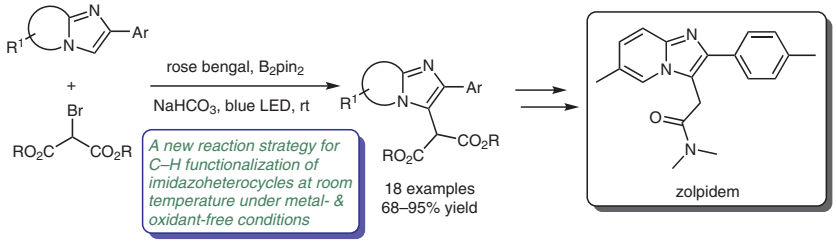
Synthesis N. R. Chaubey et al. Paper

Organophotoredox-Catalyzed C–H Alkylation of Imidazoheterocycles with Malonates: Total Synthesis of Zolpidem

Narendra R. Chaubey[*a]
Anant R. Kapdi[a]
Biswanath Maity[b]

[a] Institute of Chemical Technology, Department of Chemistry, Nathalal Parekh Road, Matunga, Mumbai 400019, Maharashtra, India
narendra581981@gmail.com
[b] Translational Cell Biology Unit, Centre of Biomedical Research, Raibareli Road, Lucknow, Uttar-Pradesh 226014, India



Received: 28.10.2020
Accepted after revision: 29.10.2020
Published online: 02.12.2020
DOI: 10.1055/s-0040-1706103; Art ID: ss-2020-t0503-op

Abstract Organophotocatalytic C–H bond functionalization has attracted a lot of attention in the past several years due to the possibility of catalyzing reactions in a metal- and peroxide-free environment. Continuing on these lines, an organophotoredox-catalyzed C–H functionalization of imidazo[1,2-*a*]pyridines and related heterocycles with bromomalonates under mild conditions is reported, providing excellent yields of the products at room temperature. This is the first report involving malonates as coupling partners leading to the synthesis of a range of functionalized products including total synthesis of zolpidem, a sedative-hypnotic drug molecule.

Key words organophotoredox, C–H functionalization, imidazoheterocycles, zolpidem, drug prejudice

Among the all known N-heterocycles, imidazo[1,2-*a*]-pyridines are widely found in biologically active natural products and pharmaceuticals. It is also considered as a 'drug prejudice' as it shows antipyretic,[1] antiviral,[2] antibacterial,[3] anticancer,[4] antiulcer,[5] and anti-inflammatory[6] properties. There are also marketed drugs such as alpidem, zolpidem, olprinone, necopidem, saripidem, and zolimidine containing imidazo[1,2-*a*]pyridines as the core of the molecule. This moiety have also shown significant importance in material chemistry due to its capabilities to exhibit excited state intramolecular proton transfer.[7] Due to all these reasons, functionalization of imidazo[1,2-*a*]pyridines at different positions by various groups has drawn considerable attention in the last few decades.[8]

In the last few years, visible-light-promoted photoredox process has emerged as a prominent tool for carrying out novel chemical transformations at room temperature.[9] Most common photocatalysts employed to carry out such transformations are ruthenium- and iridium-based complexes. These precious metal catalysts are very expensive and potentially toxic on larger scale.[10] Therefore major efforts have been made in the last few years to use organic dyes as an alternative to these expensive complexes. Recently, several reports have been published involving visible-light-promoted C–H functionalization of imidazo-[1,2-*a*]pyridines at room temperature.[11–21] However, cross coupling reaction between a moiety with C-sp^3 carbon and C-sp^2 carbon of imidazo[1,2-*a*]pyridine is still considered as a challenging task for synthetic organic chemists. Nature of the functional group or the substituent attached at the C3 position of the imidazo[1,2-*a*]pyridine regulates its biological activity. Many well-developed drugs contain methylene group directly attached to imidazo[1,2-*a*]pyridines (Figure 1). To the best of our knowledge, there is no such method for the direct coupling between active methylene compounds and imidazo[1,2-*a*]pyridines. Therefore to check the impact of the presence of an active methylene carbon at the C3 position of the imidazo[1,2-*a*]pyridine, it was decided to carry out this challenging C–C bond formation reaction under mild and sustainable conditions.

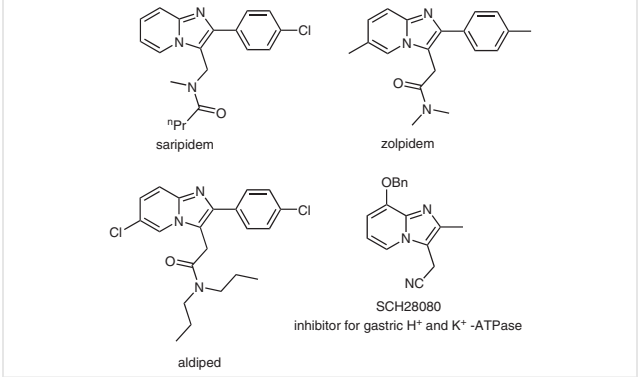
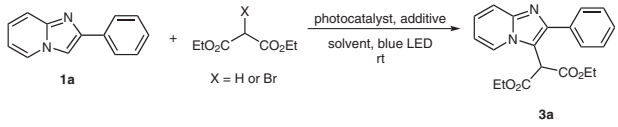


