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SYNTHESIS OF SOME NEW DERIVATIVES OF 3-SUBSTITUTED-2-BIPHENYL IMIDAZO (1,2-A)PYRIDINE WITH STUDY THEIR BIOLOGICAL ACTIVITY

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ABSTRACT
New series of 3-substituted heteocyclic compounds containing bridge head nitrogen were synthesised through multi-step reactions. In order to prepare the starting 2-substituted heteocyclic compounds of pyridine, a known procedure was used by condensation of 2-amino pyridine with (4-phenyl 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 were 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.

KEYWORDS: Imidazo/pyridine, oximes, Chalcone, Anti-microbial activity.

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 [Gayatri *et al*., 2016]. Imidazo [1, 2-a] pyridine are bridge -head nitrogen heterocycles, and compounds containing this heterocycles have been reported for various biological activities [Rajender, S. and Dalip, K. 1999 and Shrikanth *et al*., 2013] and it received considerable interest from the pharmaceutical industry like antifungal and anti microbial agents. [Bollam *et al*., 2017, John, P. and Paollimain, D. 1969, Saddik *et al*., 2017, Pravin *et al*., 2013, Kansagara, N. and Shah, V. 2015, Pravin, S. and Sakharam, B. 2013, Valentina *et al*., 2013, Ladani *et al*., 2009 and Bhatt *et al*., 2016] In order to prepare parent compound of 2-substitiuted imidazo (1, 2a) pyridine, a known procedure will be used by condensation of suitable 2-amino pyridine with α-halo ketone (4-phenyl phenacyl bromide) in refluxing ethanol as described by Roe [John, P. and Paollimain, D. 1969] to give 2-(4- phenyl phenyl) imidazo (1, 2-a) pyridine and introduce it in different reactions [Bollam *et al*., 2017]. The susceptibility of π-excessive system of these fused rings to elecrophilic 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 $CHCl_3$.[John, P. and Paollimain, D. 1969] Moreover, Hydrazone derivatives of imidazo pyridine have ported to have interesting bioactivity such as anti bacterial. [Pravin, S. and Sakharam, B. 2013] anti fungal [John, P. and Paollimain, D. 1969, Saddiki *et al*., 2017; Pravin *et al*., 2013; Kansagara, N. and Shah, V. 2015; Pravin, S. and Sakharam, B. 2013] here in this research have designed and synthesized hydrazones, semicarbazones and oximes dervatives of imidazo [1,2-a] pyridine [John, P. and Paollimain, D. 1969] 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.[Saddiki, R. and *et al*., 2017, Pravin, S. and *et al*., 2013 and Kansagara, N. and Shah V., 2015] 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 [Pravin *et al*., 2013], anti microbial [Kansagara, N. and Shah, V. 2015], antiviral, anti HIV, antitumor and anticancer [Bollam *et al*., 2017, John, P. and Paollimain, D. 1969, Saddiki, R. and *et al*., 2017, Pravin, S. and *et al*., 2013 and Kansagara, N. and Shah, V. 2015]. 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 [Ladani, M. and *et al*., 2009]. These active compounds have been synthesized by cyclocondesation of chlcones with urea and thiourea [Rajender, S. and Dalip K. 1999, Shrikanth *et al*., 2013, Bollam *et al*., 2017, John, P. and Paollimain, D. 1969,

Saddiki *et al*., 2017, Pravin *et al*., 2013; Kansagara, N. and Shah, V. 2015 and Pravin, S. and Sakharam, B. 2013]. The aim of the research is synthesis new compound of imidazo (1, 2-a) pyridine and study their bioactive entities, especially with pharmacological activities bearing heterocyclic ring system namely imidazo [1, 2- a] pyridine.

