Synthesis and Antimicrobial screening of Chalcones containing imidazo [1,2-a] pyridine nucleus

Pravin S. Bhale, Sakhamaram B. Dongare, Umakant B. Chanshetti
Department of Chemistry, Arts, Science and Commerce College, Naldurg, Tq-Tuljapur, Dist.-Osmanabad-413 602, Maharashtra, INDIA,
Available online at: www.isca.in, www.isca.me
Received 22nd November 2013, revised 28th November 2013, accepted 15th December 2013

Abstract
A series of chalcones were prepared by reacting various acetophenones with 2-(4-bromophenyl)imidazo[1,2-a]pyridine-3-carbaldehyde in the presence of alcoholic alkali. The structures of these compounds were confirmed on the basis of spectral data. All the title compounds were screened for their antimicrobial activities. The screening data indicated that tested compounds showed good antimicrobial activity.

Keywords: Imidazo[1,2-a]pyridine; Imidazo[1,2-a]pyridine-3-carbaldehyde chalcones; antifungal activity; antibacterial activity.

Introduction
Design and synthesis of new compound with appropriate therapeutic importance is a major challenge in medicinal chemistry. Recently, imidazo [1,2-a] pyridines have significant importance in the pharmaceutical industry owing to their various interesting biological activity displayed over a broad range of therapeutic classes; these molecules exhibit antiviral (anticytomegalovirus and antivaricella-zoster virus), anti-inflammatory, analgesic, antipyretic, antiulcer, and antibacterial properties. They are also β-amyloid formation inhibitors, GABA and benzodiazepine receptor agonists and cardiotonic agents. Drug formulations containing imidazo[1,2-alpyridine that are currently available on the market include alpidem (anxiolytic), zolpidem (hypnotic) and olprinone (PDE-3 inhibitor). Acuña and co-workers were the first to report that imidazo[1,2-alpyridines possessing a 2-hydroxyphenyl substituent at position 2 display excited-state intramolecular proton transfer (ESIPT).

The non-benzodiazepines are generally used as sedatives, anticonvulsants, hypnotics, anxiolytics and muscle relaxants as they show less adverse effects compared to classical benzodiazepines. In fact, imidazopyridines are the major class of non-benzodiazepines, acting upon various central nervous systems (CNS) disorders. Several imidazo[1,2-alpyridine nucleus already in market which include alpidem has sedative and anxiolytic properties and zolpidem is a hypnotic drug. Both alpidem and zolpidem have higher affinity for benzodiazepine-1 than for benzodiazepine-2 receptors and their interaction with various receptors has been reported. Some imidazo[1,2-alpyridine containing drugs are as follow:
Further, it is also revealed that, selectivity of imidazo [1,2-a]
aldazines towards benzodiazepine receptors can be enhanced
by incorporating a 4-halophenyl ring at 2nd position and a
hydrophobic unit at 8th position. Inspired by this observation,
ich the expectation of improved pharmacological
activity.

Chalcones are well known intermediates for synthesizing
various heterocyclic compounds. The compounds with
backbone of chalcones have been reported to possess various
biological activities such as antibacterial, anti-inflammatory,
anti-malarial, antioxidant, anti-HIV, and antitubercular.
The presence of a reactive α,β-unsaturated keto function in
chalcones was found to be responsible for their anti-
inflammatory activity. It was envisaged that the two
pharmacophores if linked together would generate novel
molecular templates which are likely to exhibit interesting
biological properties. We were designed and synthesized
various chalcone containing imidazo[1,2-a] pyridine nucleus.

![Chemical Structure](image)

Where,

3a: R₁=R₂=R₃=H; 
3b: R₁=R₂=H, R₃=-OCH₃ 
3c: R₁=R₂=R₃=Br; 
3d: R₁=R₂=H, R₃=Cl 
3e: R₁=H, R₂=-CH₃, R₃=-OH; 
3f: R₁=-OH, R₂=H, R₃=-CH₃ 
3g: R₁=H, R₂=R₃=-OCH₃

Scheme-1
Reagents and Condition: (a) Ethanol, 10% Aq. KOH, RT for 6-8 hrs

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Mol. Formula</th>
<th>Mol. weight</th>
<th>M.P. (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>C₁₂H₁₃BrN₂O</td>
<td>403.27</td>
<td>122-124</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>C₁₂H₁₇BrN₂O₂</td>
<td>433.30</td>
<td>168-170</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>C₁₂H₁₄BrN₂O</td>
<td>482.17</td>
<td>220-224</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>C₁₂H₁₄BrClN₂O</td>
<td>437.72</td>
<td>210-212</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>C₁₂H₁₇BrN₂O₂</td>
<td>433.30</td>
<td>178-180</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>C₁₂H₁₇BrN₂O₂</td>
<td>433.30</td>
<td>190-192</td>
<td>54</td>
</tr>
<tr>
<td>7</td>
<td>3g</td>
<td>C₁₄H₁₉BrN₂O₃</td>
<td>463.32</td>
<td>156-158</td>
<td>68</td>
</tr>
</tbody>
</table>
Material and Methods

Experimental: All commercially available chemicals and reagents were purchased from Aldrich and used without further purification. All the solvents were dried and distilled before use. The melting points were determined in open capillary tube and are uncorrected. The IR spectra of synthesized compounds were recorded on Shimadzu 8400-S FT-IR Spectrophotometer using potassium bromide. The 1H NMR were recorded in CDCl₃ or DMSO-d₆ using NMR Varian-Mercury 300 MHz spectrometer and chemical shifts are reported as parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. The IR spectra of synthesized compounds were purchased from Aldrich and used without further purification. All commercially available chemicals and reagents were purchased from Aldrich and used without further purification.

Antibacterial activity:

Research Journal of Chemical Sciences _____________ ______________________________________________

Experimental:

General procedure for the preparation of Chalcone of Imidazo[1,2-a]Pyridine nucleus: Acetophenone / Substituted acetonaphone (0.5mmol) dissolved in 5ml of ethanol and to this 10% aqueous KOH (1 ml) solution were added and stirred for 15-20 minutes at room temperature. To this mass 2-(4-bromophenyl)Imidazo[1,2-a]Pyridine-3-carbaldehyde 0.5mmol were added. Stirred the above reaction mass for 6-8 hours at room temperature. Reaction was monitored by TLC. After completion of reaction, reaction mass was poured in ice cold water and neutralized with acetic acid, filtered off to obtain desired product. The resulting product was purified by column chromatography on silica gel (Merck, 60–120 mesh) using gradient of hexanes/ethyl acetate as eluent.

Spectral data of representative compound: (E)-3-(2-(4-bromophenyl)Imidazo[1,2-a]pyridine-3-yl)-1-(4-methoxyphenyl) prop-2-en-1-one (3b): Yellow Solid, IR (KBr): 3017, 2864, 1680, 1604, 1570, 1221, 1170, 650cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ = 8.48(d, 1H), 8.10(d, J=8Hz, 2H), 7.90(d, 1H), 7.70(d, 4H), 7.55(d, 1H), 7.40(d, 1H), 7.20(t, 1H), 7.10(d, J=8Hz, 2H), 6.80(t, 1H), 3.84(s, 3H); LCMS( ESI): m/z 435.28(M+2).

Antibacterial activity: The purified products were screened for their antibacterial activity using cup-plate agar diffusion method. The nutrient agar broth prepared by the usual method were inoculated aseptically with 0.5 ml of 24 hr. old subcultures of Baccillus coccus, Staphylococcus aureus, Aerogenes, Pseudomonas aeruginosa in separate conical flasks at 40-50°C and mixed well by gentle shaking. About 25 ml content of the flask was poured and evenly spreaded in a petridish (13 cm diameter) and allowed to set for 2 hr. The cups (10 mm diameter) were formed by the help of borer in agar medium and filled with 0.04ml (40mg) solution of sample in DMF. The plates were incubated at 37°C for 24 hr. and the control was also maintained with 0.04ml of DMF in a similar manner and the zone of inhibition of the bacterial growth were measured in millimeter and recorded in table-2.

Antifungal activity: Aspergillus niger was employed for testing antifungal activity using cup-plate agar diffusion method. The culture was maintained on sabourauds agar slants sterilized sabourauds agar medium was inoculated with 72 hr old 0.5ml suspension of fungal spores in a separate flask. About 25 ml of the inoculated medium was evenly spreaded in a Petridish (13cm diameter) and allowed to set for 2 hr. the cups (10mm diameter) were punched. The plates were incubated at 30°C for 48 hr. After the completion of incubation period, the zone of inhibition of growth the form of diameter in mm was measure.

Along the test solution in each petridish one cup was filled up with solvent, which acts as control. The zone of inhibition of test solution are recorded in table-3.

Table-2

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>B. coccus</th>
<th>S. aureus</th>
<th>Aerogenes</th>
<th>P. aeruginosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>18</td>
<td>11</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>3b</td>
<td>14</td>
<td>19</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>3c</td>
<td>16</td>
<td>14</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>3d</td>
<td>13</td>
<td>12</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>3e</td>
<td>10</td>
<td>14</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>3f</td>
<td>19</td>
<td>13</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>3g</td>
<td>13</td>
<td>12</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>25</td>
<td>25</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>20</td>
<td>15</td>
<td>22</td>
<td>16</td>
</tr>
</tbody>
</table>

Table-3

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>A. niger</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>18</td>
</tr>
<tr>
<td>3b</td>
<td>12</td>
</tr>
<tr>
<td>3c</td>
<td>13</td>
</tr>
<tr>
<td>3d</td>
<td>18</td>
</tr>
<tr>
<td>3e</td>
<td>19</td>
</tr>
<tr>
<td>3f</td>
<td>20</td>
</tr>
<tr>
<td>3g</td>
<td>13</td>
</tr>
<tr>
<td>Greseofulvin</td>
<td>26</td>
</tr>
</tbody>
</table>

Results and Discussion

A series of chalcones (3a-3g) were prepared by reacting various substituted acetophenones with 2-(4-bromophenyl)imidazo[1,2-a]pyridine-3-carbaldehyde in the presence of alkali (scheme-1 and table-1). The structures of newly synthesized compounds characterized by IR, 1H NMR, Mass and physical data.

The formation of chalcones (3a-3g) was confirmed by IR and NMR spectra. The presence of a band around 1570 cm⁻¹ due to
C=C stretch. The appearance of characteristic band at 1680cm\(^{-1}\) is due to carbonyl C=O stretch. The band at 650 cm\(^{-1}\) shows halide C-Br stretch. In \(^1H\) NMR spectrum of chalcones doublet at \(\delta 8.48(3H)\) suggested the presence of protons behind nitrogen in imidazo[1,2-a]pyridine ring and singlet at \(\delta 3.84(3H)\) shows -OCH\(_3\) group proton.

Synthesized compounds were evaluated for their antibacterial screening against \textit{B. coccus}, \textit{S. aureus}, \textit{P. aeruginosa} and \textit{Aerogenes}. Compound 3a and 3f shows moderate activity against \textit{B. coccus}. Compound 3b showed maximum zone of inhibition against bacteria \textit{S. aureus} and \textit{P. aeruginosa}. Compound 3d shows maximum zone of inhibition against \textit{Aerogenes} but less than standard used for screening.

Compound 3e and 3f for their antifungal screening shows maximum zone of inhibition against fungi \textit{A. niger} but less than the standard used for screening.

**Conclusion**

The structures of synthesized compounds were confirmed by IR and NMR spectroscopy. Investigation of antibacterial and antifungal screening data revealed that the compound 3b showed maximum zone of inhibition against bacteria \textit{S. aureus} and \textit{P. aeruginosa} and Compound 3f showed maximum zone of inhibition against fungi \textit{A. niger}. Further bioassay, optimization and structure-activity relationship of the title compounds are underway.

**Acknowledgment**

The authors are thankful to Principal, A. S. C. College, Naldurg, Dist.- Osmanabad for providing laboratory facilities.

**References**

1. Hanson S.M., Morlock E.V., Satyshur K.A., Czajkowski C. Structural requirements for eszopiclone and zolpidem binding to the gamma-aminobutyric acid type-A (GABAA) receptor are different, \textit{J. Med. Chem.}, 51(22), 7243-52 (2008)