Figure 1 Drug molecules containing imidazoheterocycles

We commenced our study with 2-phenylimidazo[1,2-*a*]pyridine (**1a**; 0.5 mmol) and diethyl malonate (1 mmol) in DMSO (5 mL) as reacting partners. When **1a** and diethyl malonate were made to react under 10 W blue LED in the presence of 2 mol% of eosin Y, decomposition of starting material was observed (Table 1, entry 1). No reaction was observed when 1.5 equivalents of bis(pinacolato)diboron (B_2pin_2) was used as an additive, but this time **1a** was not decomposed and recovered from the reaction mixture (entry 2). Similar observation was reported when this reaction was carried out in acetone (entry 3). Use of *N*-hydroxysuccinimide (NHSI) or *N*-hydroxyphthalimide (NHPI) as the HAT catalyst along with eosin Y/B_2pin_2 system could not produce the required product (entry 4, 5). Similar result was observed with $Ru(bpy)_3(PF_6)_2$ photocatalyst (entry 6). Ferrocene/TBHP and rose bengal/TBHP system were also attempted to get the required result (entries 7 and 8, respectively). Later, it was decided to attempt the desired coupling reaction by in situ conversion of diethyl malonate into its iodo derivative and a reaction was carried out in the presence of I_2/K_2CO_3 along with B_2pin_2. This effort also did not produce any fruitful result (entry 9). Replacing eosin Y with $Ru(bpy)_3(PF_6)_2$ along with $I_2/K_2CO_3/B_2pin_2$ system did not yield the desired result (entry 10). After these unsuccessful efforts, it was decided to use diethyl bromomalonate (**2a**; 0.5 mmol) instead of diethyl malonate as the coupling partner. When **1a** and **2a** were subjected to $Ru(bpy)_3(PF_6)_2/NPh_3/B_2Pin_2$ system in the presence of 10 W blue LED, a poor yield of the desired coupling product was observed (entry 12). Yield of the reaction was improved to 47% in 1,4-dioxane (entry 14). The product **3a** was obtained with an improved yield of 65% when rose bengal was used as the photocatalyst (entry 15). We were surprised to observe an excellent yield of 95% by using sodium bicarbonate as the base (entry 16). No reaction was observed in the absence of rose bengal or blue LED light. Hence, we were successful in developing a metal- and peroxide-free condition for coupling an active methylene carbon with 2-phenylimidazo[1,2-*a*]pyridine (**1a**).

After achieving the optimized reaction conditions, our next move was to explore the scope of the reaction. Initially, the reaction was examined with different substituents on

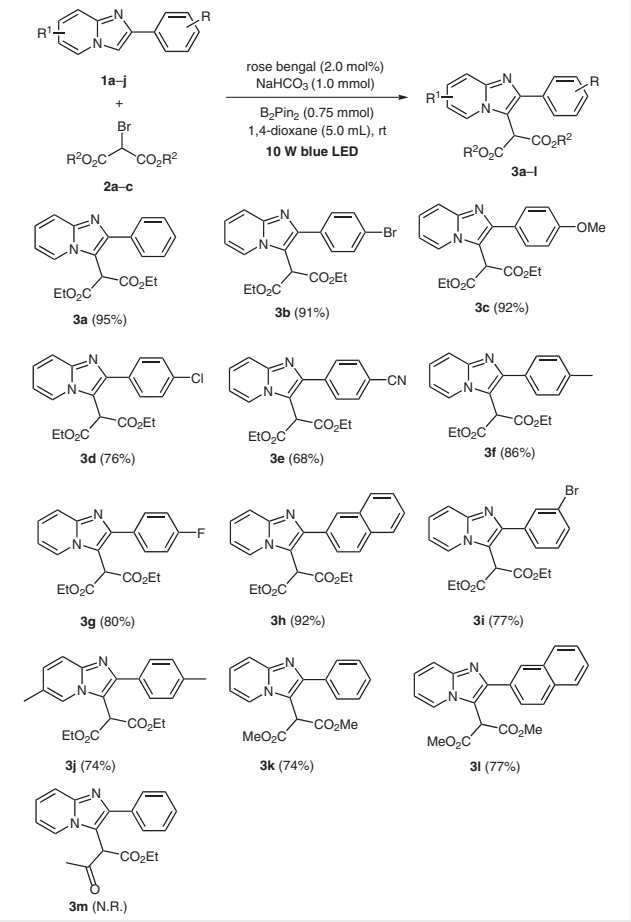
Table 1 Optimization of the Reaction Conditions



Entry	Photocatalyst (2 mol%)	Additive	Solvent	Yield (%)[a]
1	eosin Y	–	DMSO	N.R.
2	eosin Y	B_2pin_2 (1.5 equiv)	DMSO	N.R.
3	eosin Y	B_2pin_2 (1.5 equiv)	acetone	N.R.
4	eosin Y	NHSI (0.2 equiv)/B_2pin_2 (1.5 equiv)	EtOAc	N.R.
5	eosin Y	NHPI (0.2 equiv/B_2pin_2 (1.5 equiv)	EtOAc	N.R.
6	$Ru(bpy)_3(PF)_6$	NHPI (0.2 equiv/B_2pin_2 (1.5 equiv)	EtOAc	N.R.
7	–	TBHP (2 equiv)/ferrocene (0.2 equiv)	EtOAc	N.R.
8	rose bengal	TBHP (2 equiv)	$ClCH_2CH_2Cl$	N.R.
9	eosin Y	I_2 (1 equiv)/ K_2CO_3 (1.5 equiv)/B_2Pin_2 (1.5 equiv)	DMSO	N.R.
10	$Ru(bpy)_3(PF)_6$	I_2 (1 equiv)/ K_2CO_3 (1.5 equiv)/B_2Pin_2 (1.5 equiv)	DMSO	N.R.
11	$Ru(bpy)_3(PF)_6$	NBS (1.1 equiv)/NPh_3 (2 equiv)/B_2Pin_2 (1.5 equiv)	DMSO	N.R.
12	$Ru(bpy)_3(PF)_6$	NPh_3 (2 equiv)/B_2Pin_2 (1.5 equiv)	DMSO	20[b]
13	$Ru(bpy)_3(PF)_6$	NPh_3 (2 equiv)/B_2Pin_2 (1.5 equiv)	MeCN	32[b]
14	$Ru(bpy)_3(PF)_6$	NPh_3 (2 equiv)/B_2Pin_2 (1.5 equiv)	1,4-dioxane	47[b]
15	rose bengal	NPh_3 (2 equiv)/B_2Pin_2 (1.5 equiv)	1,4-dioxane	59[b]
16	**rose bengal**	**$NaHCO_3$ (2 equiv)/B_2Pin_2 (1.5 equiv)**	1,4-dioxane	95[b]
17	–	$NaHCO_3$ (2 equiv)/B_2Pin_2 (1.5 equiv)	1,4-dioxane	trace[b]
18	rose bengal	$NaHCO_3$ (2 equiv)/B_2Pin_2 (1.5 equiv)	1,4-dioxane	N.R.[b,c]

