Synthesis of some New 3-Substituted Heterocyclic Compounds Containing Bridgehead Nitrogen from 2-Amino Pyridine with Study Their Biological Activity

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Abstract

New series of 3-substituted heterocyclic compounds containing bridge head nitrogen were synthesized through multi-step reactions. In order to prepare the starting 2-substituted heterocyclic compounds of pyridine, a known procedure was used by condensation of 2-amino pyridine with (4-bromo phenacyl bromide). Carbaldehyde group was introduced at position-3 of prepared 2-substituted imidazo / pyridine rings by Vilsmeier-Haack reaction. 3-Carbaldehyde derivatives underwent Claisen condensation with different aryl ketons to give unsaturated ketones of these derivatives, which on cyclization with urea and thiourea afforded 3-cyclic oxopyrimidines and thiopyrimidines derivatives of imidazo / pyridine rings. In addition, 3-carbaldehyde derivatives was reacted with hydrazine, semicarbazide and hydroxyl amine hydrochloride to yield new hydrazone, semicarbazone and oxime derivatives of imidazo / pyridine rings. All prepared compounds were characterised via FT-IR spectroscopy, some of them were characterised by ^{1}H-NMR spectroscopy. These new 3-subistituted derivatives of imidazo /pyridine rings were tested in different species bacterial and fungi. Some of tested compounds showed strong activity while the other showed moderate against. Interestingly, All these new prepared compounds showed high activity against fungi. [DOI: 10.22401/ANJS.00.1.04]

Keywords: Imidazo/pyridine, oximes, Chalcone, Anti-microbail activity.

1. Introduction

One of the most important imidazole compounds are aza-indolizidine, which are contains a phenyl ring fused to a imidazole ring, which also known as imidazo (1,2-a) pyridine, [1].

Imidazo [1,2-a] pyridine are bridge-head nitrogen heterocycles, and compounds containing this heterocycles have been reported for various biological activities [2,3] and received considerable interest from the pharmaceutical industry like antifungal [8,12] and anti-microbial agents, [3,10]. In order to prepare parent compound of 2-substitiuted imidazo (1,2-a) pyridine, a known procedure will be used by condensation of suitable 2-amino pyridine with different α-halo ketones in refluxing ethanol to give 2-substitstied imidazo (1,2-a) pyridine and introduce it in different reactions, [4].

The susceptibility of π-excessive system of these fused rings to electrophilic attack permitted the preparation of a variety of 3-substituted fused rings of pyridines. Therefore, the second step will be introduced aldehyde group at position-3 by Vilsmeier-Haack reaction with using mixture of $POCl_3$ and DMF in presence of $CHCl_3$, [5]. Moreover, Hydrazone derivatives of imidazo pyridine have ported to have interesting bioactivity such as anti-bacterial [9], anti-fungal [5,9] here in this research have designed and synthesized hydrazones, semicarbazones and oximes dervatives of imidazo [1,2-a] pyridine, [5]. In addition, new chalcones derivatives of imidazo (1,2-a) were synthesized. Chalcones have been proved to be an important intermediate for the synthesis of many heterocyclic compounds in organic chemistry, [6,8]. These facts encouraged us to synthesis some new chalcone derivatives bearing imidazo [1,2-a] pyridine nucleus, which were reported to possess various biological activaties such as anti-bacterial [7], anti-microbial [8], antiviral, anti HIV, antitumor and anticancer, [4,8]. The chalcones have been discovered to be useful for the synthesis of variety of heterocyclic compounds such thiopyrimidines and

oxopyrimidines. It is worth to mention oxypyrimidine and thiopyrimidines derivatives represent one of the most important class of compounds having a wide range of biological activities such as anti HIV, antiviral and herbicidal, [11]. These active compounds have been synthesized by cyclocondesation of chlcones with urea and thiourea, [2,9]. The aim of the research is synthesis new compound of imidazo (1,2-a) pyridine and study their bioactive entities, especially with pharma-cological activities bearing heterocyclic ring system namely imidazo [1,2-a] pyridine.

2. Materials and Methods

1. Melting points recorder using electro thermal melting point apparatus.
2. All the (^{1}H and ^{13}C NMR) spectra were recorded on bruker ultra-shield 400 MHz spectrometer using DMSO-d6 as solvent as an internal standard Chemical shift values are listed in δ scale
3. The IR spectra were recorded on Schimadzu FTIR spectrophotometer by using potassium bromide discs.

3. Instrumentation

General procedure for Synthesis of 2-(4-bromo phenyl) imidazo[1,2-a] pyridine.1, [1]

A mixture of 2-amino pyridine (0.94 gm, 0.01 mol) 4-bromo phenacyl bromide (2.77 gm,0.01 mol) are dissolved in (20 ml) of ethanol. The mixture was heated under reflux in water bath for 6 hours. Then, the solution was cooled and basified with (5% NaoH) until pH 10. The resulting solid washed with water, filtered and Recrystallized with ethanol. All physicall properties are listed in table [1].

