INTRODUCTION

Among the nitrogen derivatives, imidazo-fused heterocycles are becoming more important in medicinal and organic chemistry, as they exhibit a broad spectrum of pharmacological and biological activities, such as antiviral, antibacterial, anti-fungal and anti-inflammatory properties [1]. The significance of imidazopyridine scaffolds in the drug discovery sector is well appreciated because of the appealing benefits they offer. Imidazole fused polyheterocycles containing ring junction nitrogen have attracted considerable interest in medicinal chemistry in view of their uses as anti-inflammatory [2], anticancer [3], antibacterial [4] and antituberculosis [5] agents. The importance of imidazo[1,2-a]pyridine is evident from the fact that it is prevalent in several marketed drugs such as olprinone (cardio tonic agent, a phosphodiesterase-PDE 3 inhibitor) [6,7], zolpidem (hypnotic) [8], levamisole (anticancer) [9,10], alpidem (a nonsedative anxiolytic) [11-13], zolimidine (anti-inflammatory) [14,15]. They are also used in molecular recognition and bio-imaging probes due to their structural characteristics [16-18], sedative agents (saripidem & necopidem) [19,20]. Functionalized heterocyclic scaffolds derived from imidazo[1,2-a]pyridines have shown broad therapeutic properties such as treatment of heart disease [4], migraines [21], digestive disease [22,23] and viral disease [24].

In this paper, we report the synthesis of some novel imidazo[1,2-a]pyridine derivatives, a straightforward, isocyanide based Groebke-Blackburn-Bienayme [25-27], three component reactions in which aldehyde, 2-aminopyridine and isocyanide are condensed in presence of green parameters such as (i) ZnO nanoparticles/ZnFe2O4 nanoparticles (reusable heterogeneous catalysts), (ii) 2-methyltetrahydrofuran (green solvent) and (iii) microwave irradiation (energy efficiency reducing time period of the reaction). Furthermore, these derivatives were further evaluated for their antidiabetic studies.

EXPERIMENTAL

All the chemicals were commercially procured from Alfa Aesar. Microwave assisted experiments were conducted using a CEM discovery system in a closed vessel under magnetic stirring. 5 mL reaction vial, microwave tube: 10 mL pressure vessel, pyrex were used. Melting points were determined in open glass capillaries on a Stuart SMP30 apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellets on a Shimadzu FTIR 8400S spectrophotometer. 1H NMR (400 MHz) spectra were recorded on a Bruker DPX 400 spectrophoto-
meter using tetramethyldisilane (TMS) as internal standard, CDCl₃ and DMSO-d₆ as solvents. HRMS spectra were recorded on a Xevo QT of mass spectrometer. Silica gel 60 F24 of Merck pre-coated plates were employed for their thin layer chromatography (TLC) analysis to check the purity of the compounds, the spot being located under UV light and iodine vapoors.

**Synthesis of ZnO nanoparticles:** 2.5 g of Zinc nitrate \([\text{Zn(NO}_3\text{)}_2\cdot 4\text{H}_2\text{O}]\) was dissolved in 300 mL distilled water. The pH of the solution was brought to 8.0 by drop wise addition of ammonium hydroxide solution (20%). The reaction mixture was then stirred for 1 h at room temperature and transferred to a Teflon lined steel autoclave and maintained at 100 to 120 °C for different time periods ranging from 6 to 24 h. The autoclave was sealed and maintained at 165 °C for 16 h in the furnace and then allowed to reach the room temperature. Finally, the brown precipitated solution was coarsely stirred for 0.5 h and transferred to 50 mL of Teflon lined autoclave. The autoclave was sealed and maintained at 165 °C for 16 h in the furnace and then allowed to reach the room temperature. Finally, the brown precipitated solution was washed several times with distilled water, filtered and dried at 80 °C overnight. The reaction can be scaled without any change in phase and morphology of the samples.

**Synthesis of ZnFe₂O₄ nanoparticles:** Ferric nitrate (4.87 g), Zinc nitrate (3.75 g) and sodium hydroxide (3.28 g) were mixed together and dissolved in 40 mL of distilled water. Then 2 mL of polyethylene glycol (PEG) was added dropwise in the solution under constant stirring at room temperature and the pH level was maintained around 11. The mixture was continuously stirred for 0.5 h and transferred to 50 mL of Teflon lined autoclave. The autoclave was sealed and maintained at 165 °C for 16 h in the furnace and then allowed to reach the room temperature. Finally, the brown precipitated solution was washed several times with distilled water and absolute ethanol. Then the brown precipitates were collected and dried at 60 °C for 6 h in hot air oven and characterized.

