ONE POT GREEN SYNTHESIS OF 2-ARYL/HETERYL-BENZIMIDAZOLE AS ANTI-INFLAMMATORY AGENTS

Anna Pratima Nikalje*, Mangesh Ghodke

Department of Pharmaceutical Chemistry, Y. B. Chavan College of Pharmacy, Dr. Rafiq Zakaria Campus, Aurangabad. 431001. MS. India.

ABSTRACT

Benzimidazole derivatives constitute an interesting class of organic compounds with diverse pharmacological activities. In view of the observations and in continuation of previous synthetic programme on the synthesis of chalcones and their derivatives, present study report the synthesis of some new benzimidazole derivatives which have been found to possess an interesting profile of anti-inflammatory activity. The present study reports an eco-friendly, one pot, microwave-assisted expeditious synthesis of 2-aryl/heteryl-substituted benzimidazole derivatives and their anti-inflammatory activity. The one pot synthesis was carried out under microwave irradiation, by condensing phenylene diamine with aryl and/or heteryl aldehydes in solvent-free conditions using zirconium oxy chloride as catalyst in borosil beaker and irradiated in synthetic microwave oven at 700W for 3-6 min. The reaction was carried out at 70°C- 85°C. The products were obtained in good yields and in shorter reaction times. The synthesized compounds were evaluated for in-vivo anti-inflammatory activity on Wistar albino rats in carrageenan induced rat paw edema model. After 1hr compound no. 3e, after 2hr compound no. 3b, 3d and after 3hr compound no. 3d, 3e and 3h have exhibited more percentage of inhibition of anti-inflammatory activity.

Key Words: Green synthesis, eco friendly, benzimidazole, carrageenan, anti-inflammatory activity, indomethacin.
INTRODUCTION

Inflammation is defined as the local response of living mammalian tissues to injury due to any agent. Non steroidal anti-inflammatory drugs (NSAIDs) are one kind of therapeutics, widely used in the world because of their high efficacy in reducing pain and inhibiting inflammation. NSAIDs drugs such as Celecoxib, Diclofenac can inhibit the enzyme cyclooxygenase (COX-1 and COX-2), which catalyze the biotransformation of arachidonic acid to prostaglandins (PGs) and to Thromboxane A2. These are the mediators of pain, inflammation, fever. Hence, the development and discovery of new agents that can inhibit the COX-1 and COX-2 activity will be of importance for the controlling inflammation. Many pharmaceuticals are synthetic compounds, and a large number of them are heterocycles.

Benzimidazoles constitute an important group of heterocyclic compounds and contains the benzene ring fused to the imidazole ring and they exhibit wide range of biological activities such as antifungal, antiviral antibacterial, anticancer, antiulcer and anti-inflammatory. Their potential biological activity encouraged us to prepare some new heterocyclic derivatives as these heterocycles can be easily synthesized under laboratory condition. The present study describes green, expeditious synthesis of 2-substituted benzimidazole derivatives by condensation of phenylene diamine with aldehydes in solvent-free conditions and in presence of zirconium oxy chloride as catalyst under microwave irradiation. Solvent free reactions occur more efficiently and more selectively. Such green reactions are simple to handle, reduce pollution, avoid use of harmful solvents, are economic and protect environment from pollution and are especially important in industry. The synthesized novel derivatives were evaluated as anti-inflammatory agents in Wistar albino rats using carrageenan induced rat paw edema model.
MATERIALS AND METHODS

All the chemicals used were of Merck make. The reactions were carried out in synthetic microwave oven; CATA R. Melting points was determined in open capillaries using melting point apparatus and were uncorrected. The purity and homogeneity of compounds were checked using TLC technique. Infra Red spectra were recorded on Fourier Transform Infra Red JASCO 4000 in KBr powder. \(^1\)H NMR were recorded on Brucker advance II 400 Nuclear Magnetic Resonance spectrophotometer in CDCl\(_3\). Mass spectra were recorded on TOS MS +484 spectrophotometer. Compounds were synthesized in open borosil beakers in solvent-free conditions avoiding use of costly solvents and their drainage in contrast to conventional method where refluxing of 4-6 hrs is required.

