Synthesis, Spectral, Bio Assay, Chromatographic - Studying of New Imidazole Reagents Via Three Components Reaction

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Abstract

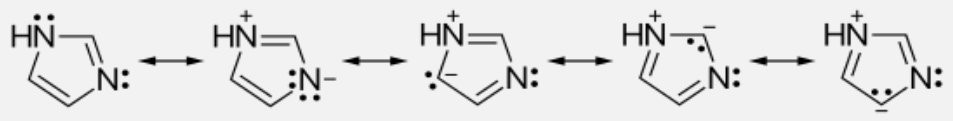
Imidazoles are part of the theophylline Reagent, found in tea leaves and coffee beans, which stimulates the central nervous system. It is found in the anti-cancer drug mercaptopurine, which fights leukemia by interfering with DNA systems. A number of prepared imidazoles, including clotrimazole, are selective inhibitors of nitric oxide synthase, which makes them interesting drug targets in inflammation, respiratory diseases and tumors of the nervous system. Other biological activities of the drug carrier imidazole relate to deregulation of the intracellular fluxes of (Ca and K) ions. Novel imidazole –heterocyclic reagents were created via cyclization process then condensation process., followed by investigation of all created new reagents via a number of spectral performances (FT.IR, H.NMR)–spectrophotometric, other physical and chemical properties, and chromatographic study with microbial studying for all new created imidazole reagents.

Key Words: Imidazole, Thiadiazole, Triazole, Antimicrobial, Heterocyclic, Chromatography, Thiazole, Three Components Reaction.

DOI Number: 10.14704/nq.2021.19.7.NQ21092 **NeuroQuantology 2021; 19(7):115-122**

Introduction

Imidazole was first prepared in 1858 by German chemist Heinrich Debus, although various imidazole derivatives were discovered as early as the (1840)s. It turns out that glyoxal, formaldehyde, ammonia condenses to form imidazole (glyoxaline, as it was originally called). This reaction, while producing relatively low ratios., Imidazoles are a highly polar Reagent (Nagham Aljamali 2015), as evidenced by its (3.67 D) electrode dipole moment. It is highly soluble in water. The Reagent is classified as aromatic due to the presence of a planar ring containing (6 π) electrons (a pair of electrons from a protonated nitrogen atom and one from each of the remaining four atoms of the ring) (S. Padhan. 2007). Some of the resonance structures of imidazoles are shown below:



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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 16 May 2021 **Accepted:** 20 June 2021

Imidazole derivatives prepared with hybrid groups or atoms are of value in the treatment of many systemic fungal infections. Imidazoles belong to the class of azole antifungals (Thomas. L et al 1997)., which include ketoconazole, miconazole, and clotrimazole. For comparison, another group of azoles is the triazoles, which includes fluconazole (Nagham Aljamali., 2020), Itraconazole, and Voriconazole. The difference between imidazoles and triazoles involves the mechanism of cytochrome P450 inhibition (Matheus M 2007). The N3 of the imidazole complex binds to the heme iron atom of the ferric cytochrome P450, while the N4 of the triazole binds to the Heme group. Triazole has been shown to have a higher specificity for cytochrome P450 than imidazole, which makes it more effective than imidazole (Edon. V .et al, 2014., Wang. G., et al 2017).

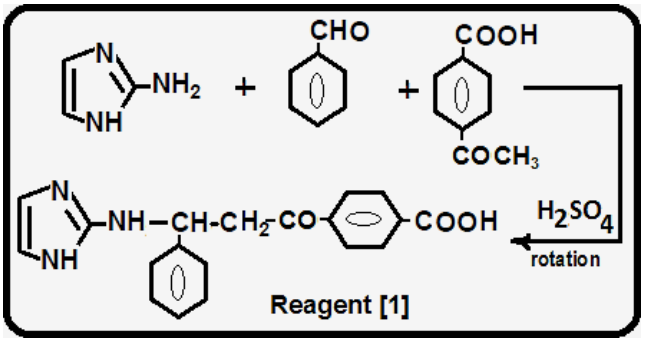
Practical Part

Various technical performances have been smeared to detect the created reagents like ((FT-IR spectra -8300 Shimadzu) in the variety (400-4000) cm^{-1} with KBr-discs., ^{1}H.NMR–Spectra in (DMSO)–solvent., chromatography separation., also to antimicrobial assay.

Creation Paths

Preparation Path of Reagent{1}

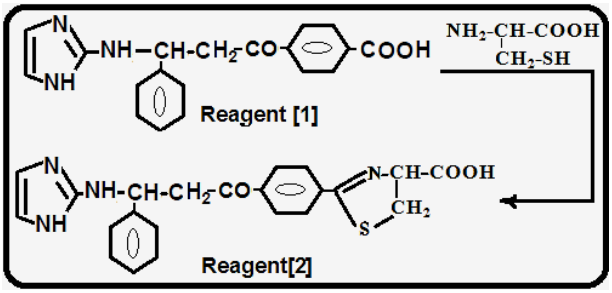
The first reagent[1] was prepared from the reaction of amino imidazole (0.01 mole) with benzaldehyde (0.01 mole) in an acidic medium of sulfuric acid, then para-acetobenzoic acid (0.01 mole) was mixed with mechanical rotation for (3hrs) at laboratory temperature by following studies (Nagham Aljamali.2019, Emad .K et al , 2020) , then the solution was cooled, filtered, dried and recrystallized to produce reagent [1].



