performed as the melting points were determined by melting point apparatus. Solubility and Thin Layer Chromatography was used for monitoring the progress of reaction. UV/Visible spectra were run on JASCO / SIMADZU spectrophotometer. FTIR spectra were recorded in KBr powder on a Jasco V460 IR Spectrometer by diffused Reflectance technique. ^{1}H- NMR spectra were measured in d6-DMSO on a Bruker II Avance 400 MHz NMR spectrometer. The reported chemical shifts were against TMS. Mass spectra were recorded on a JEOL JMS600 spectrum.

Synthetic scheme:



Synthetic Procedure:-

Step 1:- Synthesis of 1-(1-hydroxyNaphthalene-2-yl) ethanone

In 80 ml hot glacial acetic acid, 50 gm zinc chloride was added and the reaction mixture was refluxed till it dissolved. Then 30 gm of 1-naphthol was added to reaction mixture and was refluxed for 8 hours. The reaction mixture was cooled and poured in acidulated water. The crude product was filtered, washed with water and recrystallized from ethanol to obtain pure product of 95.02 % w/w yield having melting point range 80-82 ºC[5]. Solvent System: - Petroleum Ether: Ethyl Acetate (8:1).

Step 2:- Synthesis of 2-acetylNaphthalene-1-yl substituted benzoate

In 100 ml of two necked RBF having dropping funnel and calcium guard tube, place 1.86 gm (0.01 mole) of 1-(1-hydroxyNaphthalene-2-yl) ethanone and 0.015 mole of substituted benzoic acid in 3.72 ml of pyridine. Stirr the mixture at 0º-10º C for near about 15 minutes. Add 1.49 ml (2.46 gm, 0.016 mole) of phosphorus oxychloride drop wise during 2 hours. When the addition was over, the mixture was poured with good stirring into ice-cold hydrochloric acid, followed by small volume of ice-cold water[6]. The product was collected on a Buchner funnel. Washing was continued till no more pyridine was present. The product was air-dried at room temperature and recrystallized from methanol. Solvent System: - hexane: Ethyl Acetate (95:05).

Step 3:- Synthesis of 1-(1-hydroxyNaphthalene-2-yl)-3-substituted propane-1, 3-

Dione:

Solution of 0.01 mole of 2-acetylNaphthalene-1-yl substituted benzoate in 11 ml of dry pyridine was prepared in 100 ml RBF and warmed to 50ºC.To this solution 1 gm of grind KOH was added. The mixture was stirred for 15-30 minutes, during which time a copius precipitates of the yellow potassium salt of 1-(1-hydroxyNaphthalene-2-yl)-3-substituted propane-1, 3-dione formed. The mixture was cooled to room temperature and acidified with 100 ml of 10 % acetic acid[7].The diketone separated which was collected on a filter, dried and recrystallized the dried product with methanol. Solvent system-chloroform: benzene (70:30).

Step 4:- Synthesis of 2-(5-substituted Phenylisoxazole-3-yl)napthalen-1-o[1]

To Take 1(-1-Hydroxynaphthlen-2-yl)-3-sustituted propane-1,3-dione (0.02 mol) and add Hydroxylamine Hydrochloride (0.02 mol) in the presence of KOH in absolute ethanol (25 ml) was refluxed on a oil bath for above 12 hrs[8-10]. Then reaction mixture was neutralised with acetic acid and whole contents

were poured in ice cold water which result the formation of creamish to light brown precipitate. Solvent system- Ethyl acetate:hexane (70:30).

Anti-bacterial activity:

All the compounds synthesize in the present investigation were screen for their anti-bacterial activity by Cup plate Method. Antibacterial activities were test on nutrient medium against, *Staphylococcus aureus* and *Escherchia coli* which are representative types of gram positive and gram negative organisms respectively. The antibacterial activities of the compounds were assessing by disc-diffusion method[11].

Method of Testing:

The sterilize media were cool to 45^{0}C with gentle shaking to bring about uniform cooling and then inoculate with 18-24 hrs old culture under aseptic conditions, mixwell by gentle shaking. This was pouring in to sterile Petri dishes (properly labeled) and allows the medium to set. After solidification all the Petri dishes were transfer to laminar flow unit[12-15]. Then the discs which were previously prepared were carefully kept on the solidified media by using sterilized forceps. These Petri dishes were kept as it is for one-hour diffusion at room temperature and then for incubation at 37^{0}C for 24 hours in an incubator. The extent diameter of inhibition after 24 hours was measure as the zone of inhibition in millimetres.

RESULT AND DISCUSSION:

Physical Characteristics:

All the synthesized compounds were light creamish to brown coloured crystalline solids. Most of the compounds are freely soluble in chloroform and other solvents like methanol, ethanol. The melting point of the compounds was in the range of 70ºC to 250ºC.

Spectral Characteristics:

IR spectra of all compounds were recorded on FT-IR 8400S Shimadzu spectrophotometer using KBr. All the synthesized compounds have shown characteristic stretching and bending in desired range. Mass spectra were obtained using. All the spectra were taken by direct infusion mass with ESI and APCI in positive and negative mode ionization ranging from 500-2000 m/e. All the compounds possess a molecular ion M^+, M+1 peak. The ^{1}H-NMR spectra of some of the compounds were studied in d6-DMSO on a Bruker II Avance 400 MHz NMR spectrometer. All the compounds show characteristic chemical shift from TMS in terms of δ ppm. δ value obtained in the desired range which signifies the presence of aromatic ring.