EXPERIMENTAL

A. Experimental Instruments

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

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

A mixture of 2-amino pyridine (0.94 gm, 0.01 mol) 4-phenyl phenacyl bromide (2.74 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. orange Solid, Yield 89%, m.p. 208, Elemental Analysis Calcd for $C_{19}H_{14}N_2$: IR (KBr/Cm-1):: 3035, 3002, 1633, 1597, 1564, 742cm-1; 1H- RMN, 300 MHz(DMSO-d6) δppm: δ 6.83-6.78 (d, 2H, Ar-H),δ 7.22-7.18 (d, 2H, Ar-H) ,δ7.66-7.55 (m, 4H, Ar-H) ,δ 7.56_7.59 (d, H, -CH),δ 8.14-8.11 (d, H, Ar-H).

C. General procedure for Synthesis of 2-(4-biphenyl) 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 C since an exothermic reaction takes place. To the reaction mixture, an ice-cold solution of 2-**(**4- phenyl phenyl bromide) imidazo [1,2-a] pyridine (1gm, 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 aceton and ethanol. Offbrown Solid, Yield 83%, m.p. 190 ,Elemental Analysis Calcd for $C_{20}H_{16}N_2O$: IR (KBr/Cm-1):: 3059, 2956, 2850, 1653, 1614, 1560, 1551, 759 cm-1; 1H-RMN, 300 MHz(DMSO-d6) δppm:δ 7.19-7.15 (d, 2H, Ar-H) δ 7.28 (d, 2H, Ar-H),δ7.85-7.61 (m, 4H, Ar-H),δ 7.56_7.59 (s, 1H, -CHO) ,δ 9.69-9.67 (d, H, Ar-H).

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

2-(4-biphenyl) imidazo [1, 2-*a*] pyridine -3-carbaldehyde (1gm, 0.0033 mol) was added to a refluxing solution of (95%) NH_2 NH_2 (1ml) In (15ml) 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. Offyellow Solid, Yield 90%, m.p. 175, Elemental Analysis Calcd for $C_{20}H_{16}N_4$: IR (KBr/Cm-1): 3321, 3188, 3029, 2921, 1631, 1608, 1585, 1537 , 754cm-1; 1H-RMN, 300 MHz(DMSO-d6) δppm: δ 1.5 (s, abroad, NH_2) δ 6.97-6.95 (d, 2H, Ar-H),δ7.30(d,2H,Ar-H),δ7.67-7.7.63 (m,4H, Ar-H) , δ 9.0 (s,H,CH=N<u>H</u>), δ 9.49-9.47(d, 1H, Ar-H)

E. General procedure for Synthesis of 2-(4- biphenyl) imidazo [1, 2-*a*] pyridine -3-semicarbazone 4.[5]

Semicarbazide hydrochloride (0.04 gm, 0.0004 mol) and NaAOC (0.02 gm, 000.3mol) were added to a solution of 2-(4- biphenyl) imidazo [1, 2-*a*] pyridine -3-carbaldehyde (1 gm, 0.0033 mol) in boiling 50% aqueous solution of EtOH (10ml). 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. Offyellow Solid, Yield 87%, m.p. 215, Elemental Analysis Calcd $C_{20}H_{17}N_5$: IR (KBr/Cm-1): 3343, 3261, 3074, 3047, 1677, 1635, 1581 , 1541, 754 cm-1; 1H-RMN, 300 MHz(DMSO-d6) δppm: δ 10.04 (s ,1H, NH), δ7.74-7.7.71 (m,4H, Ar-H), δ 7.38 (s, H, CH=N<u>H</u>) , δ 9.70-9.68 (d, 1H, Ar-H).

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

$NH_2OH.HCl$ (0.5 gm,0.0007mol) in H_2O (5ml) was added to a solution of 2-[biphenyl] imidazo [1, 2-a] pyridine -3-carbaldehyde (1 gm,0.0033mol) 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.White Solid, Yield 77%, m.p. 230,Elemental Analysis Calcd $C_{20}H_{15}N_3O$: IR (KBr/Cm-1):: 3431, 3082, 2923, 1625, 1496, 1456,761, cm-1; 1H-RMN, 300 MHz(DMSO-d6) δppm: δ7.74-7.7.71 (m,4H, Ar-H) ,δ 7.38 (s, H, CH=N<u>H</u>) ,δ 9.29-9.27 (d,H, Ar-H).

