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Spectroscopy-based Confirmation of Three Novel Isoxazole Combinations

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Abstract: *Isoxazoles possess numerous pharmaceutical, agricultural and industrial properties. They are antivirus, antitumor, blood pressure lowering agents, anti-Parkinson, anti-Alzheimer etc. the present research paper studies three synthetized combinations: one combination from oximes family and two combinations pertaining to isoxazoles. At first, 4-methylbenzaldehyde was transformed to 4-methylbenzaldoxime (combination 1) using hydroxylamine pyridine hydrochloride, as the solvent. Then, the resulting oxime (combination 1) was transformed to nitrile oxide with the increase in sodium hypochlorite at the same time with which process [3+2] cycloaddition was carried out using propargyl alcohol and (3-para-tolyl isoxazole-5-yl)-methanol (combination 2) was prepared. Esterification was the result of the effect of pantothenic acid in dichloromethane solvent on Combination 2 and (3-para-tolyl-isoxazole-5-yl)-methyl pentanoate was produced. The structures of the synthetized combinations were verified using spectroscopy, ^{1}H NMR FT-IR and ^{13}C NMR.*

Keywords: *Synthesis, Isoxazole, Oxime, Spectroscopy*

INTRODUCTION

Heterocycles constitute an important set of organic compounds that are widely applied. They account for a large quotient of various types of compounds used in pharmaceutics, veterinary and phytochemistry. Isoxazoles with such substitutions as amino-, alkyl, halogens, nitro-, methoxy, hydroxyl and acyl have been discovered in a great many of important biological molecules. Isoxazole derivatives possess many biological properties and act as intermediates in natural biologics like peptides, steroids, terpenes and so forth (Gilkerist, 2001). Isoxazoles are utilized as block structures in organic synthesis. They can be transformed to numerous important synthetic units like ß-hydroxy ketones, γ-amino alcohols, unsaturated α- and ß-oximes and ß-hydroxy nitriles (Yavari et al., 2006).

Isoxazole chain system contains a steroid part that can be used to produce substances of a high medical importance (Gupta et al., 1999). Some of the novel steroid isoxazoles are applied as estrogen synthase inhibitors. Estrogen synthase system (aromathase) is responsible for the human estrogen hormones' biosynthesis. Estrogens are vital to the normal body growth and development but they are also known to increase breast cancer risk. Almost 30% to 50% of the breast cancers are hormone-associated. Estrogen biosynthesis has accordingly been increased as an effective treatment method. This leads to the expansion of the site-activated inhibitors possibly of a potential for the breast cancer control (Li et al., 1998).

There are two important methods for the isoxazole chain synthesis. One is the reaction of hydroxylamine with a three-carbon compound like 1, 3-diketone with one unsaturated α- and ß-ketone and the other is the

reaction of one nitrile oxide with an alkene or alkyne. Nitrogen's cycloaddition reaction, as well, results in the isoxazoles chain formation in a lower oxidative level. The reaction between hydroxyl amines and 1, 3-deketones is an appropriate method for procuring 3,5Disubstituted isoxazoles.

The reaction progress is documented using FT-IR spectroscopy. Isoxazole products are currently obtained through automatic and parallel synthesis. Intramolecular nitrogen cycloaddition reactions are the strongest synthetic methods for combining the derivatives of fused bicycle isoxazoles (Shang et al., 2002).

Chemically, Isoxazoles behave more similar to pyridine than other heterocycle compounds but they perform electrophilic substitution a lot faster than pyridine. Isoxazoles' behavioral similarity to pyridines can be very closely exampled in furan's behavior towards benzene (Davis, 1997). Isoxazoles' derivatives have been largely investigated as contingent pharmaceutical agents. For instance, structures with 3-aryl-5-methylisoxazole-4-carboaxamide half have been recognized as regulators of ghrelin-receptors, α-adrenergic receptors, selective antagonists and glutamate receptor v-antagonists (Zhu et al., 2011). Isoxazole and pyrazole derivatives are interesting irregular heterocyclic compounds because of demonstrating properties belonging to a vast array of pharmaceuticals, including anti-inflammatory, anticancer, antibacterial, antivirus and antidiabetic, antimicrobial and antifungal. Some isoxazoles and pyrazoles show agricultural chemistry properties and are used in pesticides (Li et al., 2007). Oxime intermediate is seminally synthetized from 4-(decyloxy)-benzaldehyde or 4-bromo using hydroxylamine chloride and potassium hydroxide in ethanol/water in room temperature (Han, 2009).

