EXPLORING THE EFFECTS OF NEWER THREE COMPONENT AMINOBENZYLATED REACTIONS OF TRIPHENYL IMIDAZOLE MOTIF AS POTENT ANTIMICROBIAL AND ANTI-INFLAMMATORY AGENTS

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ABSTRACT

An elegant synthesis of newer desired aminobenzylated triphenyl imidazole hybrids is described. Cyclization of benzal with appropriate aromatic aldehydes in the presence of ammonium acetate yielded 2-substituted - 4, 5-diphenyl imidazole entities, which further undergoes mannnich condensation reaction with benzaldehyde and various aromatic secondary amines afforded the title compounds. The constituents of the newly synthesised compounds have been established on the basis of their physical and spectral data. All the newly synthesised heterocycles have been screened for in vitro antimicrobial and anti-inflammatory activities. Among the synthesized compounds, the compound TPI-IV exhibited good anti-inflammatory activity and better anti-microbial activity against bacterial strains Staphylococcus aureus, Pseudomonas aeruginosa and fungal strain Candida albicans.

Keywords: Triphenyl imidazole hybrids, Synthesised heterocycles, Mannich condensation, in vitro antimicrobial activity, Anti-inflammatory activity.

INTRODUCTION

Triphenyl imidazole is a privileged structural motif, which has played a pivotal role in the drug discovery process. Nitrogen containing heterocycles paved way for the active research in Pharmaceutical Chemistry. The study of triphenyl imidazole derivatives has been a developing field within the realm of heterocyclic chemistry for the past several decades because of their ready accessibility through synthesis, wide range of chemical reactivity and manifold biological activities. This structural template shows remarkable pharmacological activities such as antibacterial1,2, antireactivity and manifold biological activities. This structural template ready accessibility through synthesis, wide range of chemical compounds. Base could furnish better therapeutic results. To our knowledge antiviral8, antitumour9, antispasmodic10, antioxidant11 and anti-inflamatory3,4, anticonvulsive5, anthelmintic6, antiulcer7, antiallergic activities. 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MATERIALS AND METHODS

All the reagents used were of analytical grade. Melting points of the title compounds were determined using Vego-Digital VMP-D melting point apparatus and are uncorrected. Infra red spectra (cm⁻¹) were recorded on Perkin-Elmer spectrophotometer as pellets on KBr discs. The ¹HNMR (400MHz) spectra were recorded on Bruker-Avance II spectrometer in DMSO-d6 using TMS as an internal standard (chemical shifts in δ ppm). The splitting patterns are designated as follows: s, (singlet), d, (doublet), t, (triplet), m, (multiplet). Mass spectra were recorded on Shimadzu LCMS-SL2010A (70ev) mass spectrometer. The reactions were monitored by thin layer chromatography (TLC) using precoated silica gel G plates of E-Merck. The spots were developed in iodine chamber.

Synthesis of 4,5-diphenyl-2-(2,3,4-trimethoxyphenyl)-4H-imidazole DPI

Benzil (25mmol, 5.25g) and 2,3,4-trimethoxy benzaldehyde (25mmol) were refluxed with ammonium acetate (10g) and glacial acetic acid (5 ml) for 4 hr afforded 2-substituted 4, 5-diphenyl imidazole. After refluxing, the reaction mixture was left overnight and filtered. The filtrate was neutralized with ammonium hydroxide and the second crop of the precipitate were combined and recrystallised from ethanol. Yield 67%, m.p 136°C, Rf value 0.69.

Synthesis of N-((4,5-diphenyl-2-(2,3,4-trimethoxyphenyl)-1H-imidazol-1-yl)phenyl)methyl)substituted amine (TPI-I-TPI-V)

4,5-diphenyl-2-(2,3,4-trimethoxyphenyl)-4H-imidazole derivatives were dissolved in methanol and undergoes mannnich condensation reaction with benzaldehyde and appropriate aromatic secondary amines yielded the corresponding N,N-disubstituted - 2,4,5-triphenyl-1H-imidazol-1-yl methanamine analogues by refluxing for 2 hr. Volatiles are removed under reduced pressure and the resulting dense oily product was recrystallised from ethanol to afford a white solid substance. The physicochemical parameters of the target compounds were tabulated in Table 1.

N-((4, 5- diphenyl-2-[2, 3, 4-trimethoxyphenyl]-1H-imidazol-1-yl) phenyl) methyl)-N-phenyl benzenamine (TPI-I).

IR (KBr) cm⁻¹: 3083.60 (Aromatic -CH stretching), 2933.57 (Aliphatic -CH stretching), 1519.64 (aromatic C=C stretching), 1432.44 (C≡N stretching), 1401.84 (C-N stretching), 1243.44 (C-O-C stretching).¹HNMR(400 MHz,DMSO-d6) δ ppm: 6.14 (s,1H,CH), 3.84 (s,9H,(OCH₃)), 6.54+8.26 (m,27H,Ar-H). Mass: m/z 643.
N-((4, 5-diphenyl-2, 3, 4-trimethoxyphenyl)-1H-imidazolyl) phenyl methyl piperazine (TPI-II).

IR (KBr) cm⁻¹: 3030.48 (Aromatic –CH stretching), 2926.82 (Aliphatic –CH stretching), 3010.71 (Aromatic –CH stretching), 2992.28 (Aliphatic –CH stretching).