Physical and Spectral Characteristics of 2-(5-substituted Phenylisoxazole-3-yl) napthalen-1-ol (IIIa-c):

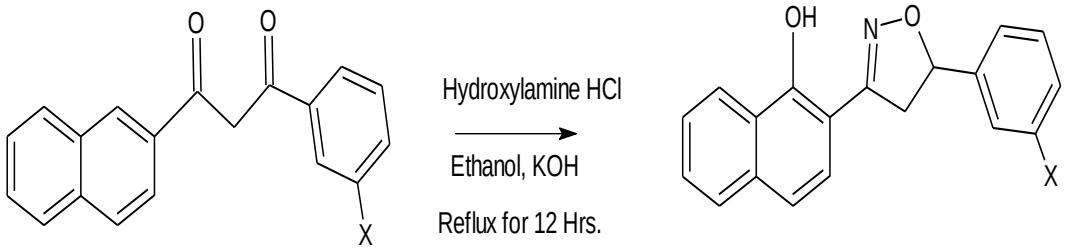


Table 1: Physical Characteristics

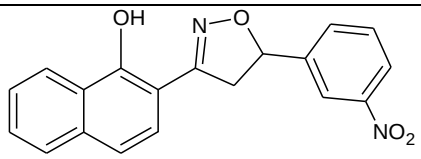
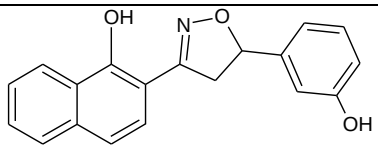
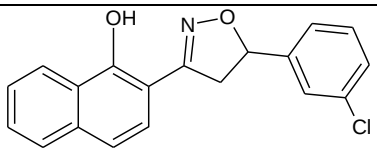
Compound	code	Mol. formula	Mol. Wt. gm/mole	Melting point (ºC)	% Yield (w/w)	Rf value
	IIIa	$C_{19}H_{14}N_2O_4$	334	147-149	72.6	0.50
	IIIb	$C_{19}H_{14}O_3$	290	153-155	68.5	0.59
 Comp-IIIc	IIIb	$C_{19}H_{13}ClO_2$	308	123-125	63.4	0.65

Table 2: Spectral Characteristics

Compound	IIIa		
Fun. group assigned	**Group frequency in Wave number (cm^{-1})**	**^{1}H-NMR**	**Mass value**
Aromatic C-H stretching	2958.90, 2885.10,2673.67	4.712 Singlet 1H, OH δ7.981-8.245, Multiplet 4H, Ar-H 7.342-7.786, Multiplet 6H, Ar-H 4.982 Singlet NO_2	The molecular weight of the compound is 334and the mass spectral data matching the same as 334.0 m/e it shows that the m+ peak.
NO_2	1558.66		
C=O	1708.95,1663.66		
C-N	1385.90		
IIIb			
Aromatic C-H stretching	2974.33,2949.26	4.781 Singlet 1H, OH δ7.934-8.287 Multiplet 4H, Ar-H δ7.421-7.864 Multiplet 6H, Ar-H δ5.134 Singlet 1H, OH	The molecular weight of the compound is 290 and the mass spectral data matching the same as 290.1 m/e it shows that the m+ peak
OH	3327.26		
C-N	1527.67		
IIIc			
Aromatic C-H stretching	2853.78,2923.22, 2956.11	5.413 Singlet 1H, OH 7.237-7.876, Multiplet 4H, Ar-H 7.893-8.457 Multiplet 6H, Ar-H 5.134 Singlet 1H, OH	The molecular weight of the compound is 308 and the mass spectral data matching the same as 308.6 m/e it shows that the m+ peak.
Cl	717.13		
C-N	1323.21		

Screening of Anti-Microbial Activity:

Table 3: Anti-bacterial activity data of synthesized compounds

Sr.No	compound	Concentration µg/ml	E.coli	S.Aureus
1	Comp-IIIa	50	12	14
		100	15	17
2	Comp-IIIb	50	9	11
		100	12	11
3	Comp-IIIc	50	9	10
		100	13	14
4	Amoxicillin	50	24	25
		100	25	25

Zone of inhibition of synthesized compounds:

* 6-8 mm poor activity, 9-11 mm moderate activity, 12-15 above good.

CONCULSION:

Brief introductions of anti-inflammatory activity and pharmacological importance, chemistry and properties of isoxazole have been summarized. All the synthesized compounds were characterized by IR, Mass and ^{1}H-NMR spectroscopy. All the compounds were evaluated for antimicrobial activity against gram positive bacteria, *Staphylococcus aureus*, gram negative bacteria *Escherichia coli.* The presence of electron withdrawing group is important for the antimicrobial activity. All the three compounds showed above good antibacterial and good antifungal activity. The presence of nitro group at position 5 is important for antifungal activity.

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