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

To a solution of *p*-chloro acetophenone (0.5 gm, 0.003 mol) in ethanol (15ml) and (1ml) of 40% NaOH was added till the solution become basic and stirred for 20-25 min., and then 2-(4- biphenyl) imidazo [1,2-*a*] pyridine-3-carbaldehyde (0.85gm 0.003 mol) was added. The reaction mixture was stirred for 24 hrs. The content poured on crushed ice and neutralized with concerated acetic acid. The solid was separated, filtered and crystallized from mixture of ethanol and chloroform. Brown Solid, Yield 64%, m.p. 198, Elemental Analysis Calcd $C_{22}H_{14}BrN_2OCL$: IR (KBr/Cm-1): : 3082, 3033, 1681, 1633, 1587, 1525, 740, cm-1; 1H-RMN, 300 MHz(DMSO-d6) δppm: δ 6.62 (d, 2H, Ar-H), δ 6.75 (d, 2H, Ar-H) ,δ 6.93-6.90(d, H, -CH) ,δ7.36-7.22 (m,4H, Ar-H), δ 7.56_7.59 (d, H, -CH) , δ 7.71-7.75 (d, 4H, Ar-H)

H. (2*E*)-3-[2-(4-biphenyl) imidazo [1,2-*a*] pyridine-3-yl]-1-(4-hydroxy phenyl)-prop-2-en-1-one.6a: White Solid, Yield 59%, m.p. 178, Elemental Analysis Calcd $C_{22}H_{15}BrN_2O_2$: IR (KBr/ Cm-1):: 3431, 3078, 2956, 1631, 1596, 1558, 1522, 773 cm-1

I.(2*E*)-3-[2-(4-biphenyl)imidazo[1,2-*a*]pyridine-3-yl]-1-(4-nitro phenyl)-prop-2-en-1-one.6b: Orange Solid, Yield 76%, m.p. 184, Elemental Analysis Calcd $C_{22}H_{14}BrN_3O_3$: IR (KBr/Cm-1):: 3082, 3055, 1674, 1631, 1595, 1517, 846, 744 cm-1

J. 2*E*)-3-[2-(4-biphenyl)imidazo [1,2-*a*] pyridine-3-yl] -1-(3,5-di methoxy phenyl)-prop-2-en-1-one.6d: Yellow Solid, Yield 71%, m.p. 202,Elemental Analysis Calcd. $C_{24}H_{19}BrN_2O_3$: IR (KBr/Cm-1):: 3064, 2929, 1652, 1577, 1541, 1520, 767, 750 cm-1

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

A mixture of 2-(4- phenyl 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 (0.25 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. White Solid, Yield 56%, m.p. 164,Elemental Analysis Calcd $C_{23}H_{14}BrN_4CLS$: IR (KBr/Cm-1):: 3353, 3060, 2921, 1650, 1566, 1491 cm-1; 1H-RMN, 300 MHz(DMSO-d6) δppm:δ 7.41 (d, 2H, Ar-H),δ 7.19 (d, 2H, Ar-H), δ7.36(m,4H,Ar-H),δ7.35-7.33(d,H,Ar-H),δ7.70-7.68 (d, H, Ar-H), δ 8.92 (s, H, Ar-NH) ,δ 8.03 (s, H, Ar-H)

L. 6-[2-(4-biphenyl) imidazo [1,2-*a*]pyridine-3-yl] -4-hydroxy pyrimidin-2(1*H*)-thione.7a

White Solid, Yield 53%, m.p. 151, Elemental Analysis Calcd $C_{23}H_{15}BrN_4Os$: IR (KBr/Cm-1) IR (KBr/Cm-1): :3417, 3272, 3043, 2926, 1616, 1542, 1467cm-1