Han et al (2009) designed and synthetized a new set of isoxazoles used in anticancer drugs and subjected it to biological evaluation (Suryawanshi et al., 2012). Ejlali (2008) synthetized a number of 3 and 5-substituded isoxazoles. They made use of [2+3] cycloaddition method for isoxazole ring synthesis. Yataneg et al synthetized some 3-substituded derivatives of isoxazoles and showed that these compounds can be used as herbicide against weeds. In 2012, Suryawanshi synthetized retinoid compounds, including isoxazoles and amide derivatives thereof. The retinoid structure can be per se divided to three parts: hydrophobic part, linked part and carboxylate part. Synthesized heteroretinoid and its derivatives work against leishmanial activity. Kumar et al (2012) succeeded in isoxazole-benzoquinone compounds. In this regard, 2-nitrobenzaldehyde (Gilkerist, 2001) is the initiator that reacts with hydroxylamine and hydrochloride (HCL and NH2OH) and produces an oxime derivative (Yavari et al., 2006). Combination 2 is subjected to 1, 3-dipolar cycloaddition reaction with phenyl acetylene in the presence of ET2N/Naocl in DCM, as the solvent. The isoxazole 3 formed using Huisgn-click reaction through subjecting the combination 3 to cycloaddition reaction is transformed to benzoquinone. In doing so, the nitro group if amine 4 derivative is reduced following which the benzoquinone is ready for synthesis.

Experimental Section:

The present empirical research paper was conducted in Islamic Azad University, Tabriz Branch. At first, 4-methyl benzaldoxime (Combination 1) was prepared from reacting 4-methyl benzaldehyde with hydroxyl amine hydrochloride. The obtained oxime was converted to the corresponding nitrile oxide in an attacking reaction with sodium hypochlorite and also in reaction with propargyl alcohol during (3-para-tolyl-isoxazole-5-yl)-methanol cycloaddition reaction (combination 2). Next, (3-para-tolyl-isoxazole-5-yl)-methyl pentanoate was transformed to combination 2 through adding pentanoic acid in the presence of sulfuric acid. The materials and solvents used in this reaction were procured from Merck Company. The specimens' melting points were determined using melting point measurement device. The purity rates of the solvents were ascertained through determining their boiling points and refraction coefficients using refractometer device.

Preparation of 4-Methylbenzaldoxime (Combination 1):

4-methylbenzaldehyde, hydroxylamine hydrochloride and pyridine were poured into a two-neck 250-milliliter flask equipped with reflux column and magnetic stirrer for amounts equal to 9.85g (82 millimoles), 25.25g (365 millimoles) and 25 milliliters, respectively. The reacting mixture was refluxed for four hours. The mixture was allowed to cool down in a cold room after the termination of the reaction time following which it

was removed of its solvent and the residual part of the mixture was extracted using ethyl acetate and distilled water. The organic phase of the mixture was dried by dehydrated sodium sulfate. A green solid body was obtained after filtering the solution following the solvent removal. The intended material was obtained for an amount equal to 12.15g (a 95.7-percent gain) with an 82-degree-centigrade melting point. The information pertinent to ^{1}H NMR and IR is as below:

IR (KBr) cm^{-1}:
3500, 3200, 3110, 3026, 2985, 2914, 1631, 1511, 1436, 1605, 959, 871, 815, 776, 719, 575, 514

^{1}H NMR ($CDCl_3$, 400 MHz):
8.81 (s, 1H), 8.13 (s, 1H), 7.18 - 7.47 (m, 4H), 2.36 (s, 3H)

(3-para-tolyl- isoxazole-5-yl)-methanol (Combination 2) Synthesis:

4-methylbenzaldoxime (combination 1), propargyl alcohol and dichloromethane were poured for values equal to 11.75 grams (87 millimoles), 10 milliliters (179 millimoles) and 50 milliliters, respectively, into a two-neck 250-milliliter flask equipped with a dropping funnel and a magnetic stirrer. Then, 120ml 5.5% sodium hypochlorite was added drop by drop following which the mixture was stirred for 48 hours in room temperature. Next, the flask's content was poured in the 250ml separating funnel and the organic phase was separated from the aqueous phase. The separated organic phase was dried using sodium sulfate. After being subjected to filtering and solvent extraction, an amount of 12.52g (92-percent gain) of a solid and pure brown matter with a melting point of 97°C was obtained. The ^{1}H NMR and IR spectroscopy information is as below:

IR (KBr) cm^{-1}:
3500, 3200, 3100, 2900, 2800, 1607, 1569, 1431, 1361, 1170, 831, 805, 639

^{1}H NMR ($CDCl_3$, 400 MHz):
2.33 (m, 3H), 2.36 - 2.42 (m, 1H), 4.72 (s, 2H), 6.47 (s, 1H), 7.13 - 7.59 (m, 4H)

(3-para-tolyl- isoxazole-5-yl)-Methyl Pentanoate (Combination 3) Synthesis:

