ISSN: 0067-2904

Anti-Breast Cancer Activity of Some Synthesized Pyrazole Derivatives Bearing Imidazo[1,2a]pyridine Moiety

Amera H. Hamd* , Naeemah Al-Lami
Department of chemistry, college of science, University of Baghdad, Baghdad, Iraq

Received: 24/2/2022 Accepted: 14/10/2022 Published: 30/7/2023

Abstract

A novel series of pyrazole derivatives containing imidazo[1,2-a]pyridine **D1**-**D8** moiety has been synthesized. The reaction of 2-aminopyridine with 4-phenylphenacyl bromide and 4-bromophenacyl bromide gave the products **A** and **A1**, respectively. These products then reacted with DMF and $POCl_3$ to obtain new aldehyde derivatives B and B1. These two aldehydes were condensed with various acetophenone substitutes to yield the corresponding chalcone derivatives **C1**-**C10**. Following this, the cycloaddition reaction with hydrazine hydrate provided new pyrazole derivatives **D1**-**D8**. The prepared compounds were verified by FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. Two of these derivatives (**C5** and **D1**) were chosen to investigate their cytotoxic efficacy against breast cancer using the MTT assay.

Keywords: Chalcones, [1,2a]imidazo pyridine, Pyrazole, Anticancer.

الفعالية المضادة لسرطان الثدي لبعض المشتقات الجديدة للبايرزول المحملة بحلقة الايمدازوبريدين

أميرة حسين حمد* , نعيمة اللامي
قسم الكيمياء, كلية العلوم, جامعة بغداد, بغداد, العراق

الخلاصة

تم تحضير سلسلة من مشتقات البيرازول الجديدة التي تحتوي على نواة ايميدازو[1,2a] بيريدين **D1**-**D8**. تفاعل 2-امينو بيريدين مع 4- فنيل فينيسيل بروميد و4- بروموفينيسيل بروميد اعطى المنتجات **A** و **A1**، على التوالي. هذه المنتجات فوعلت مع DMF و $POCl_3$ للحصول على مشتقات ألديهايد جديدة **B** و **B1**. هذه المركبات كثفت مع مركبات الاسيتوفينون المعوضة لانتاج مشتقات الجالكون المقابلة **C1**-**C10**. بعد ذلك، غلق مع الهيدرازين المائي زود مشتقات البيرازول الجديدة **D1**-**D8**. تم التحقق من المركبات المحضرة بواسطة. تم التحقق من هذه المركبات بواسطة طيف الاشعة تحت الحمراء و طيف الرنين النووي المغناطيسي للهيدروجين و الكاربون. اثناء من هذه المشتقات (**C5** و **D1**) تم اختيارهم للتحقق من الفعالية السامة للخلايا ضد سرطان الثدي.

1. Introduction

*Email: hussainamera47@gmail.com

Compounds with only a nitrogen-bridgehead fused heterocyclic bearing an imidazole ring are bioactive important due to their flexibility of biological action, such as antibacterial [1], anticancer [2], antimicrobial [3], anti-inflammatory [4], and anticorrosion inhibitors [5]. Imidazole[1,2-a]pyridines have proved to be more selective pharmacologically as sedative-hypnotic (Zolpidem) and anxiolytic (Alpidem) agents [6]. Pyrazoles are a family of five-membered heterocycles that are particularly valuable in chemical synthesis [7]. Among the azole family, they are one of the most investigated classes of chemicals. Over the years, several synthesis methods and synthetic analogues have been documented. The presence of the pyrazole nucleus in various structures leads to a wide range of uses in technology [8], medicine, and agriculture [9]. They are classified as protein glycation inhibitors [10], antibacterial, antifungal [11], anticancer [12], antidepressant [13], anti-inflammatory [14], anti-tuberculosis [15], antioxidant [16], and antiviral agents [17]. Chalcones and pyrazole have a wide range of pharmacological effects [18], including anti-inflammatory [19], antimicrobial [20], antihypertensive [21], analgesic, antitumor, antiviral, antibacterial, anti-HIV, anticancer, and anticonvulsant properties [22]. Because of chaconne's biodynamic activities and their usefulness as good synthesizers for various components that are heterocyclic, it is beneficial to develop a couple of new chalcones. It was decided to prepare some novel pyrazole and α,β-unsaturated carbonyl compounds, which could possess anticancer and antibacterial properties. This will be accomplished by reacting 2-aminopyridine with 4-phenyl phenacyl bromide and 4-bromo phenacyl bromide in the presence of sodium bicarbonate, yielding imidazo[1,2a]pyridine **A** and **A1**. The products **B** and **B1** were then synthesized by reacting **A** and **A1** with $POCl_3$ in the presence of DMF (Vilsmeier conditions) [23]. The research aims to focus on the introduction of chemical diversity into the molecular framework in order to synthesize therapeutic active molecules of various compositions.

2. Materials and methods

2.1. Instruments and chemicals

Melting points were measured using digital melting point equipment and are uncorrected. All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ultra-shield 400 MHz spectrometer with DMSO-d_6 as an internal standard. The FT-IR spectral data were recorded on a Shimadzu FT-IR spectrophotometer using potassium bromide discs. All chemicals used in this work were supplied by FDC Limited, CDH, BDH, Fluka, and Merck.

