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Synthesis and identification of (Imidazole- thiadiazol) derivatives and study the biological activity as antibacterial

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Abstract

In this study, the synthesis of heterocyclic derivatives originating from imidazole was conducted. Initially, the process involved the synthesis of 3-((1H-imidazol-2-yl)diazenyl)-4-methoxybenzoic acid (1) through a coupling reaction. This reaction was facilitated between 4-methoxy benzoic acid-3-diazonium chloride and imidazole in an alkaline alcoholic solution. Subsequently, the azo derivative (1) underwent a reaction with thiosemicarbazide, employing POCl3 as a solvent, resulting in the formation of 5-(3-((1H-imidazol-2-yl)diazenyl)-4-methoxyphenyl)-1,3,4-thiadiazol-2-amine (2). The subsequent phase involved reacting compound (2) with chloroacetyl chloride, leading to the synthesis of 5-(3-((1H-imidazol-2-yl) diazenyl)-4-methoxyphenyl)-N-(3-chloroprop-1-en-2-yl)-1,3,4-thiadiazol-2-amine (3). The concluding step entailed the reaction of the derivative (3) with various amines, including 2-Aminothiazole, 2-Amino-6-methoxybenzothiazole, 2-Amino-4,5-dimethylthiazole, 4-Chloro-2-nitroaniline, and 2-Amino pyrimidine, to yield imidazole derivatives (4-8). Characterization of these compounds was achieved through FTIR, ^{1}H-NMR, and ^{13}C-NMR. Furthermore, biological activity of all produced heteroaromatic derivatives was evaluated against two types of bacteria: *Staphylococcus aureus* and *Escherichia coli*.

Key words: Imidazole, - thiadiazol, heterocyclic compounds.

تحضير و تشخيص مشتقات (إيميدازول – ثيادايازول) ودراسة فعاليتها البيولوجية كمضادات بكتريا

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الخلاصة

تضمن هذا البحث تحضير مادة مشتقة حلقية غير متجانسة من الإيميدازول. و تضمنت الخطوة الأولى تحضير 3-((إيميدازول-2-ديازونيل)-4-ميثوكسي حامض البنزويك (1) بتفاعل الاقتران بين 4-ميثوكسي حامض البنزويك -3-كلوريد الديازونيوم مع الإيميدازول في محلول كحولي قلوي، ثم تضمنت الخطوة الثانية تفاعل مشتق الآزو (1) مع الثيوسيميكاربازيد باستخدام المذيب POCl3 للحصول على 5-(3-إيميدازول-2-ديازينيل) -4-ميثوكسي فينيل)4,3,1--

ثياديازول-2-أمين (2). وتضمنت الخطوة الثالثة تفاعل (2) مع كلورو أسيتيل كلورايد للحصول على 5- (3-((إيميدازول ديازينيل)-4-ميثوكسي فينيل-3)-N-(كلوروبروب-1-2-1,3,4- ثياديازول -2-أمين(3). وتضمنت الخطوة النهائية مشتق التفاعل (3) مع العديد من أنواع الأمينات (2-أمينوثيازول، 2- أمينو- 6 -ميثوكسي بنزوثيازول، 2-أمينو-4،5-ثنائي ميثيل ثيازول، 4-كلورو-2-نيتروانيلين، 2-أمينو بيريميدين). للحصول على مشتقات الإيميدازول (4-8). تميزت جميع هذه المركبات بمطياف الأشعة تحت الحمراء (FT-IR)، ^{1}H-NMR و^{13}C-NMR، ثم قمنا بدراسة النشاط البيولوجي لجميع مشتقات الحلقات غير المتجانسة تجاه نوعين مختلفين من البكتيريا (المكورات العنقودية الذهبية) و(الإشريكية القولونية).

1. Introduction

Azo derivatives are organic dyes containing (-N=N-) group [1]. The azo compounds are contained the thiadiazole make this very important class having application in multiple fields such as biological activity , pharmaceutical , industrial [2,3] for that in this research we study the biological activity as inhibition and killing of bacteria [4,5]. also, we added thiazole and pyrimidine to azo-thiadiazole derivatives by many steps of reactions to incrze the activite of compounds, that Heterocyclic compounds that have (N, S) as hetero atoms are important it have veriose applications [6-9]. The chemistry thiazole and pyrimidine derivatives have been of great interest because of its various biological activity it used as anti – inflammatory antitumor, vasodilator, anti-tubercular, antifungal , antimicrobial, anticancer ,anti-diabetic and anti-bacterial activities [1—12]

2.Materials

The Fourier Transform Infrared (FTIR) spectra, ranging from 400 to 4000 cm^{-1}, were obtained using a SHIMADZU FTIR-8400S instrument, employing KBr discs for sample preparation. ^{13}C NMR and ^{1}H NMR analyses were performed on a Varian Agilent system, operating at 500 MHz, utilizing DMSO-d6 as the solvent. These measurements were conducted at the Department of Chemistry, Al-Basra University, Iraq.

2.1preparation of the compound(1)[13]

The azo compound was prepared by dissolving (3-amino-4-methoxybenzoic acid) (0.0072mol,1.203g) In a solution consisting of (5ml HCl) and 20mal distilled water and cooled to (0-5^{O}C), then a solution of sodium nitrite is added by dissolving (0.0072mol, 0.4993g) of sodium nitrite in 5mal distilled water. Added drop by drop to the mixture. After that, the mixture is left for 20 minutes to complete the process. Then add this solution to a solution consisting of (0.0072mol, 0.49g). Imidazole and 1g sodium hydroxide dissolved in 50ml distilled water and 5ml ethanol at a temperature (0-5^{O}C) gradually, and after completing the addition, the solution is left for one hour, while observing the pH adjustment at pH=6, after which the solution is filtered to obtain a precipitate and washed With distilled water several times .