Two grams of the combination 2 was poured into a 150ml beaker to which 10cc pentanoic acid along with sulfuric acid was added. The mixture was stirred and allowed to rest for 3-4 hours in room temperature. Separation operation begins with the addition of distilled water so as to separate organic phase from aqueous phase. A solid matter with the melting point of 54°C was obtained 24 hours after solvent extraction and crystallization. The ^{13}C NMR, ^{1}H NMR and IR information is as below:

IR (KBr) cm^{-1}:
1433 - 1612 - 1740 - 2871 - 2954 - 3032 - 3132

^{1}H NMR ($CDCl_3$, 400 MHZ):
0/87 (t ، 3H). 1/28-1/58- 2/21 (m ، 2H). 2/33 (s ، 3H). 5/19 (s ، 2H) 6/59 (s ،1H)
7/18 (d ، 2H). 7/56 (d ، 2H)

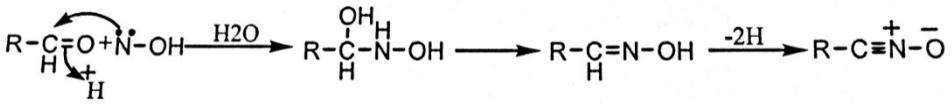
^{13}C NMR ($CDCl_3$. 100 MHZ):
12/4، 20/0 ، 20/9، 25/5، 32/3، 54/9، 97/8، 100/8، 125/4، 128/3 ، 139/0، 191/2، 165/9

Discussion and Conclusion:

Isoxazole ring is formed through [3+2] cycloaddition reaction. There are five paths based on the atoms' arrangements on rings in every preliminary member: path [3+2], path [4+1], path [5+0], path [3+3+1] and path [2+2+1]. It is most often based on [3+2] path that such reactions as (CCC+NO) and (CNO+CC) form. The

method of nitrile oxide reaction with an alkene or an alkyne is a different way of constructing isoxazoles because the substituents on every member can be changed. The reaction may also encompass and eliminative reaction.

In the meantime, nitrile oxide can be prepared using hydroxyl amine plus aldehyde during the following reaction and mechanism.



The H-taking method in the presence of sodium hypochlorite is as below:

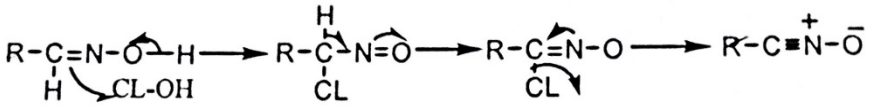
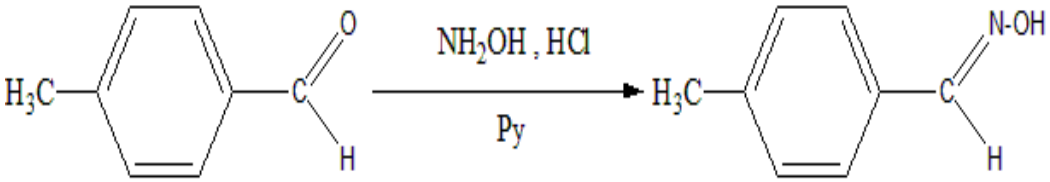


Diagram (3-3): schematic view of nitrile oxide synthesis stages

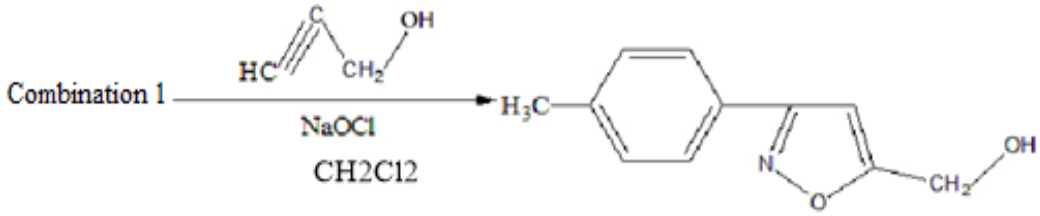
Nitrogen cycloaddition reaction, as well, leads to the formation of isoxazoles but in a lower oxidative level. The reaction between hydroxylamine and a three-carbon member is amongst the well-known reactions (diagram (3-4).