M.6-[2-(4-biphenyl)imidazo [1,2-*a*] pyridine-3-yl]-4-nitro pyrimidin -2(1*H*)-thione.7b. Orange Solid, Yield 61%, m.p. 211,Elemental Analysis Calcd. $C_{23}H_{14}BrN_5O_2s$: IR (KBr/Cm-1) IR(KBr/ Cm-1)::3386, 3070, 2923, 2926, 1631, 1558, 1494cm-1

N.General procedure for Synthesis of 6-[2-(4-biphenyl) imidazo[1,2-*a*]pyrimidin-3-yl]-4-chloropyridine-2(1*H*)-one. 8c. [11]

A mixture of 2-(4-biphenyl 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 (0.26 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. White Solid, Yield 56%, m.p. 205, Elemental Analysis Calcd $C_{23}H_{14}BrN_4OCL$: IR (KBr/Cm-1):: 3375, 3076, 2920, 1629, 1629, 1492 cm-1; 1H RMN, 300 MHz (DMSO-d_6) δppm: δ 7.14 (d, 2H, Ar-H) δ7.38 (d,2H,Ar-H), δ7.46 (m,4H,Ar-H), δ7.56-7.54 (d,H,Ar-H) ,δ7.80-7.77(d, H, Ar-H), δ7.64 (s,H,Ar-NH) ,δ6.22 (s,H,Ar-H).

O.6-[2-(4-biphenylphenyl)imidazo[1,2-*a*]pyridine-3-yl]-4-hydroxypyrimidin-2(1*H*)-one.8a

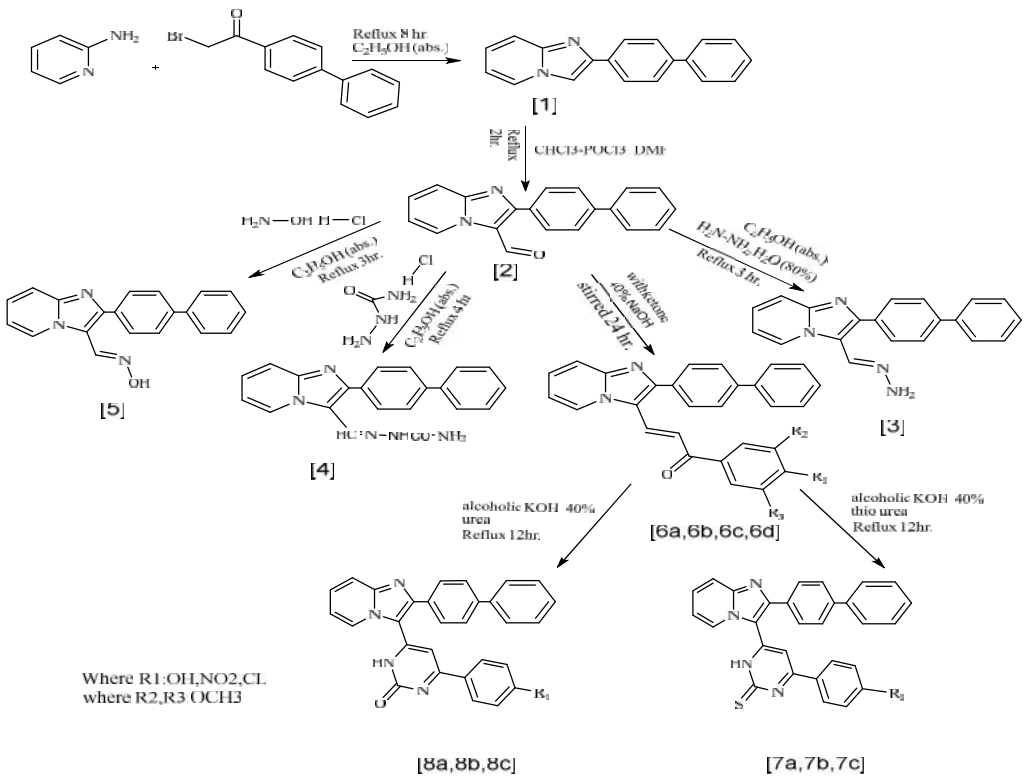
White Solid, Yield 53%, m.p. 221,Elemental Analysis Calcd $C_{23}H_{15}BrN_4O_2$: IR (KBr/Cm-1):: 3406, 3339, 3082, 1629, 1654, 1487cm-1