2.2 preparation of compound(2)[14]

The synthesis of the thiadiazole derivative was conducted in a two-necked round-bottom flask, outfitted with a condenser and a magnetic stirrer. A quantity of

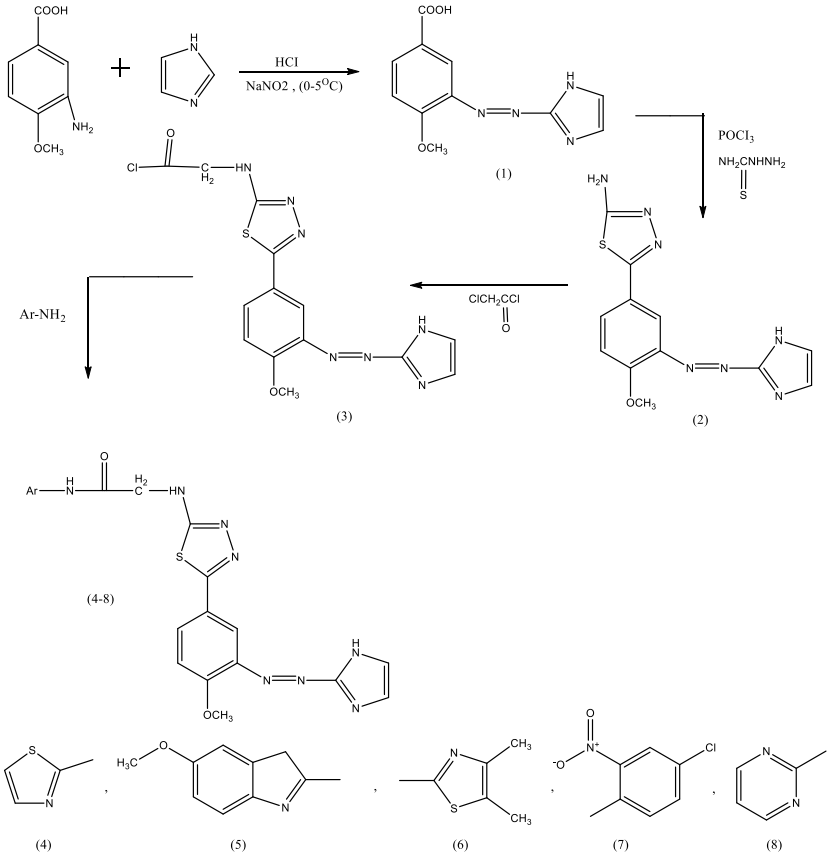
the precursor derivative (1), specifically 0.0043 mol or 1.0578 g, along with 0.3918 g of thiosemicarbazide, were combined and dissolved in 8 mol of POCl3 under continuous agitation for a duration of 3 hours. Subsequent to this period, the reaction mixture was allowed to cool. Following cooling, 40 mL of distilled water was incrementally introduced to the mixture. After the addition was completed, stirring was maintained for an additional 4 hours. The mixture was then subjected to filtration, and the filtrate was neutralized using a potassium hydroxide solution until a neutral pH was achieved. The resultant precipitate was isolated via filtration, rinsed with distilled water, dried, and recrystallized using absolute ethanol. The progression of the reaction was monitored through Thin Layer Chromatography (TLC) employing a mobile phase composed of methanol and gasoline in a ratio of 4:1.

2.3,preparation of compound(3)[15]

added (0.46 mal)(0.0059 mol) from chloroacetyl chloride in the form of drops to (0.0059ml)(1.76g) of derivative 2 dissolved in 30mal 1-4 dioxane with continuous stirring using a magnetic stirrer at room temperature for 3 hours, after which the precipitate te is filtered, dried, and recrystallized with absolute ethanol.

2.4preparation of compound(4-8)[16]

(0.001mol) of derivative 3 dissolved in (25mol) of absolute ethyl alcohol was added to (0.001mol) (2-Aminothiazole, 2-Amino-6-methoxybenzothiazole , 2-Amino-4,5 dimethyl thiazole, 4-Chloro-2-nitroaniline , 2-Amino pyrimidine) The mixture was heated in a round flask for 30 minutes, then cooled and the precipitate was collected, then recrystallized with absolute ethanol to get (4-10) derivatives.

