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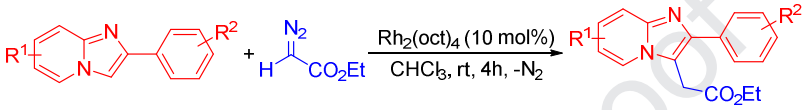

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ABSTRACT

An efficient and environment-friendly C3-ethoxycarbonylmethylation of imidazo[1,2-a]pyridines with ethyl diazoacetate in the presence of a Rh(II) catalyst was developed. Such strategy not only enables the synthesis of zolpidem, but also provides a way to generate synthetic intermediates to afford cellular active anticancer agents.

1. Introduction

Imidazo[1,2-a]pyridines represent privileged scaffolds in azaheterocycle chemistry and medicinal chemistry [1], and have been found to be the core structure of many natural products and marketed drugs [2], including alpidem, necopidem, saripidem, zolpidem (Ambien®), olprinone, DS-1, minodronic acid, divalpon, and zolimidine. As imidazo[1,2-a]pyridines exhibit privileged drug-like properties and favorable pharmacokinetics profiles, more and more efforts have been made to develop new drug candidates based on imidazo[1,2-a]pyridine scaffold. Veken group discovered a novel class of urokinase plasminogen activator (uPA) inhibitors with C3-aminated imidazo[1,2-a]pyridine scaffold for cancer therapy [3]. Maekawa lab reported C3-methylated imidazo[1,2-a]pyridine derivatives as melanin-concentrating hormone receptor 1 (MCHR1) antagonist used as antiobesity agents [4]. Trigewell and coworkers developed a series of efficacious insulin-like growth factor-1 receptor (IGF-1R) kinase inhibitors derived from C2-heteroarylimidazo[1,2-a]pyridine scaffold with improved cellular anticancer activities and favorable pk properties [5]. Heckmann et al identified a first- in-class autotaxin inhibitor based on the 2,3,6 trisubstituted imidazo[1,2-a]pyridine, which is currently being evaluated in an exploratory phase 2a study for the treatment of idiopathic pulmonary fibrosis [6]. Merk group designed and developed a high-affinity farnesoid X receptor (FXR) modulator comprising imidazo[1,2-a]pyridine core scaffold for nonalcoholic steatohepatitis (NASH) treatment, which showed extraordinary selectivity for FXR and favorable metabolic stability compared to steroidal FXR agonists [7]. Taken together, imidazo[1,2- a]pyridine scaffold represents a promising area for identification of lead structures towards drug discovery.

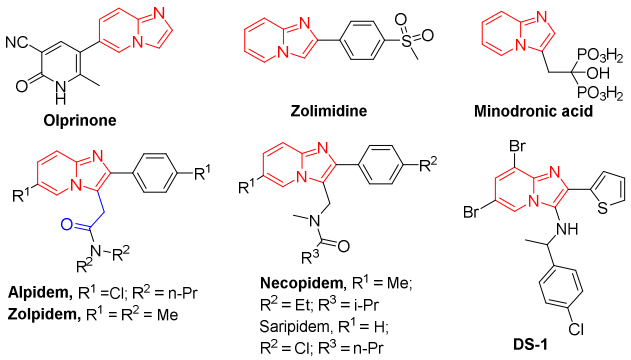

Figure 1. Therapeutic agents derived from imidazo[1,2-a]pyridine.

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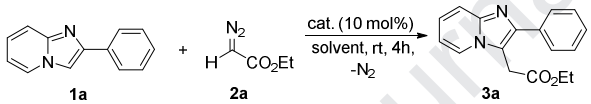
Recently, through the high-throughput computational screening and structure-based drug design, we identified a new series of cellular active signal transducer and activator of transcription 3 (STAT3) inhibitors with the core structure of C3-ethoxycarbonylmethylated imidazo[1,2-a]pyridine, which is an ester analogue of zolpidem and alpidem (Fig. 1). Previously, such a structural motif can be prepared through C3-alkylation of imidazo[1,2-a]pyridine with xanthates under the mechanism of xanthate-based radical addition reaction [8]. However, high temperature and several equivalents of oxidants were utilized in the process. Therefore, a more effective and environment-friendly approach to achieve C3-ethoxycarbonylmethylimidazo[1,2-a]pyridine is still needed.

Inspired by the nucleophilicity of C-3 position of imidazo[1,2-a]pyridines [9] and electrophilicity of the carbene intermediates generating from the Rh(II) catalyst and diazo compounds [10], we envisioned that direct C3-ethoxycarbonylmethylation of imidazo[1,2-a]pyridines with ethyl diazoacetate might be achieved in the presence of a Rh (II) catalyst. Therefore, in continuation of our e□orts on the development of expeditious methods for the synthesis of imidazo[1,2-a]pyridine analogues to generate promising lead compounds for drug discovery [11], we started a campaign to develop an expeditious approach to access C3-ethoxycarbonylmethylated imidazo[1,2-a]pyridines. Most notably, Lee et al. reported a Rh (II)-catalyzed regioselective C3-alkylation of 2-arylimidazo[1,2-a]pyridine with aryl α-diazoesters this year [12]. Herein, we report an efficient and environment-friendly C3-ethoxycarbonylmethylation of imidazo[1,2-a]pyridines with ethyl diazoacetate in the presence of Rh (II) catalyst.