Experimental

General procedure for the preparation of 2-aryl benzimidazole, 3(a-h)

In this method Ortho phenylene diamine (0.01mol), substituted aldehyde (0.01mol) and a pinch of catalyst zirconium oxy chloride were triturated, transferred to 50 ml borosil beaker and irradiated in synthetic microwave oven at 700W for 3-6 min. The temperature of the reaction was measured with the help of temperature probe. The reaction was carried out at 70\(^{0}\)C- 85\(^{0}\)C. The reaction was monitored by the TLC. The time required for completion of reactions was recorded. At the end of reaction, the reaction mixture was washed with cold water to remove catalyst. The product was filtered, dried and recrystallized from ethanol. All the compounds 3(a-h) were prepared following this method as per the scheme and were recrystallized from ethanol

\[
\text{NH}_2 \quad \text{Ar-CHO} \quad \text{MW} \quad \text{b} \quad \text{NH}_2
\]

Where, Ar = Aryl / heteryl

b = Zirconium oxy chloride, Solvent free

Scheme: Synthetic method for target compounds

Synthesis of 2-(4-Methoxyphenyl)-benzimidazole (3a)

Yellowish -green solid. IR (KBr, cm\(^{-1}\)) : 3097, 2928, 2334, 1693; \(^1\)H NMR(CDCl\(_3\), \(\delta\) ppm ) : 3.83(s, 1H, CH3), 6.83-7.97 (m, 8H, Ar-H), 12.81(s, 1H, N-H); MS m/z: 223(M+1); Anal
Synthesis of 2-Phenyl-benzimidazole (3b)
Yellow solid. IR (KBr, cm\(^{-1}\)): 3097, 2900, 2335, 1693; \(^1\)HNMR (CDCl\(_3\), \(\delta\) ppm): 7.3-8.3 (m, 9H, Ar-H), 12.81 (s, 1H, N-H); MS m/z: 192 (M+1); Anal Calcd. For C, 80.39; H, 5.19; N, 14.42; Found C, 78.30; H, 4.13; N, 12.02.

Synthesis of 2-(4-Chlorophenyl)-benzimidazole (3c)
Yellow solid. IR (KBr, cm\(^{-1}\)): 3097, 2800, 2334, 1693, 725, 600; \(^1\)HNMR (CDCl\(_3\), \(\delta\) ppm): 7.33-8.3 (m, 8H, Ar-H), 12.81 (s, 1H, N-H); MS m/z: 227 (M+1); Anal Calcd. For C, 68.28; H, 3.97; N, 12.25; Found C, 66.28; H, 3.47; N, 11.25.

Synthesis of 2-(2-Hydroxyphenyl)-benzimidazole (3d)
Yellow solid. IR (KBr, cm\(^{-1}\)): 3756, 3097, 2340, 693, 602; \(^1\)HNMR (CDCl\(_3\), \(\delta\) ppm): 5.0 (s, 1H, Ar-OH), 6.79-8.23 (m, 8H, Ar-H), 12.81 (s, 1H, N-H); MS m/z: 210.08 (M+1); Anal Calcd. For C, 74.27; H, 4.79; N, 13.33; Found C, 72.27; H, 3.79; N, 12.33.

Synthesis of 2-(Pyridine-2-yl)-benzimidazole (3e)
Brown solid. IR (KBr, cm\(^{-1}\)): 3097, 2928, 2335, 1693, 610; \(^1\)HNMR (CDCl\(_3\), \(\delta\) ppm): 7.55-8.33 (m, 8H, Ar-H), 12.81 (s, 1H, N-H); MS m/z: 195.08 (M+1); Anal Calcd. For C, 73.83; H, 4.65; N, 21.52; Found C, 72.27; H, 3.69; N, 20.33.

