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Antioxidant Activity of New Tetrazole, Thiazolidin-4-one, and Aza-beta Lactam Linking to Secondary Imines of Imidazopyridine

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Abstract

In this contribution, new derivatives of bicyclic fused rings with a bridgehead nitrogen atom were synthesized from the imidazo[1,2-a]pyridine derivatives **C1** by reacting two moles of 2-aminopyridine and 4-aminoacetophenone with iodine in a one-pot reaction. This compound (**C1**) was then condensed with 2-nitrobenzaldehyde and 2,4-dichlorobenzaldehyde to form new derivatives of Schiff bases (**C2** and **C3**). These Schiff bases were then cyclized to synthesize thiazolidin-4-one derivatives (**C4** and **C5**), tetrazole derivatives (**C6** and **C7**), and aza-β-lactam derivatives (**C8** and **C9**) through the reactions with thioglycolic acid, sodium azide, and 1-naphthylisocyanate, respectively. FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy were used to characterize these new compounds. In the second part of this work, the antioxidants of these compounds were measured, and results ranged from good to medium.

Keywords: Fused ring; Imidazo[1,2-a]pyridine, Tetrazole, Thiazolidin-4-one, Aza-beta lactam.

النشاط المضادة للأكسدة للتيترازول والثايوزوليدينون والأزا بيتا لاكتام الجديدة المرتبطة بأمينات ثانوية من ايميدازوبريدين

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الخلاصة

في هذا العمل حضرت مركبات جديدة من مشتقات الحلقات الثنائية الملتحمة الاميدازو [1,2-a] بيريدين التي تحتوي في تركيبها على ذرة نيتروجين جسريه. **C1** تم تحضيره من خلال تفاعل مولين من 2-أمينوبيريدين و مول واحد من 4-أمينو أسيتوفينون مع اليود في تفاعل ذات الوعاء الواحد. قواعد شيف **C2** ، **C3**حضرت من خلال تكثيف المركب **C1** مع 2-نايتروبنزلديهايد و 2،4-ثنائي كلورو بنزلديهايد. وباستخدام تفاعلات الاضافة الحلقية لقواعد شيف لتحضير مشتقات ثيازوليدينون **C4** ,**C5** ومشتقات تترازول **C6** ، **C7** ومشتقات الازا-بيتا لاكتام **C8** ، **C9** من خلال التفاعل مع حامض الثايوكلايكولك وأزايد الصوديوم و 1 -

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نفثال ايزوسيانيت على التوالي.شخصت هذه المركبات الجديدة بالتحليل الطيفي FT−IR, ^{1}H−NMR, ^{13}C−
(NMR) ثم قياس مضادات الأكسدة لهذه المركبات ، وظهرت النتائج من جيدة إلى متوسطة.

1. Introduction

Heterocyclic molecules with a bridge nitrogen atom in their structure are essential compounds in medicinal chemistry applications [1]. Compounds containing imidazo[1,2-a]pyridine-fused rings are of remarkable importance, as researchers in the pharmaceutical industry and academics have been keenly interested in the synthesis of these heterocyclic fused rings, which contributed to the discovery of modern medicines and led to the development of pharmaceutical compounds [2,3]. Biological studies of the prepared compounds demonstrated numerous activities against anti-cancer [4,5], anti-bacterial [6], anti-microbial [7], anti-tubercular [8], anti-fungal, anti-inflammatory, antiviral, anti-protozoal, anti-pyretic, analgesic, anti-apoptotic, hypnoselective, and anxioselective activities [9-12]. They also act as β-amyloid formation inhibitors, benzodiazepine receptor agonists, and cardiotonic agents. Numerous medications, including zolpidem for treating insomnia, alpidem for treating anxiety, olprinone for treating acute heart failure, zolimidine for treating peptic ulcers, necopidem, and saripidem for treating peptic ulcers, as well as others, are available on the market and contain imidazo[1,2-a]pyridine [13]. Also, the key physicochemical properties of imidazo[1,2-a]pyridine derivatives include those used in other critical technological fields and their multiple applications, such as corrosion inhibitors for metals. These compounds were synthesized by several methods, the most important of which are the multicomponent reactions (MCRs) or the reactions of 2-aminopyridine with *p*-aminoacetophenone and I_2 [14]. Schiff's bases are among the compounds that are classed as being the key to organic chemistry to launch into the synthesis of many other compounds that express therapeutic importance in pharmaceutical chemistry. These compounds contain an imine group, or the so-called azomethine, which is synthesized when a primary amine and a carbonyl group from a ketone or aldehyde react together in the presence of glacial acetic acid [15]. The cyclization addition reaction is one of the important reactions in organic synthesis to form many heterocyclic rings, which is of great importance in different biological and industrial fields. Tetrazole, thiazolidinedin-4-one, and beta-lactams are examples of heterocyclic rings, which are prepared from Schiff bases. The aim of this work is to synthesize fused-ring compounds (imidazo/pyridine) that contain heteroatoms and measure some of the biological activities of these compounds as antioxidant activity (*in vitro*) of some prepared compounds using the DPPH radical scavenging method.

