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Antioxidant and Antimicrobial Activities of Some New Synthesized Triazole, Thiazolone, and Thiazine Containing Fused Rings of Imidazopyridine

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Abstract

Several heterocyclic compounds bearing an imidazo(1,2a)pyridine moiety have been synthesized in this work, including triazole, thiazol, and thiazolone. This was done by condensation of 2-aminopyridine with 2-aminopyridine with 4-bromophencyl bromide or 4-phenylphencyl bromide to produce 2-substituted phenyl imidazo(1,2a)pyridine compounds **1** and **2**. The Vilsmeier-Haak reaction was used to create the aldehyde group at position 3 of the 2-substituted phenyl imidazo(1,2a)pyridine ring (**3** and **4**). The reaction of compounds **3** and **4** with thiosemicarbazide afforded thiosemicarbazone derivatives **5** and **6** in 66 and 70% yields, respectively. These derivatives (**5** and **6**) were then subjected to three different cyclization reactions to obtain 1,3-thiazolone (**7** and **8**), 1,2,4-triazole (**9** and **10**), and 1,3-thiazole (**11** and **12**) derivatives. The FT-IR spectroscopy was used to confirm the structure of these derivatives, and the ^{1}H NMR spectroscopy was used for some of them. A few of the produced compounds were examined for antimicrobial and antioxidant activities

Keywords: Imidazo[1,2a]pyridine, Heterocyclic compounds, Antimicrobial activity, Antioxidant activity

الفعالية المضادة للاكسدة والميكروباتل بعض المركبات الجديدة (الثايزين و الثايوزولون و الترايزول) الحاوية على حلقات مدمجة من إيميدازو بيريدين

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الخلاصة

تم تحضير مركبات حلقية غير المتجانسة (تريازول و ثيازين و ثيازولون) ,و الحاوية على نواة الإيميدازو (1,2 a) بيريدين عن طريق سلسلة من التفاعلات. حيث، تم تحضير 4–فينيل إيميدازو (1,2 a) بيريدين عن طريق تكاثف 2–أمينو بيريدين مع 4–برومو فيناسيل بروميد أو 4–فينيل بروميد الفينسايل .ثم تم تحضير الالديهايد عن طريق تفاعل فيلز–مايرهوك من تفاعل فينيل إيميدازو(1,2 a)بيريدين مع ثنائي مثيل فورمامايد و .POCl3 . تم تحضير مشتقات الثايوسيميكاربزون (قواعد شيف) عن طريق التكاثف مع 3– مشتقات كربالديهايد مع ثايوسيميكاربازايد. بعد ذلك تم غلق مشتقات الثايوسيميكاربزون مع 4–برومو فيناسيل

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بروماید، حامض الهیدروکلوریك واحادي كلورو كلوريد الحامض في وجود أسيتات الصوديوم اعطت مشتقات 1،3–ثيازين، 1،2،4–تريازول و 1،3–ثيازولون على التوالي. تم تشخيص المشتقات الجديدة عن طريق التحليل الطيفي للاشعة تحت الحمراء و طيف الرنين النووي المغناطيسي للبروتون والكاربون. و كذلك تم اختبار بعض هذه المشتقات كمواد مضادة للميكروبات و مضادة للاكسدة .

1. Introduction

One of the most important core structures in organic compounds is the imidazol-fused heterocyclic. It can be found in many natural products and physiologically active compounds that have antibacterial properties [1], anticancer [2], antimicrobial [3,4], antifungal [5], antiviral [6], and anti-inflammatory activities [7]. These are structural themes of different medications that are commercialized [8], such as divaplon and fasiplon [9]. Imidazo-fused pyridines are crucial to the pharmaceutical business due to their vast variety of fascinating pharmacological activities [10]. There are many different heterocyclic compounds that can be produced using the intermediate thiosemicarbazone [11]. The compounds were then cyclized using a variety of reagents and conditions to create some new heterocyclic substances (thiazolone, thiazein, and 1,2,4-triazole) with an imidazol/pyridine moiety. Thiazolone is a five-membered heterocyclic structure composed of sulfur, nitrogen, and oxygen atoms [12]. It has a number of isomers, including thiazol-4-one and thiazol-5-one [13]. The biological functions of the thiazolone system are broad, including anti-cancer [14], anti-hypertensive [15], anti-oxidant [16], anti-bacteria [17], anti-fungal activities [18], and as herbicides [19]. Thiazole (1,3-thiazol) is an aromatic five-membered heterocycles with sulfur and nitrogen atoms. Different products containing this ring were found in both natural and therapeutic [21], peptides [22], and chlorophyll [23], and showed a wide variety of biological activities [20]. Numerous biological actions of thiazole compounds exist, such as antioxidant [24,25], antitubercular [26], and antibacterial properties [27]. Many medications used in the pharmaceutical industry, including meloxicam, dasatinib (antineoplastic), abafungin (antifungal), and nitazoxanide (antiparasitic), include an athiazole core (anti-inflammatory) [28]. Another type of organic heterocyclic complex is a triazole, which has two carbon and three nitrogen atoms, making up the five members of this ring. Triazoles come in two isomeric groups: 1,2,4-triazol, and 1,2,3-triazole [29]. Triazole derivatives contain a variety of pharmacological characteristics, including anti-malarial activities. [30], anti-cancer [24,31,32], antibacterial [34]. In addition, a variety of medications have triazole rings, including fluconazole [33]. In our work, new 1,3-thiazole-4-one, 1,2,4-triazole, and 1,3-thiazine derivatives bearing imidazo(1,2a)pyridine moieties will be prepared in four steps starting from 2-aminopyridine, then investigate their antimicrobial and antioxidant activities.

2. Material and methods

2.1. Instruments and chemicals

All the chemicals utilized were purchased from Sigma Aldrich, Fluka chemical, and Chemical central drug houses companies. The FT-IR spectral data were recorded using a Shimadzu FT-IR-8400 at the College of Science, University of Baghdad. The ^{1}H NMR and ^{13}C NMR spectral data were recorded using an ultra-shield (500 MHZ spectrometer) at the Central Laboratory of Tehran University. Chemical shifts are expressed in ppm downfield from tetramethylsilane (TMS) as an internal standard or deuterated DMSO as a reference. Melting points are uncorrected and were recorded in open capillary tubes using Gallenkamp melting point equipment.

2.2. Chemistry

*2.2.1. Synthesis of 2-([1,1'-Biphenyl]-4-yl)imidazo[1,2-a]pyridine (**1**) and 2-(4-bromophenyl)imidazo[1,2-a]pyridine (**2**) [34]*

2-Aminopyridine (10 mmol) was combined with 4-bromophencyl or 4-phenylphencyl bromide (10 mmol) in sodium bicarbonate (10 mmol). This mixture was refluxed for 8 hours before cooling and basifying with NaOH (1.0 M) to obtain pH 9, as measured by pH paper. The reaction mixture was poured onto crushed ice. The solid crude material was then filtered and recrystallized from ethanol to afford the desired products **1** and **2**.

*2.2.2. Synthesis of 2-([1,1'-Biphenyl]-4-yl)imidazo[1,2-a]pyridine-3-carbaldehyde (**3**) and 2-(4-bromophenyl)imidazo[1,2-a]pyridine-3-carbaldehyde (**4**) [1].*

In a round-bottom flask, DMF (0.6 mL) and $POCl_3$ (1 mL) were mixed and vigorously stirred for 10 minutes at 10 °C. Compound **1** (9 mmol) and compound **2** (20 mmol) were then added to the reaction mixture. The reaction mixture was heated at 60 °C for 12 hours. After cooling, the reaction mixture was poured on top of the ice cubes. The solid crude material was then filtered, recrystallized from the ethanol, and thoroughly rinsed with water to give the title products **3** and **4**.

*2.2.3.Synthesis of 2-((2-([1,1'-Biphenyl]-4-yl) imidazo[1,2-a]pyridin-3-yl) methylene) hydrazine-1-carbothioamide (**5**) and 2-((2-(4-bromophenyl)imidazo[1,2-a]pyridin-3-yl)methylene) hydrazine-1-carbothioamide (**6**) [35]*

A mixture of aldehydes (**3** and **4**) (0.01 mol) and thiosimecarbazide (0.01 mol) in absolute ethanol (25 mL) with a few drops of glacial acetic acid was refluxed for 8 hours. After the reflux process was complete, the mixture was cooled to room temperature, and the solid crude material was filtered and recrystallized from ethanol to afford the desired products **5** and **6**.

*2.2.4.Synthesis of 2-(2-([1,1'-Biphenyl]-4-yl) imidazo [1,2-a]pyridin-3-yl) methylene) hydrazineylidene) thiazolidin-4-one (**7**) and 2-(2-(4-bromophenyl)imidazo [1,2-a]pyridin-3-yl)methylene)hydrazineylidene)thiazolidin-4-one (**8**) [36]*

A mixture of thiosemicarbazone derivatives (**5** and **6**) (0.01 mol) and chloroacetic acid (0.01 mol) in absolute ethanol (25 mL) in the presence of anhydrous sodium acetate was heated at 60°C for 12 hours. The solid crude material was then filtered and recrystallized from ethanol to produce the title compounds **7** and **8**.

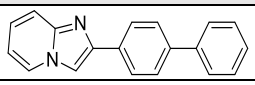
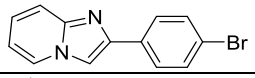
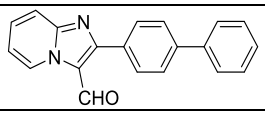
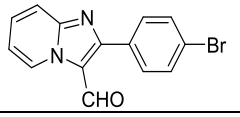
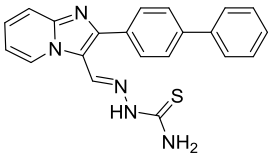
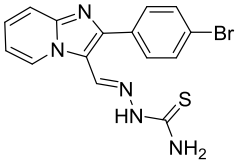
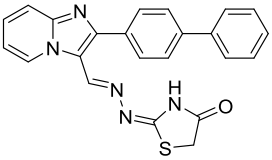
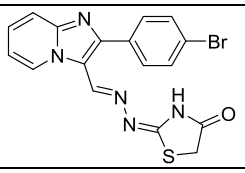
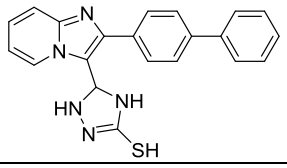
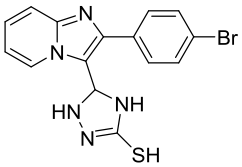
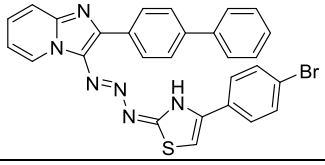
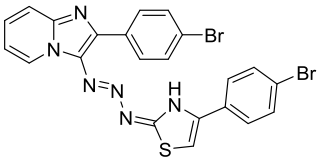
*2.2.5. 5-(2-([1,1'-biphenyl]-4-yl)imidazo[1,2-a]pyridin-3-yl)-4,5-dihydro-1H-1,2,4-triazole-3-thiol (**9**) and 5-(2-(4-bromophenyl)imidazo[1,2-a]pyridin-3-yl)-4,5-dihydro-1H-1,2,4-triazole-3-thiol (**10**) [37]*

To a solution of thiosemicarbazone derivatives (**5** and **6**) (0.01 mol) in absolute ethanol (25 mL), a few drops of HCl were added before being refluxed for 8 hours. After cooling and water dilution, the solid crude material was then filtered, washed with water, dried, and refined with ethanol to yield the desired products **9** and **10**.