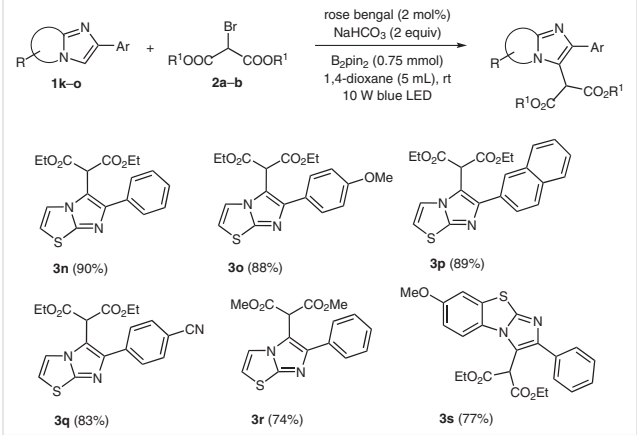
[a] Isolated yield; N.R.: no reaction.
[b] Reaction was carried out with diethyl bromomalonate (**2a**).
[c] Reaction was carried out in the absence of 10 W blue LED.

the phenyl ring of 2-arylimidazo[1,2-*a*]pyridines. For this purpose, diethyl bromomalonate (**2a**) was treated with different 2-arylimidazo[1,2-*a*]pyridines **1a–j**. All the *para*-substituted 2-arylimidazo[1,2-*a*]pyridines with electron-donating substituents (such as Me, OMe, and halogens) and electron-withdrawing substituents on phenyl ring of acetophenone part (**1b–g**) tolerated the reaction conditions with moderate to excellent yields (68–92%) (Scheme 1). Similarly, 2-(2-naphthyl)imidazo[1,2-*a*]pyridine (**1h**) also underwent the reaction to furnish the product **3h** in 92% yield. To check the effect of *meta* substitution, 2-(3-bromophenyl)imidazo[1,2-*a*]pyridine (**1i**) was treated with **2a** under the optimized reaction conditions. Without any surprises it also reacted smoothly to produce the product **3i** in a yield of 77%. When dimethyl bromomalonate (**2b**) was used instead of diethyl bromomalonate (**2a**), it also sustained the reaction condition and yielded the products **3k** (74%) and **3l** (77%) in very good yields. In order to explore the scope of the protocol with another active methylene compound, **1a** was treated with ethyl 2-bromo-3-oxobutanoate (**2c**) but no reaction was observed under the present reaction conditions.



Scheme 1 Scope of the reaction with different 2-arylimidazo-[1,2-*a*]pyridines

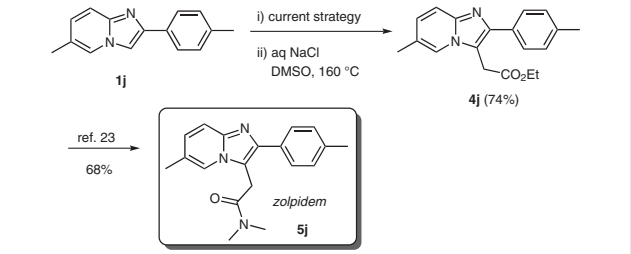
In the process of further exploration of this protocol, it was decided to study the scope of the reaction with other class of imidazoheterocycles. For this purpose, different 6-arylimidazo[2,1-*b*]thiazoles were synthesized following the reported procedure.[22] When 6-phenylimidazo[2,1-*b*]thiazole (**1k**) was treated with **2a** under present conditions, the product **3n** was obtained in a very good yield (90%) (Scheme 2). Similarly, 6-(4-methoxyphenyl)imidazo[2,1-*b*]-thiazole (**1l**) and 6-naphthylimidazo[2,1-*b*]thiazole (**1m**) also reacted well with diethyl bromomalonate (**2a**) to furnish the desired products **3o** (88%) and **3p** (89%) in excellent yields. The presence of electron-withdrawing group on phenyl ring was tolerated well under these conditions as 4-(imidazo[2,1-*b*]thiazol-6-yl)benzonitrile (**1n**) gave product **3q** (83%) in a very good yield. Dimethyl bromomalonate (**2b**) also reacted smoothly with 6-phenylimidazo[2,1-*b*]thiazole (**1k**) under our conditions. Next, it was decided to use benzo[*d*]imidazo[2,1-*b*]thiazole as the heterocycle counterpart. For this purpose diethyl bromomalonate (**2a**) was treated with 7-methoxy-2-phenylbenzo[*d*]imidazo-[2,1-*b*]thiazole (**1o**) to produce the corresponding alkylated product **3s** in 77% yield.



Scheme 2 Scope of the reaction with other imidazoheterocycles

We have also proved the synthetic utility of this protocol by carrying out a total synthesis of the drug molecule zolpidem (**5j**) (Scheme 3). The crude product **3j** (obtained from reaction between **1j** and **2a**) was subjected to Krapcho decarboxylation to produce **4j** (74%), which on further hydrolysis and then condensation with amine gave zolpidem (**5j**).[23]

