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Original Article

Antioxidant Activity of New Synthesized Pyrazole and 2-Oxo-3*H*-pyrimidine Derivatives Containing Imidazo(1,2-a) Pyridine

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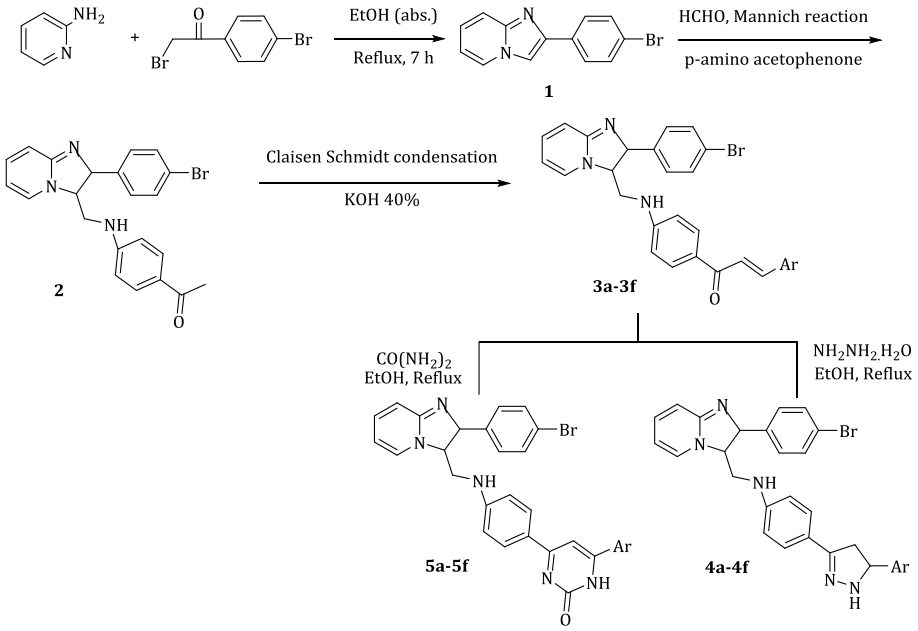
ABSTRACT

In this research, chalcone, cyclic pyrazole, and oxo-pyrimidine compounds were prepared from the reaction of start material 2-amino pyridine with bromo phenacyl bromide constituted in the first step 2(4-bromo phenyl) imidazole (1,2-a) pyridine compound (1). In the following step, compound (1) was treated with 4-amino acetophenone in the presence formaldehyde giving Mannich base (2). In the third step compound (3) condensed with aromatic aldehydes under cross aldol reaction to give the new chalcones from 3A to 3E. In the last step, chalcone derivatives were cyclized by hydrazine hydrate and urea compounds for giving pyrazole and oxo-pyrimidine rings (4A-4E), (5A-5E), respectively. All the prepared compounds were subjected to FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopies, and also, they were evaluated as antioxidant.

GRAPHICAL ABSTRACT



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Introduction

Many of reagent compounds are the important major objectives of organic synthesis, one of heterocyclic compound's an imidazo (1,2-a) pyridine is an important of fused bicyclic 5-6 hetero-cycles including divers physicochemical properties [1]. It has great importance in the biological activity such as anti-tubercular [2] and antimicrobial [3] Mannich reaction compounds are the organic compounds contain from amino alkylation and a carbonyl functional group [4]. The primary or secondary amine as 4-amino aceto phenone or ammonia groups reacted with cyclic imidazo (1,2-a) pyridine. Studies have proven that Mannich base have biological activity such as antibacterial, antifungal, anti-nociceptive, and analgesic [5].

Chalcone is the organic compound. It is an α, β-unsaturated ketone prepared under a base catalyzed via condensation Claisen–Schmidt, a variety of important biological compounds and various pharmacological effect such as antimalarial and anti-HIV [6]. Chalcone can be synthetically manipulated of heterocyclic compounds corresponding to pyrazole and oxo-pyrimidine [7]. Pyrazole is an organic compound with formula $C_3H_3N_2H$. It has five-membered ring with two adjacent nitrogen atoms. The derivatives of pyrazole are used in medicine, for their analgesic, anti-inflammatory, and antipyretic [8] Pyrimidine is a heterocyclic compound consists of six-membered ring with two nitrogen atoms in positions 2 and 3 inside the ring. Pyrimidine derivatives have a wide pharmaceutical significance in various drugs, for examples Thiamine, Talbutal, and Gemcitabine [9]. Pyrazole and pyrimidine were synthesized by reaction the hydrazine hydrate and urea with α, β unsaturated carbonyl under the suitable condition [10].

