PEG Mediated Synthesis, Characterization And Cytotoxicity Evaluation of Novel Imidazo[1,2-a] Pyridines Chalcones

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Abstract: A series of condensed Novel Imidazo [1,2-a] Pyridine Chalcones (5a-f) have been synthesized by Claisen–Schmidt condensation reaction using various acetyl heterocyclic ketones and 3-formyl-2-phenyl Imidazo [1,2-a] pyridine in PEG-400 as green solvent. Imidazo[1,2-A]-Pyridine Chalcones are associated with immense biological activities like anticancer, antitumour, antituberculosis, antianflammatory, antioxidant, analgesics. Initially we have synthesized 3-formyl-2-phenyl imidazo[1,2-a]pyridine by aerobic oxidative coupling reaction using 2-aminopyridines and cinnamaldehydes in presence of Copper bromide as catalyst, directly led to the formation of appropriate Imidazo [1,2-a] pyridine carbaldehyde. The structures of the compounds were characterized by IR, ^{1}H NMR and screened for their cytotoxicity evaluation. The cytotoxity was premeditated by the brine-shrimp lethality assay methods, utilizing brine shrimp (Arternia salina LEACH). Brine shrimp lethality is a rapid general bioassay for identifying toxic dose of a bioactive compound. Bioavailabilities of chalcones were firmly recommended by in vitro cytotoxicity study and confirmed to be nontoxic. Almost all the synthesized Chalcones specially Chalcone 5c and 5f shows highest Cytotoxicity activity.

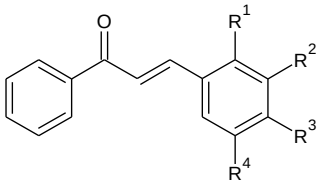
***Index Terms*: 3-formyl-2-phenyl- Imidazo [1,2-a] pyridine, Acetyl heterocyclic ketones, PEG-400, Imidazo [1,2-A] pyridines Chalcones, Brine shrimp lethality and Cytotoxicity activity.**

I. INTRODUCTION

Heterocyclic compounds containing nitrogen are known to possess a diverse range of pharmacological activities.[1-2] Imidazo [1,2-a] pyridine is one of the medicinally important fused heterocyclic moiety are forthcoming interesting objects for the synthesis of Imidazo [1,2-a] Pyridine derivatives and has long been therapeutically used to cure various diseases as an important drugs. 3-formyl imidazo[1,2-a]pyridine as one of the key intermediates in making anxiolytic drugs zolpidem and alpidem.[3] There are several reports on the synthesis of imidazo[1,2-a]pyridine. Earlier formation of Imidazo [1,2-a] pyridines is carried out in two steps. In first step reaction between 2-aminopyridine and phenacyl bromide and in second step formylation using using DMF/$POCl_3$ by Vilsmeier–Haack formylation method.[4-5] But in the present investigation we have synthesized 3-formyl imidazo[1,2-a] pyridinesin one step by aerobic oxidative coupling of 2-aminopyridines with cinnamaldehydes in presence of CuBr catalyst[6].

Chalcones containing the Imidazo [1,2-A] Pyridines moieties plays an important role as powerful pharamacophore units. Synthesized new series of Imidazo[1,2-A]-Pyridine chalcone system possess potent biological activities that could be further developed as important drug in medicinal chemistry. Imidazo [1,2-a] Pyridine compounds have broad scope to synthesize large number of new chemotherapeutic agent and these are used in remedying new compounds which useful in scientific medicines as drugs. Intensively a great idea has been developed behind the synthesis and biological activities of the condensed Imidazo [1,2-a] pyridines have been reported. This framework has been used as antifungal, antibacterial, herbicides, anti-inflammatory, antimicrobial, antitumor and anticancer[7-8].

In the structure of chalcone there are two aromatic rings are in unsaturation coupled together by a three-carbon α, β-unsaturated carbonyl system (Structure- 1). Basically chalcones are belonging from the subclass of flavonoid family introduced by Kostanecki and Tabor. They contain two aromatic rings with an unsaturated chain in which two aromatic rings are joined by a three-carbon α, β-unsaturated carbonyl systems as shown in following Structure Structurally, being double bond in chalcone results in *cis* and trans isomeric forms of which the *trans* form is thermodynamically stable.

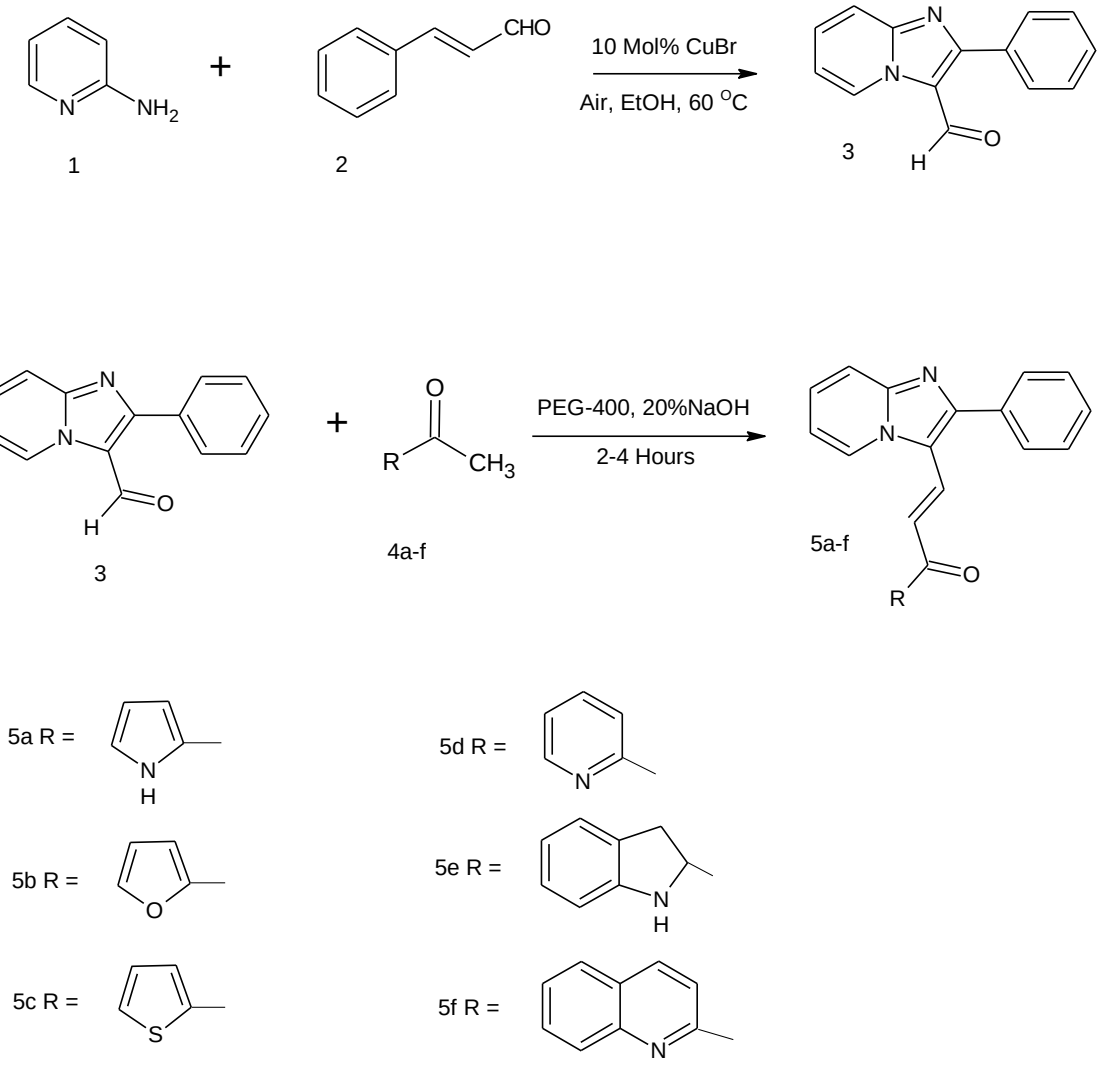


Structure- 1

Synthesis Imidazo[1,2-A]-Pyridine chalcones have been carried out using poly ethylene glycol PEG-400 which is found to be an green solvent economical, easily accessible, thermally stable, recyclable, biological comfortable, nontoxic.[9-11] Further the cytotoxity of the synthesized chalcones were determined the brine-shrimp lethality assay methods , utilizing brine shrimp (Arternia salina LEACH).[12-13]Brine shrimp lethality is a rapid general bioassay for identifying toxic dose of a bioactive compound found to be non-toxic. Bioavailabilities of chalcones were firmly recommended by in vitro cytotoxicity study and confirmed to be nontoxic.[14-15]

II. MATERIAL AND METHODS

SCHEME- 1



III. GENERAL

3.1 Instrumentation

IR spectra were recorded on FT-IR spectrometer (Perkin Elmer, Maharashtra, India) using KBr disk method. 1HNMR spectra were recorded on 1HNMR (Varian-NMR-mercury 300 MHz) spectrometer in $CDCl_3$ as solvent. All chemical shifts (d) are quoted in parts per million downfield from TMS and coupling constants (J) are given in hertz. Abbreviations used in the splitting pattern were as follows: s = singlet, d = doublet, t = triplet, q = quintet and m = multiplet. All the reagents and solvents were used of analytical grade and used as supplied unless otherwise stated. Thin layer chromatography was performed on silica gel coated plates for monitoring the reactions. The spots could be visualized easily under UV light.

3.2 General procedure for synthesis of Imidazo[1,2-a]pyridine carbaldehydes (3) :

In 250 ml round bottom flask 2-aminopyridine 1 (1.0 equiv.) and cinnamaldehyde 2 (1.2 equiv.) in ethanol was added 10 mol% CuBr and the reaction mixture was refluxed and stirred at 60 °C for 8 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered, dried on a rotavapor and extracted with water and ethyl acetate. The EtOAc layer was dried over anhydrous sodium sulphate and evaporated on a vacuo rotavapor to get the crude product. The crude product was purified by silica gel (#100–200) column chromatography using n-hexane and EtOAc as eluents to obtain pure products.[6] The yield of the crude product obtained in the range of 80–90% yield.

2-Phenyl-imidazo[1,2-a]pyridine-3-carbaldehyde (3) [6]

Yellow solid; m.p. 122–123 °C; 1H NMR (CDCl3, 400 MHz): δ 10.07 (s,1H), 9.68 (d, J = 8.0 Hz, 1H), 7.85–7.81 (m, 3H), 7.61–7.53 (m,4H), 7.14 (t, J = 8.0 Hz, 1H); 13C NMR (CDCl3, 100 MHz): δ 179.7, 158.4, 147.8, 132.3, 130.5, 129.9, 129.8, 128.9, 128.8, 120.8, 117.5, 115.4; IR (CHCl3): νmax 2924, 1646, 1634, 1494,1407, 1326, 1248 cm−1;

3.3 Synthesis of Imidazo[1,2-a]pyridine Chalcones (5a-f) :

A mixture of various heterocyclic ketones (4a-f) such as acetyl pyrrole, acetyl furan, acetyl thiophene, acetyl pyridine, acetyl indole and acetyl quinoline respectively and 2-Phenyl-imidazo [1,2-a]pyridine-3-carbaldehyde 3 (1 mmol) was dissolved in 15 ml PEG-400. To this mixture, sodium hydroxide (20%, 1ml) was added and the reaction mixture was stirred at 40-50 ^{0}C temperature for 1 hr. The reaction mixture was then poured into 100 ml ice cold water. The product was separated out, it was filtered and processed out. The obtained products were recrystallised (5a-f) from ethanol to afford pure compounds.[9-12]

3.4 The spectral data of synthesized Imidazo[1,2-a]pyridine Chalcones compounds(5a-f) :

5a - (2*E*)-3-(2-phenyl imidazo [1,2-*a*] pyridin-3-yl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one :

1H NMR (CDCl3, 300 MHz): δ 7.51 (d, 1H) aromatic C_1, δ 7.03 (d,1H) aromatic C_2, δ6.69 (d,1H) aromatic C_3, δ 8.09 (d,1H) aromatic C_4,δ 7.48(d,1H) C_{12} & C_{16} aromatic benzene ortho coupling J= 6.9 Hz, δ 7.32 (d,1H) C_{13}& C_{15} aromatic benzene ortho coupling J= 6.9Hz, δ 7.22 (d,1H) C_{13} aromatic benzene, δ 7.54 (d,1H)) C_5 unsaturated C=C-C==O J= 15.5 Hz, δ 6.98 (d,1H), δ 6.67 (d,1H) C_6 unsaturated - C=C-C==O J= 15.3 Hz , Pyrrole C_{8-} aromatic, δ 6.32 (d,1H),Pyrrole C_{9-} aromatic, δ 7.23 (d,1H), pyrrole C_{10-} aromatic, δ 5.0 (d,1H) exchangeable withD_2O.

5b - (2*E*)-1-(furan-2-yl)-3-(2-phenyl imidazo [1,2-*a*] pyridin-3-yl)prop-2-en-1-one :

1H NMR (CDCl3, 300 MHz):δ 7.51 (d, 1H) aromatic C_1, δ 7.03 (d, 1H) aromatic C_2, δ 6.69 (d,1H) aromatic C_3, δ 8.09 (d, 1H) aromatic C_4, δ 7.48 (d ,1H) C_{12}& C_{16} aromatic benzene ortho coupling J= 6.9 Hz, δ 7.32 (d, 1H) C_{13}& C_{15} aromatic benzene ortho coupling J= 6.9 Hz, δ 7.22 (d,1H) C_{13} aromatic benzene, δ 7.54 (d,1H)) C_5 unsaturated C=C-C==O J= 15.5 Hz, δ 6.98 (d,1H), δ 6.67 (d,1H) C_6 unsaturated - C=C-C==O J= 15.3 Hz , Pyrrole C_{8-} aromatic, δ 6.32 (d,1H), furan δ 7.23 (d,1H),C_8 , δ 6.61(d,1H) C_9, δ 7.72 (d,1H) C_{10}.

5c - (2*E*)-3-(2-phenyl imidazo [1,2-*a*] pyridin-3-yl)-1-(thiophen-2-yl)prop-2-en-1-one :

1H NMR (CDCl3, 300 MHz): δ 7.51 (d, 1H) aromatic C_1, δ 7.03 (d, 1H) aromatic C_2, δ 6.69 (d,1H) aromatic C_3, δ 8.09 (d, 1H) aromatic C_4, δ 7.48 (d ,1H) C_{12}& C_{16} aromatic benzene ortho coupling J= 6.9 Hz, δ 7.32 (d, 1H) C_{13} & C_{15} aromatic benzene ortho coupling J= 6.9 Hz, δ 7.22 (d,1H) C_{13} aromatic benzene, δ 7.54 (d,1H)) C_5 unsaturated C=C-C==O J= 15.5 Hz, δ 6.98 (d,1H), δ 6.67 (d,1H) C_6 unsaturated - C=C-C==O J= 15.3 Hz ,Thiophene δ 7.61 (d,1H), δ 7.06 (d,1H), δ 7.65 (d,1H).

5d - (2*E*)-3-(2-phenyl imidazo [1,2-*a*] pyridin-3-yl)-1-(pyridin-2-yl)prop-2-en-1-one :

1H NMR (CDCl3, 300 MHz):δ 7.51 (d, 1H) aromatic C_1, δ 7.03 (d, 1H) aromatic C_2, δ 6.69 (d,1H) aromatic C_3, δ 8.09 (d, 1H) aromatic C_4, δ 7.48 (d ,1H) C_{12}& C_{16} aromatic benzene ortho coupling J= 6.9 Hz, δ 7.32 (d, 1H) C_{13}& C_{15} aromatic benzene ortho coupling J= 6.9 Hz, δ 7.22 (d,1H) C_{13} aromatic benzene, δ 7.54 (d,1H)) C_5 unsaturated C=C-C==O J= 15.5 Hz, δ 6.98 (d,1H), δ 6.67 (d,1H) C_6 unsaturated - C=C-C==O J= 15.3 Hz , Pyridine - δ 8.31 (d,1H), δ 8.17 (d,1H), δ 7.88 (d,1H), δ 9.03 (d,1H).

5e - (2*E*)-1-(1*H*-indol-2-yl)-3-(2-phenyl imidazo [1,2-*a*] pyridin-3-yl)prop-2-en-1-one :

1H NMR (CDCl3, 300 MHz):δ 7.51 (d, 1H) aromatic C_1, δ 7.03 (d, 1H) aromatic C_2, δ 6.69 (d,1H) aromatic C_3, δ 8.09 (d, 1H) aromatic C_4, δ 7.48 (d ,1H) C_{12}& C_{16} aromatic benzene ortho coupling J= 6.9 Hz, δ 7.32 (d, 1H) C_{13}& C_{15} aromatic benzene ortho coupling J= 6.9 Hz, δ 7.22 (d,1H) C_{13} aromatic benzene, δ 7.54 (d,1H)) C_5 unsaturated C=C-C==O J= 15.5 Hz, δ 6.98 (d,1H), δ 6.67 (d,1H) C_6 unsaturated - C=C-C==O J= 15.3 Hz , Indole - δ 7.38 (d,1H), δ 7.55 (d,1H), δ 7.00 (d,1H), δ 7.08 (d,1H),), δ 7.40 (d,1H),), δ 10.1 (d,1H) replacable with D_2O.

5f - (2*E*)-3-(2-phenyl imidazo [1,2-*a*] pyridin-3-yl)-1-(quinolin-2-yl)prop-2-en-1-one :

1H NMR (CDCl3, 300 MHz):δ 7.51 (d, 1H) aromatic C_1, δ 7.03 (d, 1H) aromatic C_2, δ 6.69 (d,1H) aromatic C_3, δ 8.09 (d, 1H) aromatic C_4, δ 7.48 (d ,1H) C_{12}& C_{16} aromatic benzene ortho coupling J= 6.9 Hz, δ 7.32 (d, 1H) C_{13} & C_{15} aromatic benzene ortho coupling J= 6.9 Hz, δ 7.22 (d,1H) C_{13} aromatic benzene, δ 7.54 (d,1H)) C_5 unsaturated C=C-C==O J= 15.5 Hz, δ 6.98 (d,1H), δ 6.67 (d,1H) C_6 unsaturated - C=C-C==O J= 15.3 Hz , Quinoline - δ 8.19 (d,1H), δ 8.42 (d,1H), 7.68 (d,1H), δ 7.43 (d,1H),), δ 7.61 (d,1H),), δ 8.05 (d,1H) .

IV. RESULT AND DISCUSSION

In the present study, the synthesis of title compounds Imidazo [1,2-a] pyridine Chalcones (5a-f) by Claisen Schmidt condensation has been carried out successfully by using selected heterocyclic ketones like acetyl pyrrole, acetyl furan, acetyl thiophene, acetyl pyridine, acetyl indole and acetyl quinoline and 2-Phenyl-imidazo[1,2-a]pyridine-3-carbaldehyde 3 (1 mmol) was dissolved in 15 ml PEG-400 according to literature methods (Scheme 1) [9-11]. The purity of the newly synthesized compounds was recognized by TLC. The characterization of all the listed synthesized Chalcones were made by IR , NMR spectral analysis. Chalcones showed the IR absorptions characteristics of carbonyl >C=O (1685-1600 cm-1) and aromatic C=C (1580-1400 cm-^{1}) functionalities. The IR of 2-Phenyl-imidazo[1,2-a]pyridine-3-carbaldehyde (3) shows the various band at vmax 2924, 1646, 1634, 1494,1407, 1326, 1248 cm−1; due to C-N, C=N, CHO, aromatic benzene ring respectvely etcs. The ^{1}H NMR spectra of chalcones displayed multiplet due to aromatic protons at 6.92-8.00 δ (m, Ar-H).and unsaturation at 7.54- 6.67 δ due to unsaturated C=C-C==O, having an Coupling constant J= 15.5 Hz. Particulars of the methods and conditions are described in experimental section.

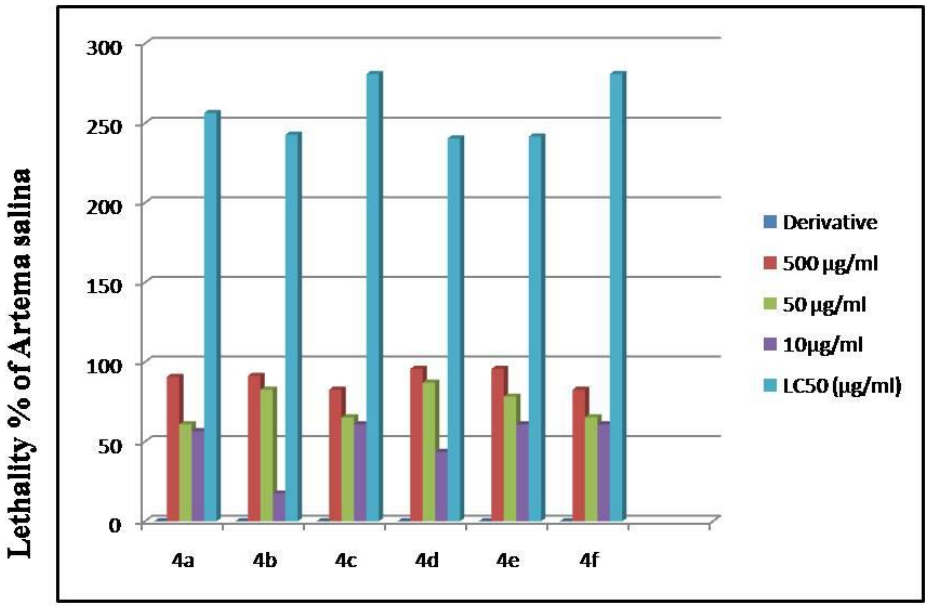
V. CYTOTOXICITY ACTIVITY

5.1 Brine Shrimp Lethality Test

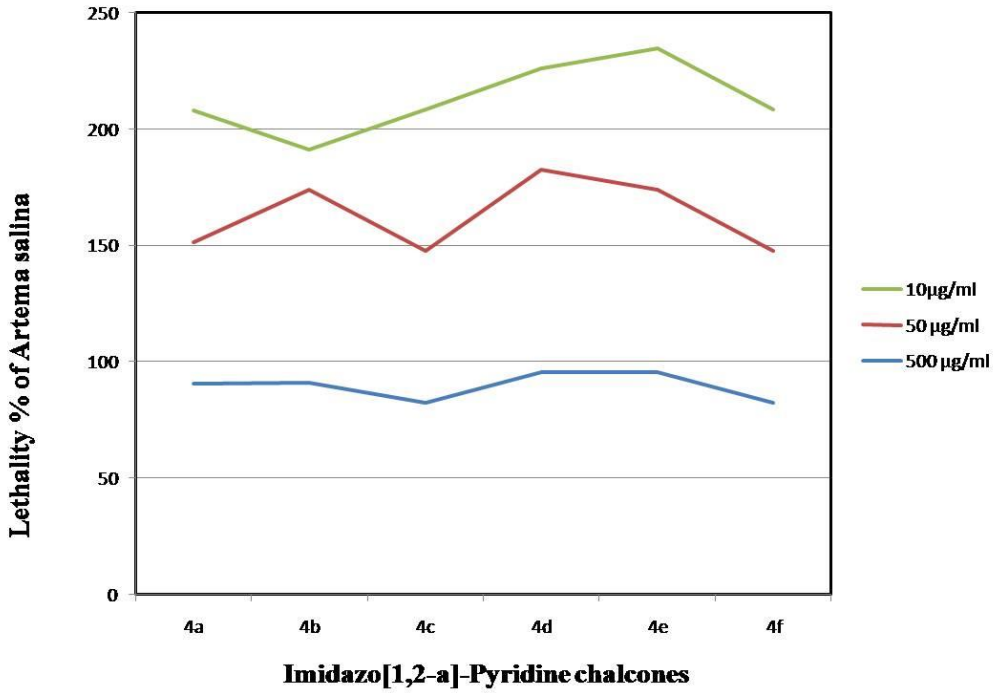
The *in vitro* cytotoxic activity of each synthesized compounds (5a-f) was studied by the brine-shrimp lethality assay method. Brine-shrimp (*Artemia salina*) eggs were hatched in artificial sea water (40 g sea salts/L) at room temperature (22-29 ºC). After two days these shrimps were transferred to vials (10 shrimps per vial) containing artificial sea water (5 mL) with 500, 50 and 10 µg/mL final concentrations of each compound taken from their stock solutions of 20 mg/mL in DMSO. After 24 hours number of surviving shrimps was counted. Data was analyzed with computer programme (Probit analysis) to determine LC50 values.