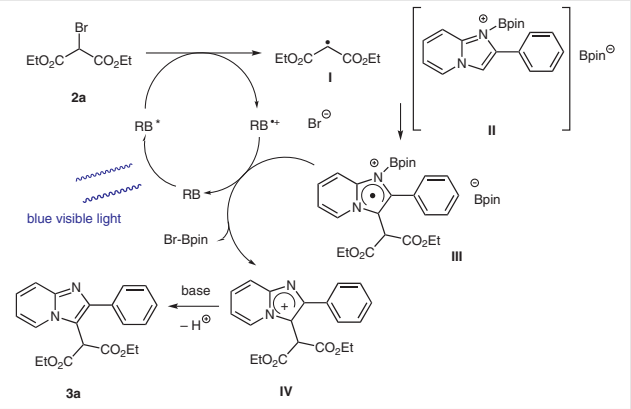
Few control experiments were carried out to examine the mechanism of this reaction strategy. When 2-phenylimidazo[1,2-*a*]pyridine (**1a**) and diethyl bromomalonate (**2a**) were treated in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) under the proposed reaction conditions, the desired product **3a** was not formed. A similar result was observed when the same reaction was carried out in the presence of 2,6-di-*tert*-butyl-4-methyl-



Scheme 3 Total synthesis of zolpidem

phenol (BHT). These results clearly indicated that the reaction probably proceeds through a radical pathway. From the optimization studies it was very much clear that 2-phenylimidazo[1,2-*a*]pyridine (**1a**) decomposes in the absence of B_2pin_2 and is an essential additive to get desired reaction.

From the above results and previous literature,[16,24] a plausible reaction mechanism is proposed for this reaction protocol (Scheme 4). In the presence of blue LED, rose bengal (RB) is converted into its excited state RB*, which helps in the generation of carbon radical species **I** from **2a**. 2-Phenylimidazo[1,2-*a*]pyridine (**1a**) gets activated by B_2pin_2 to intermediate **II**. The carbon radical **I** reacts with intermediate **II** to produce the radical intermediate **III**, which gets converted into the intermediate **IV**. This intermediate **IV** undergoes abstraction of proton by base to produce the final product **3a**.



Scheme 4 Plausible reaction mechanism

In conclusion, we have developed a metal- and peroxide-free reaction strategy for the coupling of imidazoheterocycles with malonates at room temperature.[25] This is a new reaction protocol and also the first report for the synthesis of most of these molecules. Resulting molecules of this protocol can create new possibilities for probable drug candidates as these molecules can be easily converted into new highly functionalized compounds. The substrate scope of this protocol is sufficiently good and the yields of the products are excellent. This protocol has also been applied for the total synthesis of zolpidem.

^1H and ^{13}C NMR spectra were recorded on a Varian (^1H NMR at 500 or 400 MHz, ^{13}C NMR at 125.7 or 100 MHz) FTNMR spectrometer. Chemical shifts for protons are reported in parts per million downfield from TMS and are referenced to residual deuterium in the solvent (^1H NMR: $CDCl_3$ at 7.26 ppm). Chemical shifts for carbons are reported in parts per million downfield from TMS and are referenced to the carbon resonances of the solvent peak (^{13}C NMR: $CDCl_3$ at 77.0 ppm). NMR data are represented as follows: chemical shift, multiplicity (standard abbreviations), coupling constant (*J*, Hz), and integration. Analytical TLC was performed on Merck Kieselgel 60 GF254 plates (thickness 0.25 mm). Visualization was performed with a 254 nm UV lamp and by staining in I_2 chamber. Organic solutions were concentrated under reduced pressure using a Heidolph rotary evaporator. Purification of the crude products was carried out by column chromatography using silica gel (100?200 mesh). All the reactions of the present protocol were carried out in a sealed vial. Yield refers to the isolated analytically pure material. The coupling reaction was carried out at rt under a 10 W blue LED light.

All the 2-arylimidazo[1,2-*a*]pyridines **1a–j** were prepared from corresponding acetophenones and 2-aminopyridines following the reported procedure.[26] Similarly, different 6-arylimidazo[2,1-*b*]thiazoles **1k–n** were synthesized from 2-aminothiazoles and the corresponding acetophenones using reported protocol.[23] 7-Methoxy-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (**1o**) was also prepared in a similar way as their thiazole counterparts. Diethyl bromomalonate and dimethyl bromomalonate were purchased from TCI Chemicals Ltd.

Diethyl 2-(2-Phenylimidazo[1,2-*a*]pyridin-3-yl)malonate (3a); Typical Procedure

To a solution of 2-phenylimidazo[1,2-*a*]pyridine (**1a**; 97 mg, 0.5 mmol) in 1,4-dioxane (5 mL), was added B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) and the resulting solution was stirred at rt for 5 min. Now diethyl bromomalonate (**2a**; 239 mg, 1 mmol, 2 equiv) was added followed by the addition of $NaHCO_3$ (84 mg, 1 mmol, 2 equiv) and rose bengal (9.7 mg, 2 mol%). The resulting reaction mixture in a closed vial was stirred at rt under 10 W blue LED for 24 h. The mixture was poured into cold H_2O (30 mL) and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The crude residue was purified by column chromatography to obtain the desired product **3a**; yield: 167 mg (95%); colorless oil.

^1H NMR ($CDCl_3$, 500 MHz): δ = 8.35 (d, *J* = 10.0 Hz, 1 H), 7.75 (d, *J* = 10.0 Hz, 2 H), 7.67 (d, *J* = 5.0 Hz, 1 H), 7.50 (t, *J* = 7.5 Hz, 2 H), 7.41 (t, *J* = 7.5 Hz, 1 H), 7.27–7.23 (m, 1 H), 5.41 (s, 1 H), 4.21–4.27 (m, 4 H), 1.25 (t, *J* = 5.0 Hz, 6 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 166.6, 146.3, 145.8, 133.8, 129.0, 128.6, 128.5, 128.2, 126.2, 125.1, 117.5, 111.9, 62.4, 49.1, 13.9.[12]

Diethyl 2-[2-(4-Bromophenyl)imidazo[1,2-*a*]pyridin-3-yl]malonate (3b)

Yield: 196 mg (91%); thick colorless oil.