Synthesis of 2-(4-Thiophene)-benzimidazole (3f)
Brown solid. IR (KBr, cm\(^{-1}\)): 3097, 2900, 2334, 1693, 631; \(^1\)HNMR (CDCl\(_3\), \(\delta\) ppm): 7.0 (d, 1H, \(=\)CH of thiophene ring), 7.1 (d, 1H, \(=\)CH of thiophene ring), 7.55-8.23 (m, 4H, Ar-H), 12.81 (s, 1H, N-H); MS m/z: 200.04 (M+1); Anal Calcd. For C, 65.97; H, 4.03; N, 13.99; S, 16.01; Found C, 62.27; H, 3.59; N, 11.33; S, 14.22.

Synthesis of 2-(4-Nitrophenyl)-benzimidazole (3g)
Yellowish -green solid. IR (KBr, cm\(^{-1}\)): 3097, 2900, 2335, 611; \(^1\)HNMR (CDCl\(_3\), \(\delta\) ppm): 7.33-8.3 (m, 8H, Ar-H), 12.81 (s, 1H, N-H); MS m/z: 184.06 (M+1); Anal Calcd. For C, 71.73; H, 4.38; N, 15.21; Found C, 70.27; H, 3.49; N, 14.33.

Synthesis of 2-(4-hydroxy-3-methoxyphenyl) benzimidazole (3h)
Yellowish -green solid. IR (KBr, cm\(^{-1}\)): 3097, 2900, 2334, 1693, 664; \(^1\)HNMR (CDCl\(_3\), \(\delta\) ppm): 3.73 (s, 3H, OMe), 5.0 (s, 1H, \(-\)OH), 6.8-8.2 (m, 7H, Ar-H), 12.81 (s, 1H, N-H); MS m/z:
239.07 (M+1), Anal Calcd. For C, 65.27; H, 3.79; N, 17.56; Found C, 63.27; H, 3.49; N, 15.56;

PHARMACOLOGY

Anti-inflammatory activity

Male or female Wistar Albino rats with body weight 100 – 200gm were taken. The animals were starved overnight before start of the study. The animals dosed with 10mg/kg body weight of the test drugs and control received the same volume of water. After 30min 0.05ml of 1% solution of carrageenan was injected into the plantar side of the left hind paw according to the reported method.[14] The paw was marked with ink at the level of lateral malleolus and immersed in mercury up to the mark to determine the paw volume. Similarly after 30 min, 1hr, 2hr and 3hr the paw volume was measured.

Evaluation: The volumes are obtained in ml and the average (mean) values are obtained by the statistical analysis. The statistical analysis is performed by using one-way ANOVA followed by Tukey’s test.

RESULTS AND DISCUSSION

Microwave assisted technology has been adopted to achieve remarkable rate enhancement and dramatic reduction in reaction times, better yields and cleaner reactions. The synthesis of 2-arylbenzimidazole by condensation of aromatic diamines with aldehydes, under microwave and solvent free condition using eco friendly catalyst is reported here. Zirconium oxy chloride is used as an eco friendly catalyst, which is an efficient Lewis acid catalyst used in various transformations, such as dehydrative cyclization. This catalyst is cheaper cost wise, soluble in water and it has been used for cyclocondensation reactions. The reaction proceeds efficiently and was completed within 3-6 min. Physical data of the synthesized compounds is presented in Table 1. All the synthesized derivatives follows Lipinski's rule i.e. not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms), not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms), a molecular mass less than 500 daltons, log P not greater than 5.
Table 1: Physical characterization data of synthesized compounds