*2.2.5.2-(2-([1,1'-Biphenyl]-4-yl) imidazo [1,2-a]pyridin-3-yl) triaz-2-en-1-ylidene)-4-(4-bromophenyl)-2,3-dihydrothiazole (**11**) and 4-(4-bromophenyl)-2-((E)-(2-(4-bromophenyl) imidazo[1,2-a]pyridin-3-yl)triaz-2-en-1-ylidene)-2,3-dihydrothiazole (**12**) [38].*

A mixture of thiosemicarbazone derivatives (**5** and **6**) (0.001 mol) and 4-bromophenacyl bromide (0.001 mol) in absolute ethanol (25 mL) in the presence of anhydrous sodium acetate (0.082 g) was refluxed for 12 hours. The solid crude material was then filtered and recrystallized to produce the title compounds **11** and **12**.

Table 1: Physical characteristics of compounds **1-12**

Compound number	Structure	Chemical formula	M.Wt. (gm/mol)	Melting Point (°C)	Color	Yield (%)
1		$C_{19}H_{14}N_2$	270.33	213-216	Yellow	90
2		$C_{13}H_9BrN_2$	273.13	192-194	Orange	92
3		$C_{20}H_{14}N_2O$	298.34	199-201	White	70
4		$C_{14}H_9Br\ N_2O$	301.14	220-222	Brown	65
5		$C_21H_{17}\ N_5S$	371	285-286	Orange	66
6		$C_{15}H_{12}BrN_5S$	372.9	290-292	Brown	70
7		$C_{23}H_{17}\ N_5SO$	411	285-287	Orange	67
8		$C_{15}H_{12}BrN_5SO$	412.9	290-292	Brown	70
9		$C_{21}H_{17}N_5S$	371	272-274	Orange	66
10		$C_{15}H_{12}BrN_5S$	372.9	243-244	Brown	75
11		$C_{29}H_{20}BrN_5S$	549.9	299-301	Orange	64
12		$C_{23}H_{15}Br_2N_5S$	551.8	320-322	Brown	72

2.3. DPPH scavenging assay

DPPH radical scavenging activity is due to their hydrogen-donating ability [29]. Radical scavenging activities are very important to prevent the deleterious role of free radicals in different diseases, including cancer. DPPH free radical scavenging is an accepted mechanism for screening the antioxidant activity of organic compounds. The test sample (1 mL) (25, 50, and 100 ppm) was mixed with 1.0 mL of DPPH (40 ppm) solution. The absorbance of the resulting solution was measured at 517 nm in a visible spectrophotometer. Ascorbic acid was used as the reference compound. A lower absorbance of the reaction mixture indicated higher free radical scavenging activity. In the DPPH assay, a violet-colored DPPH solution is reduced to a yellow-colored product, diphenylpicryl hydrazine, by the addition of organic compounds in a concentration-dependent manner. This method has been extensively used to predict antioxidant activities because of the relatively short time required for analysis. The following formula was used to calculate the sample's level of free radical inhibition, which is how radical scavenging activity was expressed.

$$\boldsymbol{Inhipition}\ (\%) = \frac{A - At}{A} \times 100$$

Where A is the absorbance of the control (blank, without sample) and A_t is the absorbance in the presence of the test samples.

2.4. Anti-bacterial activity

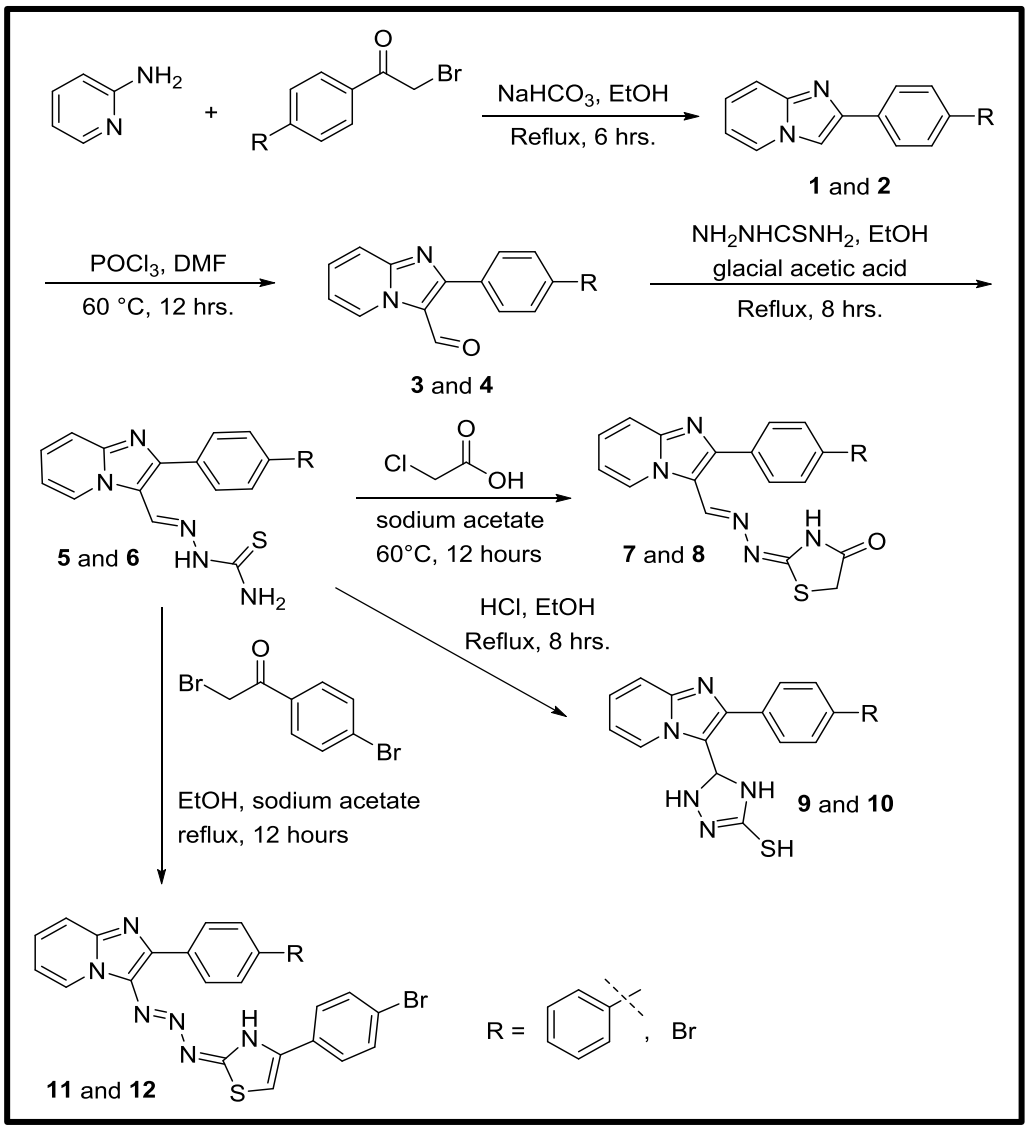
Muller Hinton Agar, the culture medium utilized for bacterial growth, was made by dissolving an amount of Muller Hinton Agar in distilled water and bringing the mixture to a boil to ensure thorough dissolution. The prepared solution was sterilized for 15 minutes using an autoclave (121 °C). The solution was then put onto clean petri dishes and allowed to cool and harden there for a period of time. One liter of distilled water was used to dissolve the nutritional broth powder, which was then well mixed and incubated for 24 hours at 37 °C after the bacteria (gram-positive and gram-negative) were cultured on the culture medium, they were swabbed by swab to cover the entire surface of the petri dishes and the biological activity of the compounds was assessed using the well diffusion method by adding 100 µL of synthetic compounds in DMSO by micropipette into the well (6 mm). The samples were incubated for 24 hours in the petri dish after being placed there. By using a caliper, the zone of bacterial growth inhibition was determined in milliliters.

3. Results and discussion

3.1. Chemistry

Scheme 1 shows the synthesis of the title products **1-12**. The synthesis of 2-substituted imidazol(1,2a)pyridine *via* condensation of 2-aminopyridine with 2,4-dibromoacetophenone or 2-bromo-4-phenylacetophenone in ethanol produced bromophenyle)imidazo(1,2-a)pyridine (**1**), and biphenyl)imidazo(1,2-a)pyridine (**2**), respectively. The FT-IR spectroscopy of these compounds showed that the C=N absorption of the cyclic imidazoles appeared at 1631 and 1635 cm^{-1}, and the amino group absorption disappeared (Table 2). In the second step, the Vilsmeier-Haack reaction was used on 2-subphenyl imidazol[1,2a]pyridine-3-carbaldehydes to afford the compounds 3 and 4. The FT-IR spectra of these derivatives **3** and **4** revealed new absorptions at 1672 and 1679 cm^{-1} due to the carbonyl group (Table 2). The compounds 3 and 4 derivatives were then reacted with thiosemicarbazide in ethanol in the presence of acetic acid as a catalyst to give the desired thiosemicarbazone derivatives **5** and **6** in **66** and 70 yields, respectively. The structure of these compounds was characterized by FT-IR spectroscopy, which showed new absorptions at 1633 and 1637 cm^{-1} due to the C=N group and absorptions at 3452, 3386 cm^{-1}, and 3432, 3288 cm^{-1} due to the amino group. Different cyclizing agents and reaction conditions were tested on the reaction of thiosemicarbazone

derivatives **5** and **6** with chloroacetic acid in the presence of anhydrous sodium salt to afford the corresponding thiozolidone derivatives **7** and **8** in 67 and 70 yields, respectively. The FT-IR spectra of these derivatives **7** and **8** showed disappearing absorption of the NH_2 group, and absorptions at 1685 and 1699 cm^{-1} belong to the carbonyl group (Table 2). Ring closure of the products **5** and **6** was then achieved successfully under acidic medium (HCl, 35%) to produce the 1,2,4-triazole-3-thiol derivatives **9** and **10** (Table 2). The FT-IR spectroscopy of compounds **9** and **10** exhibited new absorptions at 2574 and 2619 cm^{-1} due to the S-H band. Finally, thiazole derivatives **11** and **12** were produced by the cyclization of thiosemicarbazone derivatives **5** and **6** with 4-bromophenacyl bromide. The FT-IR spectroscopy of compounds **11** and **12**showed new absorptions at 1640 and 1639 cm^{-1} attributed to the C=N imine group (Table 2).



Scheme 1: The synthetic route of the products **1**-**12**

Table :2 The FT-IR spectral data (υ, cm^{-1}) of compounds **1-12**

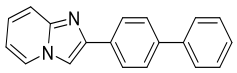
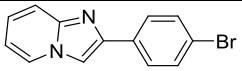
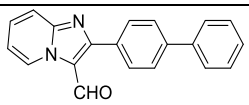
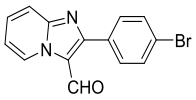
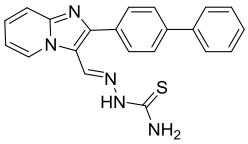
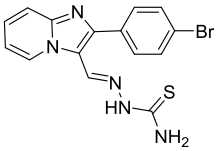
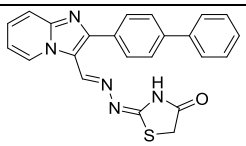
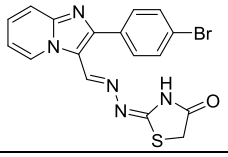
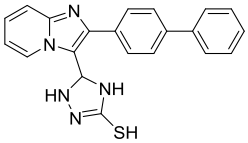
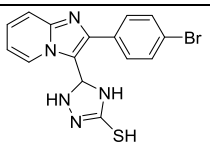
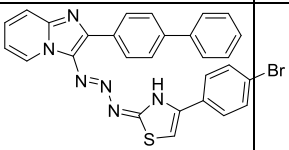
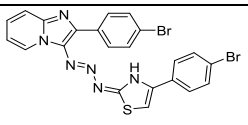
Compound number	Structure	C-H Aromatic	C-H Aliphatic	C=O	C=N	C=C	Other spectral data
1		3074 3047 3002	-	-	1633	1585 1541	-
2		3012 3072 3012	-	-	1631	1596 1564 1523	705 (C-Br)
3		3095 3058	2848 2781 (Aldehydic)	1672	1635	1562	-
4		3058 3085	2833 2792 (Aldehydic)	1689	1631	1556 1531	696 (C-Br)
5		3085	2980		1598 1629	1560 1490	3346-3305 ($C-NH_2$) 3174 (C-NH) 1278 (C=S)
6		3090	2990		1637 1600	1560 1506	3398-3336 ($C-NH_2$) 3234 (C-NH) 667 (C-Br) 1292 (C=S)
7		3080	2993	1699	1581		765 (C-S)
8		3035	2985	1703	1608		771 (C-S)
9		3040	-		1627 1573	1519 1479	3423, 3261 (NH) 2665 (S-H)
10		3082	-		1635 1612	1560 1531	2638 (S-H) 3415, 3388 (NH)
11		3035	2974		1637 1558 1490	1477 1411	3292 (C-NH) 738 (C-S-C)
12		3050 3244	2981		1639 1596 1558	1514 1471	754 (C-S-C)

Table 3: The ^{1}H NMR spectral data (δ, ppm) of compounds **5**, **9** and **11**

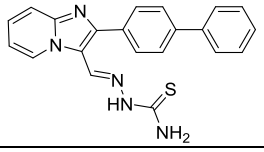
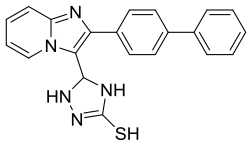
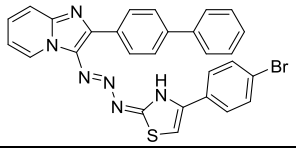
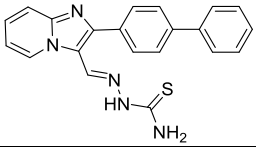
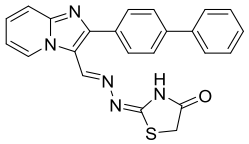
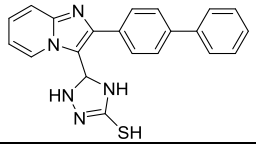
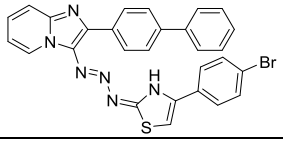
Compound number	Compound structure	Chemical shifts
5		6.92 (s, 2H, NH_2) 6.93-8.55 (m, 14H, Ar-H and HC=N) 9.60 (s, 1H, NH)
9		6.57 (s, 1H, C-H) 6.52-8.42 (m, 13H, Ar-H) 8.44 (s, 1H, N-H) 8.45 (s, 1H, N-H) 8.54 (s,1H, S-H)
11		5.25 (s, 1H, HC=N) 6.90-7.99 (m, 19H, Ar-H and =C-H ring) 8.05 (s, 1H, N-H)

Table 4: The ^{13}C NMR spectral data (δ, ppm) of compounds **5**, **7**, **9**, and **11**

Compound number	Compound structure	Chemical shifts
5		111-140 (Ar-C) 144 (C=N cyclic or C=N acyclic or C=S) 145 (C=N cyclic or C=N acyclic or C=S) 148 (C=N cyclic or C=N acyclic or C=S)
7		109-136 (Ar-C) 144 (C=N cyclic or C=N acyclic) 145 144 (C=N cyclic or C=N acyclic) 160 144 (C=S or C=O) 164 144 (C=S or C=O)
9		67.0 (C-NH) 129.2, 128.2, 127.2, 126.82 (Ar-C) 139.0, 130.8, 130.2 (C=N) 158 (C-SH)
11		114-132 (Ar-C) 144 (C=N imidazo or C=N acyclic or C=N thiazole) 145 (C=N imidazo or C=N acyclic or C=N thiazole) 160 (C=N imidazo or C=N acyclic or C=N thiazole)

3.2. Antimicrobial activity [39]

The inhibition of growth of microorganisms by compounds **5**, **6**, **7**, and **8** at concentration of 0.3 M against *Staphylococcus pneumonia and Bacillus Subtilis* (gram-positive bacteria) and *Kelbsiella pneumonia and E-coli* was assessed using the cup-plate method as the zone of inhibition created by the test substance as well as common medications (Amoxicillin). Table 5 lists the test solution's zone of inhibition.

Table 5: Antimicrobial activity of compounds **5**, **6**, **7**, and **8**

Compound Number	Zones of inhibitions in mm				
	Antibacterial activity				Antifungal activity
	Escherichia coli (-)	*Kelbsiella pneumonia (-)*	*Bacillus Subtilis (+)*	*Staphylococcus aureus (+)*	Candida
5	20	23	18	20	20
6	20	21	15	26	22
7	18	22	15	27	24
8	24	24	26	27	19
Amoxicillin	24	30	20	20	-
Posaconazole	-	-	-	-	28

3.3. DPPH scavenging assay

The results in Table 6 list some of the prepared derivatives **5-12** abilities to donate hydrogen or scavenge radicals utilizing the stable radical DPPH [40]. Figure 1 demonstrates that compound **1** and **2** present the donating group (NH_2, NH, and SH), which can behave as agents of free radicals and are capable of opposing oxidation, and exhibit the highest antioxidant activity on DPPH, whereas the other compounds exhibit moderate activity because we observed the presence of electron withdrawing groups, such as Br, and the phenyl ring exhibited the lowest antioxidant activity [24].

Table 6: Antioxidant activity of compounds **5-12**

Sample	DPPH Scavenging (%)		
	100 ppm	50 ppm	25 ppm
5	90	85.5	84
6	91	88.13	90.1
7	79.75	84	85
8	79.08	84.58	83.3
9	39.6	42.25	42.08
10	48.16	50.8	43.4
11	70.45	68,43	68.50
12	66.52	64.7	62.95
Ascorbic acid	94.95	92.43	91.50

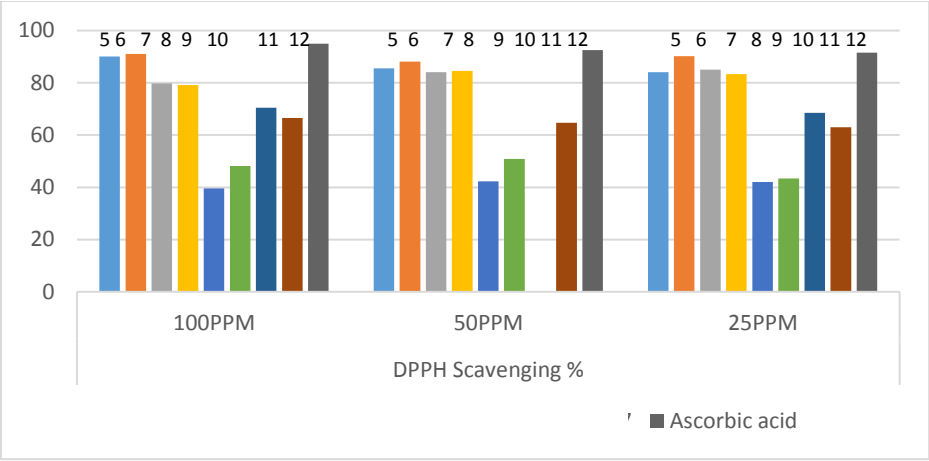


Figure 1: Diagram for antioxidant activity of several prepared compounds

4. Conclusion

New imidazo[1,2-a]pyridine derivatives containing the triazole, thiazolone, and thiazine moiety have been synthesized at position 3. The FT-IR, ^{1}H NMR, and ^{13}C NMR measurements were used to confirm the structures of these compounds **5-12**. The antioxidant activity of the created compounds was evaluated utilizing the 2,2-diphenyl-1-(2,4,6-trinitrophenyl) hydrazyl, hydroxyl, and radical scavenging assay methodologies. Compounds **5**, **6**, and **12** have strong promise as radical scavengers. The antibacterial efficacy of a few recently synthesized imidazole and pyridine derivatives against three species of pathogenic bacteria and one type of fungus was assessed. The highest activity from compounds **6**, **7**, and **8** on gram-negative bacteria was found in *Staphylococcus aureus*.

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