2.2. Synthesis

*General synthesis of 2-([1,1'-biphenyl]-4-yl)imidazo[1,2-a]pyridine and 2-(4-bromophenyl)imidazo[1,2-a]pyridine (**A** and **A1**)* [24].

A mixture of 2-aminopyridine (1 g, 1.0 mmol) / 4-bromophencyl bromide or 4-phenylphencyl bromide (1.0 mmol) was dissolved in ethanol (25 mL). The mixture was then refluxed for 8 hours. The solution was then cooled and basified with NaOH (1.0 M) until it gave a pH of 9 as determined by pH paper. The resulting solution was cooled and poured over crushed ice. The formed precipitate was filtered and purified by recrystallizing from ethanol to obtain compounds.

Synthesis of 2-(4-substituted phenyl)imidazo[1,2-a]pyridine-3-carbaldehyde (**B1** and **B2**) [23].

In a round-bottom flask, a mixture of DMF (600 □L) and $POCl_3$ (1 mL) at 10 °C, was stirred vigorously for 10 minutes. Compound A (2.5 g, 9 mmol) / A1 (2.45 g, 20 mmol) was then added to the reaction mixture. The reaction mixture was heated at 60 °C for 12 hours. After allowing the liquid to cool, it was poured over ice cubes. The solid-crude material was then filtrated and

recrystallized from ethanol and thoroughly rinsed with water to afford the desired products **B1-B2**.

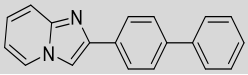
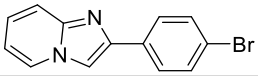
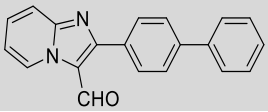
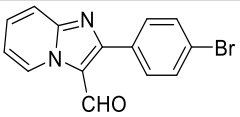
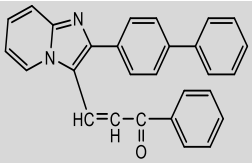
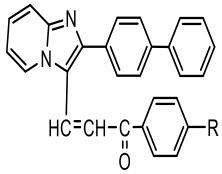
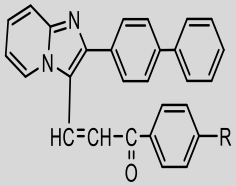
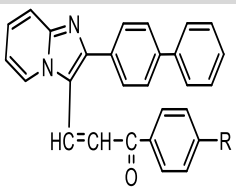
*Synthesis of 3-(2(4-substituted phenyl)imidazo[1,2-A]pyridine-3-yl)-1,(4-substituted phenyl)prop-2-en-1-one (**C1-C10**)[25].*

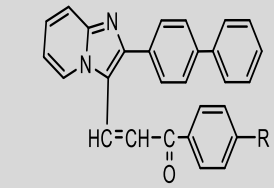
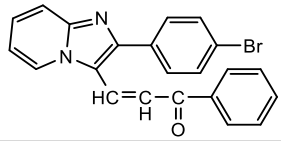
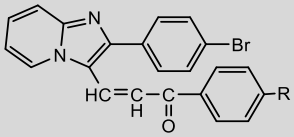
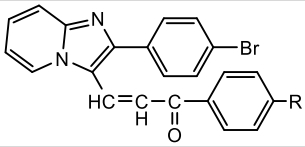
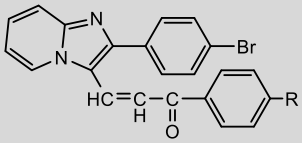
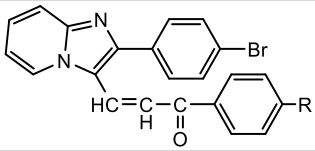
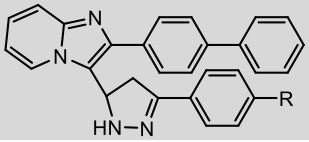
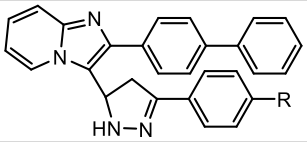
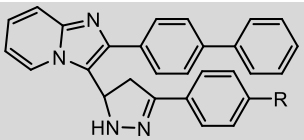
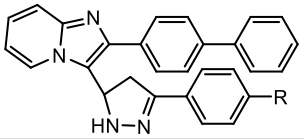
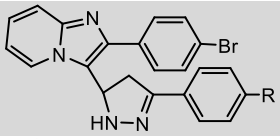
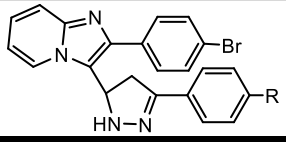
A solution of substituted acetophenones (1.6 mmol) in ethanol (10 mL) was added to a solution of **B1** (440 mg, 1.6 mmol) / **B2** (430 mg, 1.6 mmol) in ethanol (10 mL). A solution of KOH (1 mL, 40%) was then added to make the reaction mixture alkaline. The reaction mixture was stirred at room temperature for 24 hours. The solid-crude material was isolated by filtration and crystallized from ethanol to give the title products **C1-C10** [22].