Table 1

Optimization of reaction conditions[a]



1a 2a 3a

Entry	Catalyst	Solvent	Yield [%][b]
1	$Rh_2(OAc)_4$	CH_2Cl_2	71
2	$Rh_2(OAc)_4$	$CHCl_3$	79
3	$Rh_2(OAc)_4$	DCE	67
4	$Rh_2(OAc)_4$	THF	50
5	$Rh_2(OAc)_4$	Toluene	40
6	$Rh_2(OAc)_4$	CH_3CN	64
7	$Rh_2(OAc)_4$	1,4-dioxane	39
8	$Rh_2(oct)_4$[c]	$CHCl_3$	89
9	$Rh_2(TFA)_4$	$CHCl_3$	35
10	$[Rh(COD)Cl]_2$	$CHCl_3$	28
11	$[Rh(COD)OH]_2$	$CHCl_3$	15
12	$[Rh(C_2H_4)Cl]_2$	$CHCl_3$	27
13	$Rh_2(esp)_2$	$CHCl_3$	55

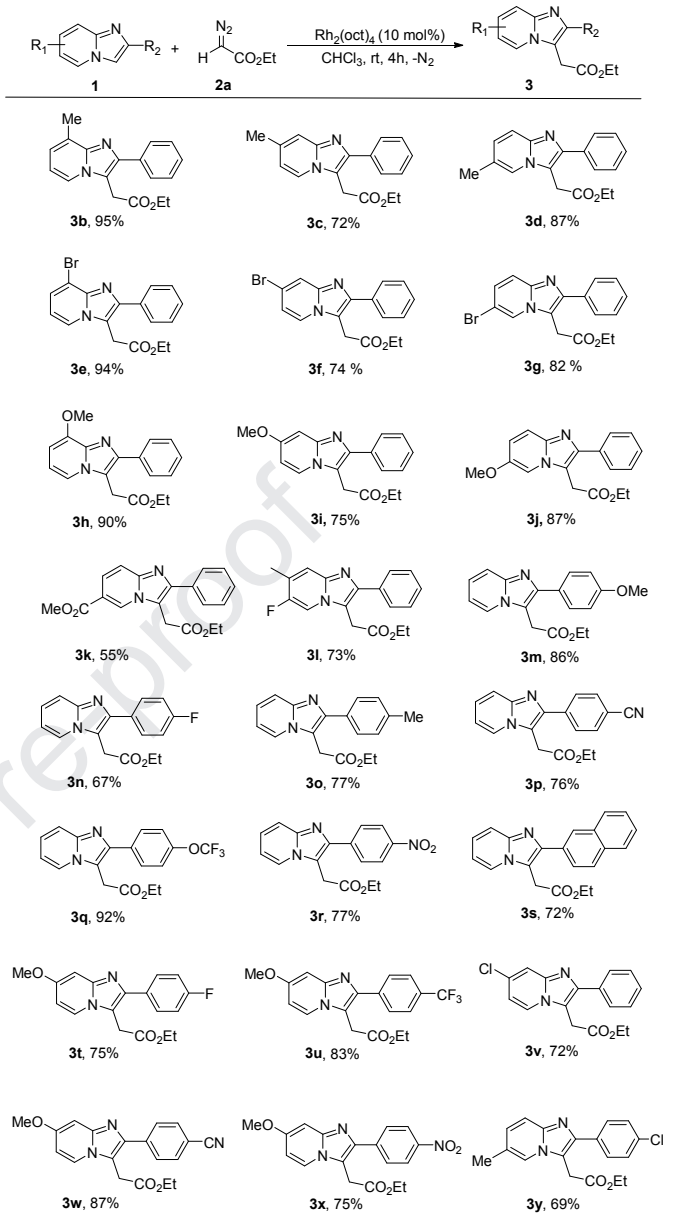
[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv) was reacted with **2a** (1.5 equiv) and catalyst (10 mol %) in solvent under a N_2 atmosphere.

[b]Isolated yields.

[c]$Rh_2(oct)_4$: $[Rh(C_7H_{15}CO_2)_2]_2$.

2. Results and discussion

Guided by the theory mentioned above, our investigation commenced with a survey of appropriate solvent using 2-phenylimidazo[1,2-a]pyridine (**1a**) and ethyl 2-diazoacetate (**2a**) as the model substrates under the influence of 10 mol% $Rh(OAc)_2$. Various solvents were tested (Table 1, entry 1-7), and chloroform (Table 1, entry 2) showed the best activity



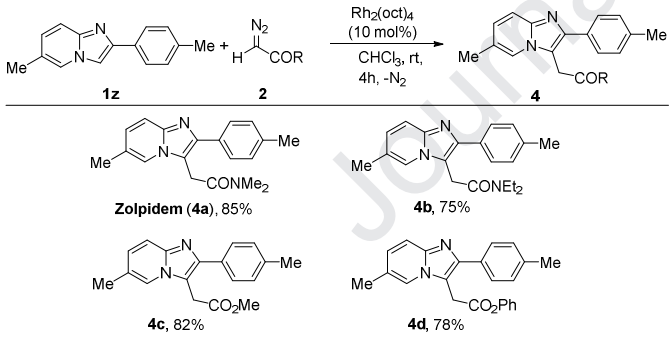
Scheme 1. Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2a** (1.5 equiv), $Rh_2(oct)_4$ (10 mol%), $CHCl_3$ (4 mL), Isolated yields.

and afforded title C3-ethoxycarbonylmethylated 2-phenyl-imidazo[1,2-a]pyridine **3a** in 79% yield. Encouraged by this result, further evaluation of a range of Rh(II) catalysts was performed (entries 8−14 in Table 1). Interestingly, the nature of the catalyst had a profound impact on the reaction and $Rh_2(oct)_4$ proved to be the most e□ective (Table 1, entry 8). The desired compound **3a** was gratifyingly afforded in 89% yield using $Rh_2(oct)_4$ and chloroform.