Diagram (3-4): schematic view of isoxazoles formation though reacting with three-carbon-membered hydroxylamine

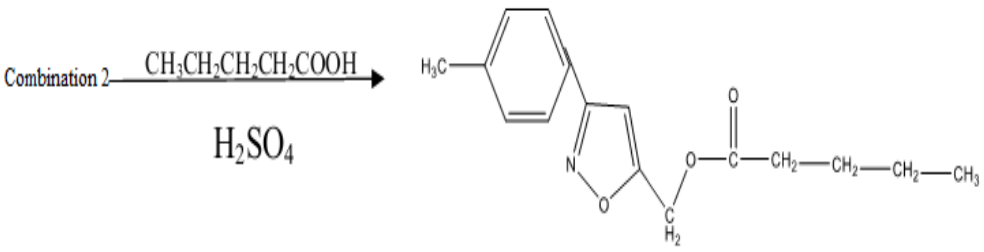
Reactions Conducted:



Combination 1

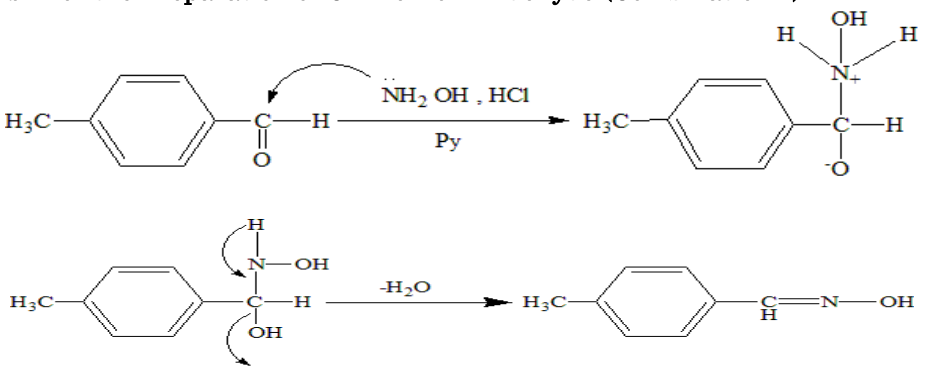


Combination 2

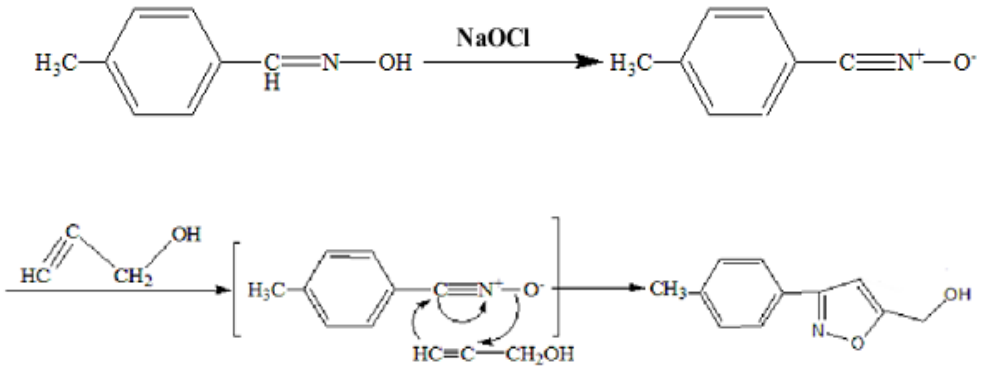


Combination 3

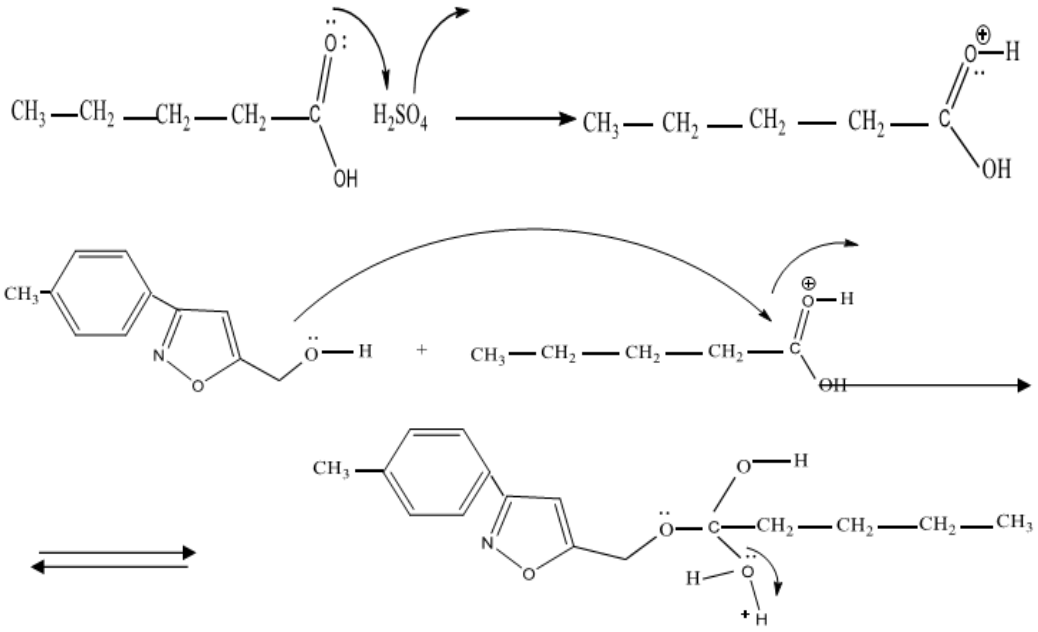
Proposed Mechanism for the Preparation of Oxime from Aldehyde (Combination 1):