Scheme 1. Creation of Reagent{1}

Preparation Path of Reagent {2}

After preparing the first reagent, the second step was followed by preparing the second reagent by taking equal moles of the reagent [1] (0.01 mole) and cysteine (0.01 mole) in ethanol through refluxing for (7 hours) by following studies (Nagham Aljamali. 2020), so we get a cyclic Reagent through the ring closure (Nagham Aljamali. 2019) of the carboxyl group with the amine and thiol groups of the amino acid cysteine, the solution cooled and filtered. It dried, recrystallized, and it was the reagent [2].



Scheme 2. Creation of Reagent {2}

Preparation Path of Reagent {3}

After preparing the first reagent, the second step was followed by preparing the reagent [3] by taking equal moles of the reagent [1] (0.01 mole) and ortho-thiolaniline (0.01 mole) in ethanol through refluxing for (7 hours) by following studies (Nagham Aljamali.2021), so we get a cyclic Reagent through the ring closure of the carboxyl group with thiol and amine group, the solution cooled and filtered. It dried, recrystallized, and it was the reagent [3].

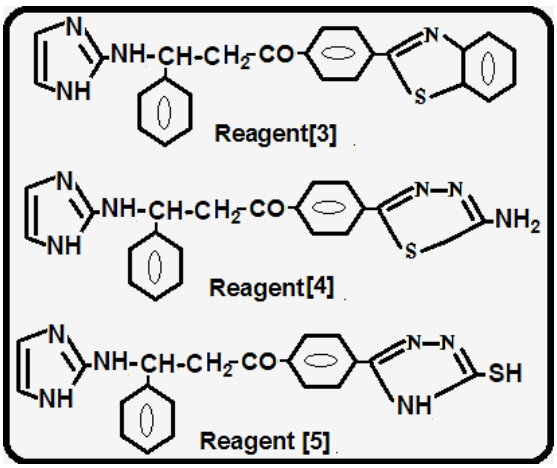
Preparation Path of Reagent {4}

After preparing the first reagent, the second step was followed by preparing the reagent [4] by taking equal moles of the reagent [1] (0.01 mole) and thiosemicarbazide (0.01 mole) in ethanol through refluxing for (7 hours) with drops of (H_2SO_4) by following studies (Nagham Aljamali. 2020), so we get a cyclic Reagent through the ring closure of the carboxyl group with thiosemicarbazide, the solution cooled and filtered. It dried, recrystallized, and it was the reagent [4].

Preparation Path of Reagent {5}

After preparing the first reagent, the second step was followed by preparing the reagent [5] by taking

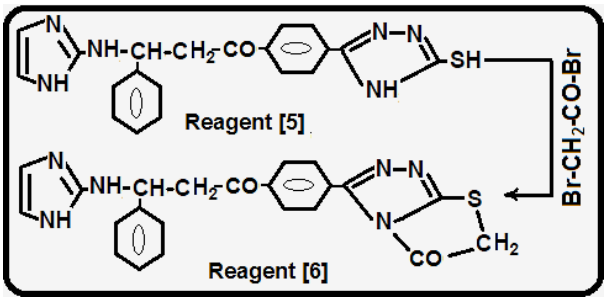
equal moles of the reagent [1] (0.01 mole) and thiosemicarbazide (0.01 mole) in ethanol through refluxing for (7 hours) with (5% of NaOH) by following studies (Nagham Aljamali. 2019), so we get a cyclic Reagent through the ring closure of the carboxyl group with thiosemicarbazide, the solution cooled and filtered. It dried, recrystallized, and it was the reagent [5].



Scheme 3. Creation of Reagents {3, 4, 5}

Preparation Path of Reagent {6}

After preparing the reagent [5], the second step was followed by preparing the reagent [6] by taking equal moles of the reagent [5] (0.01 mole) and bromoacytoyl bromide (0.01 mole) with mechanical rotation for (4 hours) with potassium carbonate by following studies (Nagham Aljamali. 2019), so we get a bicyclic Reagent, the solution cooled and filtered. It dried, recrystallized, and it was the reagent [6].



Scheme 4. Creation of Reagent {6}

Results and Discussion

The created new reagents [1-6] have been identified via numerous chemical performances, microbial:

Spectral Evidences of Formatted Reagents

FT.IR- Identification of Formatted Reagents: One of the evidence that supported the formation and preparation of new imidazole reagents is appearance of the frequencies and other frequencies disappear as a result of the formation of new reagents., all spectra explained according to reference(Nagham Aljamali., 2021):

Reagent [1]: appearance frequency at (3300)Cm^{-1} due to (NH) of amine group, band at (1702) due to carbonyl of ketone (-CO-), band at (2902) due to (CH) aliphatic, band at (1656) due to (C=N) in imidazole, band at (1725) due to carbonyl of carboxyl group (-CO-O), band at (2690-3178) due to (OH) of carboxyl group.