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Ar</th>
<th>Molecular formula</th>
<th>Molecular weight</th>
<th>Yield (%)</th>
<th>M.P (°C)</th>
<th>Rf value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>-OMe</td>
<td>C₁₄H₁₂N₂O</td>
<td>224.26</td>
<td>64</td>
<td>74</td>
<td>0.56</td>
</tr>
<tr>
<td>3b</td>
<td></td>
<td>C₁₃H₁₀N₂</td>
<td>194.23</td>
<td>68</td>
<td>68</td>
<td>0.68</td>
</tr>
<tr>
<td>3c</td>
<td>-Cl</td>
<td>C₁₃H₉ClN₂</td>
<td>228.68</td>
<td>72</td>
<td>66</td>
<td>0.44</td>
</tr>
<tr>
<td>3d</td>
<td>-OH</td>
<td>C₁₃H₁₀N₂O</td>
<td>210.23</td>
<td>65</td>
<td>81</td>
<td>0.57</td>
</tr>
<tr>
<td>3e</td>
<td></td>
<td>C₁₂H₉N₃</td>
<td>195.22</td>
<td>74</td>
<td>70</td>
<td>0.76</td>
</tr>
<tr>
<td>3f</td>
<td></td>
<td>C₁₁H₈N₂S</td>
<td>200.26</td>
<td>72</td>
<td>86</td>
<td>0.67</td>
</tr>
<tr>
<td>3g</td>
<td></td>
<td>C₁₁H₈N₂O</td>
<td>184.19</td>
<td>56</td>
<td>84</td>
<td>0.43</td>
</tr>
<tr>
<td>3h</td>
<td>-NO₂</td>
<td>C₁₃H₉N₃O₂</td>
<td>239.23</td>
<td>65</td>
<td>72</td>
<td>0.59</td>
</tr>
</tbody>
</table>

The solvent system used for TLC n-hexane : ethanol (4:2)

All the synthesized compounds were evaluated for anti-inflammatory activity and have shown promising anti-inflammatory activity. The data of anti-inflammatory activity and percentage inhibition of anti-inflammatory activity of synthesized compounds is shown in
Table 2. These observations of anti-inflammatory activity are reported in graphical form in Fig. 2-4.

Table 2: Anti-inflammatory activity of synthesized compounds

<table>
<thead>
<tr>
<th>Compound Code</th>
<th>Paw volume (in ml) ±SEM (%)</th>
<th>Inhibition of paw oedema</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 min</td>
<td>1 hr</td>
</tr>
<tr>
<td>Control</td>
<td>1.346±0.001</td>
<td>1.302±0.001</td>
</tr>
<tr>
<td>Std. Indomethacin</td>
<td>0.86±0.002</td>
<td>0.663±0.002</td>
</tr>
<tr>
<td></td>
<td>(36.10%)</td>
<td>(49.07%)</td>
</tr>
<tr>
<td>3a</td>
<td>1.143±0.003</td>
<td>1.285±0.005</td>
</tr>
<tr>
<td></td>
<td>(15.08%)</td>
<td>(1.30%)</td>
</tr>
<tr>
<td>3b</td>
<td>1.137±0.002</td>
<td>0.855±0.003***</td>
</tr>
<tr>
<td></td>
<td>(15.52%)</td>
<td>(34.33%)</td>
</tr>
<tr>
<td>3c</td>
<td>1.285±0.005</td>
<td>0.848±0.004***</td>
</tr>
<tr>
<td></td>
<td>(4.53%)</td>
<td>(34.86%)</td>
</tr>
<tr>
<td>3d</td>
<td>1.151±0.002</td>
<td>0.785±0.004***</td>
</tr>
<tr>
<td></td>
<td>(10.48%)</td>
<td>(39.70%)</td>
</tr>
<tr>
<td>3e</td>
<td>1.252±0.001</td>
<td>0.081±0.003***</td>
</tr>
<tr>
<td></td>
<td>(6.98%)</td>
<td>(93.77%)</td>
</tr>
<tr>
<td>3f</td>
<td>1.150±0.002</td>
<td>1.189±0.002</td>
</tr>
<tr>
<td></td>
<td>(14.56%)</td>
<td>(8.67%)</td>
</tr>
<tr>
<td>3g</td>
<td>1.226±0.002</td>
<td>1.218±0.003</td>
</tr>
<tr>
<td></td>
<td>(8.91%)</td>
<td>(6.45%)</td>
</tr>
<tr>
<td>3h</td>
<td>1.148±0.003</td>
<td>1.237±0.001</td>
</tr>
<tr>
<td></td>
<td>(14.71%)</td>
<td>(4.99%)</td>
</tr>
</tbody>
</table>

n = 5, The observations are mean ± SEM, **P < 0.01, *P < 0.05, as compared to control (ANOVA followed by Dunnett’s test)
Fig. 2: percentage inhibition of anti-inflammatory activity after 1hr.