**Synthesis of 2-substituted aryl/alkyl-N-aryl/alkyl imidazol[1,2-α]pyridin-3-amine derivatives (6a-f/7a-f) using ZnO nanoparticles/ZnFe₂O₄ nanoparticles:** To a microwave tube vessel containing 2-methyltetrahydrofuran (1 mL) and ethanol (catalytic quantity), was sequentially added 2-aminopyridine (50 mg, 0.53 mmol), corresponding aryl/alkyl aldehydes 4a-f (0.53 mmol), ZnO-NPs/ZnFe₂O₄ NPs (10 mol %) and phenyliso-cyanide (50 mg, 0.53 mmol) and then concentrated with a pipette. Diluted with 2-methyltetrahydrofuran (2 × 3 mL) and the combined organic phases concentrated in vacuum. The product was further purified with the help of recrystallization using isopropanol-acetate and n-heptane to obtain the desired 2-substituted aryl/alkyl-N-phenylimidazo[1,2-α]pyridin-3-amine derivatives (6a-f) in high purity with 80-85% yield. The catalyst is washed thrice with ethyl acetate, dried and the fresh reactants were introduced into the microwave dish, followed by microwave irradiation allowing the reaction to proceed for the next run.
N-Phenyl-2-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (7a) [29]: Off-white solid; Yield: 84 %; m.p.: 186-187 °C; IR (KBr, νmax, cm⁻¹): 3435 (-N-H str), 2922 (-C-H str), 1594 (-C=N str), 1493 (-C=C- str), 1151 (-C-N str); 1H NMR (400 MHz, CDCl₃): δ 2.36 (s, 3H), 6.72 (d, J = 7.2 Hz, 2H), 6.54 (d, J = 7.2 Hz, 2H), 6.70 (t, J = 7.6 Hz, 2H), 6.86 (t, J = 6.8 Hz, 1H), 7.64-7.66 (m, 2H), 7.72 (t, J = 6.0 Hz, 1H), 8.19 (d, J = 7.9 Hz, 1H), 8.28 (s, 1H, D₂O exchangeable), 8.52 (d, J = 5.4 Hz, 1H); ESI-MS: m/z 287.5 (M⁺)+. Elemental analysis C₁₆H₁₇N₃ calcd. (found) %: C 76.45 (76.41), H 6.81 (6.80), N 17.70 (17.67).

N-p-Tolyl-2-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (7b): White solid; Yield: 80 %; m.p.: 183-185 °C; IR (KBr, νmax, cm⁻¹): 3434 (-N-H str), 2928 (-C-H str), 1598 (-C=N str), 1496 (-C=C- str), 1156 (-C-N str); 1H NMR (400 MHz, CDCl₃): δ 3.78 (s, 3H), 6.68 (d, J = 6.8 Hz, 2H), 6.82 (d, J = 7.0 Hz, 2H), 6.78 (t, J = 7.6 Hz, 2H), 6.90 (t, J = 6.8 Hz, 1H), 7.71-7.76 (m, 2H), 7.76 (t, J = 6.6 Hz, 1H), 8.22 (d, J = 7.8 Hz, 1H), 8.31 (s, 1H, D₂O exchangeable), 8.48 (d, J = 5.8 Hz, 1H); ESI-MS: m/z 301.3 (M⁺)+. Elemental analysis C₁₆H₁₅N₃ calcd. (found) %: C 75.97 (75.94), H 5.36 (5.32), N 18.64 (18.62).

N-(4-Methoxy-phenyl)-2-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (7c): Yellow syrupy liquid; Yield: 80 %; IR (KBr, νmax, cm⁻¹): 3268 (-N-H str), 2971 (-C-H str), 1597 (-C=N str), 1472 (-C=C- str), 1141 (-C-N str); 1H NMR (400 MHz, CDCl₃): δ 1.38 (t, J = 6.8 Hz, 3H), 4.14 (q, J = 6.8 Hz, 2H), 6.08 (d, J = 10.0 Hz, 1H), 6.71 (t, J = 6.8 Hz, 1H), 7.04-7.13 (m, 2H), 7.50 (d, J = 9.2 Hz, 1H), 7.68-7.72 (m, 1H), 7.95 (d, J = 7.0 Hz, 1H), 8.14 (d, J = 8.2 Hz, 1H), 8.52 (d, J = 4.8 Hz, 1H); ESI-MS: m/z 293.5 (M⁺)+. Elemental analysis C₁₆H₁₄N₄ calcd. (found) %: C 73.90 (73.90), H 6.91 (6.89), N 19.14 (19.11).