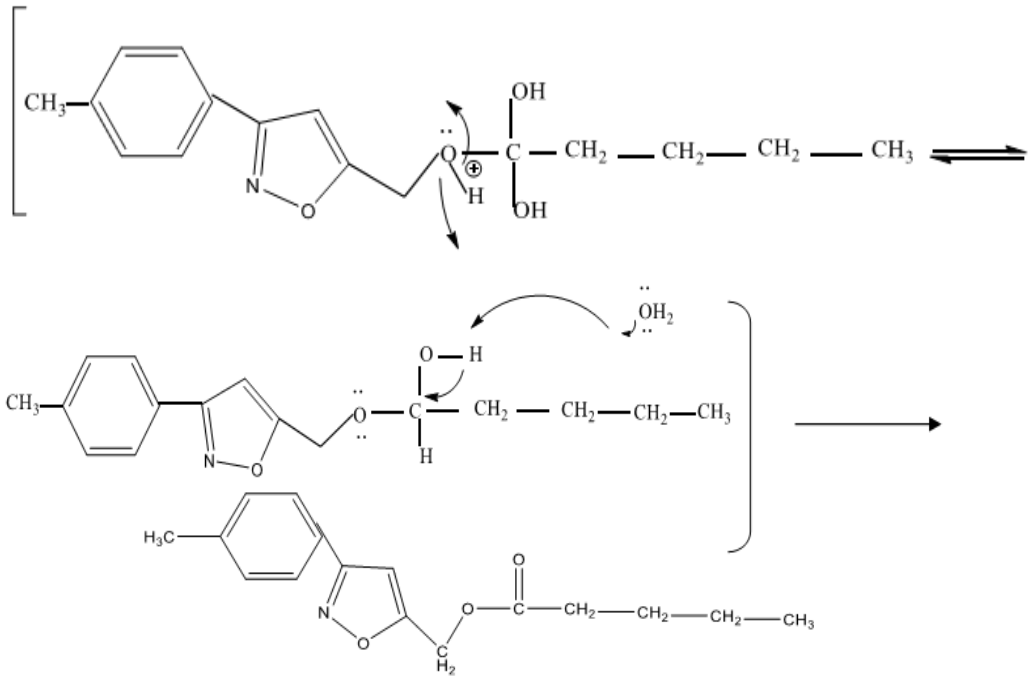


Proposed Mechanism for the Preparation of Combination 2



Proposed Mechanism for the Preparation of Combination 3

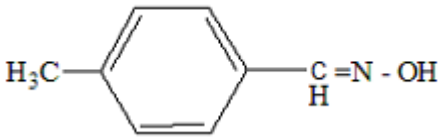




Spectrum Investigations for the Verification of the Synthetized Combinations' Structures:

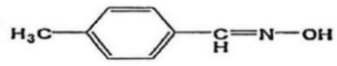
After each of the combinations was synthetized and purified using TLC method and upon the determination of the melting point, the combinations were subjected to IR and NMR spectroscopy so that their purity rates could be measured. The structures of the synthetized combinations were proved by the aid of the spectrums.

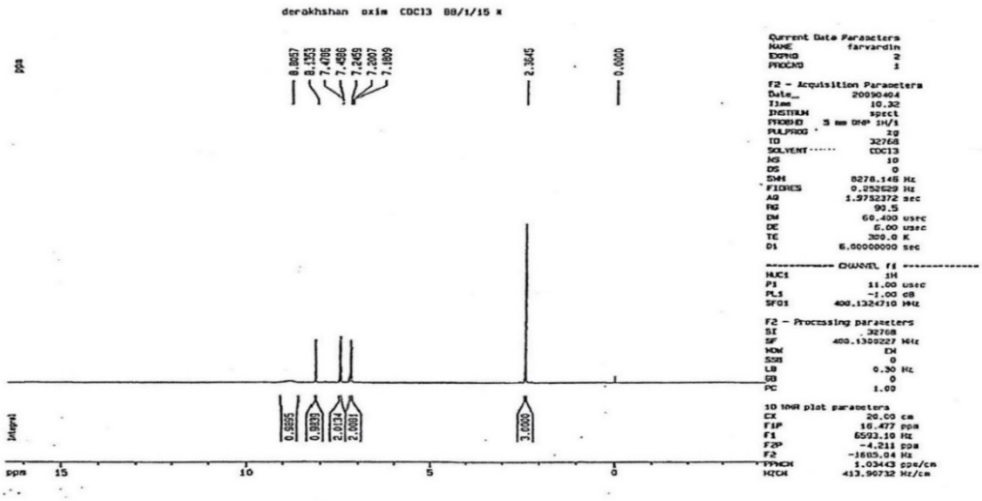
Spectral Specifications of 4-Methyl-Benzaldoxime:



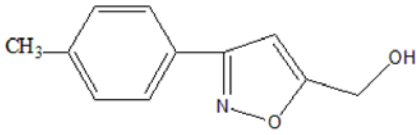
^{1}H NMR Spectroscopy ($CDCl_3$):

The peak observed in 2.36ppm pertains to methyl group protons that are attached to phenyl ring. The multiplet observed in 7.18-7.47ppm pertains to four protons from phenyl ring. The singlet observed in 8.13ppm pertains to oxime group proton. The alcohol group proton was also found resonating in 8.80ppm.

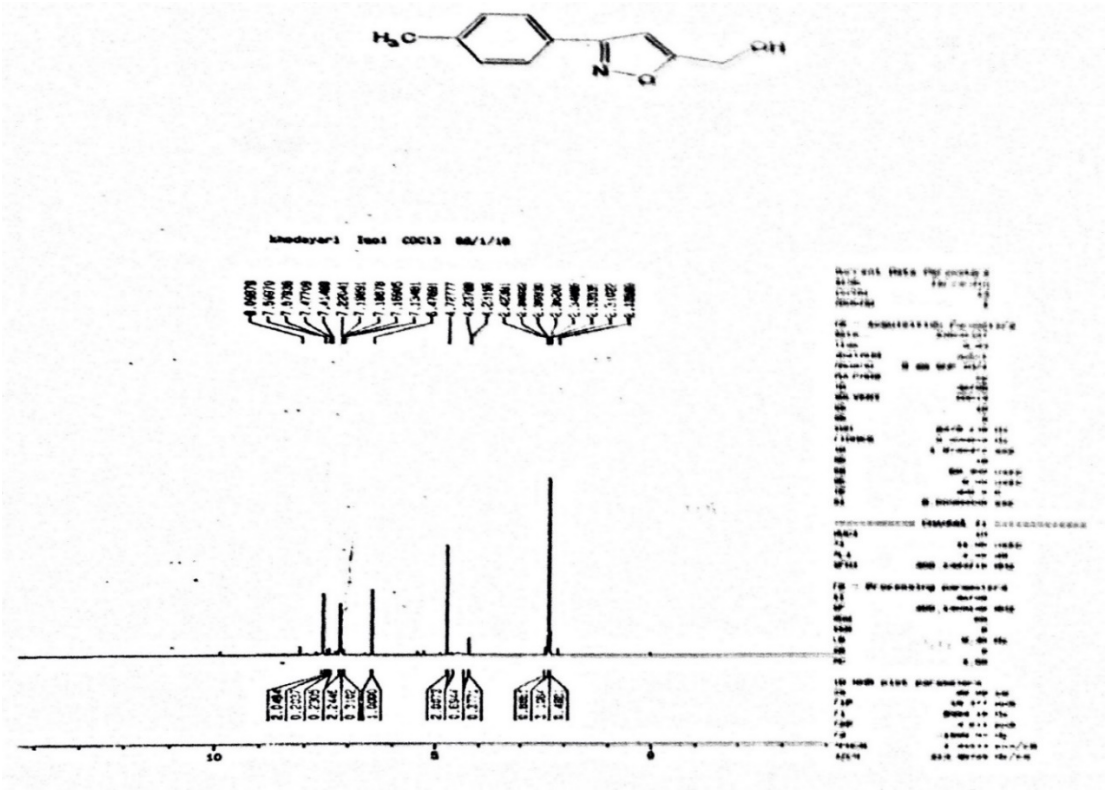




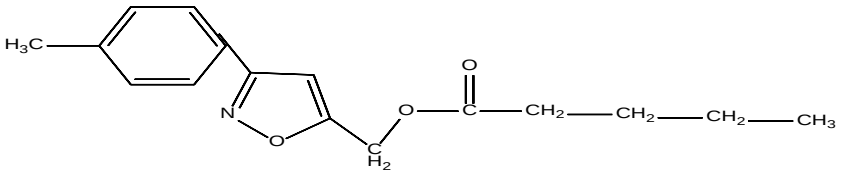
^{1}H NMR Spectroscopy of Combination 1 (400 MHz, $CDCl_3$):
Spectral specifications of (3-para-tolyl-isoxazole-5-yl)-Methanol:



^{1}H NMR Spectroscopy ($CDCl_3$):
The broad singlet observed in 2.36ppm to 2.42ppm pertains to alcohol proton resonance and the hydrogen bond has caused this peak to become broadened. The methyl group protons that are located in para-site in respect to isoxazole ring show absorption in the form of singlets in 2.33ppm. The singlet observed in 4.72ppm pertains to the resonance of the two protons of methylene group. The singlet observed in 6.47ppm pertains to the isoxazole ring proton. The four protons existent on aromatic ring have made up for two dual absorption couplets in 7.13ppm and 7.59ppm. The couplet observed in 7.13ppm pertains to meta-protons and the couplet observed in 7.59ppm pertains to ortho-protons.