Reagent [2]: appearance frequency at (3281)Cm^{-1} due to (NH) of amine group ,band at (1718) due to carbonyl of ketone (-CO-), band at (2917) due to (CH) aliphatic, band at (1650) due to (C=N) in imidazole, band at (1727) due to carbonyl of carboxyl group (-CO-O), band at (2667-3109) due to (OH) of carboxyl group., band at (783) due to (C-S) in cycle.

Reagent [3]: appearance frequency at (3290)Cm^{-1} due to (NH) of amine group ,band at (1712) due to carbonyl of ketone (-CO-), band at (2923) due to (CH) aliphatic, band at (1662) due to (C=N) in imidazole, band at (765) due to (C-S) in thiazole

Reagent [4]: appearance frequency at (3256)Cm^{-1} due to (NH) of amine group, (3204, 3284)Cm^{-1} due to (NH_2) of amine group, band at (1707) due to carbonyl of ketone (-CO-), band at (2911) due to (CH) aliphatic, band at (1658) due to (C=N) in imidazole, band at (765) due to (C-S) in thiadiazole, band at (1667) due to (C=N) in thiadiazole

Reagent [5]: appearance frequency at (3249)Cm^{-1} due to (NH) of amine group, (3197)Cm^{-1} due to (NH) of amine group in triazole, band at (1700) due to carbonyl of ketone (-CO-), band at (2921) due to (CH) aliphatic, band at (1651) due to (C=N) in imidazole, band at (2410) due to (SH) in thiol group, band at (1657) due to (C=N) in triazole.

Reagent [6]: appearance frequency at (3227)Cm^{-1} due to (NH) of amine group ,band at (1705) due to carbonyl of ketone (-CO-), band at (2921) due to (CH) aliphatic, band at (1651) due to (C=N) in imidazole, band at (2410) due to (SH) in thiol group., band at (1657) due to (C=N) in triazole according to reference (Nagham Aljamali., 2021)., Some figures (1,2):