TPI-I NHR

1H NMR(400 MHz,DMSO-d6) δ ppm: 6.42 (s,1H,CH), 3.82 (s,9H,(OCH3)3), 6.92‐8.26 (m,22H,Ar‐H). Mass: m/z 581.

N-((4, 5-diphenyl-2, 3, 4-trimethoxyphenyl)-1H-imidazolyl) phenyl methyl –N-naphthalen-1-amine (TPI-III).

IR (KBr) cm⁻¹: 3445.62 (Aromatic –CH stretching), 2926.82 (Aliphatic –CH stretching), 1588.86 (Aromatic C=O stretching), 1465.24 (C=N stretching).

Table 1: Physicochemical parameters of Triphenyl imidazole derivatives

<table>
<thead>
<tr>
<th>Compound Code</th>
<th>Ar</th>
<th>m.p (°c)</th>
<th>Yield (%)</th>
<th>Mol. formula</th>
<th>Mol. Wt.</th>
<th>Rf value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPI-I</td>
<td>N,C6H5</td>
<td>128-132</td>
<td>59.24</td>
<td>C35H36N4</td>
<td>643.77</td>
<td>0.82</td>
</tr>
<tr>
<td>TPI-II</td>
<td>N,NH</td>
<td>134-138</td>
<td>68.70</td>
<td>C35H36N4</td>
<td>650.69</td>
<td>0.73</td>
</tr>
<tr>
<td>TPI-III</td>
<td>N,NH</td>
<td>220-223</td>
<td>63.24</td>
<td>C35H36N4</td>
<td>693.83</td>
<td>0.88</td>
</tr>
<tr>
<td>TPI-IV</td>
<td>N</td>
<td>210-213</td>
<td>46.21</td>
<td>C35H36N4</td>
<td>559.71</td>
<td>0.79</td>
</tr>
<tr>
<td>TPI-V</td>
<td>C6H5</td>
<td>205-208</td>
<td>54.18</td>
<td>C47H39N3</td>
<td>581.70</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Antibacterial activity

The *invitro* antibacterial activity of the compounds was carried out by the agar cup plate method৫২. The concentration of the compound (250μg/ml) was prepared in dimethyl sulfoxide (DMSO) and olloxacin was used as standard. The antibacterial activity was evaluated using 24 hr cultures of *Staphylococcus aureus*, *Bacillus subtilis*, *Salmonella typhi* and *Escherichia coli* using Muller Hinton agar medium. The medium was sterilised by autoclaving at 120°C for 30 minutes. About 30 ml of molten nutrient agar medium inoculated with the respective strains of bacteria (final of inoculums to 30/ml of nutrient agar medium) was transferred aseptically into each sterilised petridish (10 cm diameter). The plates were left at room temperature to allow solidification of the media. In each plate 3 wells of 6mm diameter were made using a sterile cork borer. Accurately 0.1 ml of test and standard solutions were transferred to the wells aseptically by micropipette and labelled accordingly. The plates were then maintained at room temperature for 2 hr to allow the diffusion of the solution in the medium. The petridish used for antibacterial screening were incubated at 37±1°C for 24 hrs. The diameter of zone of inhibition surrounding each well was recorded.

**Antifungal activity**

*Aspergillus niger* and *Candida albicans* were employed for testing fungicidal activity using cup plate method৫২. The cultures were maintained on Sabouraud’s agar slants. Sterilised sabouraud’s agar medium was inoculated with 72 hr old suspension of fungal spores in a separate flask. About 25 ml of the inoculated medium was evenly spread in a sterilised petridish and allowed to settle down for 2 hr. The cups (10mm in diameter) were punched in petridish and loaded with sample solution in DMSO. The plates were incubated at room temperature (30°C) for 48 hr. After the completion of the incubation period, the zone of inhibition of growth of the synthesized compounds (TPI I-V) in the form of diameter in mm was measured. Along the test solution in each petridish, one cup was filled with solvent which acted as control. The antifungal activity of compounds was compared with a standard drug Griseofulvin. The results of antifungal profile were depicted in Table 2.

**In vitro anti-inflammatory activity**

The *invitro* anti-inflammatory activity was evaluated by human red blood cell membrane (HRBC) stabilisation method৫২. This method involves the stabilisation of the human red blood cell membrane by hypotonicity induced membrane lysis. The lysosomal enzymes released during inflammatory condition produces a variety of disorders. The extra cellular activity of these enzymes were said to be related to acute or chronic inflammation. The anti-inflammatory agents act by either inhibiting the lysosomal enzymes or by stabilising the lysosomal membrane, since the human red blood cell membranes are similar to lysosomal membrane components. The prevention of hypotonicity induced HRBC membrane lysis was taken as a measure of anti-inflammatory activity of the drug.

The synthesised target compounds were made into dose of 250μg/ml with 5% DMSO as solvent. Diclofenac sodium was taken as a standard drug. The percentage membrane stabilization activity was calculated by the following formula and the results were tabulated in Table 2

Percentage stabilisation = 100 – (OD of sample-OD of the product control)x 100/OD of test control
2-substituted-4,5-diphenyl imidazole root nucleus were synthesised by refluxing benzil with 2,3,4-trimethoxy benzaldehyde in presence of cyclising agents ammonium acetate and glacial acetic acid. In the next step, the prepared diphenyl imidazole analogues undergoes manich condensation reaction with benzaldehyde and various substituted aromatic secondary amines resulted in the formation of target compounds (Scheme 1).

CHEMISTRY

RESULTS AND DISCUSSION

ACKNOWLEDGEMENT

REFERENCES