Fig. 3: percentage inhibition of anti-inflammatory activity after 2 hr.

Fig. 4: percentage inhibition of anti-inflammatory activity after 3hr
It is observed that after 1hr compound no. 3e having pyridine ring, and after 2hr compound no. 3d having hydroxyl phenyl ring exhibited 93.77% and 66.81 % of inhibition, respectively. Compound no 3d (48.68%), 3e (52.88%) and 3h (41.63%) have shown better inhibition after 3hr. Thus, compounds having –OH group and–NO₂ has shown excellent activity.

A successfully facile, efficient one pot green synthesis of 2-aryl/heteryl benzimidazole performed from various aryl and heteryl aldehydes and ortho phenylene diamine. A solvent-free condition used under microwave irradiation in presence of eco friendly catalyst zirconium oxy chloride in short reaction times, 3-6 minutes to give the product 3(a-h) in excellent yields.

Lazer ES 1987, have synthesized a number of substituted 2-[(2,2,2-trifluoroethyl)sulfonyl]-1H-benzimidazoles derivatives and evaluated for anti-inflammatory activity that appears to have a mechanism distinct from typical cyclooxygenase inhibiting non-steroidal anti inflammatory drugs.[15] Mariappan et al 2011, have synthesized and biologically evaluated the Mannich bases of benzimidazole derivatives by substituting ethyl group at second position of benzimidazole , primary and secondary amines at secondary nitrogen of benzimidazole, most of the compound having good anti-inflammatory activity.[16] In present synthetic study, substituted benzimidazole derivatives are synthesized by substituting aryl/Heteryl group at second position and secondary nitrogen atom is left unsubstituted where most of the compound having good anti-inflammatory activity.

Rajasekaran et al have synthesized substituted benzimidazole oxadiazole derivatives observed that the compound with phenyl or pyridyl substituted oxadiazole ring fused to benzimidazole moiety through thioacetamide linkage.[17] The compound with phenyl substituted oxadiazole fused to benzimidazole moiety through acetamide linkage has shown least activity, while other derivatives have shown moderate activity. In present study derivatives synthesized such by substituting aryl/Heteryl group at second position instead of oxadiazone group which results in good activity.

Arora et al , have synthesized 2-pyrazoline substituted benzimidazole derivatives which have exhibited good anti-inflammatory activity.[18] Babu et al, synthesized series of isatin derivatives by condensation of N-(1H-benzimidazol-2-yl)-hydrzine carboxamide with various isatin derivatives and evaluated these compounds for in vivo (rat paw edema) for
their anti-inflammatory activity.[19] Selvakumar et al synthesized and evaluated some potent 2-substituted benzimidazolyl chalcones for analgesic, anti-inflammatory, in which most of the compounds exhibited good anti-inflammatory activity.[20] Pogula et al., have synthesized and characterized new benzimidazole 2- substituted isatin derivatives for anti-inflammatory activity.[21] Irfan N. Shaikh et al have synthesized a series of carbonyl-amide linkage based new benzimidazole derivatives from acid, aldehydes and isocyanides at ambient temperature via Passerini reaction.[22] Thus, from the previous reviews it is found that, benzimidazole derivatives were prepared, possessing aryl/heteryl group at second position have exhibited the anti-inflammatory activity and thus support the synthesis.

CONCLUSION

The methodology used here is green synthetic protocol and practically avoids use of costly solvents, the removal and drainage of solvent. This one pot, solvent free synthesis is thus eco friendly methodology. This cost effective method can be adopted for synthesis of 2-aryl/heteryl benzimidazole. The synthesized derivatives 3(a-h) possess good potential to be developed as lead molecules, after optimization these compounds can be used as anti-inflammatory agents.

ACKNOWLEDGEMENT

The authors are grateful to the Chairman of the Maulana Azad Education Trust and Principal Dr. M.H Dehghan for encouragement and support.

REFERENCES