Aim of research

1. Synthesis of new derivatives of bicyclic fused rings with bridge head nitrogen of 3-substituted imidazo/pyridine by using different methodloyies.2. Characterization of new compounds by using FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectra.
3. Evaluation of new compounds by antioxidant applications.

Materials and Methods

All chemical materials were supplied from corporations of Thomas baker, Merck, BDH, and Sigma-Aldrich. End of reaction of all compounds were checked on aluminum-coated TLC plates 60 F245 [E.MERCK] by using ethyl acetate and Petroleum ether and imagined under iodine vapor. Melting points were determined on an electro thermal melting point (Stuart Germany), and they were uncorrected. Infrared spectra resolves were done as a KBR disk in range of (400-4000 cm^{-1}). FT-IR Shimadzu was used to record at university of Bagdad /College of science. The proton ^{1}H-NMR and ^{13}C-NMR spectra operating at 400 MH_Z and 100 MH_Z, respectively in DMSO-d_6, measurements are performed at Collage Sharif University of Technology /Tehran/ Iran.

*preparation of 2(4-bromo phenyl) imidazole [1,2-a] pyridine (**1**) [11]*

2-amino pyridine (0.01 mol) was mixed with 4-phenyl phenacyl bromide (0.01 mol), and then it was dissolved in (15 mL) of abs. ethanol in the round bottom flask. Next, it was reflexed for 7 hours. After that, it was checked by TLC, purified, dried, and studied all the physical properties of the compound (**1**) represent with molecular formula: $C_{13}H_9N_2Br$, Color: Off white, Yield: 80% M.P: 265, Re-crystallization solvent: Absolut ethanol.

*Preparation of Mannich base (**2**) [12]*

0.3 mL of formaldehyde was mixed with 0.1 mL of conc. HCl, and then stirrer for 5 min, after that (0.01 m mol) of 4 amino aceto phenone was added and dissolved in absolute ethanol. Thereafter, it was flowed by refluxed for one hour. Next, (2.435 g, 0.01 mol) of the compound (**1**) was added and refluxed for 5 hours. The reaction was then checked by TLC, purified, dried, and the physical properties of the compound (**2**) was studied and represented with

molecular formula: $C_{22}H_{18}N_3OBr$, Color: Yellow, Yield: 75%, M.P.: 200 °C, Re-crystallization solvent: Absolute ethanol.

*Synthesis of chalcones derivative (**3a-3e**) [13]*

1 mol of substitution benzaldehyde with 1 mol of Mannich reaction were added to 0.5 mL of 40% sodium hydroxide as dropped with stirrer, and then the volume was completed to 5 mL of solution sodium hydroxide and stirred for 24 hours at room temperature. That reaction completion was tested by TLC.

*Compound **3a:*** Yellow solid, yield 75%, mp 250-252 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3274, 3120, 3029, 2993, 2887, 1614, 1660, 1598, 1521, 1407, 1352, 1278, 954, 767.

*Compound **3b**:* Off white, yield 70%, mp 280-282 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3253, 3103, 3093, 2989, 2833, 1658, 1596, 1616, 1413, 1359, 1282, 1178, 954, 767.

*Compound **3c**:* Yellow, yield 65%, mp 290-292 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3438, 3280, 3182, 3029, 2879, 2839, 1658, 1616, 1596, 1413, 1338, 954, 767.