With optimal reaction conditions in hand, we next turned our attention to the scope of 2-aryl-imidazo[1,2-a]pyridines that can participate in this coupling reaction (Scheme 1). Initially, we fixed the phenyl function at the C-2 position of imidazo[1,2-a]pyridine and then examined the e□ciency of the reaction with various substituents on the pyridine sca□old. As shown in Scheme 1, the C3-ethoxycarbonylmethylation of 2-phenyl-imidazo[1,2-a]pyridines tolerated a large number of substrates, furnishing the corresponding title compounds (**3b**–**3j**) in good to

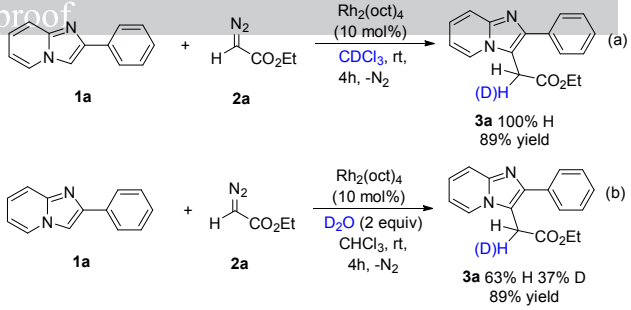
excellent yields. Incorporation of a methyl group at the C-8, C-7, and C-6 positions of imidazo[1,2-a]pyridine a□orded **3b**, **3c**, **3d** in yields of 95%, 72%, and 87%, respectively. Similarly, introduction of an electron-withdrawing group (Br) or electron-donating group (MeO) at any of the C-8/C-7/C6 position of the imidazo[1,2-a]pyridine also provided the corresponding products in good to excellent yields (**3e**–**3g** and **3h**-**3j**). Particularly noteworthy is that C-8 and C-6 substituted imidazo[1,2-a]pyridines seemed to be more reactive than C-7 substituted ones. It should also be noted that C-6 methoxycarbonylated imidazo[1,2-a]pyridine gave slightly lower yield, a□ording the corresponding **3k** in 55% yield. Interestingly, the presence of both methyl and fluoro (**3l**) was still suitable for this reaction.

Afterwards, with the pyridine sca□old of imidazo[1,2-a]pyridine unsubstituted, a series of functional groups at the para position of the C-2 phenyl ring were explored (3**m**–3**r**). It was found that all substituents either with electron-donating (OMe and methyl) or electron-withdrawing properties (F, OCF3, NO_2, and CN) were tolerated under this reaction with yields between 67 and 92%. Furthermore, steric-hindrance (**3s**) can also be tolerated in this reaction. As evident from the yield of products **3a**–**3s**, it can be concluded that electronic e□ects associated with electron-donating/withdrawing substituents on the C-2 phenyl ring and the pyridine sca□old of the imidazo[1,2-a]pyridine do not significantly a□ect the reactivity. To confirm this conclusion, we incorporated diverse substituents to C-2 phenyl ring and the pyridine sca□old of the imidazo[1,2-a]pyridine and examined the reaction efficiency. As shown in scheme 3, both substituted imidazo[1,2-a]pyridine at C-2 phenyl ring and the pyridine sca□old underwent reactions smoothly and provided the products **3t**-**3y** with yields between 69 and 87%.



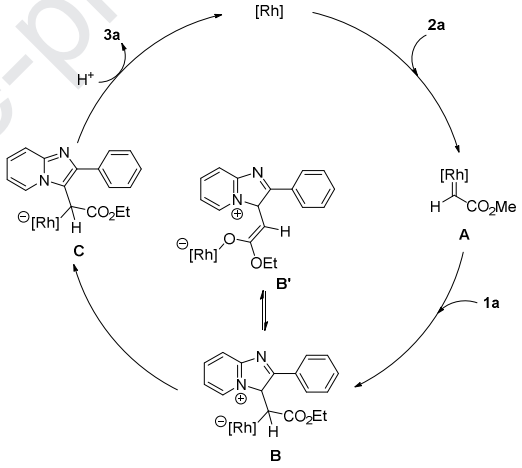
Scheme 2. Reaction conditions: **1z** (0.2 mmol, 1.0 equiv), **2** (1.5 equiv), $Rh_2(oct)_4$ (10 mol%), $CHCl_3$ (4 mL), Isolated yields.

Furthermore, the optimized reaction conditions were successfully extended to diazo compounds to expand the scope of the methodology. Under the same reaction conditions, Zolpidem (**4a**) was prepared from imidazo[1,2-a]pyridine (**1z**) and 2-diazo-N,N-dimethylacetamide in 85% yield (Scheme 2). Its ethyl analogue **4b** was also obtained in 75% yield. Methyl 2-diazoacetate and phenyl 2-diazoacetate were also well tolerated under the optimized reaction conditions and gave the title compounds, **4c** and **4d**, in 82% and 78% yield, respectively.



Scheme 3. Deuterium-labelling experiments.

To investigate the mechanism of the ethoxycarbonylmethylation reaction, we conducted deuterium-labelling experiments (Scheme 3). Firstly, the reaction solvent was changed to $CDCl_3$ from $CHCl_3$ and gave a product without deuterium, which rules out the possibility that the hydrogen atom came from the solvent (Scheme 3a). Then D_2O was added to the reaction solution, and resulted in the formation of the title compound with 37% deuterium incorporation, indicating that the hydrogen atom could be derived partly from water present in the solvent (Scheme 3b).



Scheme 4. A possible mechanism.

