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GREEN SYNTHESIS OF NEWER ISOXAZOLE DERIVATIVES AND THEIR BIOLOGICAL EVALUATION

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ABSTRACT

Isoxazole is an azole that contains nitrogen and has an oxygen atom next to it. Isoxazole rings can be found in a range of natural substances like ibotenic acid, as well as pharmaceuticals like valdecoxib, a COX-2 inhibitor. Many lactamase-resistant antibiotics, such as cloxacillin, dicloxacillin, and flucloxacillin, contain furoxan, a nitric oxide donor that contains the isoxazolyl group. The artificial danazol, an androgenic steroid, also has an isoxazole ring. The biological actions of substituted isoxazoles have been widely documented in the literature. Disubstituted and trisubstituted isoxazoles have been found to have a wide range of biological actions, including antibacterial, analgesic, anti-inflammatory, antioxidant, and anticancer properties, agonistic activity, inhibitory activity, antihypertensive activity, and glutamate transporter activity, as well as CNS (central nervous system) activity, anti-tubercular activity, and other activities such as GABA (-amino butyric acid) agonistic activity, inhibitory activity, antihypertensive activity, and glutamate transporter activity. The current review compiles the most recent data on the biological activity of isoxazole analogs. Green synthesis is an environmentally friendly method for synthesizing variety of medicinal substances.

**Keywords: Isoxazole [1], Antimicrobial activity, Green synthesis, chalcones,
heterocyclic**

INTRODUCTION

Isoxazole is a heterocyclic molecule with five members isoxazole have a unique position.

Chalcones [10] are prepared by the ClaisenSchmidt condensation method. In this method, acetophenone is condensed with an aldehyde in presence of an aqueous sodium hydroxide solution and gives chalcone.

Isoxazoles play's a crucial role in medicinal chemistry, as one of a large spectrum of heterocycles that have been studied for creating pharmacologically relevant compounds. Isoxazole is a nitrogen-containing azole with an oxygen particle adjoining it. Isoxazoles are fragrant heterocyclic mixtures with three carbon particles, one oxygen iota, and one nitrogen molecule in their ring. Hantzsch offered the term "isoxazole" for the title five-membered completely unsaturated heterocycles because it was the isomer "oxazole" that was identified initially. The Hantzsch Widman system of naming is used for the trivial name: The prefix "iso" stands for isomer, "oxa" stands for oxygen, "aza" stands for nitrogen, and the suffix "ole" stands for the ring size. Isoxazole is the derived name for a five-membered compound. This name has been accepted by the International Union of Pure and Applied Chemistry (IUPAC) and has been used in chemical abstracts. The alternate

systematic name for 1,2-oxazole is also used in chemical abstracts. Isoxazolines are its slightly saturated analogs, and isoxazolidine is its entirely saturated analog Isoxazole, isoxazoline, and isoxazolidine structures. A large number of five-membered heterocycles containing a nitrogen atom and oxygen atoms were synthesized in the lab, with medicinal and other applications in mind. Pharmacotherapeutic activities are a type of pharmacotherapy that involves the use of drugs to by modifying the structure of the single lead molecule, some effective synthetic analogs with improved therapeutic action can be created. The isoxazole nucleus has undergone numerous alterations during the previous few years.

Isoxazole-containing compounds are a rich source of valuable medications that are used to treat infections and disorders of various etiologies. Therefore, we wanted to concentrate solely on research on the antimicrobial effects of drugs containing the isoxazole ring involving several gram positive and gram negative strains.

Unsaturated aromatic heterocyclic compounds with a ring of three carbon atoms and one oxygen atom are known as isoxazoles. The impacts of the substituent at position 1 and one nitrogen atom at position 2 can change the behavior of the isoxazole. Isoxazoles have a wide range of

pharmacological and biological effects, including, anticancer [2], antinociceptive, and anti-inflammatory [3] properties. Immunomodulatory, antithrombotic, antifungal [4], antibacterial, anti-viral [5], and anti-tubercular [7] anti-analgesic [8] properties, and antagonist of dopamine D4 receptors. The chalcones are reactive intermediates in the production of isoxazole, a compound with diverse biological properties. Because of the presence of α -unsaturated carbonyl, chalcone molecules are more physiologically active. We designed several more isoxazole derivatives and tested them for antibacterial activity in light of the foregoing findings.