**RESULTS AND DISCUSSION**

Xu et al. [28] reported the synthesis of compounds 6a, 6b using zinc iodide catalyzed conditions, Lacerda et al. [29] synthesized compound 6c, 7a using AcOH catalyzed reaction condition, Shinde et al. [31] reported the synthesis of compound 6d using LaCl₃·7H₂O. Kiseliev [32] reported the synthesis of compound 6e using N-fluoropyridinium salts, Dam et al. [33] reported the synthesis of 7d using Montmorillonite K-10 clay as catalyst. To the best of our knowledge, the synthesis of compounds 6f, 7b, 7c, 7e-7f are new and have not been reported in the literature so far. Apart from the above mentioned reagents, in general imidazo[1,2-a]pyridines have been reported to be synthesized by different methodologies for this type of condensation reactions such as Sc(OtBu)₃ [38], ZnCl₂ [39], MgCl₂ [40], ZrCl₄ [41], SnCl₂·2H₂O [42], HClO₄, AcOH [28], p-TSA [43], montmorillonite K-10 [44], cellulose sulfuric acid [26], catalyst free and solvent free reaction condi-
Most of these methods have many limitations in terms of lower product yields, toxicity, longer reaction time, higher energetic reaction conditions or use of hazardous and volatile organic solvents like acetonitrile, toluene, chloroform etc. Moreover, most of those catalysts are not reusable.

Our primary objective is to develop a green synthetic protocol using recyclable and reusable heterogeneous catalyst, green solvent and energy efficiency methods with benign reaction condition. The synthesis of final targets imidazo[1,2-a]pyridines derivatives (6a-f and 7a-f) is illustrated in Scheme-I. These compounds were synthesized via three component condensation reaction between aryl-alkyl-aldehydes (4a-f), 2-aminopyridines and aryl-alkyl isocyanides (5a-f) utilizing reusable nanocrystalline ZnO/ZnFe₂O₄ as catalyst in presence of green solvent 2-methyltetrahydrofuran and catalytic quantity of ethanol (Scheme-I) under microwave irradiation conditions.

The condensation reaction was successful (in presence of ZnO NPs) even without microwave irradiation but took longer reaction time (10-18 h) for the completion of the reaction [29]. In order to reduce the reaction time, attempted microwave conditions in presence of ZnO NPs/ZnFe₂O₄ NPs was successful by reducing the reaction time to 2-5 min. The yields and quality of the products improved to a greater extent than the previously reported literature procedures. The salient features of our work lies in establishing the essential green principle ingredients such as usage of ZnO NPs/ZnFe₂O₄ as a reusable heterogeneous catalyst, 2-methyltetrahydrofuran and catalytic quantity of ethanol (Scheme-I) under microwave irradiation conditions.

Antidiabetic activity: Compilation of the antidiabetic activity results of the synthesized imidazo[1,2-a]pyridine derivatives (6a-f/7a-f) is tabulated in Table-1. All these derivatives exhibited significant hypoglycemic property, but with a certain degree of variation. A major increase in blood glucose was determined in diabetic rats. All the compounds 6a-f/7a-f had shown a significant reduction in blood glucose as compared to control diabetic rats at 50 mg/kg body weight for 3rd and 7th days. Insulin was used as a standard drug for the purpose of the study and showed 68.88 % blood glucose lowering activity at the dose of 50 mg/kg.p.o. From Table-1, it is observed that 7a-f imidazo[1,2-a]pyridine series of compounds exhibited significant hypoglycemic activity when compare to 6a-f series of imidazo[1,2-a]pyridine. Compounds 7d (67.0 %), 7e (65.54 %) and 7f (64.64 %) with substitution R = cyclohexyl, ethyl and isopropyl showed nearly equivalent hypoglycemic activity similar to the standard drug insulin (50 mg/kg b.w) in reducing the blood glucose level, while the compounds 7a (58.06 %), 7b (57.84 %), 7c (57.62 %), 7e (57.62 %) and 7f (57.62 %) were found to be comparable with control diabetic rats.

1H NMR: The proton resonating at 7.81 ppm (d, 1H), 7.60 ppm (d, 1H), 7.15-7.20 ppm (m, 3H, with overlap of phenyl proton) is assigned to the pyridine ring while the protons resonating at 6.50 ppm (d, 2H), 6.70 ppm (d, 1H), 6.82 ppm (t, 1H) and 7.15-7.20 (m, 1H) corresponds to the phenyl ring protons. The protons resonating in the aliphatic region 1.33 ppm (d, 6H) and 3.10-3.20 ppm (m, 1H) is assigned to the isopropyl group while the proton resonating at 5.30 (s, 1H, D₂O exchangeable) is assigned to the –NH group, respectively.
In general, it is concluded that in the main scaffold of imidazo[1,2-a]pyridine series, all the compounds exhibited significant hypoglycemic activity. In case of imidazo[1,2-a]pyridine derivatives, most of the compounds viz., compounds 6a (55.02 %), 6b (55.20 %), 6c (54.95 %), 6d (56.20 %), 6e (R = 55.64 %) and 6f (54.93 %) displayed moderate hypoglycemic activity.