Based on our above experimental results and previous reports,[13] a possible mechanism for the C3-ethoxycarbonylmethylation of imidazo[1,2-a]pyridines with ethyl diazoacetate is proposed in Scheme 4. Initially, a carbene complex **A** is formed from **2a** in the presence of rhodium (II) catalyst, followed by electrophilic attack at the C3-carbon of the imidazo[1,2-a]pyridine **1a** resulting in the formation of rhodium-bound zwitterionic intermediate **B**. Deprotonation of intermediate **B** furnished intermediate **C**, which underwent proton transform to afford compound **3a**.

3. Conclusion

In summary, we have developed a highly effective and environment-friendly strategy for the regioselective C3-ethoxycarbonylmethylation of imidazo[1,2-a]pyridines with ethyl diazoacetate in the presence of a Rh(II) catalyst. Such method not only enables the synthesis of zolpidem, but also provides a way to generate synthetic intermediates to achieve cellular active STAT3 inhibitors. Further e□orts on the structure-activity study of STAT3 inhibitors derived from this scaffold will be reported in due course.

4. Experimental section

4.1 General experimental details

^{1}H NMR spectral data were recorded on Varian Mercury 400 NMR spectrometer and ^{13}C NMR data were recorded on Varian Mercury 100 NMR spectrometer. Chemical shifts were quoted in parts per million (ppm) referenced to the residual undeuterated solvent peak or 0.0 ppm for tetramethylsilane, and the signals are described as br (broad singlet), d (doublet), dd (doublet of doublet), m (multiple), q (quarter), s (singlet), and t (triplet). Coupling constants (*J* values) are given in Hz. Low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded at an ionizing voltage of 70 eV on a Finnigan/MAT95 spectrometer. Column chromatography was carried out on silica gel (200–300 mesh). Analytical TLC was performed silica gel plates and visualized under ultraviolet light (254 nm).

4.2 *General procedure for the preparation of compounds **3** and **zolpidem***

A dried flask was charged with imidazo[1,2-a]pyridine (0.2 mmol, 1.0 equiv.), Ph2(oct)4 (0.02 mmol, 10 mol%), and CHCl3 (4 mL). Diazoester **2** (0.3 mmol, 1.5 equiv.) was added into the mixture dropwise under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 4h and then concentrated in vacuum. The crud product was purified by chromatography (EtOAc:Hexane=1:2) to yield corresponding imidazo[1,2-a]pyridine.

5. Spectrum

Ethyl 2-(2-phenylimidazo[1,2-a]pyridin-3-yl)acetate **(3a).** Yellow solid (89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 6.9 Hz, 1H), 7.85 (d, *J* = 7.2 Hz, 2H), 7.67 (d, *J* = 9.1 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.24 (t, 1H), 6.88 (td, *J* = 6.8, 0.9 Hz, 1H), 4.26 – 4.22 (q, 2H), 4.06 (s, 2H), 1.29 (t, 3H); ^{1}D NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 6.8 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 2H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.23 (t, 1H), 6.86 (t, *J* = 6.8 Hz, 1H), 4.24 (q, 2H), 4.05 (s, 1H), 4.03 (s, 1H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{1}H NMR ($CDCl_3$) (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 6.9 Hz, 1H), 7.85 (dd, *J* = 5.1, 3.3 Hz, 2H), 7.67 (d, *J* = 9.1 Hz, 1H), 7.48 (dd, *J* = 10.4, 4.7 Hz, 2H), 7.41 – 7.37 (m, 1H), 7.25 – 7.20 (m, 1H), 6.86 (td, *J* = 6.8, 1.0 Hz, 1H), 4.23 (q, 2H), 4.05 (s, 0.66H), 4.03(s,0.60H)1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 145.0, 144.6, 134.0, 128.6 (d, *J* = 4.4 Hz), 127.9, 124.5, 123.7, 117.6, 113.0, 112.3, 77.3, 77.1, 76.8, 61.6, 30.8, 14.1; MS(EI) m/z 281.12 (M^+); HRMS calcd for $C_{17}H_{16}N_2O_2$ (M^+) 281.1285, found:281.1280.

Ethyl 2-(8-methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)acetate **(3b).** Yellow solid (95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 6.8 Hz, 1H), 7.88 – 7.84 (m, 2H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 1H), 7.02 (d, *J* = 6.8 Hz, 1H), 6.78 (t, *J* = 6.8 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 4.03 (s, 2H), 2.69 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 145.4, 144.1, 134.3, 128.8, 128.5, 127.7, 127.5, 123.3, 121.5, 113.3, 112.3, 61.5, 30.9, 17.1, 14.1; MS(EI) m/z 295.14 (M^+); HRMS calcd for $C_{18}H_{18}N_2O_2$ (M^+) 295.1441, found:295.1434.

Ethyl 2-(7-methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)acetate **(3c).** Yellow solid (72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.0 Hz, 1H), 7.84 – 7.80 (m, 2H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.42 (s, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 6.70 (dd, *J* = 7.0, 1.5 Hz, 1H), 4.21 (q, 2H), 4.01 (s, 2H), 2.42 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 145.4, 144.1, 135.5, 134.1, 128.5 (d, *J* = 4.2 Hz), 127.7, 122.9, 115.8, 115.0, 112.3, 61.5, 30.7, 21.2, 14.1; MS(EI) m/z 295.14 (M^+); HRMS calcd for $C_{18}H_{18}N_2O_2$ (M^+) 295.1441, found:295.1433.