The use of parallel synthesizer microwave assisted synthesis as a form of synthesis are examples of green synthesis. Green synthesis [9], an environmentally friendly method for synthesizing variety of medicinal ingredients and products, as its own set of benefits, such as lowering solvent and chemical usage, lowering emissions of specific gases and shortening reaction time.

MATERIALS

All the necessary chemicals and raw ingredients are obtained from commercial vendors and used without further purification or as received form. Benzaldehyde, acetophenone, sodium hydroxide, hydrochloride salt of ammonium hydroxide, trimethylamine,

ethanol sodium oxalate parallel synthesizer, IR spectroscopy

METHODS

Synthesis of substituted chalcones: A General procedure:

In 100ml RBF the equimolar amount of substituted benzaldehydes (0.02M) and various substituted acetophenones 10ml were taken. Then after well stirred dropwise addition of trimethylamine 80ml were initiated and completed in 5 minutes at room temperature, 20ml of methanol was added under parallel synthesizer of the reaction mass. TLC was examined after the production of solid precipitate using n-hexane as the mobile phase and water in 9:3 ratio. parallel synthesizers is discontinued after the reaction is completed (40 minutes) as determined by TLC. The precipitates were poured in ice cold water, and recrystallizes from 20% alcohol. It offers the purest form of the related chalcones

Synthesis of isoxazole derivatives; A General procedure:

In 100ml RBF, a solution of substituted chalcones (1Gm) and alcohol (10ml) was successfully synthesized. After that sodium oxalate (1.5gms) and hydrochloride salt of ammonium hydroxide (10ml) were added to the reaction mass. Then the reaction mass was then synthesized in parallel synthesizer for the duration of 20mins at (60-65 °C) TLC with mobile phase n-

hexane, water 9:3 ratio was used to monitor the progress of the reaction, after completion, After the TLC reaction the product should be determined then parallel synthesizer used to stop the reaction. For the final work up, the reaction mass was taken. The reaction mixture was then

filtered after being treated with cold alcohol, yielding a solid product that was crystallized from alcohol, mixture to obtain pure product. Some of the products were described in detail by analyzing their physical and spectral data, such as IR