In general from the determined results, it is concluded that in the main scaffold of imidazo[1,2-a]pyridine nucleus, inclusion of pyridine ring in the second position and N-substituted aryl/alkyl moieties viz., compounds (7a-f) reduced the glucose level in diabetic rats. However, the impact of 7d, 7e and 7f is more pronounced in alloxan induced diabetic rats.

Further exploration of the above established results towards the synthesis, toxicity studies and mode of action of hypoglycemic activity may lead to the development of an efficient drug candidate for diabetes mellitus.

**Conclusion**

The present paper illustrates the green synthesis of imidazo[1,2-a]pyridine derivatives (6a-f/7a-f) using the green parameters such as (i) ZnO nanoparticle/ZnFe2O4 (a magnetically separable heterogeneous catalyst), (ii) 2-methyltetrahydrofuran (green solvent) and (iii) microwave irradiation (energy efficiency reducing time period of the reaction) utilizing the raw materials viz., such as aryl/alkyl-aldehydes, 2-aminopyridine and aryl/alkyl isocyanides. Evaluation of antidiabetic activity of the synthesized imidazo[1,2-a]pyridine derivatives 6a-f/7a-f revealed that most of the compounds exhibited significant hypoglycemic property when compare to insulin as the reference drug. In general, it is concluded that in the main scaffold of imidazo[1,2-a]pyridine nucleus, inclusion of pyridine ring in the second position and N-substituted aryl/alkyl moieties such as compounds 7d (67.0 %), 7e (65.54 %) and 7f (64.64 %) with substitution R = cyclohexyl, ethyl and isopropyl reduced the glucose level in diabetic rats.

**ACKNOWLEDGEMENTS**

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<table>
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<tr>
<th>Treatment (mg/kg b.w p.o)</th>
<th>Day-0</th>
<th>Day-3</th>
<th>Day-7</th>
<th>Hyperglycemic activity (%)</th>
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<tr>
<td>Control (0.5 % CMC)</td>
<td>345.0 ± 2.48</td>
<td>376.30 ± 3.54**</td>
<td>395.1 ± 3.03**</td>
<td>68.88</td>
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<td>Insulin</td>
<td>354.0 ± 1.96</td>
<td>146.30 ± 2.74**</td>
<td>110.14 ± 2.46</td>
<td>54.57</td>
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<tr>
<td>6a</td>
<td>346.5 ± 2.46</td>
<td>262.10 ± 2.26</td>
<td>157.40 ± 3.46</td>
<td>55.02</td>
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<tr>
<td>6b</td>
<td>343.0 ± 3.25</td>
<td>255.10 ± 2.72</td>
<td>154.64 ± 2.46</td>
<td>54.95</td>
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<tr>
<td>6c</td>
<td>353.4 ± 2.27</td>
<td>282.3 ± 3.65</td>
<td>159.20 ± 1.69</td>
<td>54.95</td>
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<tr>
<td>6d</td>
<td>352.6 ± 2.26</td>
<td>280.20 ± 3.80</td>
<td>154.42 ± 1.92</td>
<td>56.20</td>
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<tr>
<td>6e</td>
<td>354.3 ± 2.46</td>
<td>246.50 ± 3.13</td>
<td>157.30 ± 1.46</td>
<td>56.64</td>
</tr>
<tr>
<td>6f</td>
<td>342.4 ± 1.88</td>
<td>282.3 ± 3.65</td>
<td>154.30 ± 3.06</td>
<td>54.93</td>
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<tr>
<td>7a</td>
<td>357.3 ± 2.37</td>
<td>262.35 ± 1.68</td>
<td>154.89 ± 3.01</td>
<td>58.06</td>
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<tr>
<td>7b</td>
<td>325.8 ± 2.25</td>
<td>207.21 ± 3.13</td>
<td>120.42 ± 2.19</td>
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<tr>
<td>7c</td>
<td>334.6 ± 2.05</td>
<td>183.50 ± 1.94</td>
<td>125.30 ± 2.66</td>
<td>62.55</td>
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<tr>
<td>7d</td>
<td>348.5 ± 2.86</td>
<td>239.44 ± 2.16</td>
<td>114.72 ± 1.98</td>
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<tr>
<td>7e</td>
<td>338.6 ± 2.40</td>
<td>225.28 ± 2.46</td>
<td>117.35 ± 1.60</td>
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<tr>
<td>7f</td>
<td>339.3 ± 3.39</td>
<td>239.22 ± 2.13</td>
<td>116.50 ± 3.99</td>
<td>64.64</td>
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</table>

Values are represented as mean ± SEM. Data were analyzed using analysis of variance and group means were compared with Tukey-Kramer Post ANOVA test. The values were considered when P < 0.01. **P < 0.001; Tabulated data are expressed as mean ± SEM; (n = 6).

**REFERENCES**