Ethyl 2-(6-methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)acetate **(3d).** Yellow solid (87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 6.7 Hz, 1H), 7.84 (d, *J* = 7.1 Hz, 2H), 7.47 (dd, *J* = 14.2, 6.5 Hz, 3H), 7.38 (t, *J* = 6.8 Hz, 1H), 6.72 (d, *J* = 6.1 Hz, 1H), 4.24 (q, 2H), 4.02 (s, 2H), 2.43 (s, 3H), 1.29 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.48 (s), 145.48 (s), 144.26 (s), 135.49 (s), 134.17 (s), 128.56 (d, *J* = 10.8 Hz), 127.76 (s), 122.95 (s), 116.00 (s), 115.01 (s), 112.38 (s), 68.23 (s), 61.53 (s), 61.00 (s), 30.82 (s), 21.26 (s), 14.14 (s); MS(EI) m/z 295.14 (M^+); HRMS calcd for $C_{18}H_{18}N_2O_2$ (M^+) 295.1441, found:295.1444.

Ethyl 2-(8-bromo-2-phenylimidazo[1,2-a]pyridin-3-yl)acetate **(3e).** Yellow solid (94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 5.6 Hz, 1H), 7.84 (d, *J* = 6.9 Hz, 2H), 7.48 (dd, *J* = 14.2, 6.4 Hz, 3H), 7.40 (d, *J* = 6.1 Hz, 1H), 6.75 (d, *J* = 6.7 Hz, 1H), 4.24 – 4.22 (q, 2H), 4.03 (s, 2H), 1.27 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 165.0, 145.4, 142.9, 133.6 (d, *J* = 3.1 Hz), 129.8, 128.9, 128.6, 128.1, 126.9, 123.1, 114.8, 112.3, 111.7, 61.7, 61.3, 31.0, 14.1(d, *J* = 6.3 Hz); MS(EI) m/z 359.03 (M^+); HRMS calcd for $C_{17}H_{15}BrN_2O_2$ (M^+) 359.0390, found:359.0395.

Ethyl 2-(7-bromo-2-phenylimidazo[1,2-a]pyridin-3-yl)acetate **(3f).** Yellow solid (74%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.3 Hz, 1H), 7.87 (s, 1H), 7.81 (d, *J* = 7.3 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 1H), 6.96 (dd, *J* = 7.2, 1.6 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.01 (s, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 145.1, 133.5, 128.6 (d, *J* = 12.2 Hz), 128.2, 124.1, 119.8, 118.3, 116.2, 113.3, 61.8, 30.7, 14.1; MS(EI) m/z 359.03 (M^+); HRMS calcd for $C_{17}H_{15}BrN_2O_2$ (M^+) 359.0390, found:359.0389.

Ethyl 2-(6-bromo-2-phenylimidazo[1,2-a]pyridin-3-yl)acetate **(3g).** Yellow solid (82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 1.0 Hz, 1H), 7.85 – 7.81 (m, 2H), 7.59 (d, *J* = 9.5 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.31 (dd, *J* = 9.5, 1.8 Hz, 1H), 4.28 (q, 2H), 4.05 (s, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 165.2, 145.4, 143.4, 133.5, 129.8, 128.6 (d, *J* = 8.9 Hz), 128.1, 127.9, 124.0, 118.2, 113.5, 107.1, 61.8, 61.2, 30.7, 14.0(d, *J* = 17.6 Hz); MS(EI) m/z 359.03 (M^+); HRMS calcd for $C_{17}H_{15}BrN_2O_2$ (M^+) 359.0390, found:359.0384.

Ethyl 2-(8-methoxy-2-phenylimidazo[1,2-a]pyridin-3-yl)acetate **(3h).** Yellow solid (90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.2 Hz, 2H), 7.73 (d, *J* = 6.8 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 1H), 6.74 (t, *J* = 7.2 Hz, 1H), 6.49 (d, *J* = 7.6 Hz, 1H), 4.21 (q, 2H), 4.01 (d, *J* = 3.7 Hz, 5H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 149.1, 143.7, 139.4, 134.0, 128.7, 128.4, 127.7, 116.5, 114.0, 112.3, 100.7, 61.5, 55.8, 31.0, 14.1; MS(EI) m/z 311.13 (M^+); HRMS calcd for $C_{18}H_{18}N_2O_3$ (M^+) 311.1390, found:311.1396.

Ethyl 2-(7-methoxy-2-phenylimidazo[1,2-a]pyridin-3-yl)acetate **(3i).** Yellow solid (75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.93 (m, 1H), 7.81 (d, *J* = 7.2 Hz, 2H), 7.46 (dd, *J* = 10.3, 4.9 Hz, 2H), 7.37 (d, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 1.7 Hz, 1H), 6.58 (dd, *J* = 7.4, 2.4 Hz, 1H), 4.21 (q, *J* = 7.1, 3.2 Hz, 2H), 3.98 (s, 2H), 3.86 (s, 3H), 1.27 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 157.8, 146.3, 143.6, 134.1, 128.5, 128.2, 127.6, 124.2, 111.7, 107.1, 94.5, 61.4, 55.4, 30.6, 14.0; MS(EI) m/z 311.13 (M^+); HRMS calcd for $C_{18}H_{18}N_2O_3$ (M^+) 311.1390, found:311.1397.

Ethyl 2-(6-methoxy-2-phenylimidazo[1,2-a]pyridin-3-yl)acetate **(3j).** Yellow solid (87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.2 Hz, 2H), 7.67 (s, 1H), 7.58 (d, *J* = 9.6 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.03 (d, *J* = 9.6 Hz, 1H), 4.23 (q, *J* = 6.9 Hz, 2H), 4.01 (s, 2H), 3.86 (s, 3H), 1.28 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 149.4, 144.5, 142.0, 134.0, 128.5 (d, *J* = 18.0 Hz), 127.7, 119.6, 117.6, 113.8, 105.7, 61.6, 56.2, 31.1, 14.2; MS(EI) m/z 311.13 (M^+); HRMS calcd for $C_{18}H_{18}N_2O_3$ (M^+) 311.1390, found:311.1388.