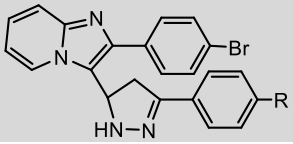
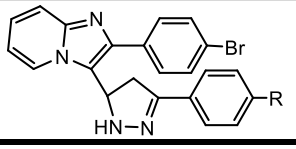
Synthetic of 2-([1,1'-subphenyl]-4-yl)-3-(3-(4-subphenyl)-4,5-dihydro-1H-pyrazol-5-yl)imidazo[1,2-a]pyridine[26].

A mixture of chalcones (10 mmol) and hydrazine hydrate (2 mL, 40 mmol) was refluxed for 10-11 hours. The resulting solution was poured on crushed ice, and the solid-crude material product was filtrated before recrystallization from ethanol to afford the desired products **D1-D8**.

Table 1: Physical properties of compounds **A-D8**

Compound number	Structure	Chemical Formula	R	M.Wt. (gm/mol)	Melting Point (°C)	Color	Yield (%)
A		$C_{19}H_{14}N_2$	-	270.33	213-216	Yellow	90
A_1		$C_{13}H_9BrN_2$	-	273.13	192-194	Orange	92
B		$C_{20}H_{14}N_2O$	-	298.34	199	White	70
B_1		$C_{14}H_9BrN_2O$	-	301.14	220	Brown	65
C_1		$C_{28}H_{20}N_2O$	-	400.47	157-158	Yellow	60
C2		$C_{28}H_{19}N_3O_3$	NO_2	445.47	173-175	Brown	71
C3		$C_{28}H_{20}N_2O_2$	OH	416.47	167-169	Green	67
C4		$C_{28}H_{19}N_2OBr$	Br	479.37	164-166	Off white	69

C5		$C_{28}H_{19}N_2OCl$	Cl	434.92	163-165	Yellow	64
C6		$C_{22}H_{15}N_2OBr$	H	403.27	169-171	White	68
C7		$C_{22}H_{14}N_3O_3Br$	NO_2	448.27	174-176	Off white	70
C8		$C_{22}H_{15}N_2O_2Br$	OH	419.27	170-172	Yellow	76
C9		$C_{22}H_{14}N_2OBr_2$	Br	482.17	188 -191	White	60
C10		$C_{22}H_{14}N_2OClBr$	Cl	437.72	176-178	Yellow	69
D1		$C_{28}H_{21}N_5O_2$	NO_2	459.50	190	Yellow	64
D2		$C_{28}H_{22}N_4O$	OH	430.50	188	Yellow	61
D3		$C_{28}H_{21}N_4Br$	Br	493.40	180	White	62
D4		$C_{28}H_{21}N_4Cl$	Cl	448.95	176	Off white	65
D5		$C_{22}H_{16}N_5O_2Br$	NO_2	462.30	190	Yellow	64
D6		$C_{22}H_{17}N_4OBr$	OH	433.30	188	Yellow	61

D7		$C_{22}H_{16}N_4Br_2$	Br	496.20	180	White	62
D8		$C_{22}H_{16}N_4ClBr$	Cl	451.75	176	Off white	65

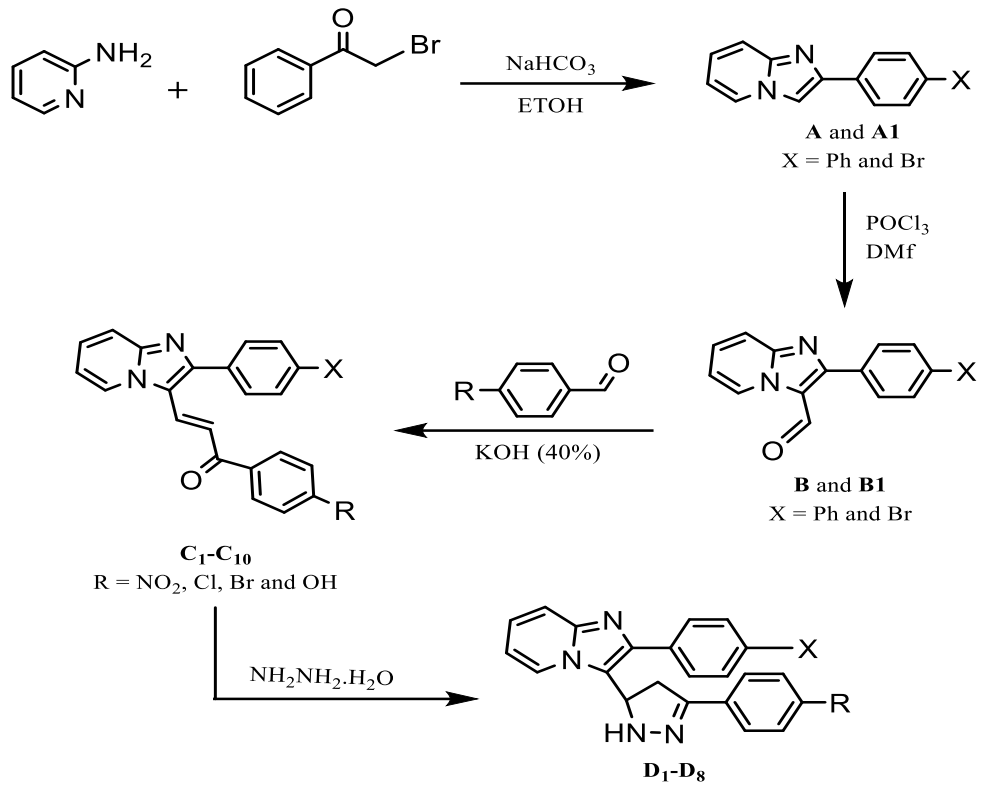
3. Cytotoxic effect of compounds C5 and D4 on the MCF-7 cell line (breast cancer) *in vitro* using the MTT assay

The 3-(dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) test was used to investigate the cytotoxic effects of compounds C5 and D4 on a breast cancer cell line (MCF-7). The cell viability and inhibition rate of the tumor cell line were assessed by the MTT test using a range of concentrations for compounds C5 and D4. The proportion of live cells was determined by comparing treated cells to the untreated cell line WRL-68. In concentrations ranging from 12.5 to 400 g/mL, compounds C5 and D4 were cytotoxic to MCF-7 cells [26] (Tables 5 and 6).

4. Results and discussion

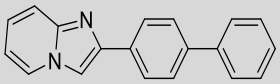
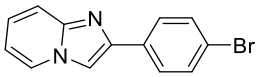
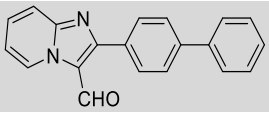
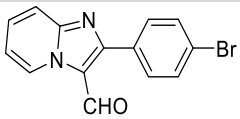
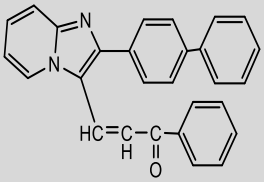
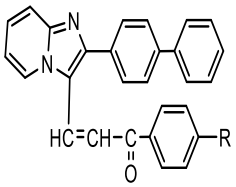
4.1. Chemistry

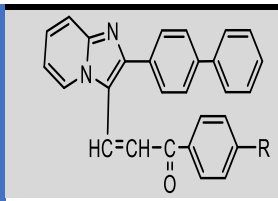
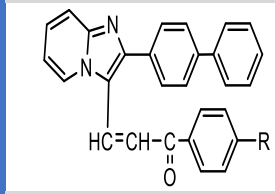
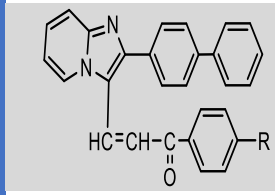
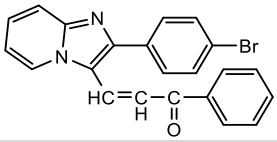
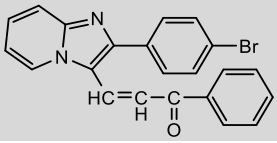
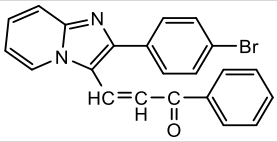
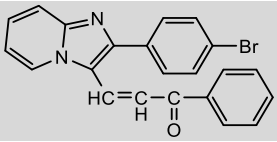
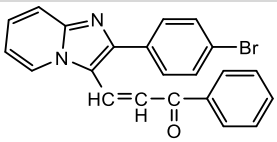
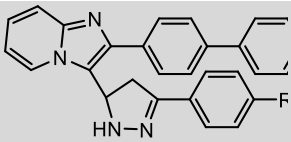
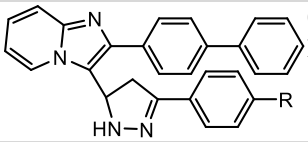
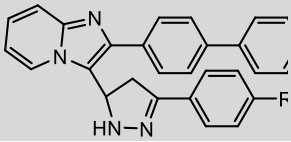
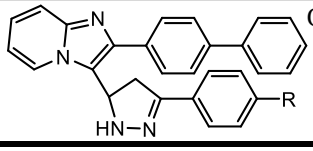
The synthesis of pyrazole derivatives **D1**-**D8** was achieved by the cycloaddition reaction of chalcones **C1**-**C10** with hydrazine hydrate. The Claisen-Schmidt reaction was used to prepare α,β-unsaturated carbonyl derivatives by treating aldehyde with acetophenone derivatives. The structure of the products **C1**-**C10** was confirmed by FT-IR spectroscopy, which showed absorptions for the =C-H group between 2781 and 2966 cm^{-1}. The ^1H NMR showed signals from 8.69 to 6.68 ppm belonging to the protons of the α,β-unsaturated ketone at **C1**-**C10**. The FT-IR spectral data of compounds D1-D8 confirms the presence of the NH of the pyrazole ring at 3319-3180 cm^{-1}. Furthermore, C-H stretching vibrations of the α,β-unsaturated ketone disappeared, which is considered good evidence for the formation of the pyrazole moiety. The ^1H NMR spectra showed signals between 8.15 and 8.21 ppm attributed to the NH proton of the pyrazole ring.



Scheme 1: Chemical synthesis of intermediate and target compounds

Table 2: The FT-IR spectral data (cm^{-1}) of all prepared compounds **A-D5**

Compound number	Structure	R	VC-H aromatic	VC-H aliphatic	VC=O	VC=N	VC=C	Others
A		-	3074 3047 3002	-	-	1633	1585 1541	-
A_1		-	3012 3072 3012	-	-	1631	1596 1564 1523	C-Br 705
B		-	3095 3058	2848 2781 aldehyde	1672	1635	1562	-
B_1		-	3058 3085	2833 2792 aldehyde	1689	1631	1556 1531	C-Br 696
C1		H	3047	2923 2852	1681	1631	1575 1498	-
C2		N O_2	3036	2925 2858	1693	1633	1604 1525	NO_2 1525 1346

C3		O H	3033	2866 2947	1662	1635	1602 1577	OH 3309-3492
C4		Br	3049	2925 2966	1650	1631	1602 1587 1544	C-Br 703
C5		Cl	3035	2845 2927	1685	1635	1600 1556 1537	C-Cl 742
C6		H	3070	2983 2881	1687	1637	1573	C-Br 590
C7		N O_2	3035	2858 2925	1693	1633	1604	NO_2 1525 1346
C8		O H	2997	2835 2889	1689	1629	1581 1544 1500	OH 3417
C9		Br	3049	2850 2981	1699	1637	1560	C-Br 644
C10		Cl	3006	2881 2996	1687	1939	1560	C-Cl 823
D1		N O_2	2956	2854 2923	-	1627 1598	1598	N-H 3319
D2		O H	3028 3056	2925	-	1629 1604	1512	N-H 318 C-OH 3382
D3		Br	3047	2923	-	1633 1575	1496	N-H 3346 C-Br 649
D4		Cl	3029	2923	-	1627 1606	1550	N-H 3406

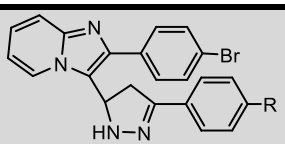
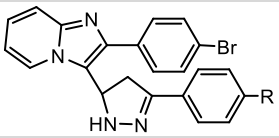
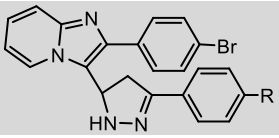
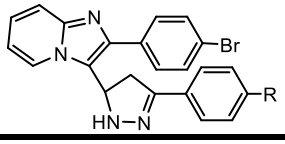
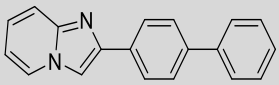
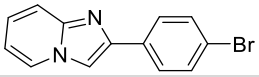
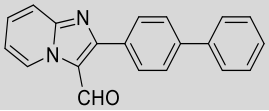
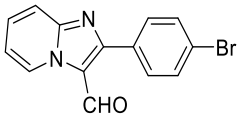
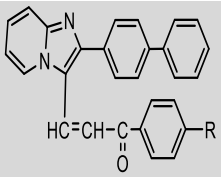
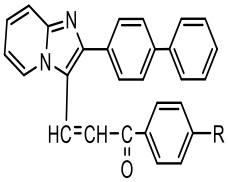
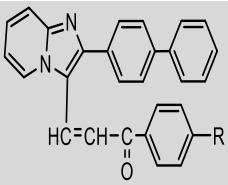
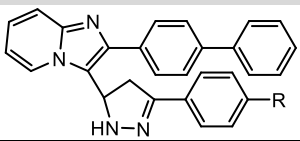
D5		N O_2	3062	2921	-	1631 1596	1560	N-H 3313
D6		O H	3068	2998	-	1627 1608	1512	N-H 3180
D7		Br	3037	2921	-	1633 1575	1500	N-H 3371
D8		Cl	3099	2977	-	1639 1558	1413	N-H 3286

Table 3: The ^{1}H NMR spectral data (δ, ppm) of compounds **A-D5**

Compound number	Structure	R	Ar-H (δ ppm) Multiple aromatic	C-H **(δ ppm)**	NH	OH
A		-	6.89-8.44	-	-	-
A_1		-	6.86-8.26	-	-	-
B		-	7.27-8.3	9.62	-	-
B_1		-	6.86-8.69	9.75	-	-
C2		NO_2	6.90-8.51	8.7 8.4	-	-
C3		OH	6.68-8.30	7.91 8.23	-	9.45
C10		Cl	6.82-7.76	8.29 8.34	-	-
D1		NO_2	6.77-8.19	4.20 4.93	8.2 1	-

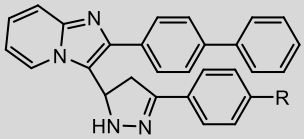
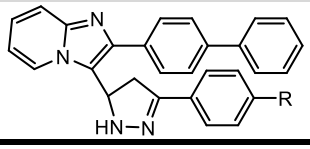
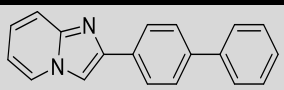
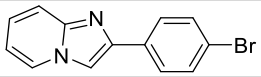
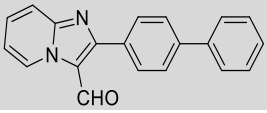
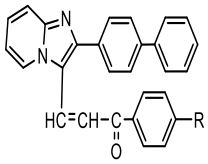
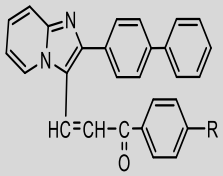
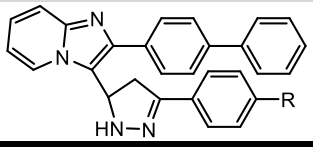
D2		OH	6.65-7.73	4.88 5.30	8.2	-
D5		NO_2	6.67-8.13	4.20 4.97	8.1 5	-

Table 4: The ^{13}C NMR spectral data (δ ppm) of compounds (**A-D5**)

Compound number	Structure	R	C=C **(δ ppm)** aromatic	C=N **(δ ppm)**	C=O	Others
A		-	127,128,129	145.1,130,113	-	-
A_1		-	126,128,129	145,134,113	-	-
B_1		-	114,126,131,129	153	188	-
C2		NO_2	114,126,128,129	145	198	-
C3		OH	114,127,128,129	145.1	189	C-OH 164
D5		NO_2	114,117,124, 128,129	144.8	-	C-NH 45.5 (C-N) 150

4.2. Biological activity

Cell viability was reduced by increasing the concentration of compounds C5 and D4, which showed a decrease in cell viability in a dose-dependent pattern. In the case of compound **C5**, the decrease in MCF-7 cell line viability (%) was noticed at 400 µg/mL (34.73 ± 0.93%), while the highest MCF-7 cell viability at 12.5 µg/mL was reached (95.14 ± 2.31%). Compound **C5** exhibited cytotoxic activity with an IC50 value of 90.97 µg/mL from the compound's effect on the MCF-7 cell line. However, an IC50 value of 147.8 µg/mL was obtained from the effect of compound **C5** on the WRI-68 normal cell line (Figure1). In terms of compound **D4**, the decrease in MCF-7 cell viability (%) was noticed at 400 µg/mL (55.29 ± 1.82%), while the highest MCF-7 cell viability at 12.5 µg/mL reached 94.83 ± 1.01%. Compound **D4** exhibited cytotoxic activity with an IC50 value of 111.0 µg/mL of the compound's effect on the MCF-7 cell line. However, an IC50 value of 115.2 µg/mL was obtained from the effect of compound **D4** on the WRI-68 normal cell line (Figure 2).

Table 5: Cytotoxicity effect of compound **C5** on MCF-7 and WRI-68

MCF-7	WRL68

Concentration	Mean ± SD	Mean ± SD
400.00	34.73±0.93	72.65±1.96
200.00	41.81±0.41	80.21±3.11
100.00	61.96±4.39	85.65±3.32
50.00	73.23±2.72	94.17±0.77
25.00	84.14±0.83	96.18±0.23
12.50	95.14±2.31	94.29±2.98

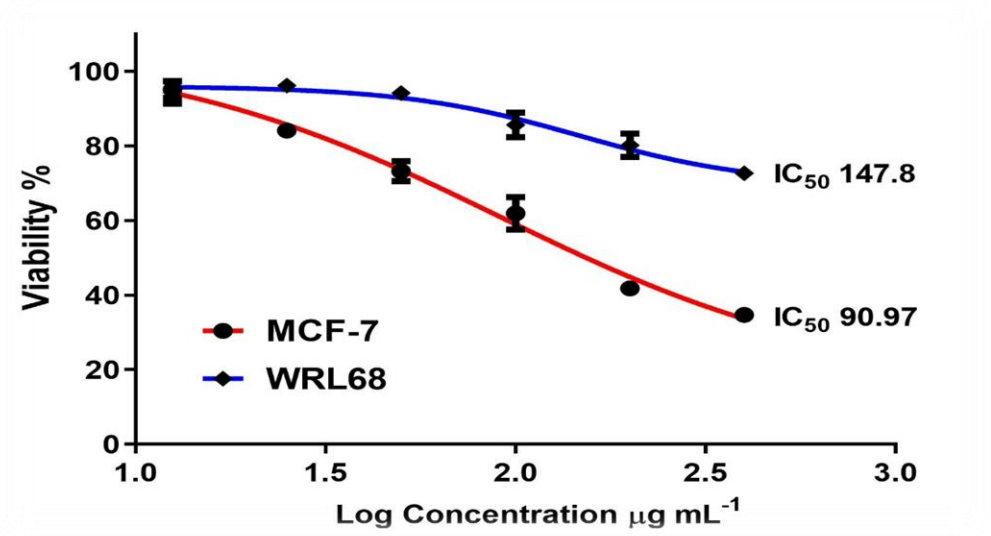


Figure 1: Cytotoxic effect of compound **C5** on MCF-7 and WRL-68 cells

Table 6: Cytotoxicity effect of compound **D4** on MCF-7 and WRI-68 cells

MCF-7		WRL68
Concentration	**Mean ± SD**	**Mean ± SD**
400.00	55.29±1.82	71.95±0.81
200.00	64.99±3.32	76.70±2.61
100.00	75.36±2.23	84.34±2.66
50.00	92.48±3.82	86.07±1.92
25.00	94.71±0.44	95.22±0.82
12.50	94.83±1.01	95.95±1.03

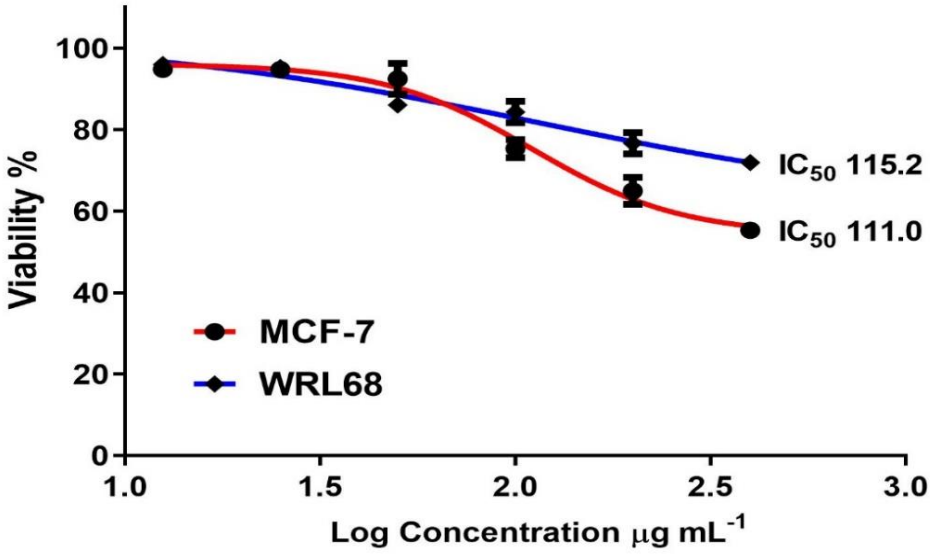


Figure 2: Cytotoxic effect of compound D4 on MCF-7 and WRL-68 cells

5. Conclusion

In this work, a variety of pyrazole-bearing imidazo[1,2-a]pyridine derivatives have been synthesized. Two of these derivatives (**C5** and **D1**) were investigated. Two chlorine-containing compounds (**C5** and **D4**) were selected for testing the cytotoxic efficacy against breast cancer using the MTT assay. As shown in Tables **5** and **6**, is possible to conclude that the values of IC50 play a critical role in determining the effect of the compounds on cancer cells since compound **C5** has a lower IC50 value. Therefore, it has the best activity on cancer cell lines compared to compound **D4**, which has a higher IC50 value. Moreover, compound **C5** is considered less toxic to normal cells since it gave a high value of IC50 compared to compound **D4**. Based on these results, compound **C5** was considered better than compound **D4** for cytotoxic activity.

Acknowledgements

We thank Ms. Munera and Mr. Andy for doing the FT-IR measurements.

References

[1] A. Siwach and P. K.Verma,"Synthesis and therapeutic potential of imidazole containing compounds," *BMC Chemistry*, vol. 15, no. 1, p. 12, 2021.

[2] S. Endoori, K. C. Gulipalli, S. Bodige, P. Ravula, and N. Seelam, Design, "synthesis, anticancer activity and in silico studies of novel imidazo[1,2-a]pyridine based 1H-1,2,3-triazole derivatives," *Journal of Heterocyclic Chemistry*, vol. 58, no. 6, pp. 1311-1320, 2021.

[3] K. A. Abrahams, J. A. Cox, V. L. Spivey, N. J. L. oman, M. J. Pallen, C. Constantinidou, R. Fernández, C. Alemparte, M. J. Remuiñán, D.Barros, L. Ballell, and G. S. Besra. Identification of novel imidazo[1,2-a]pyridine inhibitors targeting M. tuberculosis QcrB," *PloS one*, vol. 7, no. 12, p. e52951, 2012.

[4] R. B. Lacerda, C. K. de Lima, L. L. da Silva, N. C. Romeiro, A. L. Miranda, E. J. Barreiro, and C. A. F raga, "Discovery of novel analgesic and anti-inflammatory-3-arylamine-imidazo[1,2-a]pyridine symbiotic prototypes," *Bioorganic and Medicinal Chemistry*, vol. 17, no. 1, pp. 74-84, 2009.

[5] R. M. Kubba, N. M. Al-Joborry, and N. J. Al-Lami, "Theoretical and Experimental Studies for Inhibition Potentials of Imidazolidine 4-One and Oxazolidine 5-One Derivatives for the Corrosion of Carbon Steel in Sea Water," *Iraqi Journal of Science*, vol. 61, no. 11, pp. 2776-2796, 2020.

[6] M. López-Martínez, H. Salgado-Zamora, E. R. San-Juan, S. Zamudio, O. Picazo, M. E. Campos, and E. B. Naranjo-Rodriguez, "Anti-anxiety and sedative profile evaluation of imidazo[1,2-a]pyridine derivatives," *Drug Development Research*, vol. 71, no. 6, pp. 371-381, 2010.

[7] Q. Tan and B. Xu, "Chapter 9-CH Bond Activation as a Powerful Tool in the Construction of Biologically Active Nitrogen-Containing Heterocycles," in Atta ur, R. (Ed.) Studies in Natural Products Chemistry (Elsevier), pp. 299-340, 2016.

[8] G. A. Papalia, A. M. Giannetti, N. Arora, and D. G. Myszka, "Thermodynamic characterization of pyrazole and azaindole derivatives binding to p38 mitogen-activated protein kinase using Biacore T100 technology and van't Hoff analysis," *Analytical Biochemistry*, vol. 383, no. 2, pp. 255-264, 2008.

[9] A. Sapkal and S. Kamble, "Greener and Environmentally Benign Methodology for the Synthesis of Pyrazole Derivatives," *ChemistrySelect*, vol. 5, no. 42, pp. 12971-13026, 2020.

[10] Y. T. Han, K. Kim, G. I. Choi, H. An, D. Son, H. Kim, H. J. Ha, J. H. Son, S. J. Chung, H. J. Park, J. Lee, and Y. G. Suh, "Pyrazole-5-carboxamides, novel inhibitors of receptor for advanced glycation end products (RAGE)," *European Journal of Medicinal Chemistry*, vol. 79, pp. 128-142, 2014.