P.6-[2-(4-bi-phenyl) imidazo [1,2-*a*]pyridine-3-yl]-4-nitropyridimin-2(1*H*)-one.8b

Orange Solid, Yield 61%, m.p. 232,Elemental Analysis Calcd $C_{23}H_{14}BrN_5O_3$: IR (KBr/Cm-1):: 3371, 3083, 2923, 1652,1614, 1487cm-1.

RESULTS & DISCUSSION

A. *The route* for the synthesis of compounds is shown under Scheme 1. The starting materials 2_amino pyridine were reacted with (4- phenyl phenacyl bromide) in Ethanol to give 2-(4- phenyl 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 (C=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 (1633cm-1) due to carbonyl absorption of aldehyde group CHO. Carbaldehydes derivatives (2) were introduced in multi reactions such as condensation reactions using hydrazine hydrate, semicarbazide and hydroxyl amine hydrochloride reagents to afford hydrazone (**3**), semicar-bazone (4) and aldoxime (5) derivatives respectively. The FT-IR spectra of (3) compound showed absorption peaks around (1608 cm-1) due to stretching of Schiff base C=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 (3398 cm-1).On the other hand oxime (5) derivatives showed absorption peaks around (3431 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 (1681-1631 cm-1) due to stretching of carbonyl group, and another characteristic peaks at (1540-1595 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 (sheme3) afforded a different heterocycles derivatives like oxopyrimidine and thiopyrimidine. For example, the structure of compound (7) 6-[2-(4- phenyl 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 (1681 cm-1) was disappeared and other peak appeared at (3386 cm-1) belong to (N-H) group of cyclic thiopyrimidine and other peak at (1568 cm-1) for (C=S). While the 1H-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),(3),(4),(6a),(6b) and (6c) 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.



Scheme 1. Synthetic route of compounds [1-8]

B. Anti-bacterial Activity [4]:

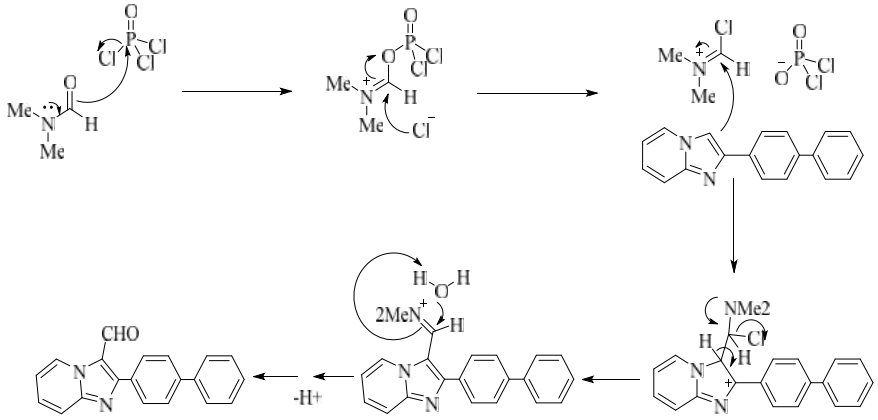
The inhibition of growth of microorganisms against *Staphylococcus aureus* (Gram +ve) and *Pseudomonas aeruginosa* (Gram –ve) was measured as the Zone of inhibition produced by test and as well as standard drugs using Cup-Plate method. The zone of inhibition of test solution is recorded in Table (1).