Methyl 3-(2-ethoxy-2-oxoethyl)-2-phenylimidazo[1,2-a]pyridine-6-carboxylate **(3k).** Yellow solid (55%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.86 – 7.83 (m, 2H), 7.80 (dd, *J* = 9.4, 1.6 Hz, 1H), 7.70 (d, *J* = 9.4 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.12 (s, 2H), 3.99 (s, 3H), 1.31 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 165.4, 146.2, 145.5, 133.3, 128.6 (d, *J* = 17.9 Hz), 128.3, 128.1, 124.2, 116.8, 116.3, 114.1, 61.8, 52.4, 30.6, 14.1; MS(EI) m/z 339.13 (M^+); HRMS calcd for $C_{19}H_{18}N_2O_4$ (M^+) 339.1339, found:339.1330.

Ethyl 2-(6-fluoro-7-methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)acetate **(3l).** Yellow solid (73%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 4.8 Hz, 1H), 7.82 – 7.79 (m, 2H), 7.48 (t, *J* = 10.5, 4.8 Hz, 3H), 7.40 – 7.36 (m, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.99 (s, 2H), 2.39 (s, 3H), 1.30 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 154.1, 152.2, 145.2, 142.9, 133.8, 128.5 (d, *J* = 17.5 Hz), 127.9, 127.3, 127.1, 117.0 (d, *J* = 5.4 Hz), 113.5, 110.1, 109.7, 61.7, 30.9, 15.2 (d, *J* = 3.1 Hz), 14.1; MS(EI) m/z 313.13 (M^+); HRMS calcd for $C_{18}H_{17}FN_2O_2$ (M^+) 313.1340, found:313.1336.

Ethyl 2-(2-(4-methoxyphenyl)imidazo[1,2-a]pyridin-3-yl)acetate **(3m).** Yellow solid (86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 6.9 Hz, 1H), 7.80 – 7.77 (m, 2H), 7.66 (d, *J* = 9.0 Hz, 1H), 7.23 – 7.18 (m, 1H), 7.03 – 6.99 (m, 2H), 6.85 (td, *J* = 6.8, 0.9 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.02 (s, 2H), 3.86 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 159.5, 144.9, 144.5, 129.8, 126.6, 124.3, 123.6, 117.4, 114.1, 112.2 (d, *J* = 12.5 Hz), 61.5, 55.3, 30.8, 14.1; MS(EI) m/z 311.13 (M^+); HRMS calcd for $C_{18}H_{18}N_2O_3$ (M^+) 311.1390, found:311.1387.

Ethyl 2-(2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl)acetate **(3n).** Yellow solid (67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.13 (m, 1H), 7.85 – 7.81 (m, 2H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.17 (t, *J* = 8.3 Hz, 2H), 6.89 (t, *J* = 6.8 Hz, 1H), 4.23 (q, *J* = 7.1, 0.8 Hz, 2H), 4.01 (s, 2H), 1.28 (t, *J* = 0.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 163.7, 161.7, 145.0, 143.6, 130.3(d, *J* = 8.1 Hz), 130.0, 124.8, 123.7, 117.5, 115.6, 115.5, 112.8, 112.5, 61.7, 30.8, 14.1; MS(EI) m/z 299.11 (M^+); HRMS calcd for $C_{17}H_{15}FN_2O_2$ (M^+) 299.1190, found:299.1183.

Ethyl 2-(2-(p-tolyl)imidazo[1,2-a]pyridin-3-yl)acetate **(3o).** Yellow solid (77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 6.6 Hz, 1H), 7.73 (d, *J* = 7.1 Hz, 2H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.29 (d, *J* = 7.4 Hz, 2H), 7.23 (t, *J* = 7.8 Hz, 1H), 6.86 (t, *J* = 6.6 Hz, 1H), 4.22 (q, 2H), 4.03 (s, 2H), 2.41 (s, 3H), 1.27 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 144.8, 144.4, 137.7, 130.9, 129.3, 128.5, 124.5, 123.7, 117.4, 112.7, 112.4, 61.6, 30.8, 21.3, 14.1; MS(EI) m/z 295.14 (M^+); HRMS calcd for $C_{18}H_{18}N_2O_2$ (M^+) 295.1441, found:295.1447.

Ethyl 2-(2-(4-cyanophenyl)imidazo[1,2-a]pyridin-3-yl)acetate **(3p).** Yellow solid (76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.14 (m, 1H), 8.02 (dt, *J* = 33.3, 16.7 Hz, 3H), 7.78 (d, 1H), 7.69 (t, *J* = 8.8 Hz, 1H), 7.31 – 7.27 (m, 1H), 6.98 – 6.87 (m, 1H), 4.25 (q, 2H), 4.04 (s, 2H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 145.3, 142.5, 138.6, 132.4 (d, *J* = 19.4 Hz), 129.0, 126.4, 125.7, 125.3 (d, *J* = 24.1 Hz), 125.2 – 125.1, 123.8, 118.8, 117.9, 114.1, 113.0 (d, *J* = 9.8 Hz), 111.4, 61.8, 30.8, 14.1; MS(EI) m/z 306.12 (M^+); HRMS calcd for $C_{18}H_{15}N_3O_2$(M^+) 306.1237, found:306.1235.