^1H NMR ($CDCl_3$, 500 MHz): δ = 8.26 (d, *J* = 10.0 Hz, 1 H), 7.57–7.61 (m, 5 H), 7.19–7.20 (m, 1 H), 6.78 (t, *J* = 10.0 Hz, 1 H), 5.24 (s, 1 H), 4.16–4.20 (m, 4 H), 1.19 (t, *J* = 7.5 Hz, 6 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 166.3, 145.8, 145.0, 132.6, 131.8, 130.5, 126.2, 125.5, 122.6, 117.5, 112.1, 111.9, 62.5, 49.0, 13.9.

HRMS: *m*/*z* calcd for $C_{20}H_{19}BrN_2O_4$ (M + H): 431.0606; found: 431.0603.

Diethyl 2-[2-(4-Methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl]malonate (3c)

Yield: 176 mg (92%); thick colorless gum.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.33 (d, *J* = 5.0 Hz, 1 H), 7.65–7.71 (m, 3 H), 7.22–7.35 (m, 1 H), 7.03 (d, *J* = 10.0 Hz, 2 H), 6.82 (t, *J* = 10.0 Hz, 1 H), 5.37 (s, 1 H), 4.21–4.28 (m, 4 H), 3.87 (s, 3 H), 1.26 (t, *J* = 7.5 Hz, 6 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 166.7, 159.7, 146.1, 145.7, 130.3, 126.2, 126.1, 125.0, 117.3, 114.2, 111.9, 111.3, 62.4, 55.3, 49.2, 14.0.

HRMS: *m*/*z* calcd for $C_{21}H_{22}N_2O_5$ (M + H): 383.1607; found: 383.1644.

Diethyl 2-[2-(4-Chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]malonate (3d)

Yield: 147 mg (76%); colorless thick oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.34 (d, *J* = 8.0 Hz, 1 H), 7.65–7.71 (m, 3 H), 7.47 (d, *J* = 8.0 Hz, 2 H), 7.25–7.29 (m, 1 H), 6.83–6.87 (m, 1 H), 5.29 (s, 1 H), 4.22–4.27 (m, 4 H), 1.26 (t, *J* = 8.0 Hz, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.4, 145.8, 145.1, 134.4, 132.2, 130.3, 128.9, 126.2, 125.4, 117.5, 112.2, 111.9, 62.5, 49.1, 14.0.

HRMS: *m*/*z* calcd for $C_{20}H_{19}ClN_2O_4$ (M + H): 387.1112; found: 387.1108.

Diethyl 2-[2-(4-Cyanophenyl)imidazo[1,2-*a*]pyridin-3-yl]malonate (3e)

Yield: 128 mg (68%); colorless thick gum.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.35 (d, *J* = 8.0 Hz, 1 H), 7.91 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 8.0 Hz, 2 H), 7.68 (d, *J* = 8.0 Hz, 1 H), 7.31 (m, 1 H), 6.83–6.89 (m, 1 H), 5.31 (s, 1 H), 4.26 (m, 4 H), 1.27 (t, *J* = 8.0 Hz, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.1, 146.0, 144.2, 138.4, 132.5, 129.5, 126.3, 125.9, 118.8, 117.8, 112.7, 112.5, 111.8, 62.7, 49.0, 14.0.

HRMS: *m*/*z* calcd for $C_{21}H_{19}N_3O_4$ (M + H): 378.1454; found: 378.1448.

Diethyl 2-[2-(*p*-Tolyl)imidazo[1,2-*a*]pyridin-3-yl]malonate (3f)

Yield: 158 mg (86%); pale yellow thick gum.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.27 (d, *J* = 10.0 Hz, 1 H), 7.58 (t, *J* = 7.5 Hz, 3 H), 7.15–7.24 (m, 3 H), 6.74 (t, *J* = 7.5 Hz, 1 H), 5.32 (s, 1 H), 4.14–4.19 (m, 4 H), 2.35 (s, 3 H), 1.18 (t, *J* = 10.0 Hz, 6 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 166.7, 145.8, 145.3, 137.1, 129.8, 128.4, 127.9, 125.2, 124.1, 116.4, 110.9, 110.6, 61.5, 48.3, 20.5, 13.1.

HRMS: *m*/*z* calcd for $C_{21}H_{22}N_2O_4$ (M + H): 367.1658; found: 367.1653.

Diethyl 2-[2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl]malonate (3g)

Yield: 148 mg (80%); pale yellow thick gum.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.34 (d, *J* = 8.0 Hz, 1 H), 7.72–7.75 (m, 2 H), 7.67 (d, *J* = 8.0 Hz, 1 H), 7.27 (t, *J* = 8.0 Hz, 1 H), 7.19 (t, *J* = 8.0 Hz, 2 H), 6.82–6.86 (m, 1 H), 5.32 (s, 1 H), 4.23–4.28 (m, 4 H), 1.25–1.29 (m, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.48, 162.9 (d, *J* = 247 Hz), 145.7, 145.4, 130.8 (d, *J* = 9 Hz), 129.7, 126.2, 125.3, 117.9, 115.7 (d, *J* = 22 Hz), 112.1, 111.7, 62.4, 49.3, 13.9.

HRMS: *m*/*z* calcd for $C_{20}H_{19}FN_2O_4$ (M + H): 371.1407; found: 371.1400.

Diethyl 2-[2-(Naphthalen-2-yl)imidazo[1,2-*a*]pyridin-3-yl]malonate (3h)

Yield: 185 mg (92%); colorless thick gum.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.40 (d, *J* = 8.0 Hz, 1 H), 8.24 (br s, 1 H), 7.94 (m, 4 H), 7.71 (d, *J* = 8.0 Hz, 1 H), 7.51 (m, 2 H), 7.27 (m, 1 H), 6.85 (t, *J* = 8.0 Hz, 1 H), 5.51 (s, 1 H), 4.25 (m, 4 H), 1.28 (t, *J* = 6.0 Hz, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.6, 146.3, 145.9, 133.3, 133.1, 131.2, 128.4, 128.3, 128.2, 127.7, 126.8, 126.4, 126.3, 126.2, 125.2, 117.9, 112.1, 112.0, 62.4, 49.2, 14.0.