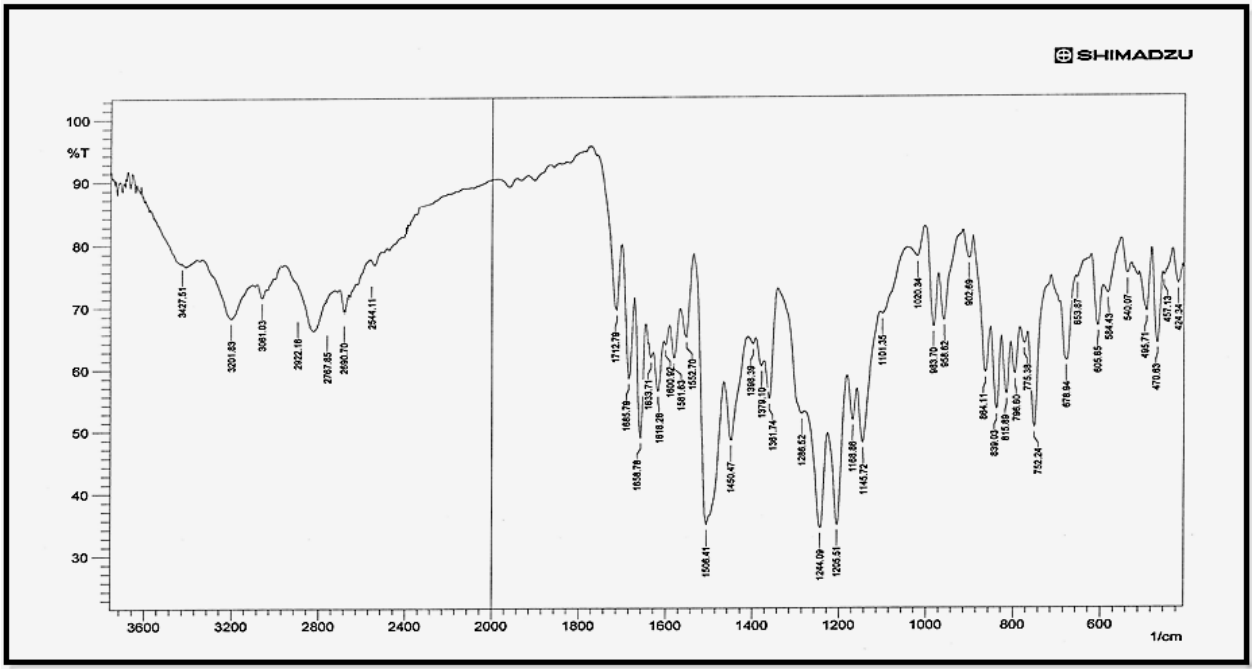


Fig. 1. I.R-Spectrum of The Prepared Reagent{3}

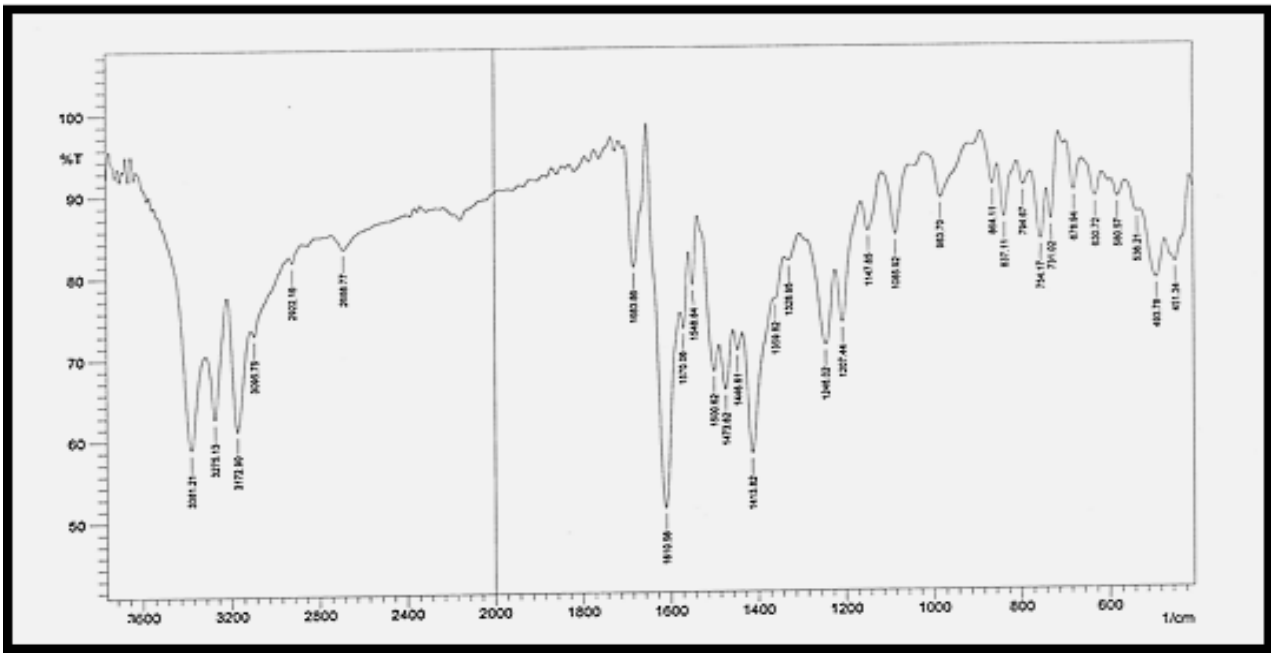


Fig. 2. I.R-Spectrum of The Prepared Reagent{4}

^{1}H.NMR-Characterization of New reagents: The other evidence that supported the formation and preparation of new imidazole reagents is appearance of the signals of other signals disappear as a result of the formation new reagents, all spectra explained according to reference[20]: All reagents gave signal at δ (5.1 to 5.23) due to proton of amine in imidazole ring (NH)., other signal at (2.05 , 2.11, 2.08) due to protons in methylene groups (-CH-CH_2-CO-)., signal at (4.92) due to proton of amine for (-NH-CH-C-)., signals at (12.89, 12.78) due to proton of carboxyl group in reagents [1,2] respectively according to reference (Nagham Aljamali., 2021), other signals at (6.94-7.76) due to protons in aromatic ring., and other signals in some figures (3,4):