Ethyl 2-(2-(4-(trifluoromethoxy)phenyl)imidazo[1,2-a]pyridin-3-yl)acetate **(3q).** Yellow solid (92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 6.7 Hz, 1H), 7.89 (d, *J* = 7.4 Hz, 2H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 6.90 (t, *J* = 6.6 Hz, 1H), 4.24 (q, *J* = 6.7 Hz, 2H), 4.03 (s, 2H), 1.29 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 149.0, 145.0, 143.2, 132.8, 129.9, 124.8, 123.7, 121.1, 117.6, 113.1, 112.6, 61.7, 30.8, 14.1.MS(EI) m/z 365.10 (M^+); HRMS calcd for $C_{18}H_{15}F_3N_2O_3$ (M^+) 365.1108, found:365.1110.

Ethyl 2-(2-(4-nitrophenyl)imidazo[1,2-a]pyridin-3-yl)acetate **(3r).** Yellow solid (77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (dd, *J* = 8.8, 1.7 Hz, 2H), 8.20 (d, *J* = 6.9 Hz, 1H), 8.10 – 8.04 (m, 2H), 7.70 (d, *J* = 9.1 Hz, 1H), 7.31 (dd, *J* = 8.5, 7.5 Hz, 1H), 6.95 (t, *J* = 6.8 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.07 (s, 2H), 1.31 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 147.2, 145.3, 142.1, 140.6, 129.0, 125.4, 123.9 (d, *J* = 6.3 Hz), 117.9, 114.4, 113.1, 62.0, 30.9, 14.1; MS(EI) m/z 326.11 (M^+); HRMS calcd for $C_{17}H_{15}N_3O_4$ (M^+) 326..1135, found:326.1135.

Ethyl 2-(2-(naphthalen-2-yl)imidazo[1,2-a]pyridin-3-yl)acetate (**3s**). Yellow solid (72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.01 (d, *J* = 6.8 Hz, 1H), 7.90 (d, *J* = 8.3 Hz, 1H), 7.84 – 7.79 (m, 2H), 7.73 (d, *J* = 6.5 Hz, 1H), 7.58 (d, *J* = 9.0 Hz, 1H), 7.37 (t, *J* = 9.0, 5.3 Hz, 2H), 7.09 (t, 1H), 6.71 (t, *J* = 6.7 Hz, 1H), 4.12 (q, 2H), 3.94 (s, 2H), 1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 145.0, 144.3, 133.4, 132.9, 131.4, 128.3 (d, *J* = 7.1 Hz), 127.6(d, *J* = 10.3 Hz), 126.5, 126.2 (d, *J* = 5.9 Hz), 124.7, 123.8, 117.4, 113.3, 112.4, 61.6, 30.8, 14.2; MS(EI) m/z 331.14 (M^+); HRMS calcd for $C_{21}H_{18}N_2O_2$ (M^+) 331.1441, found:331.1449.

Ethyl 2-(2-(4-fluorophenyl)-7-methoxyimidazo[1,2-a]pyridin-3-yl)acetate **(3t).** Yellow solid (75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.2 Hz, 1H), 7.80 (s, 2H), 7.15 (t, *J* = 8.0 Hz, 2H), 6.91 (s, 1H), 6.63 – 6.57 (m, 1H), 4.22 (q, *J* = 6.9 Hz, 2H), 3.95 (s, 2H), 3.87 (s, 3H), 1.28 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 163.5, 161.5, 158.0, 146.4, 143.1, 130.3 (d, *J* = 3.2 Hz), 130.0 (d, *J* = 8.1 Hz), 124.2, 115.6, 115.4, 111.5, 107.4, 94.6, 61.6, 55.5, 30.7, 14.1.MS(EI) m/z 329.12 (M^+); HRMS calcd for $C_{18}H_{17}FN_2O_3$ (M^+) 329.1269, found:329.1272.

Ethyl2-(7-methoxy-2-(4-(trifluoromethyl)phenyl)imidazo[1,2-a]pyridin-3-yl)acetate **(3u).** Yellow solid (83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.5 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.08 (s, 1H), 6.65 (dd, *J* = 7.5, 2.4 Hz, 1H), 4.23 (q, 2H), 3.99 (s, 2H), 3.86 (s, 3H), 1.29 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 146.6, 142.0, 137.5, 128.4, 125.7, 125.4 (d, *J* = 3.7 Hz), 124.3, 112.6, 107.9, 94.6, 61.7, 55.5, 30.6, 14.0; MS(EI) m/z 379.12 (M^+); HRMS calcd for $C_{19}H_{17}F_3N_2O_3$ (M^+) 379.1264, found:379.1272.

Ethyl 2-(7-chloro-2-phenylimidazo[1,2-a]pyridin-3-yl)acetate **(3v).** Yellow solid (72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.3 Hz, 1H), 7.80 (d, *J* = 7.4 Hz, 2H), 7.64 (d, *J* = 2.0 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 1H), 6.82 (dd, *J* = 7.3, 2.0 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.00 (s, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 145.4, 144.8, 133.5, 131.1, 128.6, 128.2, 124.1, 116.4, 114.0, 113.3, 61.8, 30.7, 14.1; MS(EI) m/z 315.08 (M^+); HRMS calcd for $C_{17}H_{15}ClN_2O_2$ (M^+) 315.0895, found:315.0890.

Ethyl 2-(2-(4-cyanophenyl)-7-methoxyimidazo[1,2-a]pyridin-3-yl)acetate **(3w).** Yellow solid (87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 11.7, 7.9 Hz, 3H), 7.75 (d, *J* = 8.3 Hz, 2H), 6.92 (d, *J* = 2.4 Hz, 1H), 6.64 (dd, *J* = 7.5, 2.4 Hz, 1H), 4.24 (q, 2H),

3.98 (s, 2H), 3.89 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 157.4, 145.7, 140.8, 137.7, 131.3, 127.6, 123.3, 118.0, 112.0, 110.0, 107.1, 93.7, 60.8, 54.6, 29.8, 13.1; MS(EI) m/z 336.13 (M^+); HRMS calcd for $C_{19}H_{17}N_3O_3$ (M^+) 336.1343, found: 336.1345.