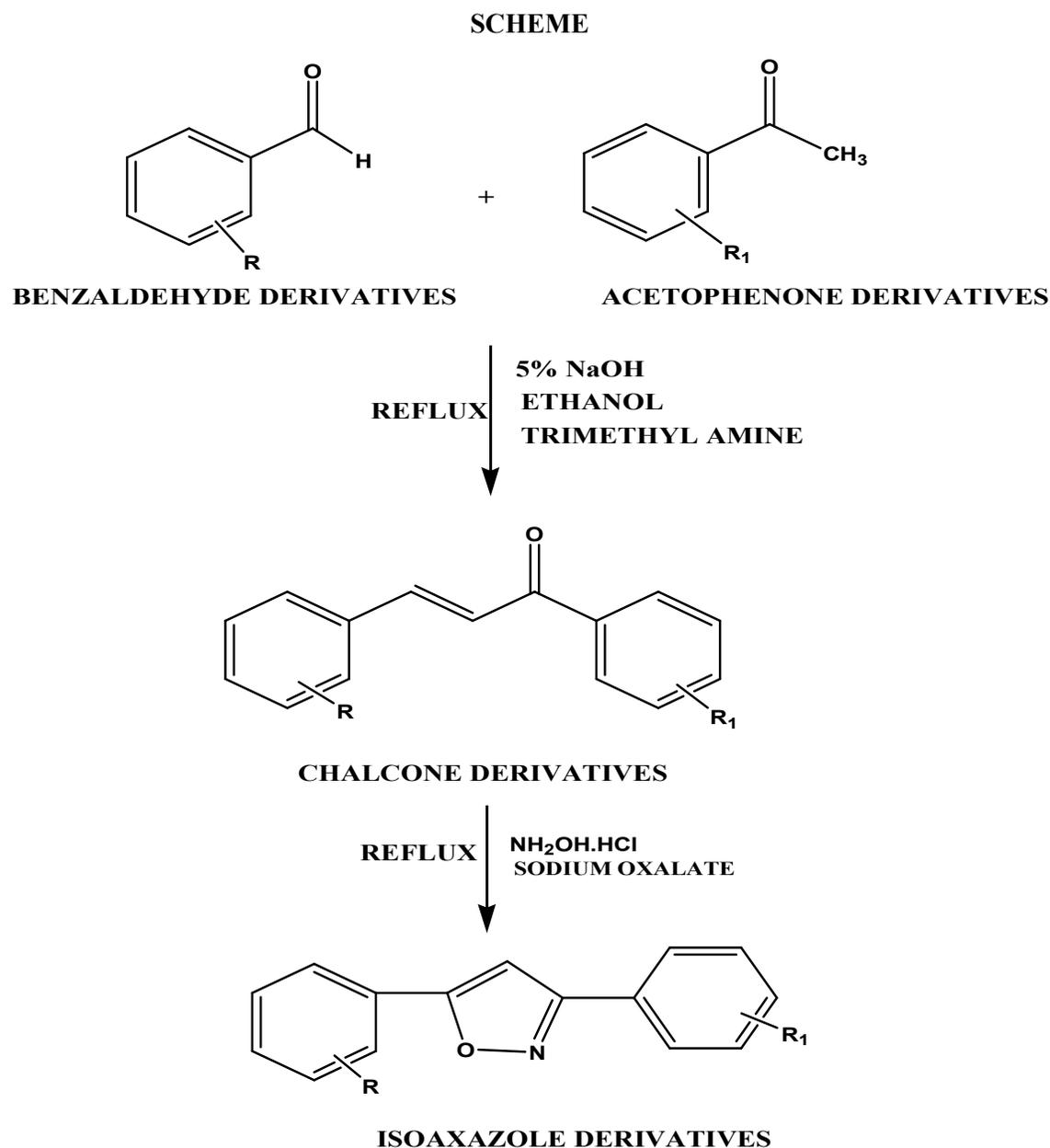


Figure 1: Isoxazole containing derivatives data

RESULTS AND DISCUSSION

The goal of this research is to create Parallel synthesizer techniques to obtain functionalized heterocycles. Synthetic tactics based on the creation of parallel synthesizer. the synthesis were carried out utilizing substituted benzaldehydes and substituted acetophenones as starting molecules. Initially trimethylamine as a base, substituted aldehydes and ketones are condensed in alcohol. As a part of chalcone derivatives in under parallel synthesizer approach as ongoing isoxazole synthesis and application of parallel synthesizer as a valuable and clean technology in chemical synthesis.

Further determination was cyclocondensation reaction between substituted chalcone derivatives hydrochloride salt of ammonium hydroxide in the presence of a catalytic quantity of sodium oxalate in a alcohol solvent to produce substituted isoxazole

To produce a fair yield of synthesized isoxazole, the present reaction was best performed under parallel synthesizer conditions in alcohol solvent at ambient temperature (60-65°C). In short period of time, derivatives 80-85% were created.

To our knowledge, this synthetic process is the best example by using parallel synthesizer it shows better promote for approach the substituted isoxazole derivatives.

Synthesis of isoxazole by using green synthesis technique with parallel synthesizer will give a better yield when compare to conventional method and parallel synthesizer is eco-friendly technique.

Table 2: isoxazole containing derivatives spectral studies

Antimicrobial property:-

The antimicrobial activity of the produced compounds was tested utilizing *E.coli* and other microorganisms *Pseudomonas aerogenosa*, *E.coli*, and *S.aureus* on nutrient agar plates, the diffusion method was utilized to test anti-bacterial activity. In a nutshell, agar (pH) is a type of agar

Table 3: Antimicrobial activity of synthesized derivatives of isoxazole

ISO-1:3-(4-methoxy-phenyl)-5-p-Tolyl-isoxazole;

$C_{17}H_{15}NO_2$ Mol wt: 265.31; IR (KBr) (cm⁻¹); 3052.78(C-H), 1785.28(C-H), 1793.24(C=O), 1672.56(C=C), 1548.35(C-O-C). M.P:174-176⁰C (GREEN SYNTHESIS YIELD):94%.