HRMS: *m*/*z* calcd for $C_{24}H_{23}N_2O_4$ (M + H): 403.1658; found: 403.1651.

Diethyl 2-[2-(3-Bromophenyl)imidazo[1,2-*a*]pyridin-3-yl]malonate (3i)

Yield: 166 mg (77%); yellow thick gum.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.35 (d, *J* = 10.0 Hz, 1 H), 7.95 (br s, 1 H), 7.68 (m, 2 H), 7.54 (m, 1 H), 7.36 (t, *J* = 7.5 Hz, 1 H), 7.27 (m, 1 H), 6.85 (t, *J* = 5.0 Hz, 1 H), 5.33 (s, 1 H), 4.25 (m, 4 H), 1.28 (t, *J* = 7.5 Hz, 6 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 166.4, 145.8, 144.8, 135.9, 132.1, 131.2, 130.2, 127.6, 126.3, 125.5, 122.1, 117.6, 112.3, 112.1, 62.6, 49.0, 14.0.

HRMS: *m*/*z* calcd for $C_{20}H_{19}BrN_2O_4$ (M + H): 431.0606; found: 431.0603.

Dimethyl 2-(2-Phenylimidazo[1,2-*a*]pyridin-3-yl)malonate (3k)

Yield: 120 mg (74%); colorless thick gum.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.32 (d, *J* = 8.0 Hz, 1 H), 7.74 (d, *J* = 4.0 Hz, 2 H), 7.68 (d, *J* = 8.0 Hz, 1 H), 7.50 (t, *J* = 8.0 Hz, 2 H), 7.42 (t, *J* = 8.0 Hz, 1 H), 7.27 (t, *J* = 8.0 Hz, 1 H), 6.85 (t, *J* = 6.0 Hz, 1 H), 5.46 (s, 1 H), 3.78 (s, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.0, 146.4, 145.8, 133.6, 129.0, 128.7, 128.3, 126.0, 125.2, 117.6, 112.3, 111.4, 53.1, 48.7.

HRMS: *m*/*z* calcd for $C_{18}H_{16}N_2O_4$ (M + H): 325.1188; found: 325.1186.

Dimethyl 2-[2-(Naphthalen-2-yl)imidazo[1,2-*a*]pyridin-3-yl]malonate (3l)

Yield: 144 mg (77%); colorless thick gum.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.36 (d, *J* = 4.0 Hz, 1 H), 8.21 (br s, 1 H), 7.98 (d, *J* = 8.0 Hz, 1 H), 7.91 (m, 3 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.52 (t, *J* = 4.0 Hz, 2 H), 7.28 (t, *J* = 6.0 Hz, 1 H), 6.86 (t, *J* = 6.0 Hz, 1 H), 5.57 (s, 1 H), 3.79 (s, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.0, 146.3, 146.0, 133.3, 133.1, 131.1, 128.5, 128.4, 128.2, 127.7, 126.7, 126.4, 126.3, 126.1, 125.3, 118.0, 112.3, 111.7, 53.2, 48.8.

HRMS: *m*/*z* calcd for $C_{22}H_{18}N_2O_4Na$ (M + Na): 397.1164; found: 397.1159.

Diethyl 2-(6-Phenylimidazo[2,1-*b*]thiazol-5-yl)malonate (3n)

Yield: 161 mg (90%); colorless thick gum.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.68 (d, *J* = 10.0 Hz, 2 H), 7.33 (m, 3 H), 6.86 (d, *J* = 5.0 Hz, 1 H), 6.26 (d, *J* = 5.0 Hz, 1 H), 4.44 (s, 1 H), 4.15 (m, 2 H), 3.98 (m, 2 H), 1.19 (t, *J* = 7.5 Hz, 3 H), 0.93 (t, *J* = 7.5 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 175.6, 168.4, 166.1, 165.6, 135.7, 128.7, 128.5, 126.4, 115.9, 110.9, 62.1, 61.4, 59.9, 13.8, 13.6.

HRMS: *m*/*z* calcd for $C_{18}H_{18}N_2O_4S$ (M + H): 359.1066; found: 359.1046.

Diethyl 2-[6-(4-Methoxyphenyl)imidazo[2,1-*b*]thiazol-5-yl]malonate (3o)

Yield: 171 mg (88%); yellow thick gum.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.59 (d, *J* = 10.0 Hz, 2 H), 6.85 (m, 3 H), 6.24 (d, *J* = 5.0 Hz, 1 H), 4.39 (s, 1 H), 4.13 (m, 2 H), 4.01 (m, 2 H), 3.77 (s, 3 H), 1.17 (t, *J* = 7.5 Hz, 3 H), 0.97 (t, *J* = 7.5 Hz, 3 H)

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 175.8, 167.8, 166.1, 165.6, 159.9, 127.7, 127.4, 115.9, 113.8, 110.8, 62.0, 61.4, 59.8, 55.3, 13.8, 13.7.

HRMS: *m*/*z* calcd for $C_{19}H_{20}N_2O_5S$ (M + H): 389.1171; found: 389.1159.

Diethyl 2-[(6-Naphthalen-2-yl)imidazo[2,1-*b*]thiazol-5-yl]malonate (3p)

Yield: 182 mg (89%); yellow thick gum.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.14 (br s, 1 H), 7.83 (m, 4 H), 7.47 (m, 2 H), 6.87 (d, *J* = 5.0 Hz, 1 H), 6.27 (d, *J* = 5.0 Hz, 1 H), 4.56 (s, 1 H), 4.18 (m, 2 H), 3.93 (m, 2 H), 1.19 (t, *J* = 7.5 Hz, 3 H), 0.81 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 175.5, 168.1, 166.2, 165.6, 133.2, 132.9, 132.8, 128.4, 128.3, 127.5, 126.6, 126.3, 125.9, 123.7, 115.9, 110.9, 62.1, 61.4, 59.7, 13.8, 13.5.

HRMS: *m*/*z* calcd for $C_{22}H_{20}N_2O_4S$ (M + H): 409.1222; found: 409.1214.

Diethyl 2-[6-(4-Cyanophenyl)imidazo[2,1-*b*]thiazol-5-yl]malonate (3q)

Yield: 159 mg (83%); colorless thick gum.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.81 (d, *J* = 10.0 Hz, 2 H), 7.75 (d, *J* = 10.0 Hz, 2 H), 7.67 (d, *J* = 5.0 Hz, 1 H), 6.86 (d, *J* = 5.0 Hz, 1 H), 5.16 (s, 1 H), 4.27 (m, 4 H), 1.30 (t, *J* = 7.5 Hz, 6 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 166.1, 151.2, 144.9, 138.5, 132.5, 128.8, 120.5, 118.8, 112.3, 111.4, 62.7, 49.8, 14.0.

HRMS: *m*/*z* calcd for $C_{19}H_{17}N_3O_4SNa$ (M + Na): 406.0837; found: 406.0832.

Dimethyl 2-(6-Phenylimidazo[2,1-*b*]thiazol-5-yl)malonate (3r)

Yield: 122 mg (74%); colorless thick gum.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.65 (d, *J* = 5 Hz, 2 H), 7.32 (m, 3 H), 6.85 (d, *J* = 5.0 Hz, 1 H), 6.24 (d, *J* = 5.0 Hz, 1 H), 4.44 (s, 1 H), 3.68 (s, 3 H), 3.48 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 175.5, 168.3, 166.5, 166.1, 135.3, 128.8, 128.6, 126.3, 115.9, 111.0, 59.8, 52.9, 52.5.

HRMS: *m*/*z* calcd for $C_{16}H_{14}N_2O_4S$ (M + H): 331.0753; found: 331.0740.

Diethyl 2-(7-Methoxy-2-phenylbenzo[*d*][2,1-*b*]thiazol-3-yl)malonate (3s)

Yield: 169 mg (77%); pale yellow thick gum.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.72 (m, 3 H), 7.46 (t, *J* = 7.5 Hz, 2 H), 7.38 (t, *J* = 10.0 Hz, 1 H), 7.19 (bs, 1 H), 6.96 (m, 1 H), 5.38 (s, 1 H), 4.22 (m, 4 H), 3.86 (s, 3 H), 1.20 (t, *J* = 7.5 Hz, 6 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 167.1, 156.8, 148.4, 147.3, 133.7, 131.4, 128.7, 128.6, 127.9, 127.4, 115.8, 115.6, 112.7, 112.7, 108.2, 62.5, 55.8, 49.6, 13.9.

HRMS: *m*/*z* calcd for $C_{23}H_{22}N_2O_5S$ (M + H): 439.1328; found: 439.1308.

Total Synthesis of Zolpidem (5j)

To a solution of 6-methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridine (**1j**; 111 mg, 0.5 mmol) in 1,4-dioxane (5 mL), was added B_2pin_2 (190 mg, 0.75 mmol, 1.5 equiv) and the resulting solution was stirred at rt for 5 min. Now diethyl bromomalonate (**2a**; 239 mg, 1 mmol, 2 equiv) was added followed by $NaHCO_3$ (84 mg, 1 mmol, 2 equiv) and rose bengal (9.7 mg, 2 mol%). The resulting reaction mixure in a closed vial was stirred at rt under 10 W blue LED for 24 h. The reaction mixture was poured into cold H_2O (30 mL) and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The crude residue of **3j** was dissolved in DMSO (0.3 mL) and a solution of NaCl (0.047 g, 0.8 mmol) in H_2O (0.3 mL) was added. The resulting mixture was heated overnight at 160 °C (oil bath). Then, the reaction mixture was cooled to rt, quenched with H_2O, and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O and dried (Na_2SO_4). After evaporation of solvent, the crude product was purified by column chromatography (30% EtOAc in hexane) to afford **4j**; yield: 114 mg (74%); off-white solid, mp 95 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.81 (br s, 1 H), 7.65 (d, *J* = 10.0 Hz, 2 H), 7.50 (d, *J* = 10.0 Hz, 1 H), 7.19–7.22 (m, 2 H), 7.01 (d, *J* = 10.0 Hz, 1 H), 7.16 (q, *J* = 7.5 Hz, 2 H), 3.94 (s, 2 H), 2.34 (s, 3 H), 2.30 (s, 3 H), 1.21 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.6, 143.8, 137.6, 131.0, 129.3, 128.4, 127.6, 122.0, 121.3, 116.7, 112.4, 61.5, 30.9, 21.3, 18.4, 14.1.[4]

The above ester **4j** (96 mg, 0.25 mmol) was converted into zolpidem (**5j**) following the reported protocol;[23] yield: 65 mg (68%); off-white colored solid; mp 194 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.99 (s, 1 H), 7.54 (d, *J* = 10.0 Hz, 3 H), 7.26 (d, *J* = 10.0 Hz, 2 H), 7.04 (d, *J* = 10.0 Hz, 1 H), 4.07 (s, 2 H), 2.94 (s, 3 H), 2.88 (s, 3 H), 2.40 (s, 3 H), 2.34 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 168.3, 144.1, 143.7, 137.4, 131.7, 129.3, 128.4, 127.5, 122.2, 121.7, 116.5, 113.6, 37.5, 35.8, 30.2, 21.2, 18.4.

Funding Information

Dr. Narendra R. Chaubey acknowledges the Research Fellowship (F. No. 45/15/2019-BIO/BMS) from Indian Council of Medical Research, Delhi, India.

Acknowledgment

We are also thankful to Dr. Biswanath Maity, CBMR, Lucknow, India for providing HRMS analysis of new molecules.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706103.

References

(1) Almirante, L.; Polo, L.; Mugnaini, A.; Provinciali, E.; Biancotti, A.; Gamba, A.; Murmann, W. *J. Med. Chem.* **1965**, *8*, 305.
(2) (a) Puerstinger, G.; Paeshuyse, J.; De Clercq, E.; Neyts, J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 390. (b) Townsend, L. B. Patent WO 9727205A1, **1997**. (c) Elhakmaoui, A.; Gueiffier, A.; Milhavet, J.-C.; Blache, Y.; Chapat, J.-P.; Chavignon, O.; Teulade, J.-C.; Snoeck, R.; Andrei, G.; De Clercq, E. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1937. (d) Gudmundsson, K. S.; Williams, J. D.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **2003**, *46*, 1449.
(3) (a) Byth, K. F.; Culshaw, J. D.; Green, S.; Oakes, S. E.; Thomas, A. P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2245. (b) Revankar, G. R.; Matthews, T. R.; Robins, R. K. *J. Med. Chem.* **1975**, *18*, 1253. (c) Fisher, M. H.; Lusi, A. *J. Med. Chem.* **1972**, *15*, 982. (d) Cheng, Y.; Moraski, G. C.; Cramer, J.; Miller, M. J.; Schorey, J. S. *PLoS One* **2014**, *9*, e87483.
(4) (a) Piantanida, M. I.; Kralj, M.; Suman, L.; Pavelicand, K.; Karminski-Zamola, G. *J. Med. Chem.* **2008**, *51*, 4899. (b) Hranjec, M.; Kralj, M.; Piantanida, M. I.; Sedic, M.; Suman, L.; Pavelic, K.; Karminski-Zamola, G. *J. Med. Chem.* **2007**, *50*, 5696. (c) Badawey, E.; Kappe, T. *Eur. J. Med. Chem.* **1995**, *30*, 327.
(5) Kaminski, J. J.; Bristol, J. A.; Puchalski, C.; Lovey, R. G.; Elliott, A. J.; Guzik, H.; Solomon, D. M.; Conn, D. J.; Domalski, M. S. *J. Med. Chem.* **1985**, *28*, 876.
(6) (a) Lacerda, R. B.; de Lima, C. K. F.; Da Silva, L. L.; Romeiro, N. C.; Miranda, A. L. P.; Barreiro, E. J.; Fraga, C. A. M. *Bioorg. Med. Chem.* **2009**, *17*, 74. (b) de Blas, C. J.; Del Prado, M.; Gruber, J.; Heinz, B. A.; Vance, L. *J. Med. Chem.* **1999**, *42*, 50.
(7) Stasyuk, A. J.; Banasiewicz, M.; Cyranski, M. K.; Gryko, D. T. *J. Org. Chem.* **2012**, *77*, 5552.
(8) Tashrifi, Z.; Mohammadi-Khanaposhtani, M.; Larijani, B.; Mahadavi, M. *Eur. J. Org. Chem.* **2020**, 269.
(9) (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (b) Shi, L.; Xia, W. *Chem. Soc. Rev.* **2012**, *41*, 7687. (c) Chen, J. R.; Hu, X. Q.; Lu, L. Q.; Xiao, W. J. *Acc. Chem. Res.* **2016**, *49*, 1911. (d) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (e) Furst, L.; Matsuura, B. S.; Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 3104.
(10) Ravelli, D.; Fagnoni, M.; Albini, A. *Chem. Soc. Rev.* **2013**, *42*, 97.
(11) Kibriya, G.; Bagdi, A. K.; Hajra, A. *J. Org. Chem.* **2018**, *83*, 10619.
(12) Mendoza, P. L.; Diaz, J. E.; Loaiza, A. E.; Miranda, L. D. *Tetrahedron* **2018**, *74*, 5494.
(13) Qu, C.-H.; Song, G.-T.; Xu, J.; Yan, W.; Zhou, C.-H.; Li, H. Y.; Chen, Z.-Z.; Xu, Z.-G. *Org. Lett.* **2019**, *21*, 8169.
(14) Sun, P.; Yang, D.; Wei, W.; Jiang, M.; Wang, Z.; Zhang, L.; Zhang, H.; Zhang, Z.; Wang, Y.; Wang, H. *Green Chem.* **2017**, *19*, 4785.
(15) Rahman, R.; Das, S.; Barman, P. *Green Chem.* **2018**, *20*, 141.
(16) Singsardar, M.; Mondal, S.; Laru, S.; Hajra, A. *Org. Lett.* **2019**, *21*, 5606.
(17) Chen, H.; Yi, H.; Tang, Z.; Bian, C.; Zhang, H.; Lei, A. *Adv. Synth. Catal.* **2018**, *360*, 3220.
(18) Zhu, Z.-Q.; Xiao, L.-J.; Zhou, C.-C.; Song, H.-L.; Xie, Z.-B.; Le, Z.-G. *Tetrahedron Lett.* **2018**, *59*, 3326.
(19) Chang, Q.; Liu, Z.; Yu, P. L.; Sun, P. *J. Org. Chem.* **2017**, *82*, 5391.
(20) Samanta, S.; Ravi, C.; Rao, S. N.; Joshi, A.; Adimurthy, S. *Org. Biomol. Chem.* **2017**, *15*, 9590.
(21) Yin, G.; Zhu, M.; Fu, W. *Heterocycl. Commun.* **2017**, *23*, 275.
(22) Liang, D.; Li, L.; Lynch, C.; Mackowiak, B.; Hedrich, W. D.; Ai, Y.; Yin, Y.; Heyward, S.; Xia, M.; Wang, H.; Xue, F. *Eur. J. Med. Chem.* **2019**, *179*, 84.
(23) Nair, D. K.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Lett.* **2012**, *14*, 4580.
(24) Usami, K.; Nagasawa, Y.; Yamaguchi, E.; Tada, N.; Itoh, A. *Org. Lett.* **2016**, *18*, 8.
(25) Chaubey, N. R.; Kapdi, A. R.; Maity, B. *ChemRxiv* **2020**, preprint DOI: 10.26434/chemrxiv.12651908.
(26) Huang, H.; Dang, P.; Wu, L.; Liang, Y.; Liu, J. *Tetrahedron Lett.* **2016**, *57*, 574.