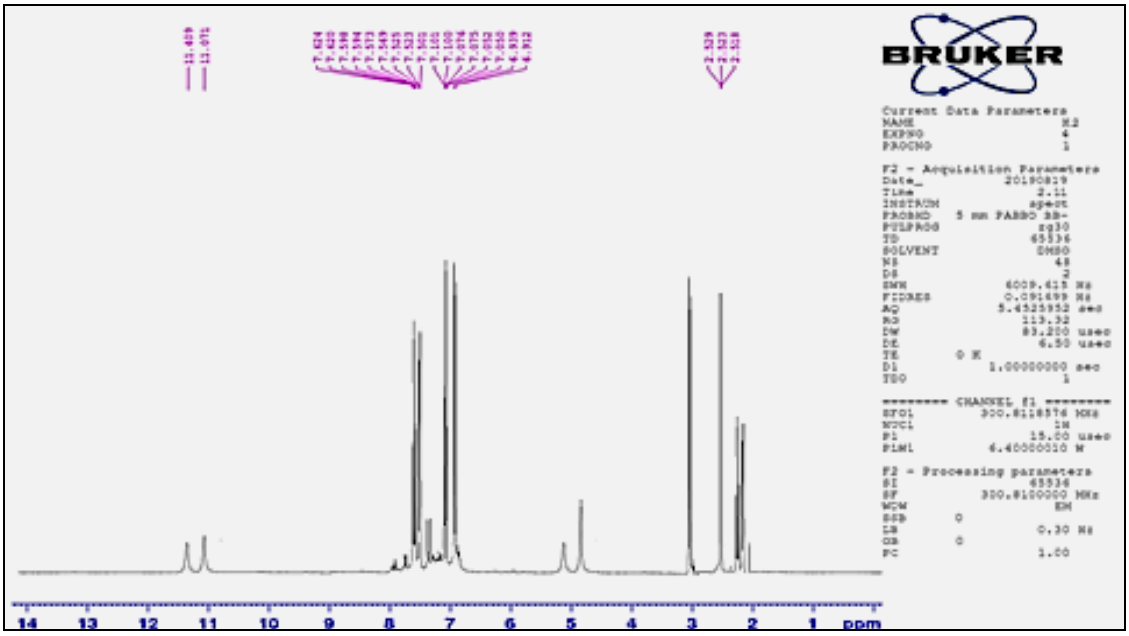


Fig. 3. H.NMR-Spectrum of Reagent{2}

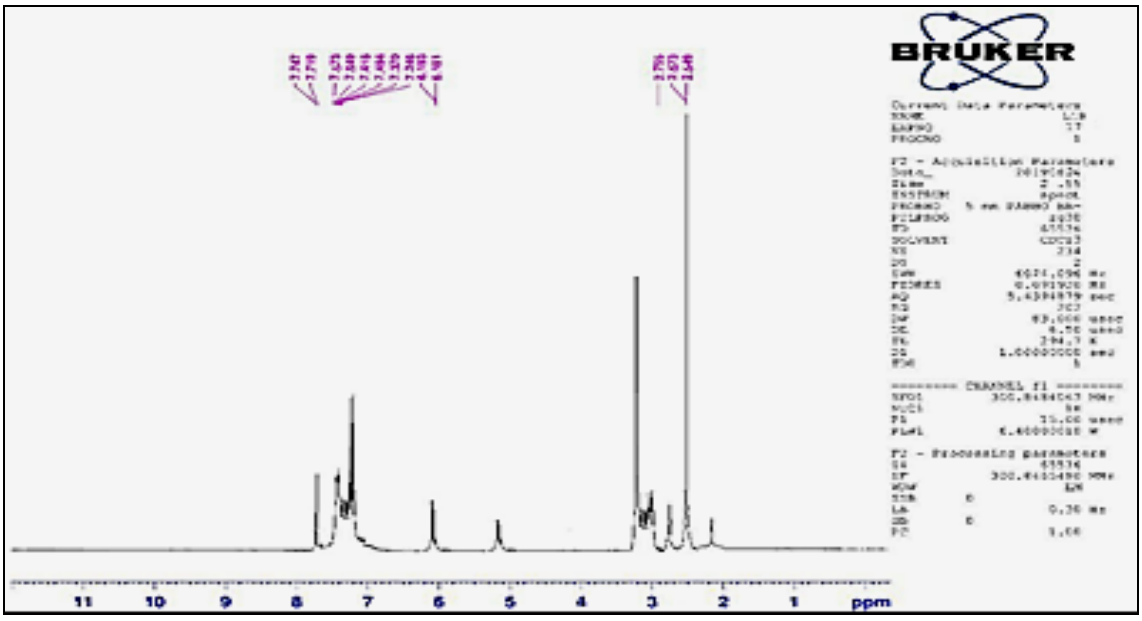


Fig. 4. H.NMR-Spectrum of Reagent{3}

Physical and Chemical Properties and Measurements

Numerous physical, chemical analysis besides to some description reported in Table (1):

Table 1. Some Physical Properties of New Reagents

Reagents	*Product %*	*Color*	*M .P (C °)*	*Rf*	*Solvents (TLC)*
{ 1 }	84	Gray	164	0.66	Ethanol : C6H6
{ 2 }	80	Reddish Yellow	196	0.68	Ethanol : C6H6
{ 3 }	72	Yellowish orange	186	0.62	Ethanol : C6H6
{ 4 }	76	Reddish Yellow	208	0.68	Ethanol : C6H6
{ 5 }	80	Orange	198	0.66	Ethanol : C6H6
{ 6 }	74	Yellowish Red	202	0.60	Ethanol : C6H6

Chromatographic Study for Reagents

One of the important applications that were carried out for the prepared reagents is the chromatographic separation (J. Zhou 2014., Mestaf M. et al 2019), which was carried out on some reagents as an application that depends on the interactions between the functional groups in the reagents and the column for the purpose of separation based on polarization (Meaaed M, et al 2018., Y. Liu 2017) (and also on molecular weights (W. She 2011)., We noted that reagent [2] is the slowest in separation, then reagent [6], and in last step reagent [3]., figures (5-7).