Table-1 : Cytotoxicity test for different Imidazo [1,2-a] pyridine Chalcones (5a-f)

Entry	500 µg/ml	50 µg/ml	10µg/ml	LC50 (µg/ml)
5a	92.65	61.76	65.52	250.41
5b	92.70	81.60	67.39	243.71
5c	92.90	64.71	66.86	281.89
5d	90.55	85.92	53.47	241.38
5e	91.65	77.25	61.86	242.54
5f	81.60	66.22	63.87	284.89



Imidazo[1,2-a]-Pyridine chalcones



From Table, most of the newly tested compounds showed potent cytotoxic activities against Brine shrimp (*Artemia salina*) lethality assay. Compound (5a-f) exhibited the higher toxicity in the brine shrimp assay for overall toxicity profile. Specially chalcones made from five membered heterocyclc ring compounds like pyrrole, furan and thiophene (5a-c) shows excellent cytotoxicity. In addition Table show that the cytotoxicity activities increase as the doses increase, therefore the 1000 µg/mL doses induced more cell death than the 10 µg/mL doses.

The lethality of a test sample in a simple zoological organism such as the shrimp (*Artemia salina*) has been utilized in the Brine Shrimp Cytotoxicity Test (BSCT)[13-14]. It is a very useful tool to screen a wide range of chemical compounds for their various bioactivities. It has been well utilized to screen and fractionation of physiologically active plant extracts as well. It has been demonstrated that BSCT correlates reasonably well with cytotoxic and other biological properties[15-16]. The brine shrimp bioassay has been established as a safe, practical and economic method for determination of bioactivities of synthetic

VI. CONCLUSIONS

In conclusion, we have successfully developed a copper(II) catalyzed aerobic oxidative coupling of 2-aminopyridines with cinnamaldehydes for one-pot synthesis of 3-formyl-2-phenyl Imidazo[1,2-a] pyridines. We have synthesized a new class of chalcones, wherein the B-ring has been replaced by an Imidazo[1,2-a] pyridine moiety. The developed method is operationally simple and could be used efficiently for the preparation of biologically important Imidazo[1,2-a] pyridines Chalcones. Almost all of the newly synthesized compounds showed potent cytotoxicity activities against Brine shrimp (Artemia salina) lethality assay. Compound (5a-f) exhibited the higher toxicity in the brine shrimp assay for overall toxicity profile. Specially Sulphur containing chalcone 5c and quinoline chalcone 5f are shows good result to cytotoxicity. However, a furtherstudy of antioxidant and antiinflammtory evaluation of Imidazo[1,2-a]pyridine Chalcones will be undertaken, concerning the structural arrangements of heterocyclic ring as it is responsible to show various biological activities.

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VIII. CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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