ISO-2:3, 5-BIS-(4-METHOXY-PHENYL)-ISOXAZOLE

$C_{17}H_{15}NO_3$ Molwt.: 281.31; IR (KBr) (cm⁻¹); 3042.78(C-H), 1775.28(C-H), 17914.24(C=O), 1672.56(C=C), 1544.35(C-O-C). M.P:176-178⁰C (GREEN SYNTHESIS YIELD):96%.

ISO-3:3-PHENYL-5-P-TOLYL-ISOXAZOLE

$C_{16}H_{13}NO$ mol wt: 235.28, IR (KBr) (cm^{-1}); 3042.78(C-H), 1775.28(C-H), 17912.24(C=O), 1674.56(C=C), 1544.35(C-O-C). M.P:74-76 $^{\circ}C$ (GREEN SYNTHESIS YIELD):93%.

ISO-4:3-(4-FLUORO-PHENYL)-5-PHENYL-ISOXAZOLE

$C_{15}H_{10}FNO$ Mol wt: 239.24, IR (KBr) (cm^{-1}); 3042.78(C-H), 1775.28(C-H), 17912.24(C=O), 1674.56(C=C), 1544.35(C-O-C).1248.72(C-F), M.P:138-140 $^{\circ}C$ (GREEN SYNTHESIS YIELD):92%.

Table 1:

Compound	Derivatives ®	Derivatives (R1)
ISO-1	CH ₃	OCH ₃
ISO-2	OCH ₃	OCH ₃
ISO-3	H	CH ₃
ISO-4	H	F

Table 2:

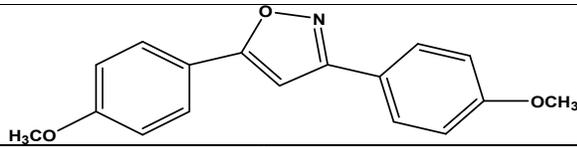
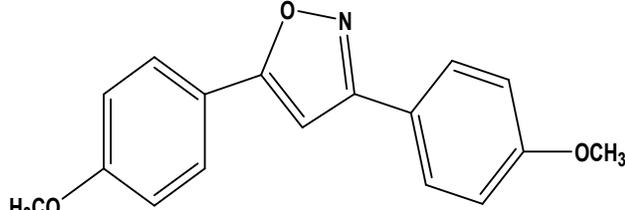
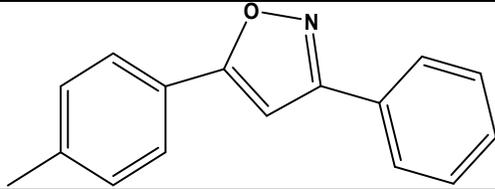
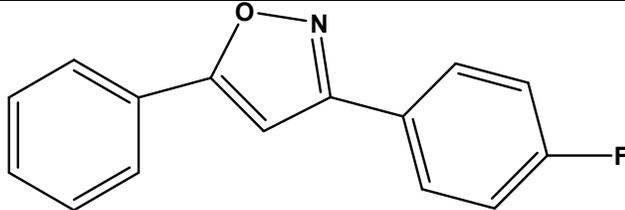
Entity	Product	Time(hr.)	%yield	M.p. $^{\circ}C$
ISO-1		1hr	94	174-176
ISO-2		1:10min	96	176-178
ISO-3		1:20mins	93	74-76
ISO-4		1:30min	92	138-140

Table 3

Compound No	<i>Bacillus Subtilis</i>	<i>Bacillus cereus</i>	<i>E.coli</i>	<i>S.pyrogenous</i>
ISO-1	6	10	9	6
ISO-2	7	11	9	5
ISO-3	7	10	8	7
ISO-4	6	9	9	6
Standard	8	11	10	7

CONCLUSION

The product was obtained by using parallel synthesizer to induce the reaction of a substituted chalcones with the hydrochloride salt of ammonium hydroxide and a catalytic quantity of sodiumoxalate at ambient condition, substituted isoxazole derivatives in good yields and short reaction times. Such as in a straight forward, basic, effective manner. Because of the wide range of biological activity. Isoxazole is a type of antibiotic that is used to treat bacterial infections

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