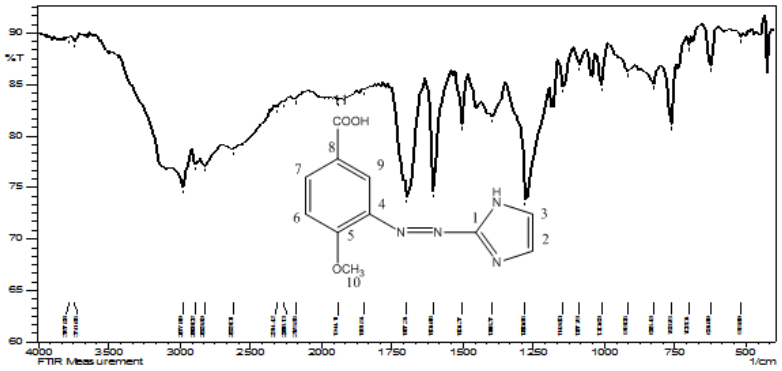


Schem1: prepare of some heterocyclic derivatives

Result and Discussion

Compound(1) :- 3-((1H-imidazol-2-yl)diazenyl)-4-methoxybenzoic acid

The infrared spectral analysis of compound (1) revealed characteristic absorption bands at specific wavenumbers: 3101 cm^{-1} attributed to N-H stretching vibrations, 3400 cm^{-1} to O-H stretching, 3055 cm^{-1} indicative of aromatic C-H stretching, 2931 cm^{-1} for aliphatic C-H stretching, 1712.67 cm^{-1} corresponding to the C=O stretch, 1550 cm^{-1} for C=N stretch, and 1450 cm^{-1} associated with N=N stretching vibrations. In the ^{1}H-NMR spectrum (DMSO-d6), observed in Figure 1b for compound (1), distinct signals were detected: a singlet at 8.8 ppm for 1H corresponding to NH, a singlet at 10.2 ppm for 1H attributed to OH, a singlet at 3.7 ppm for 3H representing OCH3, and a multiplet in the range of 7.1-8.1 ppm for aromatic hydrogens. The ^{13}C-NMR spectrum (DMSO-d_6) of compound (1), presented in Figure 1c, showed carbon resonance signals at 176 ppm for C11, 56 ppm for C10, 159 ppm for C1, 155 ppm for C4, 144 ppm for C2,3, and a range of 111-134 ppm for aromatic carbons.



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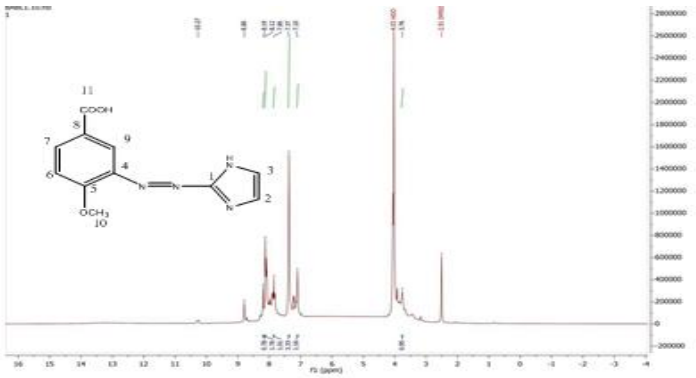

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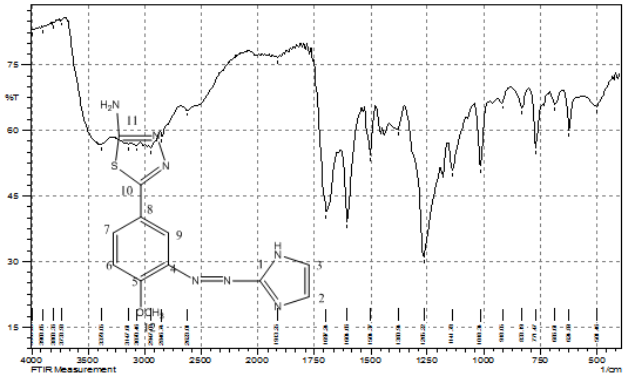
Fig. 1: spectra of compound 1: a- FTIR, b- 1H-NMR, c- 13C-NMR

compound(2):- **5-(3-((1H-imidazol-2-yl)diazenyl)-4-methoxyphenyl)-1,3,4-thiadiazol-2-amine**

The infrared spectrum data for compound (2) revealed the presence of several bands: a band ranging from 3379 to 3147 cm^{-1} was observed, indicative of NH_2 and NH groups; a band at 1697 cm^{-1} was associated with the C=N stretch; the C-H aliphatic stretch was identified at 2947.03 cm^{-1}; a C=C stretch was noted at 1604.66 cm^{-1}; and a C-O stretch was recorded at 1265 cm^{-1}. In the ^{1}H-NMR (DMSO-d6) spectrum, depicted in Figure 2, of compound (2), several peaks were observed: a singlet at 8.8 ppm corresponding to 1H of NH, a singlet at 10.6 ppm for 2H of NH_2, a singlet at 4 ppm representing 3H of OCH_3, and a multiplet in the range of 6.8-7.8 ppm for 5H of Ar-H. The ^{13}C-NMR (DMSO-d6) spectrum, presented in Figure 5, of compound (2) exhibited several chemical shifts: 56 ppm for C12, 158 ppm for C1, 150 ppm for C10, 147 ppm for C4, and a range of 110-141 ppm for aromatic carbons.



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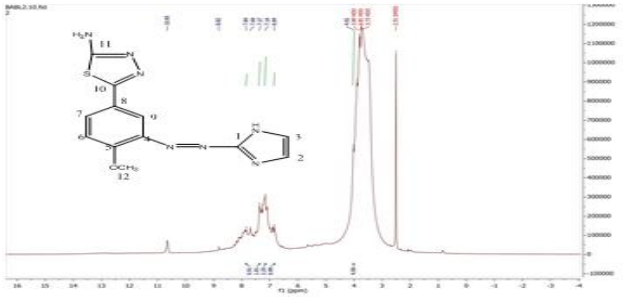

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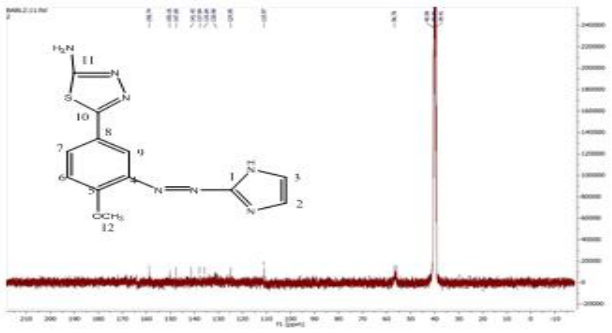

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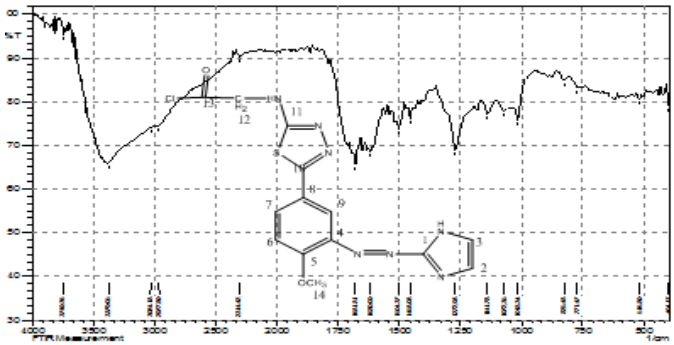
Fig. 2: spectra of compound 2: a- FTIR, b- 1H-NMR, c- 13C-NMR compound(3) (5-(3-((1H-imidazol-2-yl)diazenyl)-4-methoxyphenyl)-1,3,4-thiadiazol-2-yl)glycinoyl chloride

FTIR-spectrum analysis of compound (3) revealed distinct bands: at 3379 cm^{-1}, attributed to -N-H-stretching; at 3024 cm^{-1}, denoting -C-H aromatic stretching; at 2977 cm^{-1}, corresponding to C-H aliphatic stretching; at 1681 cm^{-1}, indicative of -C=O-stretching; at 1661 cm^{-1}, associated with -C=N-stretching; at 1504 cm^{-1}, for -N=N-stretching; at 1272 cm^{-1}, related to -C-O-stretching; and at 771.47 cm^{-1}, for -C-Cl-stretching. The ^{1}HNMR (DMSO-d_6) spectrum, as shown in Figure 3 for compound (3), identified several signals: a singlet at 9.1 ppm for the imidazole NH, a singlet at 4 ppm for an amide NH, a singlet at 3 ppm for 3H of OCH_3, a singlet at 3.9 ppm for 2H of CH_2, and a multiplet between 7.2 and 7.7 ppm for 5H of ArH. The ^{13}CNMR (DMSO-d_6)spectrum, presented in Figure 3, of compound (3) exhibited chemical shifts at 177 ppm for C12, 15 ppm for C14, 45 ppm for C13, 162 ppm for C1, 157 ppm for C11, 149 ppm for C10, and a range from 144 to 117 ppm for aromatic carbons.



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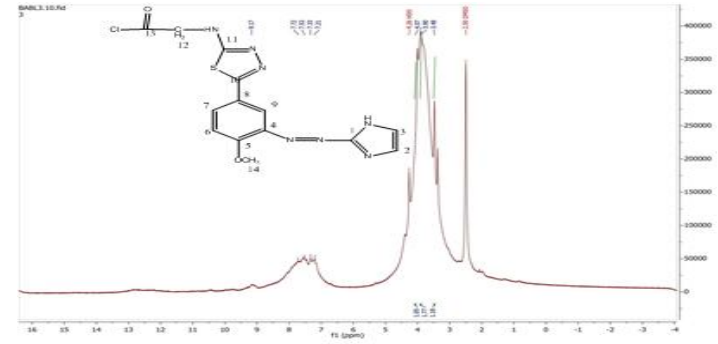

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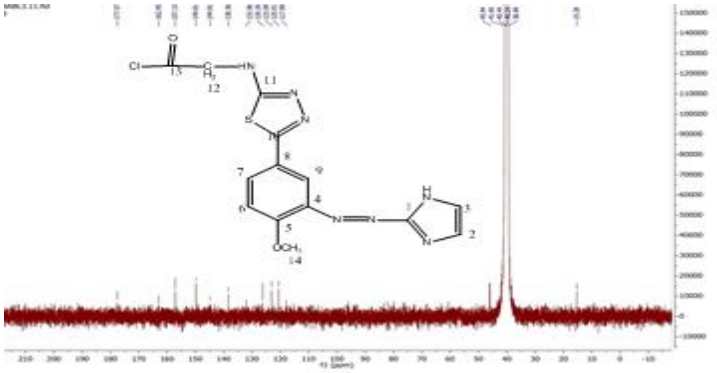

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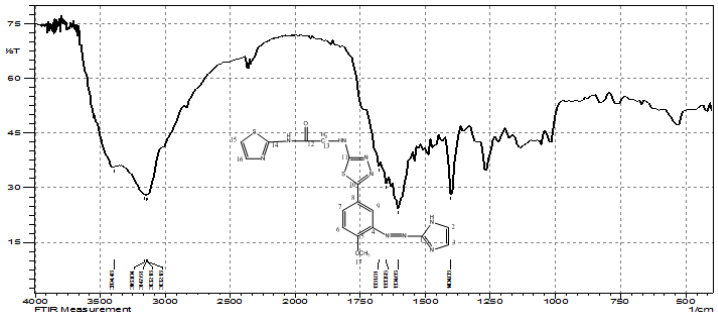
Fig. 3: spectra of compound 3: a- FTIR, b- 1H-NMR, c- 13C-NMR

compound(4) 2-((5-(3-((1H-imidazol-2-yl)diazenyl)-4-methoxyphenyl)-1,3,4-thiadiazol-2-yl)amino)-N-(thiazol-2-yl)acetamide. The infrared spectrum data of the compound (4) showed band at3409.91-3147.61 cm $^{-1}$ for (NH) 3030cm^{-1}for(C-H)arom. ,2929 cm^{-1} for (C-H)Aliph., 1570cm^{-1}(C=C)1604.66 cm $^{-1}$ for (C=N) 1450cm^{-1}(N=N),1081cm^{-1}for(C-CI).The ^{1}H-NMR(DMSO-*d6*) spectrum data Figure 4 of compound (4) show : 9.7 ppm imidazole (S,1H,NH) , 4.4,4.2 ppm (S,2H,NH),5.3ppm(S,2H,CH_2), 1.2ppm(S,3H,OCH_3) 6.7-7.8ppm (M,7H,ArH). ^{13}CNMR (DMSO-d_6)spectrum data Figure 4 of compound (4) show :170ppm(C_{12}), 31ppm(C_{17}), 55ppm(C_{13}), 154ppm(C_1), 149ppm(C_{14}) , 147ppm(C_{11}), 141ppm(C_{10}),100-138ppm(C_{Arom}).



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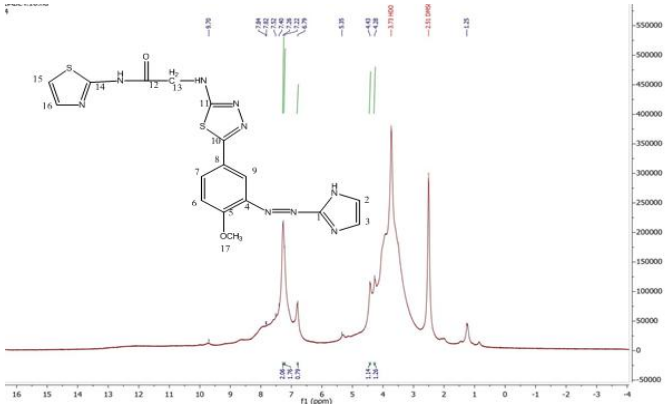

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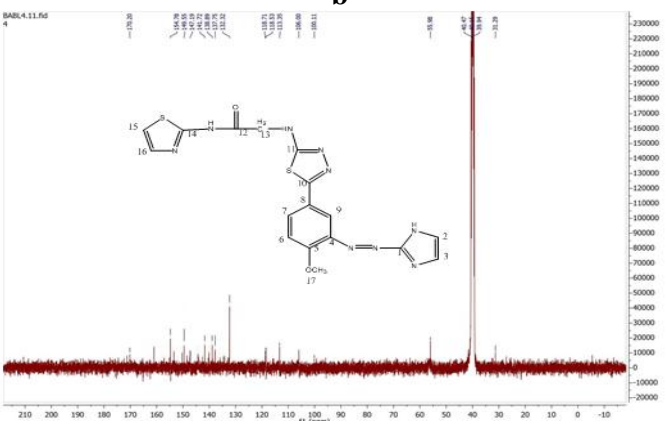

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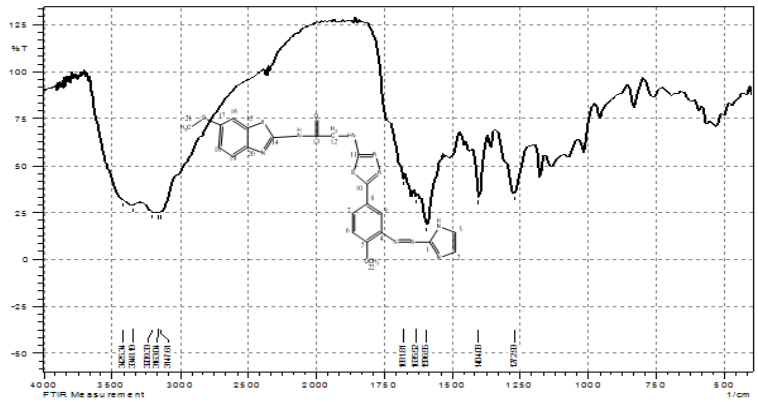
Fig. 4: spectra of compound 4: a- FTIR, b- 1H-NMR, c- 13C-NMR

Compound(5):- 2-((5-(3-((1H-imidazol-2-yl)diazenyl)-4-methoxyphenyl)-1,3,4-thiadiazol -2-yl)amino)-N-(5-methoxy-3H-indol-2-yl)acetamide

The infrared spectrum data of the compound (5) showed band at3348-3163.04cm $^{-1}$ for (NH),3022cm^{-1}for(C-H) arom.,2980cm^{-1}for(C-H) Aliph.,1679 cm^{-1} for (C=O),1512 cm^{-1} for (C=C),1272.93cm^{-1} for(C-O). The ^{1}H-NMR(DMSO-*d6*) spectrum data Figure 5 of compound (5) show: 9.6ppm imidazol (S,1H,NH),4.4ppm Amide(S,1H,NH),4.2 ppm (S,1H,NH),4 ppm(S,2H,CH_2),2.3,1.2ppm(S,6H,OCH_3) 6-7.6ppm(M,8H,ArH). The ^{13}C-NMR (DMSO-d_6) spectrum data Figure 5 of compound(5) show:172ppm (C_{12}),26ppm (C_{13}),67,68ppmC_{22},C_{21}),167ppm (C_1),165ppm(C_{14}),164ppm(C_{10}),158ppmppm(C_{11}),154ppm(C_4),112-150ppm(C_{Arom}).



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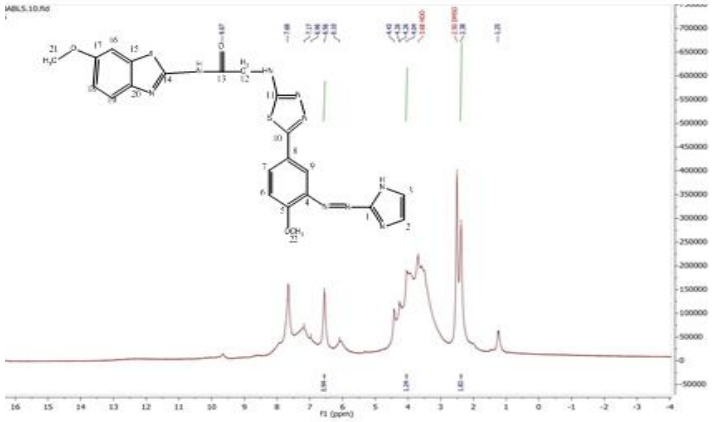

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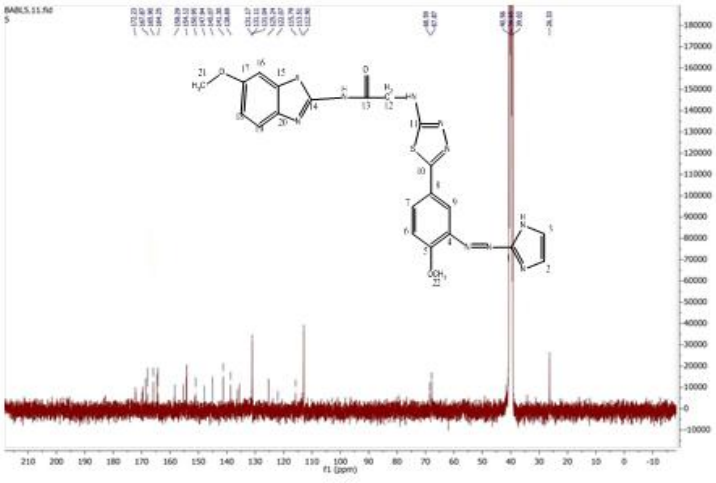

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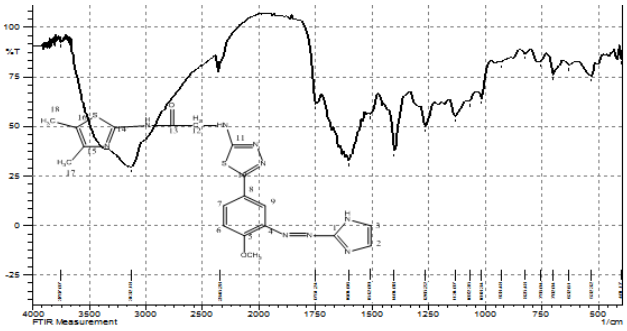
Fig. 5: spectra of compound 5: a- FTIR, b- 1H-NMR, c- 13C-NMR

compound(6) :- **2-((5-(3-((1H-imidazol-2-yl)diazenyl)-4-methoxyphenyl)-1,3,4-thiadiazol-2-yl)amino)-N-(4,5-dimethylthiazol-2-yl)acetamide**

The spectral analysis of compound (6) using infrared spectroscopy revealed the presence of various functional groups, indicated by specific absorption bands: a peak at 3132.18 cm^{-1} was attributed to the N-H stretching vibration, while bands at 1761 cm^{-1}, 1635 cm^{-1}, 1604 cm^{-1},

1512.09 cm^{-1}, and 1265.22 cm^{-1} corresponded to C=O, C=N, C=C, N=N, and C-O stretching vibrations, respectively. In the ^{1}HNMR spectrum (DMSO-d_6) of compound (6), as depicted in Figure 6, several resonances were observed: a singlet at 9.9 ppm was assigned to 1 hydrogen of the NH group; singlets at 5 and 4.8 ppm were attributed to 2 hydrogens of another NH group; a singlet at 4.4 ppm corresponded to 2 hydrogens of a -CH_2 group; singlets at 4.2 and 4 ppm were observed for 6 hydrogens of a -CH_3 group; and a singlet at 2.1 ppm was noted for 3 hydrogens of an -OCH_3 group. Furthermore, the ^{13}CNMR spectrum (DMSO-d_6) of compound (6), also shown in Figure 6, featured resonances at 174 ppm for C12, at 12 and 13 ppm for C17 and C18, at 56 ppm for C19, at 60 ppm for C13, at 168 ppm for C1, at 164 ppm for C14, at 159 ppm for C11, at 155 ppm for C10, at 151 ppm for C4, and within the range of 113-148 ppm for aromatic carbons. These spectral data provide comprehensive insights into the structural framework of compound (6), underlining the methodology's efficacy in elucidating compound composition and functional group identification.



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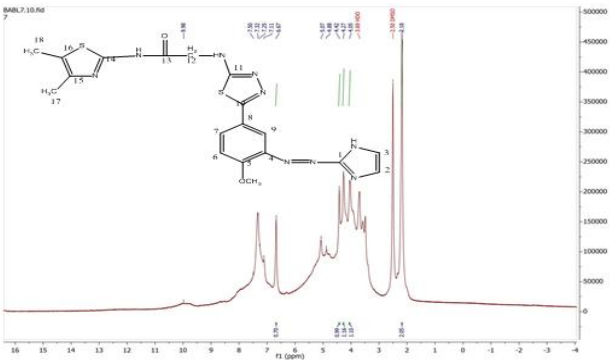

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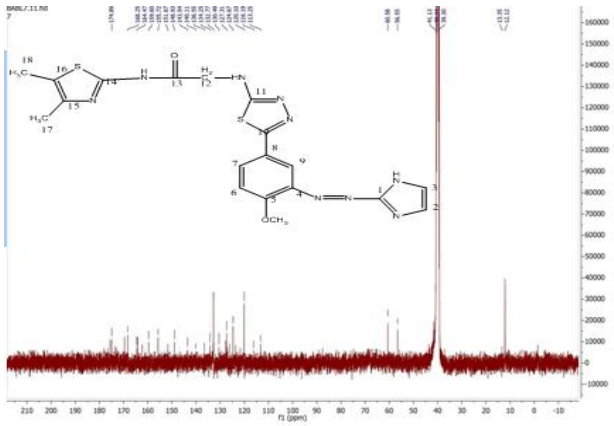

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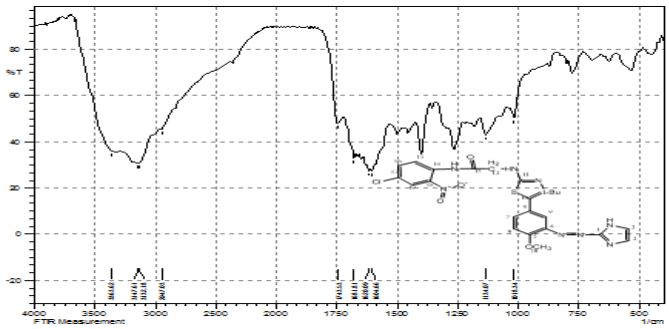
Fig. 6: spectra of compound 6: a- FTIR, b- 1H-NMR, c- 13C-NMR

Compound (7) 2-((5-(3-((1H-imidazol-2-yl)diazenyl)-4-methoxyphenyl)-1,3,4-thiadiazol-2-yl)amino)-N-(4-chloro-2-nitrophenyl)acetamide

The infrared spectrum data of the compound (7) showed band at3317-3147.61cm^{-1} for (NH),3042cm^{-1} for(C-H) arom.2947cm^{-1}(C-H) aliph. 1604cm^{-1}for(C=N),1743 cm^{-1} for (C=O), 1532.32cm^{-1} for (C=C), 1527-1342.36cm^{-1} for(NO2),1504,37 cm^{-1} for (N=N),1265.22cm-^{1} for(C-O).The ^{1}H-NMR(DMSO-d6) spectrum data Figure 7 of compound(7) show:8.9 ppm imidazole (S,1H,NH),4.4,4.2 ppm(S,2H,NH),4 ppm(S,2CH,CH_2),3.6 ppm(S,3H,OCH_3),6.5-8.2ppm(M,8H,Ar-H)The ^{13} C-NMR (DMSO-d_6) spectrum data Figure 7 of compound(7) show:169 ppm (C_{12}),65 ppm(C_{13}),68 ppm(C_{20}),167 ppm(C_1),163 ppm(C_{11}),158ppm (C_{10}),156 ppm(C_4),151 ppm(C_{14}),110-148ppm(C_{Arom}).



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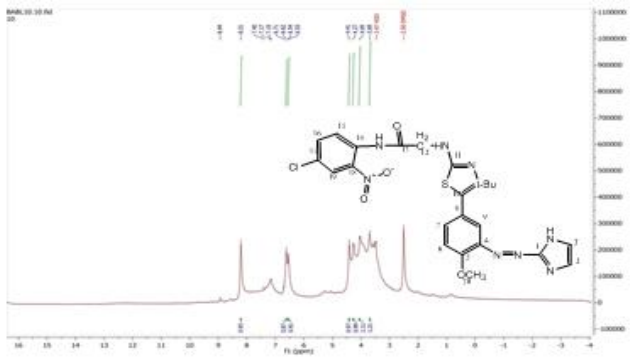

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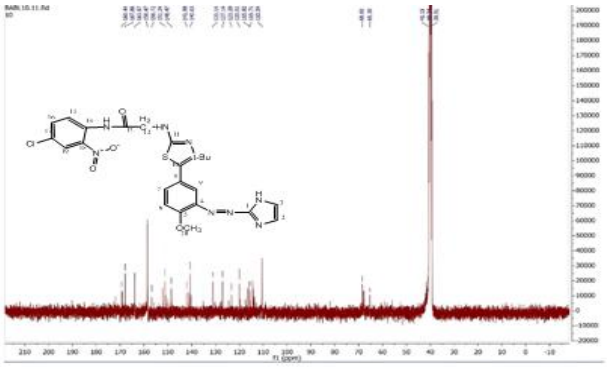
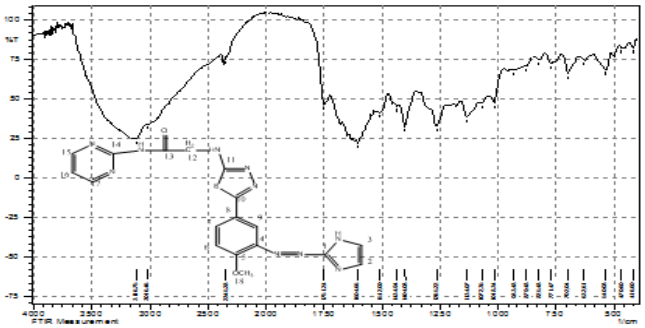


-c-

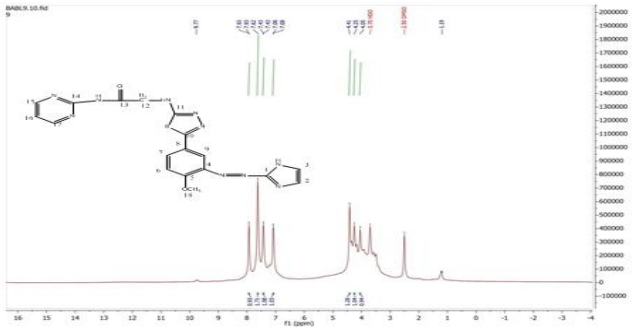
Fig. 7: spectra of compound 7: a- FTIR, b- 1H-NMR, c- 13C-NMR

Compound(8) 2-((5-(3-((1H-imidazol-2-yl) diazenyl)-4-methoxyphenyl) - 1,3,4-thiadiazol-2-yl) amino)-N-(pyrimidin-2-yl)acetamide

The infrared spectrum of compound (8) displayed distinctive absorption bands over a range of wavenumbers: a broad band stretching from 3116 to 3320 cm^{-1}, indicating -N-H-stretching vibrations, 1731 cm^{-1} for the -C=O-stretch, 1512.09 cm^{-1} for -C=C-stretching vibrations, 1604 cm^{-1} associated with -C=N-stretching, 1424 cm^{-1} for -N=N-stretching, and 1265.22 cm^{-1} indicative of C-O stretching vibrations. ^{1}H-NMR spectrum (DMSO-d_6) of compound (8), as illustrated in Figure 8, showed a singlet at 9.7 ppm for 1H related to NH, singlets at 4.4 and 4.2 ppm each for 2H corresponding to NH_2, a singlet at 4 ppm for 2H denoting CH2, a singlet at 1.1 ppm for 3H associated with OCH_3, and a multiple from 7-7.9 ppm for 8H assigned to aromatic hydrogens (ArH). In the ^{13}C-NMR (DMSO-d6) analysis of compound (8), depicted in Figure 8, carbon resonance signals were identified at 172 ppm for C12, 65 ppm for C13, 67 ppm for C18, 167 ppm for C1, 160 ppm for C14, 145 ppm for C10, 144 ppm for C11, and a range between 118 and 136 ppm for aromatic carbons (CArom), showcasing the complex structure and functional groups present in this molecule.



-a-



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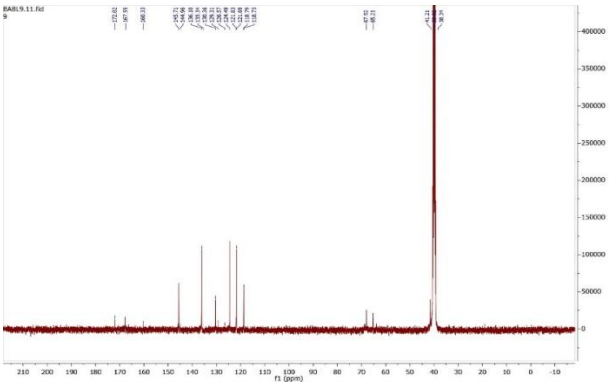

-c-

Fig. 8: spectra of compound 8: a- FTIR, b- 1H-NMR, c- 13C-NMR

Biological activity

Biological activity of the synthesized compounds was evaluated against two bacterial strains: *S.aureus* and *E.coli* (Fig.9 and Table(1)).

Table 1: Show Biological activity for compound(1-8)

Compounds No.	*E.Coli*	*S.Aureus*
1	++	++
2	+++	+
3	+++	++
4	+++	+
5	+++	+
6	+++	++
8	+++	+
7	+++	+
8	+++	+

- = No inhibition = inactive , + = (5-10) mm = slightly active , ++= (11-20) mm = moderately active , +++ = (more than 20) mm = Good active

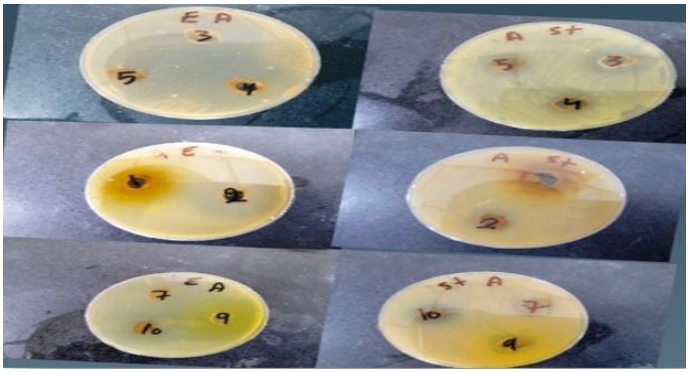

Fig. 9: pictures Show Biological activity for compound (1-8)

Table 2: Physical properties of compounds (1-8)

NO	Name of comp	M.F	M.W	M.P(C°)	R.f	Color	%
1	3-((1H-imidazol-2-yl)diazenyl)-4-methoxybenzoic acid	$C_{11}H_{10}N_4O_3$	246.2	198-201	0.4	Dark brown	90
2	5-(3-((1H-imidazol-2-yl)diazenyl)-4-methoxyphenyl)-1,3,4-thiadiazol-2-amine	$C_{12}H_{11}N_7OS$	301	211-213	0.32	Dark green	86
3	(5-(3-((1H-imidazol-2-yl)diazenyl)-4-methoxyphenyl)-1,3,4-thiadiazol-2-yl)glycinoyl chloride	$C_{14}H_{14}N_8O_2S$ CI	393.5	152-154	0.26	Dark brown	75
4	2-((5-(3-((1H-imidazol-2-yl)diazenyl)-4-methoxyphenyl)-1,3,4-thiadiazol-2-yl)amino)-N-(thiazol-2-yl)acetamide	$C_{17}H_{15}N_9O_2S_2$	441.9	123-128	0.3	Brown	70
5	2-((5-(3-((1H-imidazol-2-yl)diazenyl)-4-methoxyphenyl)-1,3,4-thiadiazol-2-yl)amino)-N-(5-methoxy-3H-indol-2-yl)acetamide	$C_{23}H_{21}N_9O_3S$	503.5	223-225	0.03 1	Light brown	86
6	2-((5-(3-((1H-imidazol-2-yl)diazenyl)-4-methoxyphenyl)-1,3,4-thiadiazol-2-yl)amino)-N-(4,5-dimethylthiophen-2-yl)acetamide	$C_{20}H_{20}N_8O_2S_2$	468.5	157-159	0.45	Brown	89
7	2-((5-(3-((1H-imidazol-2-yl)diazenyl)-4-methoxyphenyl)-1,3,4-thiadiazol-2-yl)amino)-N-(4-chloro-2-nitrophenyl)acetamide	$C_{20}H_{16}CIN_9O_4S$	513.9	167-169	0.55	Brown	79
8	2-((5-(3-((1H-imidazol-2-yl)diazenyl)-4-methoxyphenyl)-1,3,4-thiadiazol-2-yl)amino)-N-(pyrimidin-2-yl)acetamide	$C_{18}H_{16}N_{10}O_2S$	436.4	145-147	0.24	Light brown	67

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