C. Antifungal activity [4]:

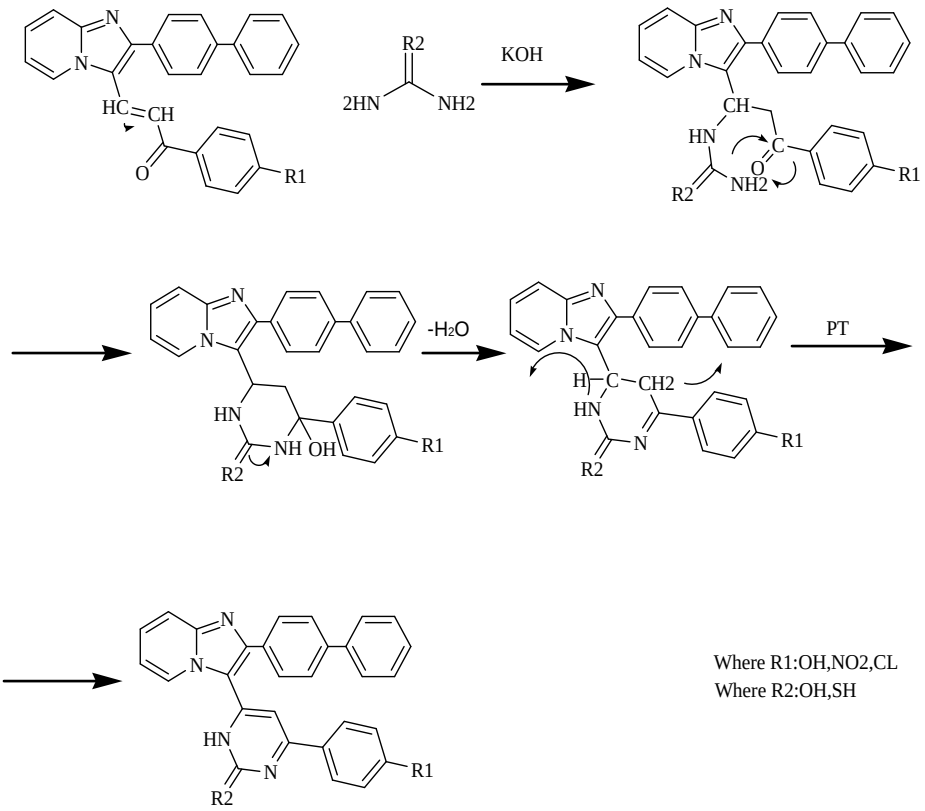
Aspergillus flavus was employed for testing antifungal activity using cup-plate agar diffusion method. The culture was maintained on Potato dextrose agar extract medium was inoculated with 72 hr. old 0.5ml suspension of fungal spores in a separate flask. The zones of inhibition of test solution are recorded in Table (1).

TABLE-1: Anti-bacterial and antigungal activity susceptibility test

com. No.	concentration	*Pseudomonas auroginosa*	*Staphylococcus aureus*	*Aspergillus flavus*
2b	40µg/ml	10	10	8
3b	40µg/ml	13	16	15
4b	40µg/ml	10	11	9
6a	40µg/ml	11	11	14
6c	40µg/ml	10	10	13



Scheme 2: Mechanism of vilsmier reaction of substituted of imidazo [1, 2-A] pyridine.



Scheme 3: Reaction mechanism of the formation of oxy and thiopyrimidine derivatives.

CONCLUSION

Designed and synthesized 15 new analogs substituted imidazo [1, 2-a] pyridine derivatives with different substitution at position 3 and characterized by physical and spectral analysis. These derivatives were evaluated for antimicrobial and antifungal activity. It can be concluded from antimicrobial and antifungal activity screening (Table-1) that compound 2, 3, 4,6a and 6c were found to be active against *Pseudomonas auroginosa, Staphylococcus aureus* and *Aspergillus***.** Further investigation with appropriate structural modification of the above compounds may result in therapeutically useful products.

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