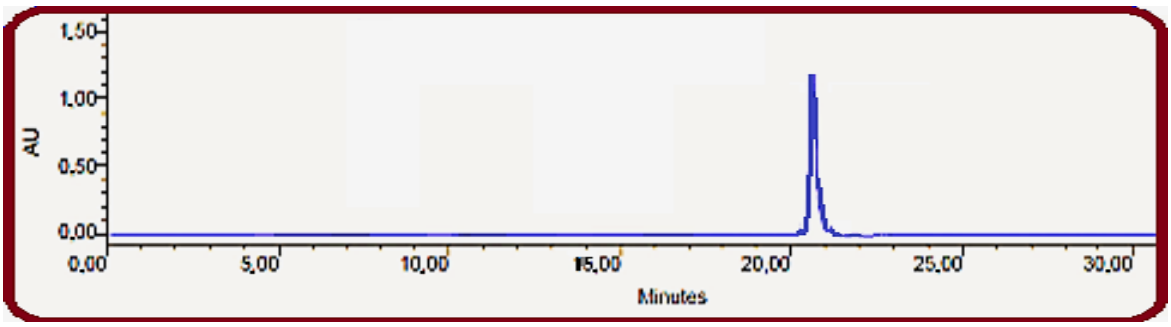


Fig. 5. Chromotogram of Reagent {2}

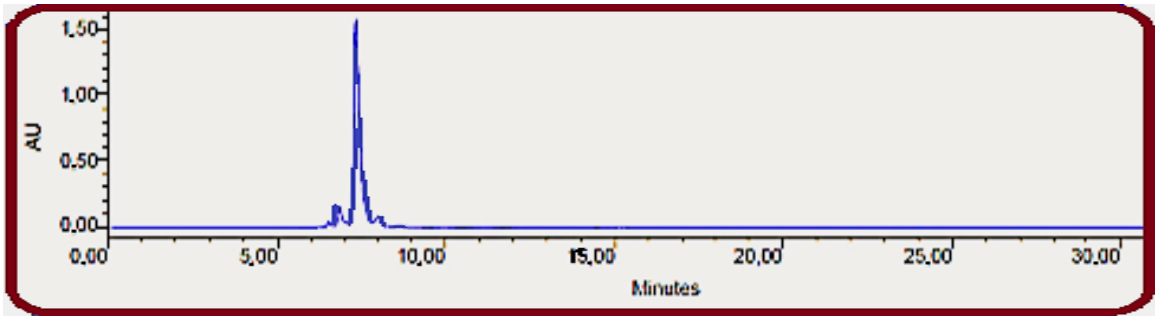


Fig. 6. Chromotogram of Reagent{3}

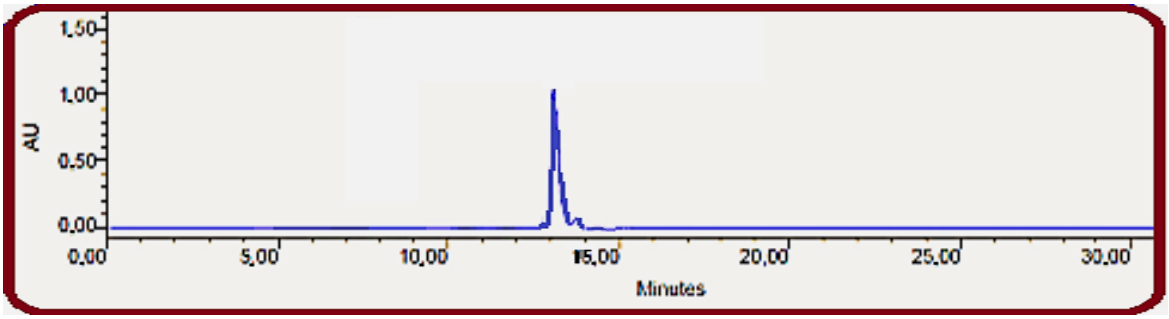


Fig. 7. Chromotogram of Reagent{6}

Antibacterial Test

All imidazole reagents studied for their effect as inhibitors via agar through the flowing a number of procedures (Mieaad M and Nagham Aljamali. 2020). The investigation of microbial inhibition performed at (three concs) (30, 50, 60 micro gram) concentrations in best solvent (DMSO) with bacteria: ***(E-Coli, St. aureus)***. The selected types of bacteria incubated for (24 hr) at (37°C). The assay of imidazole Reagents against types of bacteria gave good results with Reagents {2 and 4} more than other Reagents due to (sulfur and nitrogen) - atoms in same Reagents that participates in inhibition of bacteria (A. Ismail 2009, Hasaneen K and Nagham Aljamali., 2020) and all results explained according to references (Shireen R and Shireen R and Nagham Aljamali 2020., *Clark, Jim* 2013)., all data reported in Table (2) and photos (1,2):

Table 2. Inhibition Effect of reagents in Conc. (50 micro gram)

Reagent	*E-Coli*	*St. aureus*
Reagent {1 }	+	+
Reagent {2 }	+++	+++
Reagent {3 }	++	++
Reagent {4 }	+++	+++
Reagent {5 }	++	++
Reagent {6 }	+	+

(+): inhibition (4-6) mm
(++): inhibition (7-11) mm
(+++): inhibition (12-16) mm

Photo 1: Inhibition of Reagents on *St. aureus*

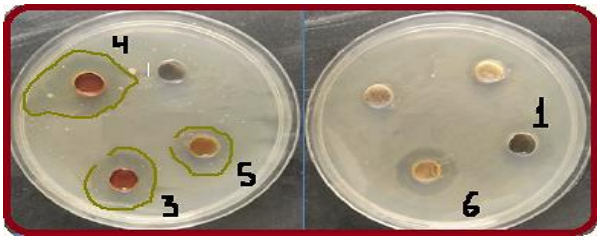


Photo 2. Inhibition of Reagents on *E. Coli*

Acknowledgments: we would like to express our heartfelt thanks to health-Lab for providing assistance samples of bacteria for studying.
Ethical clearance: Ethics committee refer that there is no plagiarism and there is no mistakes or wrong results in this work.
Conflict of interest: The authors declare that there is no conflict of interest.
Funding source: None.

References

Aljamali NM. Synthesis and chemical identification of macro compounds of (Thiazol and Imidazol). *Research Journal of Pharmacy and Technology* 2015; 8(1): 78-84. http://doi.org/10.5958/0974-360X.2015.00016.5

Pradhan, S, Xu, L, Chen, S. Janus nanoparticles by interfacial engineering. *Advanced functional materials* 2007; 17(14): 2385-2392.

Gilchrist TL. *Heterocyclic Chemistry,* 3rd ed. Addison Wesley: Essex, England 1997; 414. ISBN: 0-582-27843-0

Vitaku E, Smith DT, Njardarson JT. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among US FDA approved pharmaceuticals: miniperspective. *Journal of medicinal chemistry* 2014; 57(24): 10257-10274. https://doi.org/10.1021/jm501100b

Wang C, Yan J, Du M, Burlison JA, Li C, Sun Y, Liu J. One step synthesis of indirubins by reductive coupling of isatins with KBH4. Tetrahedron, 2017; 73(19): 2780-2785. https://doi.olrg/10.1016/j.tet.2017.03.077

Aljamali NM. *The Various Preparation Methods in Synthetic Chemistry,* 1Edt, Evincepub Publishing house, 2019. ISBN: 978-93-88277-82-2

Aljamali NM. *Reactions and Mechanisms*, 1 Edt, IJMRA Publication. 2018. ISBN : 978- 93-87176-25-6

Aljamali NM. *Experimental Methods for Preparation of Mannich Bases, Formazan, Normal and Cyclic Sulfur Reagents,* 1st edition Evince pub Publishing House 2018: ISBN: 978-93-87905-19-1.

Aljamali NM. *Alternative Methods in Organic Synthesis,* 1th–Edition, Eliva Press SRL, 2020. ISBN: 9798680201176.

Aljamali NM. *Effect of Conditions and Catalysis on Products.* 1th –Edition, Eliva Press SRL. 2021. ISBN: 9781636482286.

Aljamali NM. Synthesis and Biological Study of Hetero (Atoms and Cycles) Reagents. *Der Pharma Chemica* 2016; 8(6): 40-48.

Matheus ME, de Almeida Violante F, Garden SJ. Isatins inhibit cyclooxygenase-2 and inducible nitric oxide synthase in a mouse macrophage cell line. *European Journal of Pharmacology* 2007; 556(1-3): 200–206.

Perro A, Reculusa S, Bourgeat-Lami E, Duguet E, Ravaine S. Synthesis of hybrid colloidal particles: From snowman-like to raspberry-like morphologies. *Colloids and Surfaces A: Physicochemical and Engineering Aspects* 2006; 284: 78-83.

Pera-Titus M, Leclercq L, Clacens JM, De Campo F, Nardello-Rataj V. Pickering interfacial catalysis for biphasic systems: from emulsion design to green reactions. *Angewandte Chemie International Edition* 2015; 54(7): 2006-2021.

Alsabri IKA, Abdullabass HK, Aljamali NM. Invention of (Gluta. Sulfazane-Cefixime) Compounds as Inhibitors of Cancerous Tumors. *Journal of Cardiovascular Disease Research* 2020; 11(2): 44-55.https://doi.org/10.31838/jcdr.2020.11.02.09

Casagrande C, Fabre P, Raphael E, Veyssié M. "Janus beads": realization and behaviour at water/oil interfaces. *EPL (Europhysics Letters)* 1989; 9(3): 251-255.

Zhou WJ, Fang L, Fan Z, Albela B, Bonneviot L, De Campo F, Clacens JM. Tunable catalysts for solvent-free biphasic systems: Pickering interfacial catalysts over amphiphilic silica nanoparticles. *Journal of the American Chemical Society* 2014; 136(13): 4869-4872.

Alhashimi MTM, Muhsin NMB. Treatment of (Electric Wires and Machines)-Erosion via Engineering Materials by the Coating. *NeuroQuantology* 2019; 17(11): 11-16. https://doi.org/10.14704/nq.2019. 17.11.NQ19108

Aljamali NM. Synthesis of Antifungal Chemical Reagents from Fluconazole with (Pharma-Chemical) Studying. *Research journal of Pharmaceutical, biological and chemical sciences* 2017; 8(3): 564 -573.

Aljamali NM. *Spectral and Laboratory Diagnostics of Compounds.* 1th – Edition, Eliva Press SRL. 2021. ISBN: 9781636482118.

Mehta SL, Manhas N, Raghubir R. Molecular targets in cerebral ischemia for developing novel therapeutics. *Brain research reviews* 2007; 54(1): 34-66.