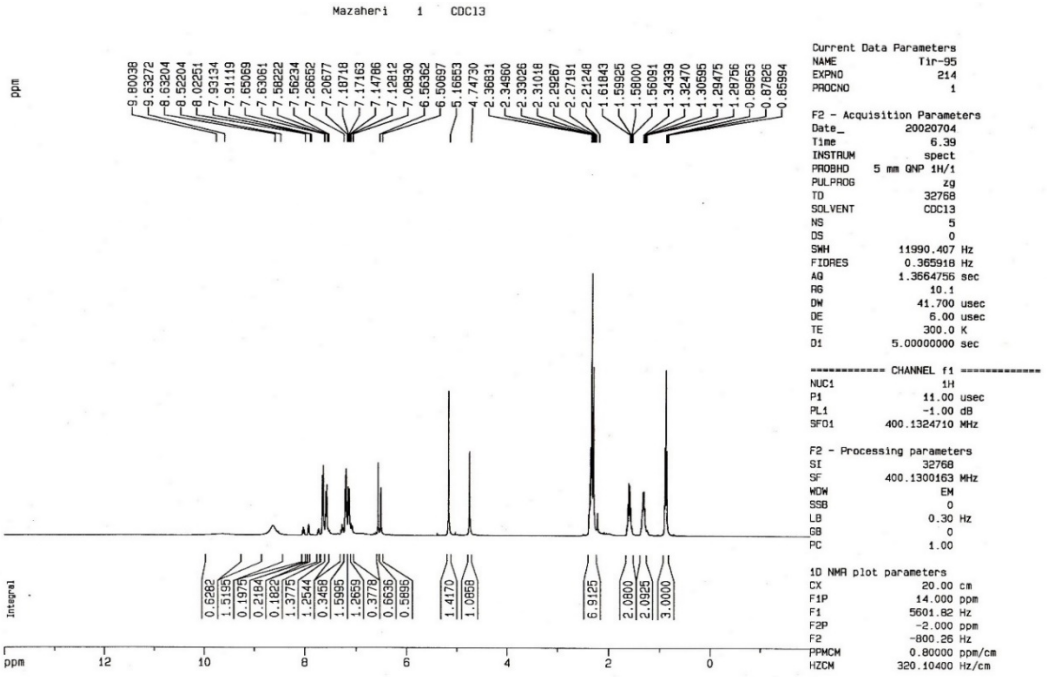


^{1}H NMR Spectroscopy of Combination 2 (400 MHz, $CDCl_3$):
Spectral specifications of (3-para-tolyl-isoxazole-5-yl)-Methylpentanoate:

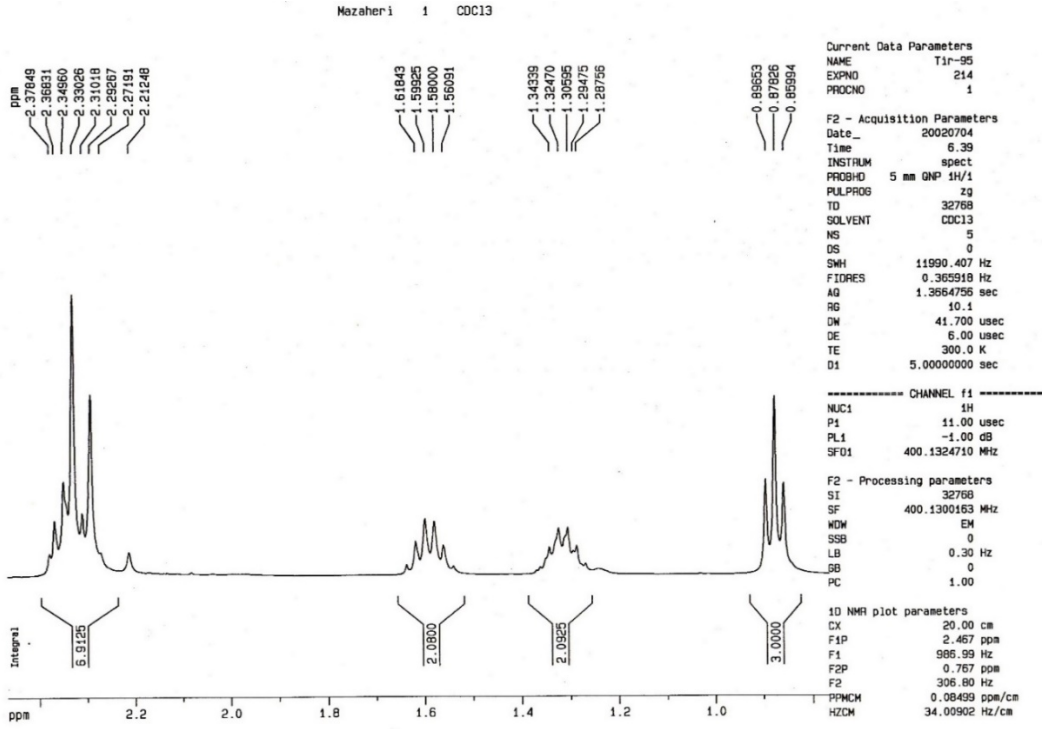


^{1}H NMR Spectroscopy ($CDCl_3$):

CH_3 protons in the form of triplets attached to CH_2 are found resonated in 0.87ppm. The two CH_2 groups attached to methyl groups are resonated in the form of multiplets in 1.58ppm and 1.28ppm. The CH_2 attached to carbonyl group is resonated in the form of couplet in 2.21ppm. The CH_3 attached to phenyl ring is resonated in the form of singlet in 2.33ppm. The CH_2 attached to isoxazole ring is resonated in the form of singlet in 5.19ppm. Isoxazole ring's proton is resonated in the form of a singlet in 6.59ppm. Phenyl ring protons are resonated in couplets in a range from 7.18ppm to 7.56ppm.



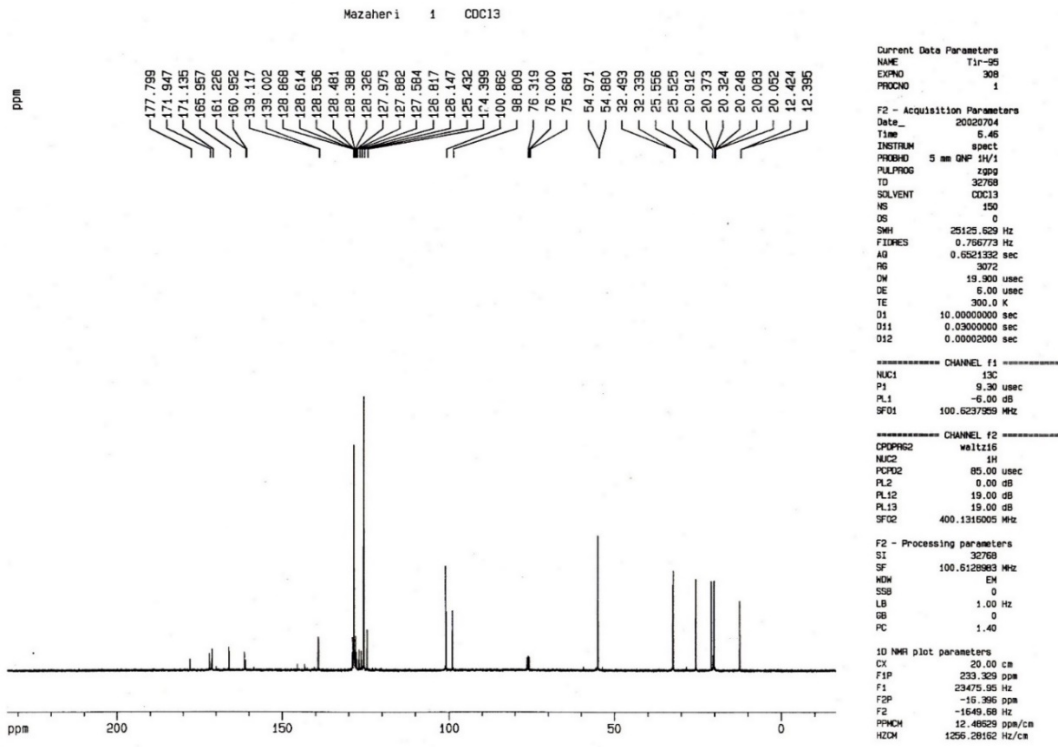
^{1}H NMR Spectroscopy of Combination 3 (400 MHz, $CDCl_3$):



^{1}H NMR (400 MHz, $CDCl_3$) Broad Spectrum of Combination 3:

^{13}C NMR Spectroscopy ($CDCl_3$):

Aliphatic carbons, reaching in number to six, have been found resonating in 12.4ppm, 20.0ppm, 20.9ppm, 25.5ppm, 32.3ppm and 54.9ppm. Aromatic carbons are resonated in 97.8ppm, 100.8ppm, 125.4ppm, 128.3ppm, 139.0ppm, 191.2ppm, 165.9ppm. Carbonyl group is resonated in 177.7ppm.



^{13}C NMR Spectroscopy of Combination 3 (100 MHz $CDCl_3$):

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