[11] S. Y. Hassan, "Synthesis, antibacterial and antifungal activity of some new pyrazoline and pyrazole derivatives," Molecules (Basel, Switzerland), vol. 18, no. 3, pp. 2683-2711, 2013.

[12] N. M. Saleh, M. G. El-Gazzar, H. M. Aly, and R. A. Othman, "Novel Anticancer Fused Pyrazole Derivatives as EGFR and VEGFR-2 Dual TK Inhibitors," *Frontiers in Chemistry*, vol. 7, 917, 2020.

[13] M. Abdel-Aziz, D. Abuo-Rahma Gel, and A. A. Hassan, "Synthesis of novel pyrazole derivatives and evaluation of their antidepressant and anticonvulsant activities," *European Journal of Medicinal Chemistry*, vol. 44, no. 9, pp. 3480-3487, 2009.

[14] R. Surendra Kumar, I. A. Arif, A. Ahamed, and A. Idhayadhulla, "Anti-inflammatory and antimicrobial activities of novel pyrazole analogues," *Saudi J. Biol. Sci*., vol. 23, no. 5, pp. 614-620, 2016.

[15] E. Meta, C. Brullo, M. Tonelli, S. G. Franzblau, Y. Wang, R. Ma, W. Baojie, B. S. Orena, M. R. Pasca, and O. Bruno, "Pyrazole and imidazo[1,2-b]pyrazole Derivatives as New Potential Antituberculosis Agents," Medicinal chemistry (Shariqah (United Arab Emirates), vol. 15, no. 1, pp. 17-27, 2019.

[16] J. R. Badgujar, D. H. More, and J. S. Meshram, "Synthesis, Antimicrobial and Antioxidant Activity of Pyrazole Based Sulfonamide Derivatives," *Indian J. Microbiol*, vol. 58, no. 1, pp. 93-99, 2018.

[17] O. I. El-Sabbagh, M. M. Baraka, S. M. Ibrahim, C. Pannecouque, G. Andrei, R. Snoeck, J. Balzarini, and A. A. Rashad, "Synthesis and antiviral activity of new pyrazole and thiazole derivatives," *European Journal of Medicinal Chemistry*, vol. 44, no. 9, pp. 3746-3753, 2009.

[18] M. F. Mohamed, M. S. Mohamed, M. M. Fathi, S. A. Shouman, and I. A. Abdelhamid, "Chalcones incorporated pyrazole ring inhibit proliferation, cell cycle progression, angiogenesis and induce apoptosis of MCF7 cell line," *Anti-Cancer Agents in Medicinal Chemistry*, vol. 14, no. 9, pp. 1282-1292, 2014.

[19] M. Mantzanidou, E. Pontiki, and D. Hadjipavlou-Litina, "Pyrazoles and Pyrazolines as Anti-Inflammatory Agents," *Molecules*, vol. 26, no. 11, p. 3439, 2021.

[20] D. S. Martsinkevich, K. F. Chernyavskaya, T. I. Ahramovich, and V. A. Tarasevich, "Synthesis and Antibacterial Activity of Novel Chalcone-derived Pyrazoles," *Russian Journal of Organic Chemistry*, vol. 58, no. 5, pp. 697-705, 2022.

[21] M. Bonesi, M.R. Loizzo, G. A. Statti, S. Michel, F. Tillequin, and F. Menichini, "The synthesis and Angiotensin Converting Enzyme (ACE) inhibitory activity of chalcones and their pyrazole derivatives," *Bioorganic and Medicinal Chemistry Letters*, vol. 20, no. 6, pp.1990-1993, 2010.

[22] N. Beyhan, B. Kocyigit-Kaymakcioglu, S. Gümrü, and F. Aricioglu, "Synthesis and anticonvulsant activity of some 2-pyrazolines derived from chalcones," *Arabian Journal of Chemistry*, vol. 10, no. 2, pp. S2073-S2081, 2017.

[23] N. Al-Lami, "New Imidazo[2,1-b]naphtha[2,1-d][1,3]thiazole Derivatives: Synthesis, Antimicrobial and Antifungal Activity, " *Iraqi Journal of Science*, vol. 56, pp. 3274-3284, 2015.

[24] A. Gueiffier, S. Mavel, M. Lhassani, A. Elhakmaoui, R. Snoeck, G. Andrei, O. Chavignon, J. C. Teulade, M. Witvrouw, and J. Balzarini, "Synthesis of imidazo[1,2-a]pyridines as antiviral agents," *Journal of Medcinal Chemistry*, vol. 41, no. 25, pp. 5108-5112, 1998.

[25] J. C. J ung, Y. Lee, M. Dongguk, M. Jung, and S. Oh, "Practical Synthesis of Chalcone Derivatives and their Biological Activities," *Molecules*, vol. 22, no. 11, pp. 1872, 2017.

[26] S. Ulloora, R. Shabaraya, S. Aamir, and A. V. Adhikari, "New imidazo[1,2-a]pyridines carrying active pharmacophores Synthesis and anticonvulsant studies," *Bioorganic and Medicinal Chemistry Letters*, vol. 23, no. 5, pp. 1502-1506, 2013.