Mohammed M, Aljamali NM, Abbas NA. Preparation, Spectral Investigation, Thermal Analysis, Biochemical Studying of New (Oxadiazole-Five Membered Ring)-Ligands. *Journal of Global Pharmacy Technology* 2018; 10(1): 20-29.

Liu Y, Hu J, Yu X, Xu X, Gao Y, Li H, Liang F. Preparation of Janus-type catalysts and their catalytic performance at emulsion interface. *Journal of colloid and interface science* 2017; 490: 357-364.

Aljamali NM. Survey on Methods of Preparation and Cyclization of Heterocycles. *International Journal of Chemical and Molecular Engineering* 2020; 6(2): 19-36.

Seh ZW, Liu S, Zhang SY, Bharathi MS, Ramanarayan H, Low M, Han MY. Anisotropic growth of titania onto various gold nanostructures: synthesis, theoretical understanding, and optimization for catalysis. *Angewandte Chemie* 2011; 123(43): 10322-10325.

Mohammed M, Aljamali NM, Shubber WA, Abdalrahman SA. New Azomethine-Azo heterocyclic ligands via cyclization of ester. *Research Journal of Pharmacy and Technology* 2018; 11(6), 2555-2560. http://doi.org/10.5958/0974-360X. 2018. 00472.9

Ismail AA, Bahnemann DW, Bannat I, Wark M. Gold nanoparticles on mesoporous interparticle networks of titanium dioxide nanocrystals for enhanced photonic efficiencies. *The Journal of Physical Chemistry C* 2009; 113(17): 7429-7435.

Abdullabass HK, Jawad AM, Aljamali NM. Synthesis of drugs derivatives as inhibitors of cancerous cells. *Biochemical and Cellular Archives* 2020; 20(2): 5315-5322.

Shafiq I, Shafique S, Akhter P, Yang W, Hussain M. Recent developments in alumina supported hydrodesulfurization catalysts for the production of sulfur-free refinery products: A technical review. *Catalysis Reviews* 2020; 1-86.

Aljamali NM, Alfatlawi IO. Synthesis of sulfur heterocyclic compounds and study of expected biological activity. *Research Journal of Pharmacy and Technology* 2015; 8(9): 1225-1242.

https://doi.org/10.5958/0974-360X.2015.00224.3

Aljamali NM, Jawd SM, Jawad ZM, Alfatlawi IO. Inhibition activity of (azo-acetyl acetone) on bacteria of mouth. *Research Journal of Pharmacy and Technology* 2017; 10(6): 1683-1686.
https://doi.org/10.5958/0974-360X.2017.00297.9

Alfatlawi IO, Salih NS, Jawad ZM, Aljamali NM. Synthesis of New Organic Compounds Via Three Components Reaction with Studying of (Identification, Thermal Behavior, Bioactivity on Bacteria of Teeth). *Journal of Global Pharma Technology* 2017; 11(9), 157-164.

Jawad AM, Aljamali NM, Jwad SM, MJ A, MJ S. Development and Preparation of ciprofloxacin Drug Derivatives for Treatment of Microbial Contamination in Hospitals and Environment. *Indian Journal of Forensic Medicine & Toxicology* 2020; 14(2): 1115-1122.

Wei H, Wang E. Nanomaterials with enzyme-like characteristics (nanozymes): next-generation artificial enzymes. *Chemical Society Reviews* 2013; 42(14): 6060-6093. https://doi.org/10.1039/C3CS35486E

Aljamali NM, Alsabri IKA. Development of Trimethoprim Drug and Innovation of Sulfazane-Trimethoprim Derivatives as Anticancer Agents. *Biomedical and Pharmacology Journal* 2020; 13(2): 613-625.
http://dx.doi.org/10.13005/bpj/1925

D'alnoncourt RN, Csepei LI, Hävecker M, Girgsdies F, Schuster ME, Schlögl R, Trunschke A. The reaction network in propane oxidation over phase-pure MoVTeNb M1 oxide catalysts. *Journal of catalysis* 2014; 311: 369-385.

Amer I, Van Reenen A, Mokrani T. Molecular weight and tacticity effect on morphological and mechanical properties of Ziegler–Natta catalyzed isotactic polypropylenes. *Polímeros* 2015; 25(6): 556-563.
http://doi.org/10.1590/0104-1428.2158

Rasool SR, Aljamali NM, Al-Zuhairi AJ. Guanine substituted heterocyclic derivatives as bioactive compounds. *Biochemical and Cellular Archives* 2020; 20(Supplement 2): 3651-3655.

DocID: https://connectjournals.com/03896.2020.20.3651.

Dub PA, Gordon JC. The role of the metal-bound N–H functionality in Noyori-type molecular catalysts. *Nature Reviews Chemistry* 2018; 2(12): 396-408.

Clark J. Types of catalysis. *Chemguide.* Bård Lindström and Lars J. Petterson (2003) "A brief history of catalysis" Cattech, 2013; 7(4): 130–38.

Li L, Guo Z, Guo Y, Ren X, Lv Q, Zhang Q. Ability of compensation for the subjects of agricultural natural disasters based on brain evoked potential experiment. *NeuroQuantology* 2018; 16(6): 554-563.