3.1 General procedure for Synthesis of 2-(4-bromo phenyl) imidazo [1,2-*a*] pyridine-3-carbaldehyde.2, [1]

To an ice cold solution of DMF (1 ml) in (5 ml $CHCl_3$), was added $POCl_3$ (2 ml) drop-wise and the temperature was maintained below 10^0 C since an exothermic reaction takes place. To the reaction mixture, an ice-cold solution of 2-**(**4-bromo phenyl bromide) imidazo [1,2-a] pyridine (1 gm, 0.0036 mol) in chloroform was added slowly. After completion of addition, the reaction mixture was refluxed in water bath for about 2 hrs. The reaction mixture was cooled and washed with ice water and filtered. The product solid obtained was purified by recrystallization from mixture of acetone and ethanol.

3.2 General procedure for Synthesis of 2-(4-bromo phenyl) imidazo [1,2-*a*] pyridine-3-hydrazone.3, [5]

2-(4-bromo phenyl) imidazo [1, 2-*a*] pyridine-3-carbaldehyde (1gm, 0.0033 mol) was added to a refluxing solution of (95%) NH_2 NH_2 (1 ml) In (15 ml) of EtOH. The mixture was refluxed in water bath for 3 hrs., and then cooled until the solid separated, this solid washed with water, filtered and purified by recrystallization from ethanol.

3.3 General procedure for Synthesis of 2- 2-(4-bromo phenyl) imidazo [1, 2-*a*] pyridine -3-semi carbazone.4, [5]

Semicarbazide hydrochloride (0.04 gm, 0.0004 mol) and sodium acetate (0.02 gm, 000.3 mol) were added to a solution of 2-(4-bromo phenyl) imidazo [1, 2-*a*] pyridine -3-carbaldehyde (1 gm, 0.0033 mol) in boiling 50% aqueous solution of EtOH (10 ml). The mixture was refluxed in water bath for 4 hrs., and then cooled to separate yellow a solid which filtered off and washed with EtOH.

3.4 General procedure for Synthesis of 2-(4-bromo phenyl) imidazo [1,2-*a*] pyridine-3–aldoxime.5, [5]

$NH_2OH.HCl$ (0.5 gm, 0.0007mol) in H_2O (5 ml) was added to a solution of 2-[bromo phenyl] imidazo [1, 2-a] pyridine-3-carbaldehyde (1 gm, 0.0033 mol) in EtOH (15 ml). The reaction mixture was refluxed on water bath for 3 hrs., and then was cooled to separate a solid and filtered off and washed with EtOH.

3.5 General procedure for synthesis of (2*E*)-3-[2-(4-bromo phenyl) imidazo[1,2-*a*] pyridine-3-yl]-1-(4-chloro phenyl)-prop-2-en-1-one.6a,6b,6c, [8]

To a solution of *p*-chloro acetophenone (0.5 gm, 0.003 mol) in ethanol (15 ml) and (1 ml) of 40% NaOH was added till the solution become basic and stirred for 20-25 min., and then 2-(4-bromo phenyl) imidazo

[1,2-*a*] pyridine-3-carbaldehyde (0.85 gm 0.003 mol) was added.

The reaction mixture was stirred for 24 hrs. The content poured on crushed ice and neutralized with concerted acetic acid. The solid was separated, filtered and crystallized from mixture of ethanol and chloroform.

3.6 General procedure for Synthesis of 6-[2-(4-bromo phenyl) imidazo [1,2-*a*] pyridine-3-yl]-4-chloropyrimidin-2(1*H*)-thione.7a,7b,7c, [11]

A mixture of 2-(4-bromo phenyl) imidazo [1,2-a] pyridine-3-yl]-1-(4-chloro phenyl) prop-2-en-1-one (1. 31 gm, 0.003 mol) and thiourea (0.25 gm, 0.003 mol) in ethanol (10 ml) was refluxed on water bath in presence of (40%) alcoholic KOH for 8 hr. The reaction mixture cooled and neutralized with 20 % HCl, and the separated solid was filtered off.

3.7 General procedure for Synthesis of 6-[2-(4-bromo phenyl) imidazo [1,2-*a*] pyridine -3-yl]-4-chloro pyridine-2(1*H*)-one.8a,8b,8c, [11]

A mixture of 2-(4-bromo phenyl) imidazo [1,2-*a*] pyridine-3-yl]-1-(4-chloro phenyl) prop-2-en-1-one (1.31 gm, 0.003 mol) and urea (0.26 gm, 0.003 mol) in ethanol (10 ml) was refluxed on water bath in presence of (40%) alcoholic KOH for 8 hr. The reaction mixture cooled and neutralized with 20 % HCl, the separated solid was filtered off, leaves the solution resulting from the filtration process for 24hrs note that crystals are from the precipitate

Anti-bacterial activity, [4]

The inhibition of growth of microorganisms against Staphylococcus aureus (Gram+ve) and Pseudomonas aeruginosa (Gram–ve) was measured as the Zone of inhibition produced by test and as well as standard drugs using Cup-Plate method. The zone of inhibition of test solution are recorded in Table (4).

Antifungal activity, [4]

Aspergillus flavus was employed for testing antifungal activity using cup-plate agar diffusion method. The culture was maintained on Potato dextrose agar extract medium was inoculated with 72 hr. old 0.5 ml suspension of fungal spores in a separate flask. The zone of inhibition of test solution are recorded in Table (4).

4. Results and Discussion

The route for the synthesis of compounds is shown under (Scheme 1). The starting materials 2-amino pyridine were reacted with (4-bromo phenacyl bromide) in Ethanol to give 2-(4-bromo phenyl) imidazo [1,2-a] pyridine derivatives (1). The FT-IR spectra of these derivatives indicated that the peak of amino group was disappeared and appeared new absorption peak at (1600-1620 cm^{-1}) owing to (CH=N) cyclic imidazole.

The second step was Vilsmeier-Haack reaction of compound (1) (Sheme 2) to give different 2-aryl imidazo (1,2-a) pyridine-3-carbaldehydes (2) in good yields. The structures of imidazo pyridine carbaldehydes were confirmed by FTIR spectral data. The compounds showed absorption peak (1633 cm^{-1}) due to carbonyl absorption of aldehyde group CHO.

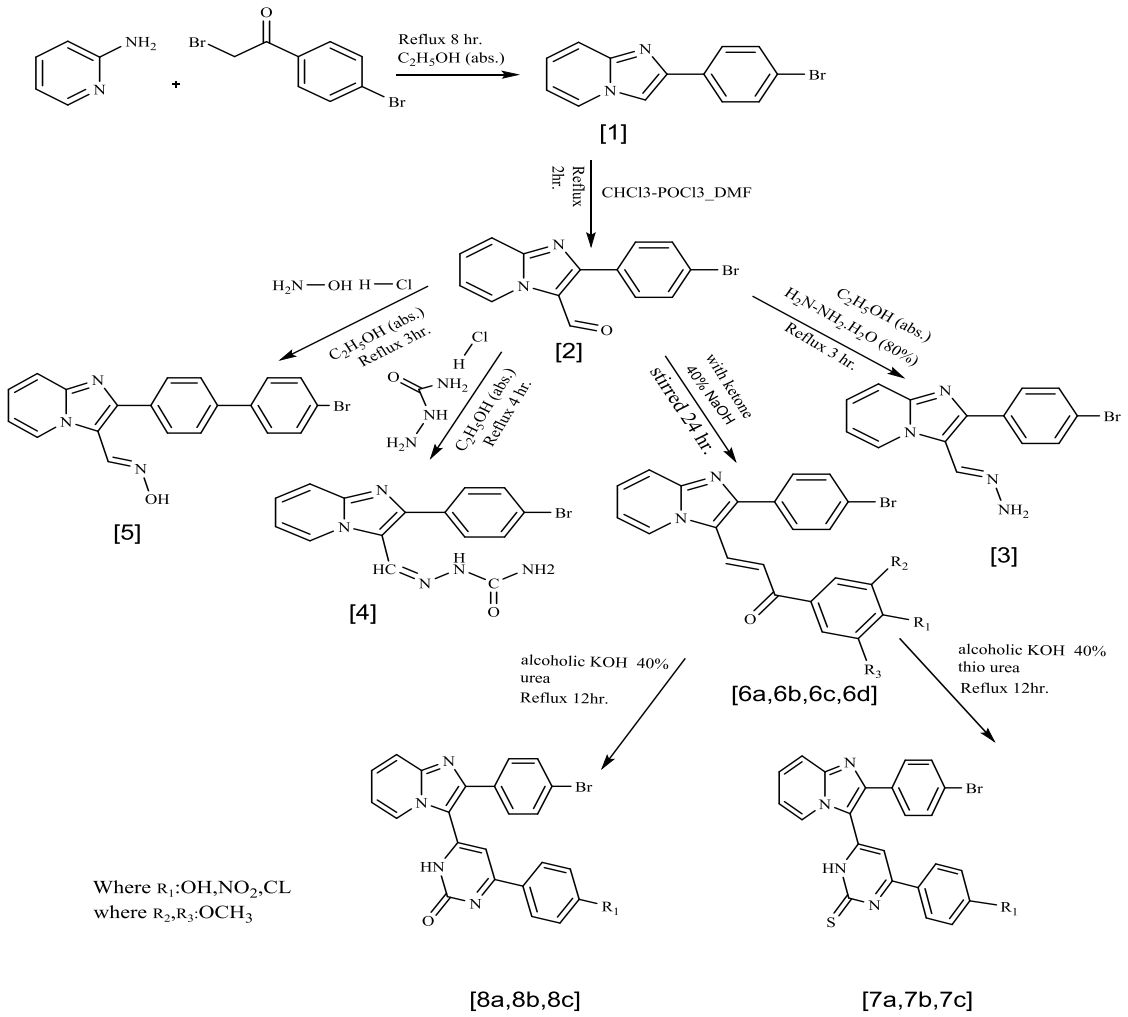
Carbaldehydes derivatives (2) was introduced in multi reactions such as condensation reactions using hydrazine hydrate, semicarbazide and hydroxyl amine hydrochloride reagents to afford hydrazine (3), semicarbazone (4) and aldoxime (5) derivatives respectively. The FT-IR spectra of (3) compound showed absorption peaks around (1632 cm^{-1}) due to stretching of Schiff base CH=N and peak at (3321 cm^{-1}) belong amine group NH_2.While the FT-IR spectra of compound (4), showed absorption peaks around (1677 cm^{-1}) owing to carbonyl of semicarbazone and peak of amino group NH_2 at (3361 cm^{-1}).On the other hand oxime (5) derivatives showed absorption peaks around (3419 cm^{-1}) due to hydroxyl group (OH) in FT-IR spectra.

Clasien-Schmidt condensation was also used in this synthetic pathway to give new chalcones derivatives (6) by reaction of 2-aryl imidazo [1,2-a] pyridine3-carbaldehydes (2) with substituted different acetophenones. The FT-IR spectra of chalcones showed strong absorption peaks at (1666 cm^{-1}) due to stretching of carbonyl group, and another characteristic peaks at (1540-1590 cm^{-1})

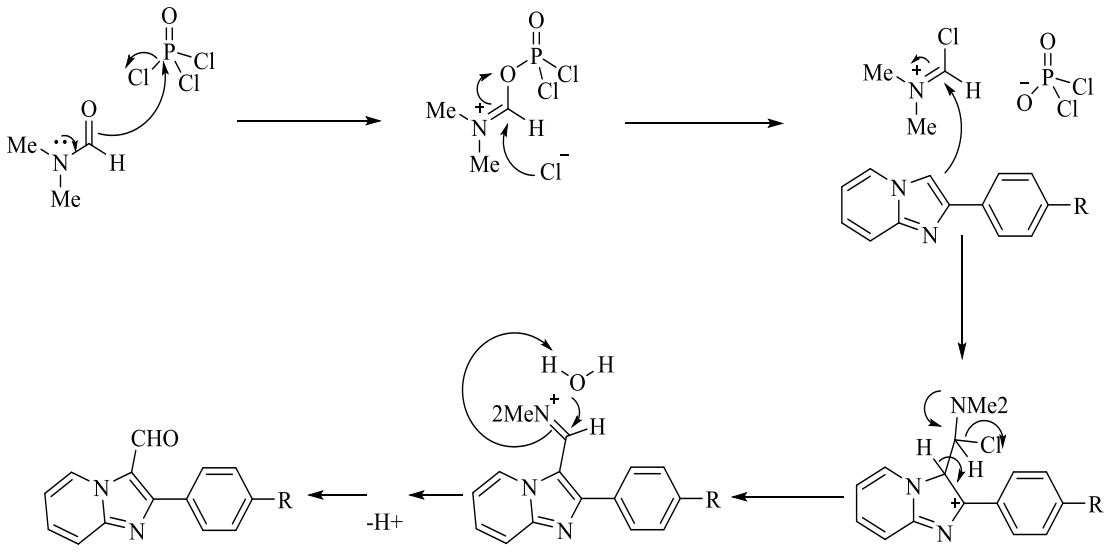
belong to alkene C=C of α, β-unsaturated ketone. The coupling constant value (J) for these olifinic protons was found to be 15.2 Hz. Similarly, for all other chalcones (6) (a-b-c-d) the 'J' values are in the range of 14.4-16 Hz, indicating that they are stereoselective and attained trans (*E*) configuration. These chalcones underwent cyclization reaction with urea, thiourea (sheme 3) afforded a different heterocycles derivatives like oxopyrimidine and thiopyrimidine. For example, the structure of compound (7) 6-[2-(4-bromo phenyl) imidazo [1,2-*a*] pyridine-3-yl]-4-nitro pyrimidin-2(1*H*)-thione (thio pyrimidines) was confirmed by FTIR, ^{1}H-NMR, ^{13}CNMR spectra, where is the absorption peak of keone C=O at (1652 cm^{-1}) was disappeared and other peak appeared at (3336 cm^{-1}) belong to (N–H) group of cyclic thiopyrimidine and other peak at (1585 cm^{-1}) for (C=S). While the ^{1}H-NMR spectra of this compound showed characteristic signal at 9.92 ppm (s, 1H, NH), and ^{13}CNMR spectra showed signal at 206 ppm belong to resonance of (C=S) group. In same manner, the formation of other compounds was confirmed. Compounds (2), (5a), (6R1b), (6R1d), (7R1b) and (8R1c) have been screened for their biological assay like antimicrobial activity in vitro towards *Staphylococcus aureus* Gram positive and *Pseudomonas aeruginosa* Gram negative bacterial strain and antifungal activity towards *Aspergillus flavus* at a concentration of 40 µg/ml. Most of these compounds showed strong activity and others moderate activity.

5. Conclusions

A series of new derivatives of 2-biphenyl-3-substitiuted imidazo (1,2-a) pyridines were synthesised starting from 2-amino pyridine. Bridgehead nitrogen compounds were synthesised from condensation reaction between 2-amino pyridine and 4-phenyl phenyl bromide to afford 2-biphenyl imidazo (1,2-a) pyrine. Latter compound underwent Vilsmeier-Haack reaction gave 3-carbaldehyde derivative. 3-Carbaldehyde derivatives underwent Claisen condensation with different aryl ketons to give unsaturated ketones of these derivatives, which on cyclization with urea and thiourea afforded 3-cyclic oxopyrimidines and thiopyrimidines derivatives of imidazo / pyridine rings. In addition, 3-carbaldehyde derivatives was reacted with hydrazine, semicarbazide and hydroxyl amine hydrochloride to yield new hydrazone, semicarbazone and oxime derivatives of imidazo / pyridine rings. All prepared compounds were characterised via FT-IR spectroscopy, some of them were characterised by ^{1}H-NMR spectroscopy. These new 3-subistituted derivatives of imidazo / pyridine rings were tested in different species bacterial and fungi. Some of tested compounds showed strong activity while the other showed moderate against. Interestingly, all these new prepared compounds showed high activity against fungi.

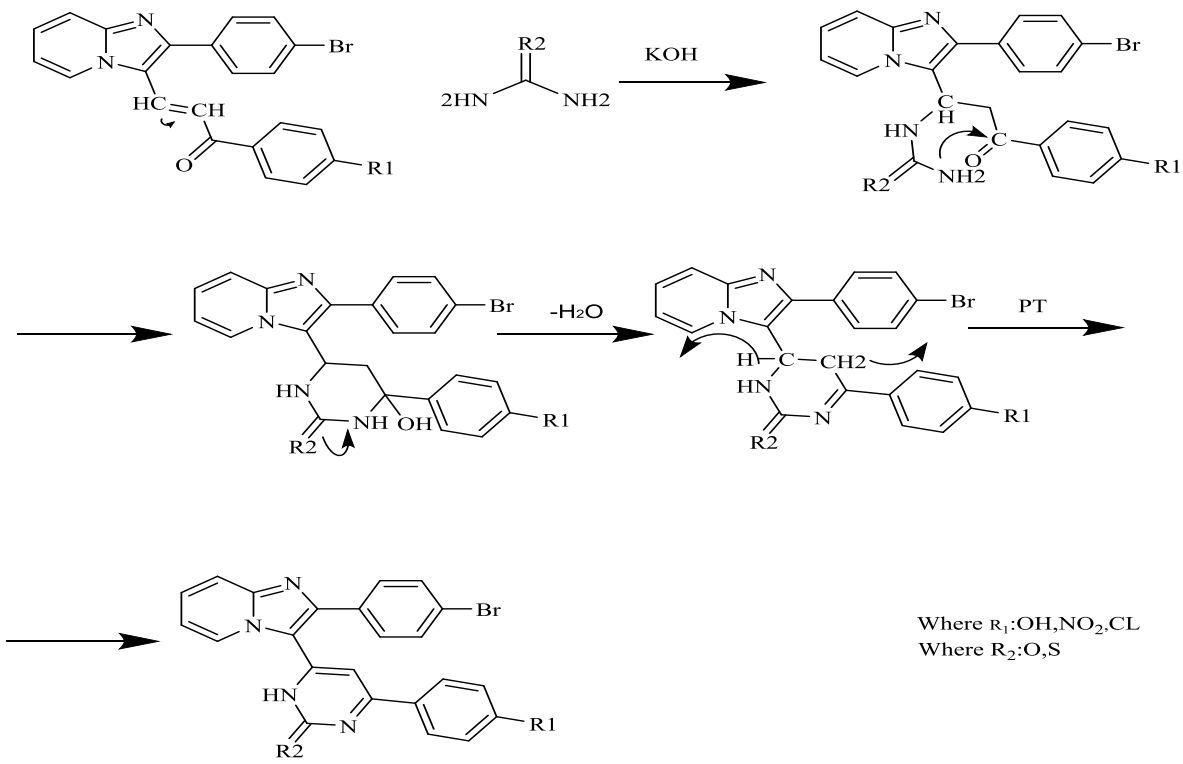


Scheme (1) Synthesis Route of Compounds, [1-8].



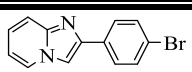
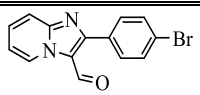
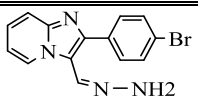
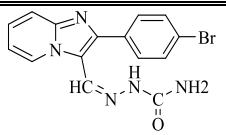
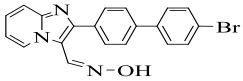
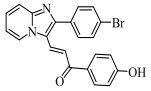
Scheme (2) Mechanism of Vilsmeier Reaction of Substituted of Imidazo [1,2-A] Pyridine.

The reaction mechanism for the formation of pyrimidine derivatives described as under.



Scheme (3) Reaction Mechanism.

Table (1)
Physical Properties of Compounds [1-2-3-4-5-6-7-8].

Com. No.	Structure	M.F.	M.P. (°C)	Color	Yield (%)
1	 2-(4-bromophenyl)imidazo[1,2-a]pyridine	$C_{13}H_9BrN_2$	216	yellow	93
2	 2-(4-bromophenyl)imidazo[1,2-a]pyridine-3-carbaldehyde	$C_{14}H_{10}BrN_2O$	193	brown	91
3	 2-(4-bromophenyl)imidazo[1,2-a]pyridine-3-hydrazone	$C_{14}H_{11}BrN_4$	220	yellow	96
4	 2-(4-bromo phenyl) imidazo [1, 2-a] pyridine -3-semi carbazone	$C_{14}H_{12}BrN_5$	206	yellow	94
5	 2-(4-bromo phenyl) imidazo [1, 2-a] pyridine -3-aldoxime	$C_{14}H_{10}BrN_3O$	218	brown	81
6a	 (E)-3-(2-(4-bromophenyl)imidazo[1,2-a]pyridin-3-yl)-1-(4-hydroxyphenyl)prop-2-en-1-one	$C_{22}H_{15}BrN_2O_2$	185	white	61

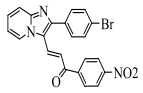
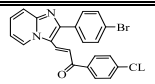
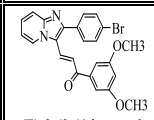
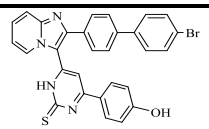
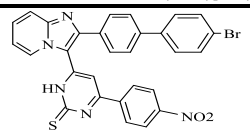
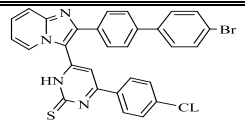
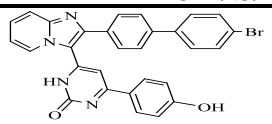
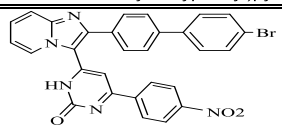
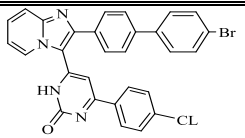
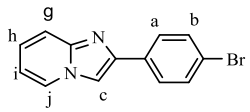
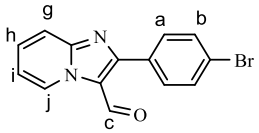
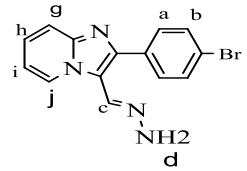
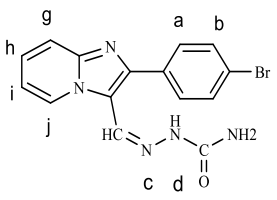
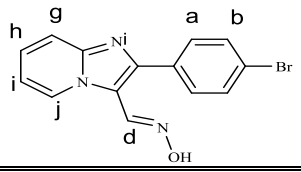
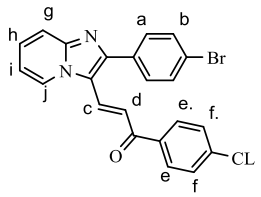
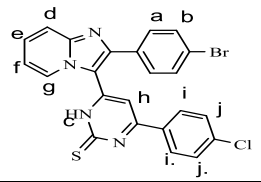
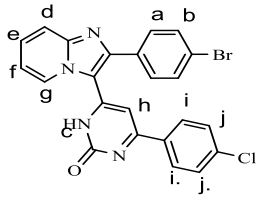
6b	 (E)-3-(2-(4-bromophenyl)imidazo[1,2-a]pyridin-3-yl)-1-(4-nitrophenyl)prop-2-en-1-one	$C_{22}H_{14}BrN_3O_3$	166	orange	89
6c	 (E)-3-(2-(4-bromophenyl)imidazo[1,2-a]pyridin-3-yl)-1-(4-chlorophenyl)prop-2-en-1-one	$C_{22}H_{14}BrN_2OCL$	208	brown	67
6d	 (E)-3-(2-(4-bromophenyl)imidazo[1,2-a]pyridin-3-yl)-1-(3,5-dimethoxyphenyl)prop-2-en-1-one	$C_{24}H_{19}BrN_2O_3$	193	yellow	81
7a	 6-(2-(4'-bromo-[1,1'-biphenyl]-4-yl)imidazo[1,2-*a*]pyridin-3-yl)-4-(4-hydroxyphenyl)pyrimidine-2(1*H*)-thione	$C_{23}H_{15}BrN_4Os$	–	white	53
7b	 6-(2-(4'-bromo-[1,1'-biphenyl]-4-yl)imidazo[1,2-a]pyridin-3-yl)-4-(4-nitrophenyl)pyrimidine-2(1H)-thione	$C_{23}H_{14}BrN_5O_2s$	211	orange	61
7c	 6-(2-(4'-bromo-[1,1'-biphenyl]-4-yl)imidazo[1,2-a]pyridin-3-yl)-4-(4-chlorophenyl)pyrimidine-2(1H)-thione	$C_{23}H_{14}BrN_4CL$	164	white	56
8a	 6-(2-(4'-bromo-[1,1'-biphenyl]-4-yl)imidazo[1,2-*a*]pyridin-3-yl)-4-(4-hydroxyphenyl)pyrimidine-2(1*H*)-thione	$C_{23}H_{15}BrN_4O_2$	221	white	53
8b	 6-(2-(4'-bromo-[1,1'-biphenyl]-4-yl)imidazo[1,2-*a*]pyridin-3-yl)-4-(4-nitrophenyl)pyrimidin-2(1*H*)-one	$C_{23}H_{14}BrN_5O_3$	232	orange	61
8c	 6-(2-(4'-bromo-[1,1'-biphenyl]-4-yl)imidazo[1,2-a]pyridin-3-yl)-4-(4-chlorophenyl)pyrimidine-2(1H)-one	$C_{23}H_{14}BrN_4OCL$	205	white	56

Table (2)
Ft-Ir Data of Prepared Compounds 1,2, 3, 4, 5, 6, 7, 8 cm^{-1}.

Comp. No.	ν C-H aromatic	ν C-H aliph	ν C=N imidazo [1,2-a] pyridine	νC=C arom	Other bands
1	3067	2927	1595	1542	CH=N pyridine 1633 C-Br 742
2	3010	2927	1596	1519	C=O aldo 1633
3	3004	2920	1596	1523	N-H sym 3321 N-H a sym 3172 CH=N shiffbase 1652
4	2921	2854	1596	1458	C=O amide 1699 NH2 3361 CH=N shiffbase 1633
5	3058	2939	1637	1552	O-H oxime 3419 CH=N shiffbase 1731
6a	3001	2877	1598	1554	C=O ketone 1631 C=C ketone 1554 OH 3460
6b	3031	2968	1587	1521	C=O ketone 1664 C=C ketone 1544 C-NO2 796
6c	3031	2925	1589	1527	C=O ketone 1666 C=C ketone 1566 C-CL 754
6d	3304	2952	1595	1521	C=O ketone 1649 C=C ketone 1573 C-OCH3 752
7a	3094	2921	1650	1485	N-H sym 3336 C=S 1585 OH 3415
7b	3041	2923	1638	1572	N-H sym 3203 C=S 1572
7c	3060	2921	1650	1491	N-H sym 3353 C=S 1566
8a	3071	2923	1635	1480	N-H sym 3346 C=O 1650 OH 3409
8b	3010	2921	1692	1497	N-H sym 3303 C=O 1660
8c	3049	2921	1631	1489	N-H sym 3346 C=O 1649

Table (3)
The ^{1}H-NMR chemical shifts of some prepared imidazo [1,2-a] pyridine derivatives.

Comp. No.	Structure	Chemical shifts in ppm
1		δ 6.83-6.78 (d, 2H, Ar-H -a) δ 7.22-7.18 (d, 2H, Ar-H -b) δ7.66-7.55 (m, 4H, Ar-H -g,h,i,j) δ 7.56_7.59 (d, H, -CH -c) δ 8.14-8.11 (d, H, Ar-H)
2		δ 7.19-7.15 (d, 2H, Ar-H -a) δ 7.28 (d, 2H, Ar-H -b) δ7.85-7.61 (m, 4H, Ar-H -g,h,i,j) δ 9.76_9.70(d, H, Ar-H) δ 10.1(s, 1H, -CHO- c)
3		δ 1.5 (s, abroad, NH_2- d) δ 6.97-6.95 (d, 2H, Ar-H -a) δ 7.30 (d, 2H, Ar-H- b) δ7.67-7.7.63 (m,4H, Ar-H-g,h,i,j) δ 9.0 (s, H, CH=NH c) δ 9.49-9.47 (d, 1H, Ar-H)
4		δ 10.04 (s ,1H, NH d) δ7.74-7.7.71 (m,4H, Ar-H-g,h,i,j) δ 7.38 (s, H, CH=NH c) δ 9.70-9.68 (d, 1H, Ar-H)

5		δ7.74-7.7.71 (m,4H, Ar-H-g,h,i,j) δ 7.38 (s, H, CH=NH d) δ 9.29-9.27 (d, H, Ar-H)
6		δ 6.62 (d, 2H, Ar-H -a) δ 6.75 (d, 2H, Ar-H -b) δ 6.93-6.90(d, H, -CH -c) δ7.36-7.22 (m,4H, Ar-H-g,h,i,j) δ 7.56_7.59 (d, H, -CH -d) δ 7.71-7.75 (d, 4H, Ar-H -e,e.,f,f.)
7		δ 7.41 (d, 2H, Ar-H -a) δ 7.19 (d, 2H, Ar-H -b) δ7.36 (m,4H, Ar-H-d,e,f,g) δ7.35-7.33 (d, H, Ar-H-i,i.) δ7.70-7.68 (d, H, Ar-H-j,j.) δ 8.92 (s, H, Ar-NH -c) δ 8.03 (s, H, Ar-H-h)
8		δ 7.14 (d, 2H, Ar-H -a) δ 7.38(d, 2H, Ar-H -b) δ7.46 (m,4H, Ar-H-d,e,f,g) δ7.56-7.54 (d, H, Ar-H-i,i.) δ7.80-7.77 (d, H, Ar-H-j,j.) δ 7.64 (s, H, Ar-NH -c) δ 6.22 (s, H, Ar-H-h)

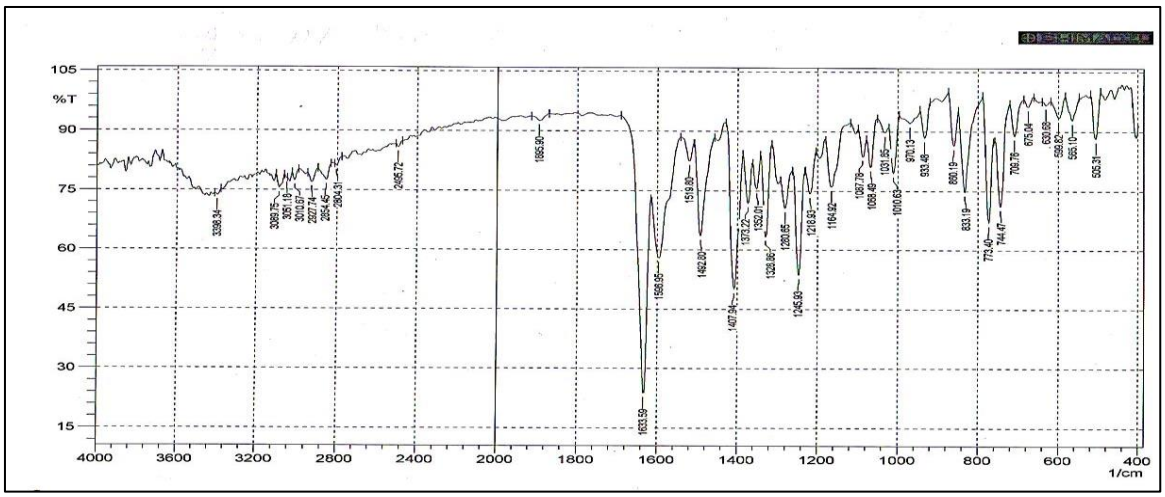


Fig.(1) FT-IR spectrum of compound [2].

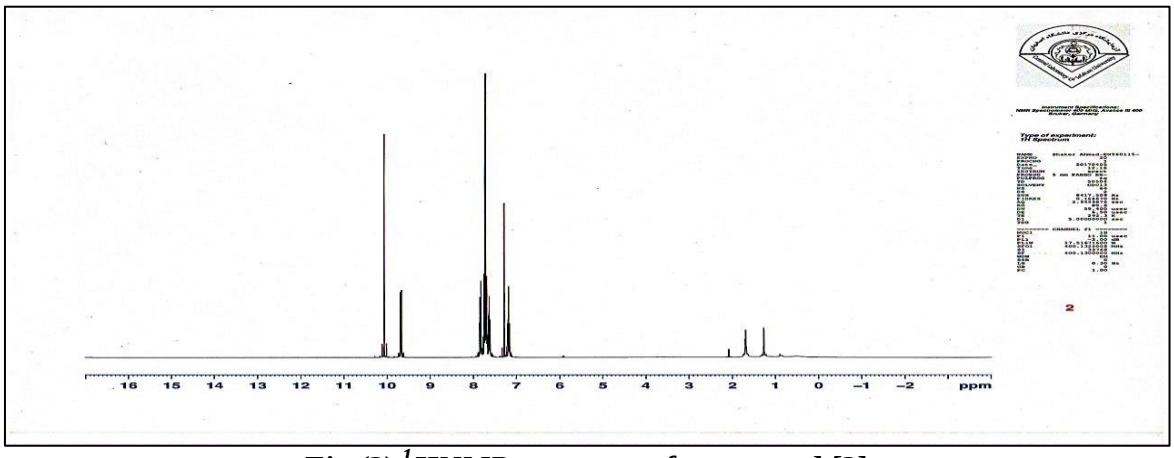


Fig.(2) ^{1}HNMR spectrum of compound [2].

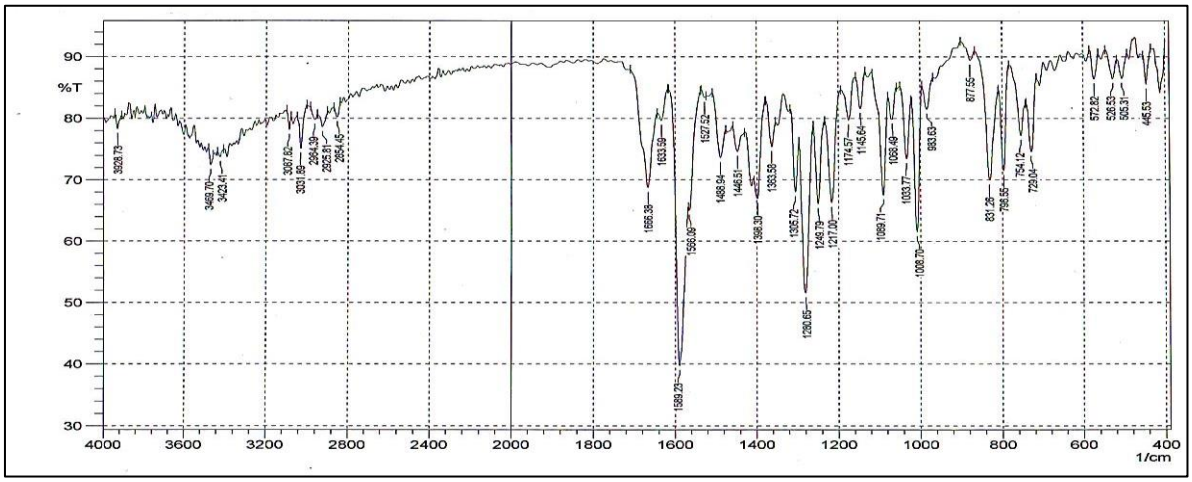


Fig.(3) FT-IR spectrum of compound [6c].

Table (4)
Anti-Bacterial and Antifungal Activity Susceptibility Test.

Com. No.	concentration	Pseudomonas auroginosa	Staphylococcus aureus	Aspergillus flavus
2a	40µg/ml	12	10	11
4a	40µg/ml	8	8	8
5a	40µg/ml	11	9	8
$6R_1$b	40µg/ml	19	10	__
$6R_1$d	40µg/ml	12	12	8
$7R_1$b	40µg/ml	10	11	8
$8R_1$c	40µg/ml	10	8	18

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