2. Experimental part

2.1. Material and instrumentation

All solvents and chemicals were supplied by Merck, Sigma-Aldrich, and CDH companies. Thin-layer chromatography (TLC) was supplied by the Merck Company, and iodine fumes were used to characterize the spots. A thermal melting point apparatus was used to measure the melting point. A Shimadzu FT-IR Spectrophotometer (FTIR-8400S) has been utilized to measure the FT-IR spectral data at the University of Baghdad/College of Sciences. Nuclear magnetic resonance spectroscopy (400 MHz) was used to record the 1H NMR and ^{13}C NMR data using DMSO-d_6 as a solvent. Chemical shifts were measured in parts per million (ppm) relative to the internal reference tetramethylsilane (TMS) at the University of Basra in Iraq.

2.2. Synthesis

*2.2.1. 2-(4-Aminophenyl)-N-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-amine [**C1**] [14-17]*

A mixture of 2-aminopyridine (0.03 mol), 4-aminoacetophenone (0.015 mol), and solid iodine (1.9 g) were dissolved in DMSO (100 mL). The mixture was then heated for 6 hours at

100 °C. The reaction was monitored by TLC (benzene / methanol, 2:1). After that reaction was finished, the mixture was added to crush-ice. A product underwent filtering, washing, and recrystallization from absolute ethanol. Table 1 lists the physical characteristics of compound **C1**. FT-IR $\upsilon_{max}(cm^{-1})$: 3433 (N-H), 3334, 3311 (NH_2), 3099 ($C\text{-}H_{aro}$), 1644 ($C{=}N_{pyridine}$), 1612 ($C{=}N_{imidazo}$), 1577, 1498 ($C{=}C_{aro}$).

2.2.2. *2-(4-((2-Nitrobenzylidene)amino)phenyl)-N-phenylimidazo[1,2-a]pyridin-3-amine [**C2**] and 2-(4-((2,4-dichlorobenzylidene)amino)phenyl)-N-phenylimidazo[1,2-a]pyridin-3-amine [**C3**]* [18-20]

A solution of 2,4-dichlorobenzaldehyde and 2-nitrobenzaldehyde (0.003 mol) in absolute ethanol (xx mL) and some drops of glacial acetic acid. After stirring for 15 minutes, compound **C1** (0.003 mol) was added to the reaction mixture before heating to reflux for 8-10 hours. When the reaction had completed, the solvent was evaporated, and the solid crude material was recrystallization from ethanol to afford the title products **C2** and **C3**. Tables 1 and 2 list the physical characteristics and FT-IR spectral data, respectively.

2.2.3.*1-(Naphthalen-1-yl)-4-(2-nitrophenyl)-3-(4-(3-(phenylamino)imidazo[1,2-a]pyridin-2-yl)phenyl)-1,3-diazetidin-2-one [**C4**] and4-(2,4-dichlorophenyl)-1-(naphthalen-1-yl)-3-(4-(3-(phenylamino)imidazo[1,2-a]pyridin-2-yl)phenyl)-1,3-diazetidin-2-one* **[*C5*]** [21]

To a solution of Schiff bases **C2** and **C3** (0.001 mol) in chloroform, 1-naphthyl isocyanate (0.001 mol) was added. The reaction mixture was refluxed for 5 hours (monitored by TLC, benzene/methanol, 2:1) before the evaporation of the solvent and recrystallization from absolute ethanol to give the desired products **C4** and **C5**. The physical properties and FT-IR spectral data are listed in Tables 1 and 3, respectively.

2.2.4.*2-(4-(5-(2-Nitrophenyl)-4,5-dihydro-1H-tetrazol-1-yl)phenyl)-N-phenylimidazo[1,2-a]pyridin-3-amine [**C6**] and 2-(4-(5-(2,4-dichlorophenyl)-4,5-dihydro-1H-tetrazol-1-yl)phenyl)-N-phenylimidazo[1,2-a]pyridin-3-amine [**C7**]* [22]

To a solution of Schiff bases **C2** and **C3** (0.001 mol) in ethanol (xx mL), NaN_3 (0.001 mol) was added. The reaction mixture was refluxed for 15 hours (monitored by TLC, benzene/methanol, 2:1) before the evaporation of the solvent. The crude material was then washed with water and recrystallized from absolute ethanol to provide the title products **C6** and **C7**. The physical properties and FT-IR spectral data are listed in Tables 1 and 4, respectively.

2.2.5.*2-(2-Nitrophenyl)-3-(4-(3-(phenylamino)imidazo[1,2-a]pyridin-2-yl)phenyl)thiazolidin-4-one [**C8**] and 2-(2,4-dichlorophenyl)-3-(4-(3-(phenylamino)imidazo[1,2-a]pyridin-2-yl)phenyl)thiazolidin-4-one [**C9**]* [23,24]

To a solution of Schiff bases **C2** and **C3** (0.01 mol) in ethanol (100 mL), mercaptoacetic acid (0.01 mol) was added. The reaction mixture was then refluxed for 12 hours. When the reaction had completed as determined by TLC (benzene / methanol, 2:1), the reaction mixture was cooled and emptied over crushed ice. The solid crude material was then filtered, dried, and recrystallized from absolute ethanol to afford the desired products **C8** and **C9**. Table 1 lists the physical characteristics, and Table 5 lists the FT-IR spectral data of these products.

Table 1: Physical properties of prepared compounds **C1-C9**

Compound number	Physical properties			Compound number	Physical properties		
	M.P (°C)	Yield (%)	Color		M.P (°C)	Yield (%)	Color
C1	173-175	70	Greenish-black	C6	>300	69	Light-beige
C2	210-212	83	Maronite	C7	>300	77	Off-white
C3	237-239	89	Yellow	C8	Oily	75	Olivaceous
C4	187-190	87	Light-brown	C9	Oily	78	Olivaceous
C5	202-204	94	Beige				

Table 2: The FT-IR spectral data of compounds **C2** and **C3**

Compound number	FT-IR spectral data (cm^{-1})						
	υ(NH)	υ(CH) Aromatic	υ(C-H) Aliphatic	υ(C=N) Imine	υ(C=N)	υ(C=C) Aromatic	Other absorption band
C2	3425	3072	2972	1637	overlap	1558 1475	1527, 1342 (NO_2 asym. and sym.)
C3	3433	3074	2983	1632	1581	1560 1471	821 (C-Cl)

Table 3: The FT-IR spectral data of compounds **C4** and **C5**

Compound number	FT-IR spectral data (cm^{-1})						
	υ(NH)	υ(CH) Aromatic	υ(C-H) Aliphatic	υ(C=O)	υ(C=N) Pyridine	υ(C=C) Aromatic	Other absorption band
C4	3282	3053	2983	1693	1647	1546	1502, 1344 (NO_2 asym. and sym.) 1598 (C=N imidazo)
C5	3284	3053	2937	1696	1645	1546	-

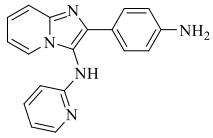
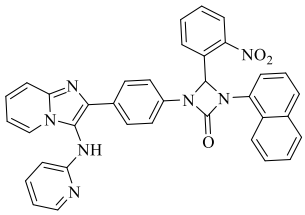
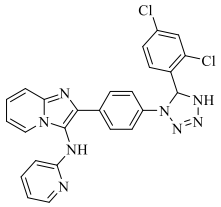
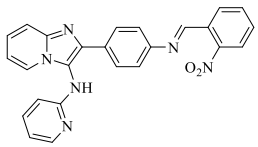
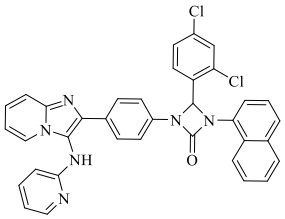
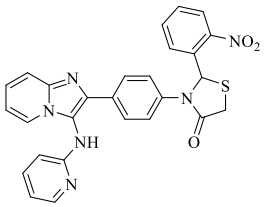
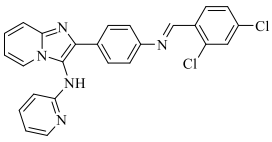
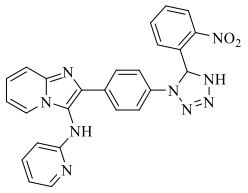
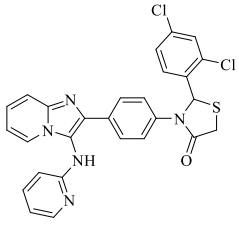
Table 4: The FT-IR spectral data of compounds **C6** and **C7**

Compound number	FT-IR spectral data (cm^{-1})						
	υ(NH)	υ(CH) Aromatic	υ(C-H) Aliphatic	υ(C=N) Imidazo	υ(N=N)	υ(C=C) Aromatic	Other absorption band
C6	3390	3056	2927	1589	1525	1568	1589 (C=N imidazo) NO_2 absorption is overlapped with C=C aromatic absorption at 1342
C7	3390	overlap	2975	overlap	1511	1571	-

Table 5 - FT-IR spectral data of compounds **C8** and **C9**

Compound number	FT-IR spectral data (cm^{-1})						
	υ(NH)	υ(CH) Aromatic	υ(C-H) Aliphatic	υ(C=O)	υ(C=N) Pyridine	υ(C=C) Aromatic	Other absorption band
C8	3423	3002	2925	1687	1649	1575	1521, 1336 (NO_2 asym. and sym.)
C9	3427	3002	2970	1682	overlap	1575	

Table 6 - The structures of prepared compounds **C1-C9**

Compound number	Structure	Compound number	Structure	Compound number	Structure
C1		C4		C7	
C2		C5		C8	
C3		C6		C9	

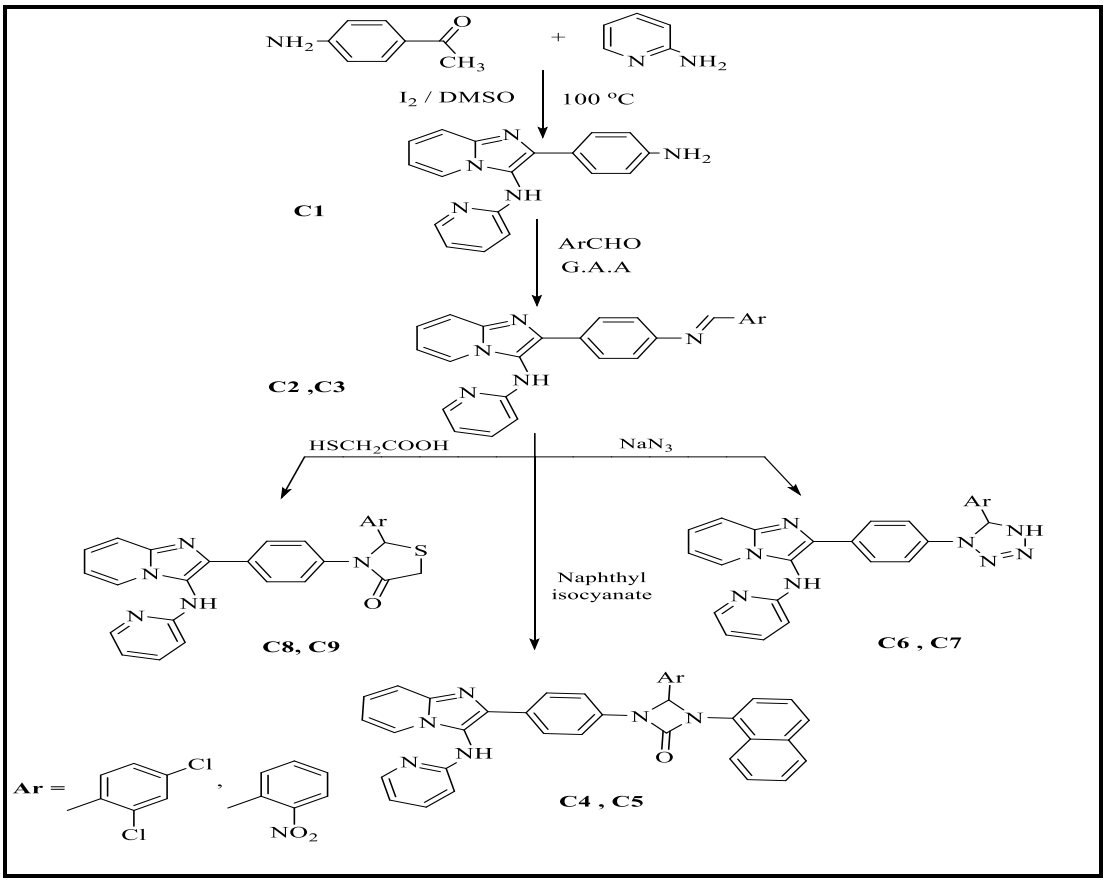
2.3. Antioxidant activity

In order to determine the antioxidant activity of some of the prepared compounds, it was used the 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) method. Ascorbic acid was used in this method as a positive standard. Free radical scavenging activity was specified according to the literature with slight modifications for three concentrations (25, 50, and 100 μg/mL). In DMSO, an extract (1 mL) was added to the DPPH solution (1 mL). To evaluate the decline of DPPH at 517 nm in 60 minutes, a blank test was used [25].

3. Results and discussion

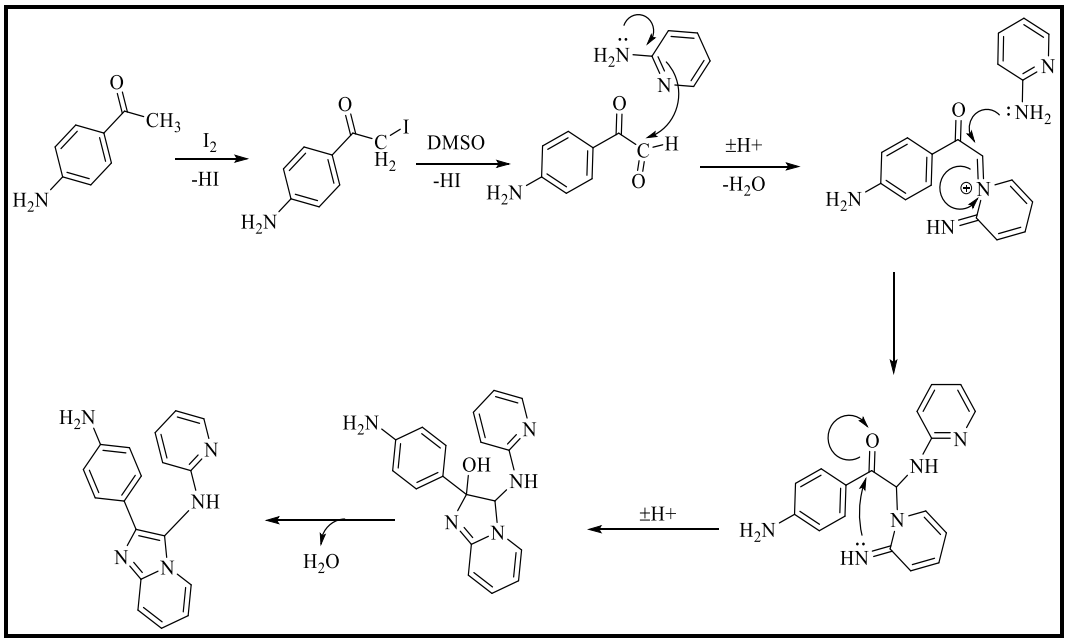
3.1. Synthesis

All the structures of the prepared compounds are listed in Table 6, and the synthetic route is shown in Scheme 1.



Scheme 1: The synthesis of compounds **C1-C9**

In the first step, fused-ring imidazo/pyridine derivatives were prepared using a one-pot reaction, where solid iodine helped form intermediate α-iodoketone in the presence of DMSO as a solvent. The compound 2-oxoacetaldehyde is formed, which is then, through a condensation reaction with 2-aminopyridine, converted into the compound **C1** as shown in the following mechanism (Scheme 2).



Scheme 2 - The mechanism for the preparation of compound **C1**

The FT-IR spectral data showed the disappearance of some bands, such as the carbonyl group of 4-aminoacetophenone in the starting material, and the appearance of new bands, such as C=N in compound **C1**. The bands from 3433 to 3311 cm^{-1} are for two groups (NH and NH_2). In addition, bands in 1654 and 1612 cm^{-1} refer to the C=N in fused rings. This is a good evidence for the formation of the compound **C1**. The ^1H NMR showed a singlet signal at 10.2 ppm belonging to the N-H proton, multiple signals between 8.6 and 6.5 ppm attributed to aromatic protons, and a singlet signal at 5.41 ppm for the NH_2 group. The second step included a condensation reaction to synthesize the Schiff base compounds **C2** and **C3**. These products were identified through the FT-IR spectra, in which a band appeared at 1637 cm^{-1} for the C=N imine and the amine band absorption in the starting materials disappeared. The ^1H NMR spectrum of the compound **C2** showed a singlet signal at 10.2 ppm due to the N-H group, multiple signals located in the range 8.8-6.9 ppm belonging to the aromatic protons in this product, and a distinct signal at 6.1 for the proton of the N=CH group. The ^{13}C NMR spectrum of compound **C2** showed signals at 159.9-119.4 ppm belonging to the aromatic carbon and 112.9 ppm belonging to the CH=N imine group. In the last step, the cyclization addition reactions of Schiff bases to prepare heterocyclic rings, including beta-lactams, tetrazoles, and thiozolidinones, were achieved successfully. The beta-lactam derivatives **C4** and **C5** were synthesized by adding 1-naphthyl isocyanate to the imine compounds **C2** and **C3**. The FT-IR spectral data showed a band at 1693 cm^{-1} corresponding to the C=O of the aza-beta-lactam ring. The ^1H NMR spectrum of the synthesized compound **C4** showed the appearance of a single signal at 9.5 ppm for NH. Several signals between 8.2 and 7.4 ppm belong to the aromatic rings, and a singlet signal at 4.1 ppm refers to the proton of the N-CH in the four-membered ring. The ^{13}C NMR showed the presence of a signal at 168 ppm belonging to the carbonyl group in the beta-lactam ring, as well as signals within the range 155.3-117.9 ppm to the aromatic carbon atom, in addition to a signal at 60.8 ppm belonging to the N-C within the four-membered ring. The products **C6** and **C7** were also synthesized by adding sodium azide, and the FT-IR analysis results showed that there are new bands at 3390 cm^{-1} belonging to the NH group, in addition to two bands in the range 2038 cm^{-1} and 1525-1511 cm^{-1} belonging to the N=N group in the tetrazole ring. The ^1H NMR spectrum for compound **C7** showed a singlet signal at 10.2 ppm belonging to NH as well as multiple signals located in the range 8.8-6.7 ppm belonging to the group of protons in the aromatic

rings. Also, two signals, one of which is single at 5.6 ppm, indicate the presence of an NH proton, and another signal at 2.6 ppm, indicates the presence of the N-CH in the heterocyclic tetrazole ring. Finally, the products **C8** and **C9** were prepared by the reaction of mercaptoacetic acid with Schiff bases to obtain a five-membered thizolidinone ring. The FT-IR results showed a band at 3423 cm^{-1} that refers to N-H and a band at 2970 cm^{-1}, and 2925 cm^{-1} that refers to C-H aliphatic. In addition, the characteristic band in the range 1781-1714 cm^{-1} belongs to the C=O group in thiazolidinone rings. Each product of **C3-C9** is likely to be a mixture of two enantiomers.

2.1. Antioxidant activity

Calculating the amount of residual radical in the medium involves dividing the absorbance of the samples by that of the DPPH control at the same time and multiplying the result by 100. A graphic calculation was made to determine how many samples were required to reduce the original DPPH concentration by 50%. The antioxidant activity of some newly synthesized compounds was evaluated by the DPPH method with some changes and compared with the standard (ascorbic acid). The compounds **C2**, **C3**, **C5**, **C6**, and **C9** were determined using a spectroscopic method with ascorbic acid as a standard. The relationship between the *in vitro* percentage inhibition and the concentration of the potent hits (25, 50, and 100 µg/mL) is summarized in Table 7 and explained in Figures 1 and 2. It is worth mentioning that the compounds with a structure containing a chloro atom and nitro group increase almost the possibilities of conjugation with the pyridine ring and aromatics. Thus, this increase caused a highly stable radical structure and the highest antioxidant activity [26].

Table 7 - Antioxidant activity of compounds **C2**, **C3**, **C5**, **C6**, and **C9**

Compound number	Scavenging %		
	25 µg/mL	50 µg/mL	100 µg/mL
C2	65.9	69.3	76.4
C3	59.6	65.0	73.4
C5	71.0	71.33	72.6
C6	58.6	64.4	69.6
C9	54.8	59.3	61.2
Ascorbic acid	89.1	97.7	98.2

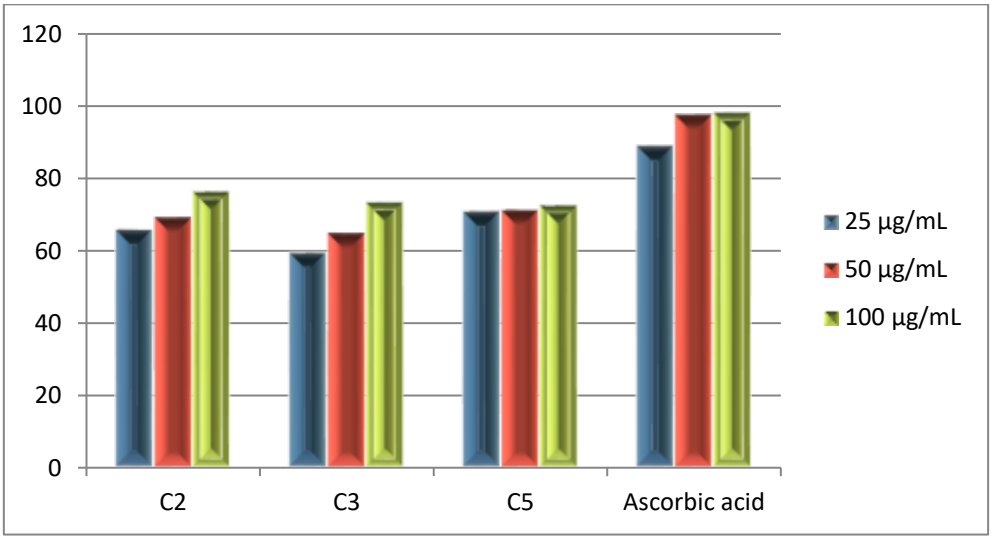


Figure 1: The percent of scavenging in compounds **C2**, **C3**, and **C5** in comparison with ascorbic acid

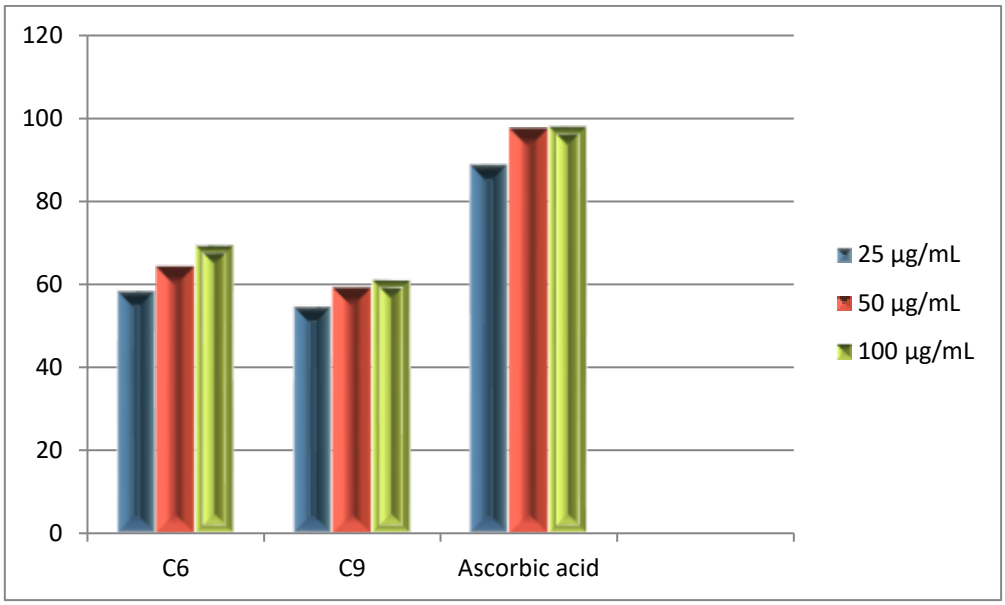


Figure 2: The percent of scavenging in compounds **C6** and **C9** in comparison with ascorbic acid

4. Conclusion

A new method was applied in this contribution, using multicomponent reactions (MCR) as a key for further reactions. The prepared imidazo[1,2-a]pyridine in the first step was used to condense with different amino aldehydes to give new Schiff bases, which were then subjected to ring closure reactions. Some of the newly prepared compounds were evaluated as antioxidant agents. The final results of antioxidant activity showed effective scavengers of free radicals.

References

[1] Y. Yuan, Z. Zhou, L. Zhang, L. Sen Li, and A. Lei, "Electrochemical oxidative C3 acyloxylation of imidazo[1,2-a]pyridines with hydrogen evolution", *Organic Letters*, vol. 23, no. 15, pp. 5932-5936, 2021.

[2] C. H. Ma, C. M. Feng, Z. W. Zhang, Y. Wang, J. Jiang, Y. Q. Yu, and Bing, "Functionalization of imidazo[1,2-a]pyridinesviaradical reactions", *New Journal of Chemistry*, vol. 45, no. 21, pp. 9302-9314, 2021.

[3] F. Paquin, J. Rivnay, A. Salleo, N. Stingelin, and C. Silva, "Multi-phase semicrystalline microstructures drive exciton dissociation in neat plastic semiconductors", *Journal of Materials Chemistry C*, vol. 3, pp. 10715-10722, 2015.

[4] I. V. Rassokhina, V. Volkova, Y. A. Kozlov, A. S. Scherbakov, A. M. Andreeva, O. E. Shirinian, V. Z. Zavarzin, and V. Igor, "Synthesis and antiproliferative activity evaluation of steroidal imidazo[1,2-A]pyridines", *Steroids*, vol. 113, pp. 29-37, 2016.

[5] D. K. Sigalapalli, G. P. Devi, G. Tokala, R. Sana, S. Tripura, Ch. Jadhav, G. S. Kadagathur, M. Shankaraiah, N. Nagesh, N. Babu, B. N. Tangellamudi, and D. Neelima, "Synthesis and biological evaluation of novel imidazo[1,2-a]pyridine-oxadiazole hybrids as anti-proliferative agents: Study of microtubule polymerization inhibition and DNA binding", *Bioorganic and Medicinal Chemistry*, vol. 43, Article ID116277, 2021.

[6] C. Wei, J. Luo, Y. Wang, Sh. Wu, S. Xing, Z. Chen, and Jixiang, "Novel amide derivatives containing an imidazo[1,2-a]pyridine moiety: Design, synthesis as potential nematicidal and antibacterial agents", *Pesticide Biochemistry and Physiology*, vol. 175, Article ID 104857, 2021.

[7] S. Kumar, N. Maurya, I. K. Verma, A. Kumar, S. Bhasin, K. K. Sharma, and K. Rohit, "Insights into selenylation of imidazo[1,2-a]pyridine: synthesis, structural and antimicrobial evaluation", *New Journal of Chemistry*, vol. 41, no. 8, pp. 2919-2926, 2017.

[8] G. Jose, T. H. S. Kumara, G. Nagendrappa, H. B. V. Sowmya, D. Sriram, P. Yogeeswari, J. P. Sridevi, T. N. G. Row, A. A. Hosamani, P. S. S. Ganapathy, N. Chandrika, and L. V. Narendra, "Synthesis, molecular docking and anti-mycobacterial evaluation of new imidazo[1,2-a] pyridine-2-carboxamide derivatives", *European Journal of Medicinal Chemistry*, vol. 89, pp. 616-627, 2015.

[9] H. C. Kwong, C. S. C. Kumar, S. H. Mah, Y. Le. Chia, T. S. Quah, C. K. Lim, G. K. Chandraju and C. Siddegowda, "Crystal correlation of heterocyclic imidazo[1,2-a]pyridine analogues and their anticholinesterase potential evaluation," *Scientific Reports*, vol. 9, no. 1, pp. 1-15, 2019.

[10] B. Li, C. Guo, N. Shen, X. Zhang, and X. Fan, "Synthesis of maleimide fused benzocarbazoles and imidazo[1,2-: A] pyridines via rhodium(iii)-catalyzed[4 + 2]oxidative cycloaddition", *Organic Chemistry Frontiers*, vol. 7, no. 22, pp. 3698-3704, 2020.

[11] S. Kumar, N. Sharma, I. K. Maurya, A. K. Bhasin, N. Wangoo, P Brandão, V. Félixd, K. K. Bhasin, and R. K. Sharma, "Facile synthesis, structural evaluation, antimicrobial activity and synergistic effects of novel imidazo[1,2-a]pyridine based organoselenium compounds", *European Journal of Medicinal Chemistry*, vol. 123, pp. 916-924, 2016.

[12] A. Nandikolla, S. Srinivasarao, Y. M. Khetmalis, B. K. Kumar, S. Murugesan, G. Shetye , Rui Ma, S. G. Franzblau, and K. V. G. C. Sekhar, "Design, synthesis and biological evaluation of novel 1,2,3-triazole analogues of imidazo-[1,2-a]-pyridine-3-carboxamide against mycobacterium tuberculosis", *Toxicology in Vitro*, vol. 74,(105237) pp. 1-11, 2021.

[13] Y. Yu, Z. Su, and H. Cao, "Strategies for synthesis of imidazo[1,2-a]pyridine derivatives: carbene transformations or C-H functionalizations", *Chemical Record*, vol. 19, no. 10, pp. 2105-2118, 2019.

[14] Z. Fei, Y. P. Zhu, M. C. Liu, F. C. Jia, and A. X. Wu, "I_2-promoted direct one-pot synthesis of 2-aryl-3-(pyridine-2-ylamino)imidazo[1,2-a]pyridines from aromatic ketones and 2-aminopyridines", *Tetrahedron Letters*, vol. 54, no. 10, pp. 1222-1226, 2013.

[15] O. A. Nief, H. N. Salman, and L. S. Ahamed, "Synthesis, characterization, biological activity studies of schiff bases and 1,3-Oxazipene derived from 1,1-bis (4-aminophenyl)-4-phenyl cyclohexane", *Iraqi Journal of Science*, vol. 58, no. 4B, pp. 1998-2011, 2017.

[16] T. A. Rehan, N. Al-Lami, and R. S. Alanee, "Anti-cancer and antioxidant activities of some new synthesized 3-secondary amine derivatives bearing imidazo[1,2-A]pyrimidine", *Eurasian Chemical Communications*, vol. 3, no. 5, pp. 339-351, 2021.

[17] A. Z. Hattab, N. Al-Lami, and J. S. Wadi, "Anticancer activity of new 3-secondary amine derivatives containing fused rings of the imidazopyridine", *Eurasian Chemical Communications*, vol. 4, no. 3, pp. 222–231, 2022,

[18] A. Mahal, P. Wu, Z. H. Jiang, and X. Wei, "Schiff bases of tetrahydrocurcumin as potential pnticancer agents", *Chemistry Select*, vol. 4, no. 1, pp. 366-369, 2019.

[19] A. Saoud, A. A. Ahmed, and E. F. Mustafa, "Synthesis, characterization and antibacterial activity of some new five-seven membered rings attached to sulfonamide compounds introducion", *Ibn AL-Haitham Journal For Pure and Applied Sciences*, vol. 27, no. 2, pp. 170–177, 2014.

[20] D. F. Hussein and J. H. Tomma, "Synthesis and characterization new schiff bases , pyrazole and pyrazoline compounds derived from acid hydrazide containing isoxazoline ring", *Ibn AL-Haitham Journal For Pure and Applied Sciences*, vol. 27, no. 3, pp. 435-447, 2014.

[21] H. D. Hanoon, H. A. A. Al Hussain, and S. K. Abass, "Synthesis and characterization of azetidin-2-one and 1,3-oxazepine derivatives using schiff bases derived from 1,1'-biphenyl-4,4'-diamine", *Journal of Physics Conference Series*, vol. 2063, no. 1, 2021.

[22] S. Leyva-Ramos and J. Cardoso-Ortiz, "Recent developments in the synthesis of tetrazoles and their pharmacological relevance," *Current Organic Chemistry*, vol. 25, no. 3, pp. 388-403, 2020.

[23] H. Al-Adhami and Suaad M. H. Al-Majidi, "Synthesis, characterization of thiazolidin-4-one, oxazolidin-4-one and imidazolidin-4-one derivatives from 6-Amino-1,3-dimethyluracil and evaluation of their antioxidant and antimicrobial agent", *Al-Qadisiyah Journal of Pure Science*, vol. 26, no. 4, pp. 59-72, 2021.

[24] G. A. Maged and A. A. Fayad, "Synthesis and spectroscopic characterization of new heterocyclic compounds derivatied from 1-(4-aminophenyl) ethan-1-oneoxime as a starting material with evaluate their biological activity", *Biochemical and Cellular Archives*, vol. 20, no. 2, pp. 5211-5222, 2020.

[25] M. S. Hussein and N. Al-Lami, "Anti-cancer and antioxidant activities of some new synthesized mannich bases containing an imidazo (2,1-B) thiazole moiety", *Iraqi Journal of Science*, vol. 63, no. 11, pp. 4620-4636, 2022.

[26] K. T. A. Al-Sultani and N. Al-Lami, "Antioxidant activity of some new synthesised benzo[d]imidazo[2,1-b]thiazole derivatives", *International Journal of Pharmaceutical Research*, vol. 12, no. 1, pp. 1819-1828, 2020.