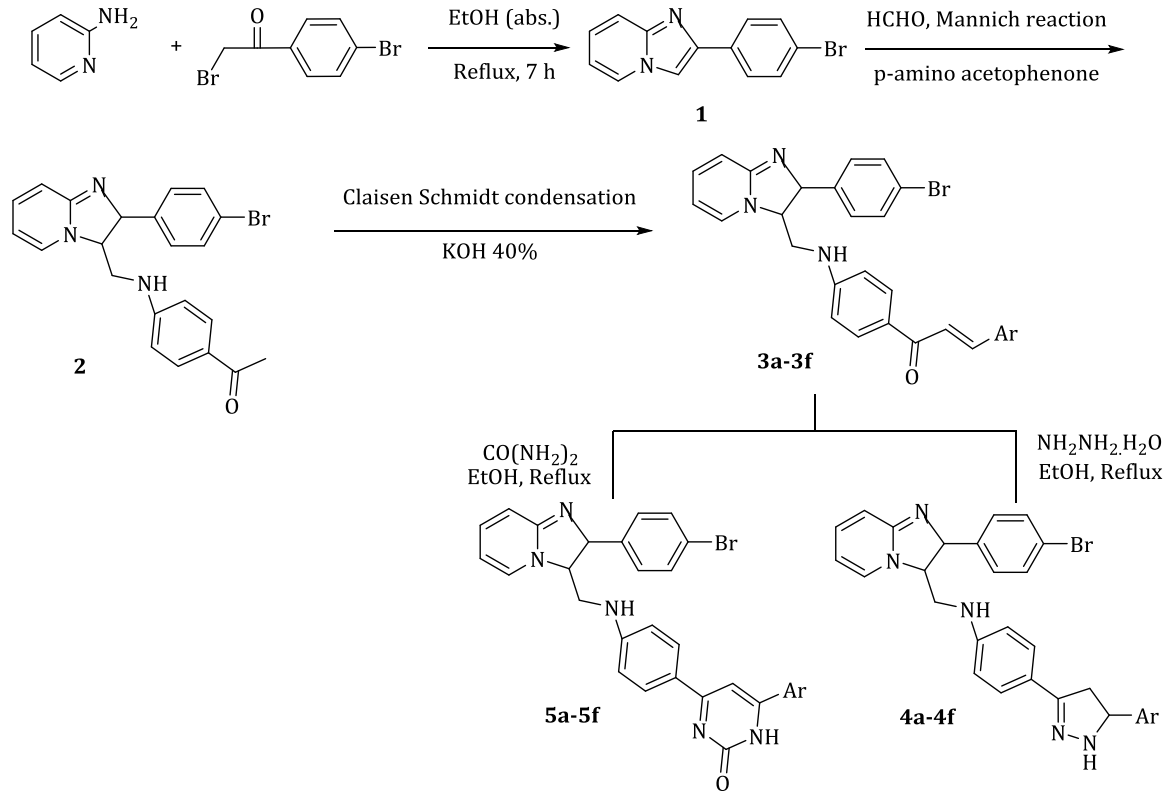
*Compound **3d**:* Off white, yield 65%, mp 240-242 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3267, 3031, 3122, 2981, 2808, 1660, 1625, 1575, 1456, 1365, 925, 748.

*Compound **3e**:* Off white, yield 65%, mp 240-242 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3481, 3263, 3147, 3029, 2938, 2866, 1652, 1614, 1564, 1407, 1352, 935, 767.

*Synthesis of pyrazole derivatives (**4a-4e**) [14]*

A mixture compound (**3**) derivatives (2.5 g, 10 mmol) and nucleophile reagents hydrazine hydrate (10 mmol) was added to 15 mL ethanol, and then a few drops of conc. HCl was added to mixture. After that, the reaction was reflexed for 6 hours, by TLC, the reaction was checked, and then filtered, purified, and dried.

*Compound **4a**:* Yellow, yield 65%, mp 190-192 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3265, 3159, 3016, 2954, 2866, 1656, 1596, 1525, 1411, 1342, 1278, 952, 767.



Ar : A = *p*-NO_2-Ph, B = *p*-OMe-Ph, C =*o*-OH-Ph, D = *p*-$N(Me)_2$-Ph, E = *p*-OH-Ph

Scheme 1: Synthesis steps of compounds **1-5**

*Compound **4b**:* Brown, yield 70%, decomposition >205 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3263, 3147, 3062, 2995, 2866, 1598, 1652, 1407, 1344, 1278, 1128, 952, 767.

*Compound **4c**:* Yellow, yield 75%, mp 220-222 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3452, 3205, 3172, 3064, 2970, 2833, 1637, 1608, 1411, 1321, 929, 786.

*Compound **4d**:* Yellow, yield 55%, mp 280-281 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3211, 3112, 3072, 2968, 2831, 1683, 1637, 1415, 1309, 950, 775.

*Compound **4e**:* Brown, yield 60%, decomposition >270 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3461, 3382, 3305, 3078, 2977, 2827, 1643, 1608, 1411, 1321, 752.

*Synthesis of Oxo pyrimidine derivatives (**5a-5e**) [14]*

The equal amounts of chalcone derivatives and urea compound were put in the amount of ethanol and sodium hydroxide (4 g NaOH and 10 mL of ethanol), and then stirred for about 5 hours. Next, it was poured into the cold water. After that, the precipitate was washed and recrystallized by a suitable solvent.

*Compound **5a:*** Yellow, yield 70%, decomposition >260 °C, IR (KBr) (ν_{max}/ cm^{-1}): 32547, 3116, 3066, 2983, 2839, 1691, 1620, 1604, 1533, 1492, 1350, 1278, 929, 717.

*Compound **5b:*** Brown, yield 65%, mp 250-252 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3498, 3263, 3161, 3004, 2981, 2891, 1662, 1573, 1421, 1323, 1245, 1151, 941, 748.

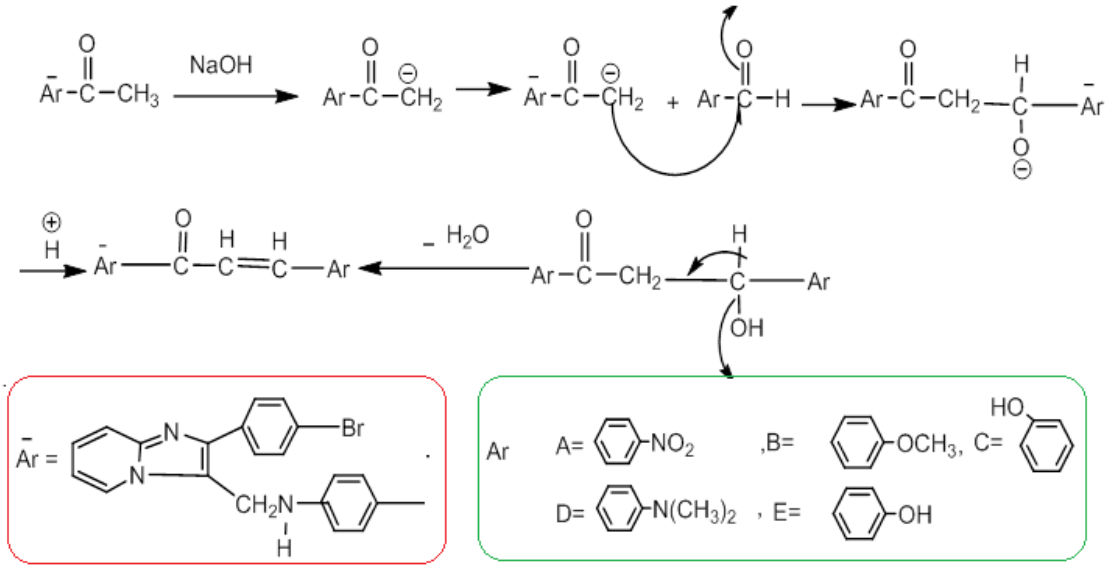
*Compound **5c:*** Orange, yield 55%, mp 200-202 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3319, 3163, 3211, 3004, 2906, 2839, 1660, 1625, 1575, 1535, 1456, 1365, 925, 748.

*Compound **5d:*** White, yield 60%, mp 240-242 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3226, 3103, 3003, 2929, 2875, 1650, 1616, 1591, 1421, 1330, 921, 769.

*Compound **5e:*** Orange, yield 65%, decomposition >220 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3479, 3286, 3177, 3013, 2889, 2869, 1654, 1610, 1404, 1357, 921, 767.

Results and Discussion

All the reactions are explained in Scheme 1. In this work, the imidazo (1,2-a) pyridine compound (**1**) was obtained from the reaction of 2-amino pyridine with bromo phencyl bromide, subjected to diagnose by the FT-IR spectrum. The absorption band at 1612 cm^{-1} belong to ν (C=N) in the imidazo pyridine ring, ν (C=C) aromatic at 1433 cm^{-1}, (C-H) aromatic at 3014-3080 cm^{-1}, ν (C-N) at 1353 cm^{-1}, and ν (C-Br) at 790 cm^{-1}. Mannich base compound (**2**) showed absorption band at 3176-3284 cm^{-1} due to ν (N-H), ν (C-H) aromatic at 3045 cm^{-1}, absorption band at 2840-2977 cm^{-1} belong to ν (C-H) aliphatic, absorption band at 1704 cm^{-1} due to ν (C=O), absorption band at 1614 cm^{-1} due to ν (C=N) in the imidazo pyridine ring, ν (C=C) aromatic ring at (1400) cm^{-1}, ν (C-N) at 1352 cm^{-1}, and ν (C-Br) at 730 cm^{-1}.
Chalcones derivatives (**3a-3e**) was prepared by Claisen Schmidt condensation using benzaldehyde and acetophenone under special states, the reaction was loss of a molecule water, the reaction involved keto-enol [15], as its mechanism is demonstrated in Scheme 2.
In ^{1}H-NMR, the results of **3a and 3d** compounds were, respectively, as follow: a singlet signal appeared at δ 4.53 ppm due to CH_2, a singlet signal appeared at δ 4.81 ppm due to NH, doubled-doubled signal at δ 7.4-7.9 ppm due to CH=CH, multiplied signal due to aromatic ring at δ 8.01-8.52 ppm. While, **3d** compound indicates a singlet signal due to two methyl group at δ 2.31 ppm, singlet signal due to CH_2 at δ 4.66 ppm, a singlet signal due to NH at δ 4.67 ppm, doubled-doubled signal at δ:(6.54-6.98) ppm due to CH=CH, and multiplied signal due to aromatic ring at 7.03-8.77 ppm.
^{13}C-NMR spectral data of compound **3d** was as follow: δ 26.42-36.47 ppm due to CH_3-N-CH_3, δ 40.65 ppm belong to CH_2NH, δ 109.39-116.29 ppm belong to CH=CH, C=C aromatic appeared multiplied single at δ 122.17- 151.22 ppm, at δ 152.64 ppm due to C=N in imidazo-pyrdine, at δ 190.38-195.83 ppm belong to carbonyl group.



Scheme 2: Mechanism steps of chalcone compound

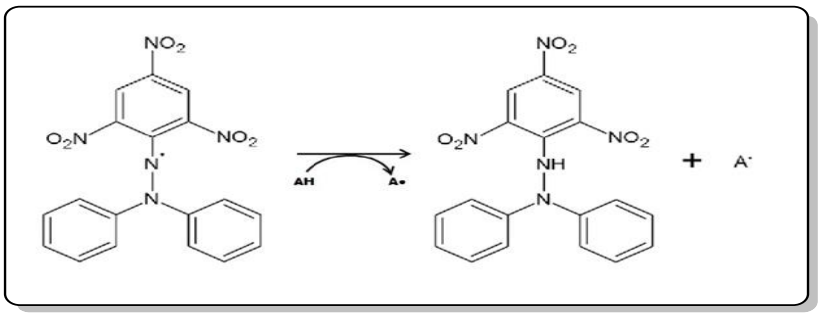
^{1}H-NMR spectra to compound **4b** was as follow: δ 2.27 ppm due to (OCH_3), signal singlet at δ 4.40 ppm due to CH_2, signal singlet at δ 4.47 ppm due to NH, CH_2, and CH in cyclic pyrazole appeared multiplied signal at δ 5.01-5.98 ppm, multiplied signal at δ 6.40-7.87 ppm due to aromatic ring, signal singlet at δ 8.30 ppm due to NH in pyrazole ring. As for the same compound diagnosed in ^{13}CNMR, the results were as follow: CH_2NH appeared signal at δ 39.64 ppm, δ 58.74 ppm due to OCH_3, δ 113.61-131.93 ppm belong to C=C aromatic, C=N in imidazole (1,2-a) pyridine appeared signal at 148.58 ppm, and in pyrazol ring (C=N) group appeared signal at δ 158.58 ppm. Compound **4e** was diagnosed by ^{1}H-NMR and it was signal singlet at δ 4.02 ppm due to CH_2, signal singlet at δ 4.04 ppm due to NH, CH_2, and CH in cyclic pyrazole appeared multiplied signal at δ 5.01-5.98 ppm, at 6.46-8.5 ppm multiplied signal belong to aromatic ring, signal singlet at δ 8.55 ppm due to NH in pyrazole ring, signal singlet at δ 8.70 ppm due to OH group. The chalcones were reacted with urea in HCl medium giving Oxo- pyrimidine. The synthesized compounds were characterized by FTIR, spectroscopy.

Compound **5a** was characterized by ^{1}H-NMR, the results were as follow: single singlet at δ 4.52 ppm due to CH_2, single singlet at δ 4.53 ppm due to NH, at δ 5.45 ppm single singlet due to CH in cyclic pyrimidine, at δ 7.05-8.52 ppm multiplied signal due to aromatic ring, at δ 9.25 ppm single singlet due to OH, in cyclic pyrimidine NH appeared single singlet at δ 9.52 ppm. In compound **5e** had diagnosed by ^{1}H-NMR and ^{13}C-NMR. The results were as follow: single singlet at δ 4.27 ppm due to CH_2, single singlet at δ 4.66 ppm due to NH, single singlet at δ 5.31 ppm due to CH in pyrimidine ring, at 6.55-8.76 ppm multiplied signal due to aromatic ring, single singlet at δ 8.77 ppm due to OH, single singlet at δ 9.04 ppm due to NH in pyrimidine ring. While, in ^{13}C-NMR to the same compound, the results were as follow: at 56.47 ppm belong to CH_2NH, multiplied signal due to carbon aromatic ring at 116.30-135.62 ppm, C=N group in pyrimidine ring, signal at 143.53 ppm, C=N group in imidazole ring gave signal at 145.22, and carbonyl group gave the singlet signal at 160.05 ppm.

Evaluation of the prepared derivatives as antioxidant [11]

In this work, the antioxidants were determined using DPPH radical scavenging activity and ascorbic acid as the positive standard. 0.5 mL of the compound extract was added to 1 ml of DPPH solution. At 517 nm, DPPH was measured versus a blank assay about 30 min. The antioxidant activity of some new synthesized compounds such as pyrazole (**4a**) and pyrimidine (**5a**) linking

with imidazo (1,2-a) pyridine was evaluated by DPPH method (Table 1 and Figure 1). The results were showed the excellent antioxidant, equal or moderate activity than the standards ascorbic acid. Scheme 3 explained the reaction of DPPH radical with antioxidant [16].



Scheme 3: The reaction of DPPH radical with antioxidant (AH)

Table 1: Values of antioxidant activity of some synthesized compounds

Compound	PPM	I%	IC50
4A	100	87.5	17.11
	50	89.84	
	25	75	
5B	100	64.45	
	50	42.53	71.85
	25	19.78	
Ascorbic acid	100	87.89	40.27
	50	87.5	
	25	17.96	

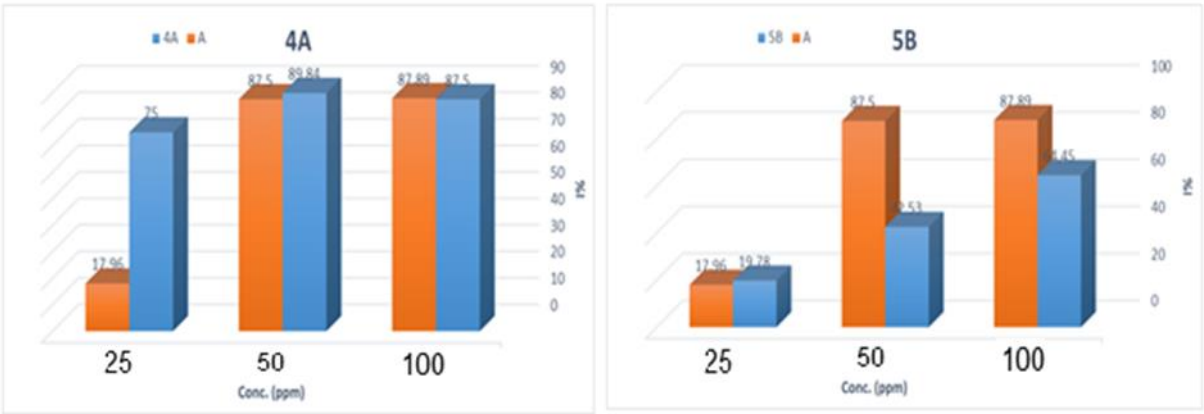


Figure 1: DPPH Scavenging activity of compound **4a** and **5b** with ascorbic acid

Conclusion

In this work, new fused ring as imidazo (1,2-a) pyridine was successfully synthesized, and also new derivatives as Schiff bases, pyrazol, and pyrmidine were prepared with characterization by FT-IR ,^{1}H-NMR, and ^{13}CNMR. The work has been enhanced by studying the application of antioxidant for the new derivatives.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

The author declared that they have no conflict of interest.

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