Ethyl 2-(7-methoxy-2-(4-nitrophenyl)imidazo[1,2-a]pyridin-3-yl)acetate **(3x).** Yellow solid (75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 8.6 Hz, 2H), 8.04 (dd, J = 11.7, 8.1 Hz, 3H), 6.94 (d, J = 2.1 Hz, 1H), 6.65 (dd, J = 7.5, 2.3 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 4.01 (s, 2H), 3.90 (s, 3H), 1.30 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 158.4, 146.9 (d, J = 17.0 Hz), 141.5, 140.8, 128.6, 124.3, 123.8, 113.4, 108.2, 94.6, 61.9, 55.6, 30.8, 14.1; MS(EI) m/z 356.12 (M^+); HRMS calcd for $C_{18}H_{17}N_3O_5$ (M^+) 356.1221, found: 356.1220.

Ethyl 2-(2-(4-chlorophenyl)-6-methylimidazo[1,2-a]pyridin-3-yl)acetate **(3y).** Yellow solid (69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.82 – 7.75 (m, 2H), 7.60 – 7.55 (m, 1H), 7.47 – 7.39 (m, 2H), 7.09 (dd, J = 8.4, 4.5 Hz, 1H), 4.22 (q, 2H), 3.98 (s, 2H), 2.38 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 144.1, 143.0, 133.8, 132.5, 129.7, 128.7, 128.0, 122.4, 121.3, 116.8, 112.7, 61.9, 30.8, 18.4, 14.1; MS(EI) m/z 328.10 (M^+); HRMS calcd for $C_{18}H_{17}ClN_2O_2$ (M^+) 329.1051, found: 329.1053.

N, N-dimethyl-2-(6-methyl-2-(p-tolyl)imidazo[1,2-a]pyridin-3-yl)acetamide **(zolpidem).** Yellow solid (85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.53 (t, J = 7.6 Hz, 3H), 7.26 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 9.1 Hz, 1H), 4.08 (s, 2H), 2.94 (s, 3H), 2.88 (s, 3H), 2.40 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 168.5, 143.3, 143.0, 136.9, 132.5, 129.5, 128.0, 127.4, 122.8, 121.0, 116.3, 115.6, 37.4, 35.7, 29.3, 21.2, 18.2; MS(EI) m/z 308.17(M^+); HRMS calcd for $C_{19}H_{21}N_3O$ (M^+) 308.1737, found: 308.1745.

N,N-diethyl-2-(6-methyl-2-(p-tolyl)imidazo[1,2-a]pyridin-3-yl)acetamide (**4b**). White solid(75%);^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 9.1 Hz, 1H), 7.20 (d, J = 7.8 Hz, 2H), 6.98 (dd, J = 9.1, 1.3 Hz, 1H), 4.00 (d, J = 2.8 Hz, 2H), 3.31 (q, J = 7.1 Hz, 2H), 3.15 (q, J = 7.1 Hz, 2H), 2.34 (s, 3H), 2.27 (s, 3H), 1.06 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.1 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 143.7, 143.0, 137.6, 131.2, 129.3, 128.3, 127.9, 122.3, 122.0, 116.0, 114.3, 42.3, 40.6, 30.2, 21.2, 18.4, 14.0, 13.0; MS(EI) m/z 334.21(M^+); HRMS calcd for $C_{23}H_{27}NO$ (M^+) 334.2134, found: 334.2145.

Methyl 2-(6-methyl-2-(p-tolyl)imidazo[1,2-a]pyridin-3-yl)acetate (**4c**). White solid (82%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.65 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 9.2 Hz, 1H), 7.21 (d, J = 7.9 Hz, 2H), 6.96 (dd, J = 9.2, 1.5 Hz, 1H), 3.93 (s, 2H), 3.68 (s, 3H), 2.32 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 144.3, 143.9, 137.4, 131.3, 129.3, 128.2, 127.5, 121.9, 121.2, 116.6, 112.1, 52.4, 30.4, 21.2, 18.3; MS(EI) m/z 293.15(M^+); HRMS calcd for $C_{20}H_{20}O_2$ (M^+) 293.1520, found: 293.1525.

Phenyl 2-(6-methyl-2-(p-tolyl)imidazo[1,2-a]pyridin-3-yl)acetate (**4d**). White solid(78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.81 (d, J = 8.1 Hz, 2H), 7.60 (d, J = 9.2 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.33 (d, J = 7.9 Hz, 2H), 7.24 (t, J = 7.4 Hz, 1H), 7.12 – 7.08 (m, 3H), 4.26 (s, 2H), 2.43 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 157.9, 150.5, 144.6, 144.1, 137.8, 131.1, 129.6 – 129.3, 128.4 127.9, 126.2, 122.3, 121.3,118.9, 116.7, 115.9, 111.8, 30.8, 21.3, 18.4; MS(EI) m/z 355.16(M^+); HRMS calcd for $C_{25}H_{22}O_2$ (M^+) 355.1623, found: 355.1642.

Declaration of competing interest

There are no conflicts to declare.

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Supplementary Material

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1. An efficient and environment-friendly C3-ethoxycarbonylmethylation of imidazo[1,2-a]pyridines was developed.

2. The drug, zolpidem, was prepared in high yield using this methodology.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: