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An expeditious microwave assisted one-pot sequential route to pyrido fused imidazo[4,5-*c*] quinolines in green media†

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An expeditious microwave assisted one-pot sequential route to synthesize pyrido fused imidazo[4,5-*c*]quinolines *via* the Pictet–Spengler cyclization strategy has been developed. In this study, substituted 2-amino pyridines are condensed with 2-bromo-2′-nitroacetophenone to generate imidazo[1,2-*a*]pyridines with nitro group functionality at C-2 position. Reduction of nitro group to its amine congener in green media followed by the Pictet–Spengler cyclization strategy with substituted aldehydes led to the formation of new C–C and C–N bonds in a one-pot sequential manner. The cyclization proceeds through the CO(carbonyl)–C(H) cleavage of the aldehyde group *via* oxidative cross-coupling, transamination, cyclization and aromatization steps. Low cost reagents and a green solvent were used to facilitate the architecturally beautiful pyrido fused imidazo[4,5-*c*]quinoline scaffolds in high yields. The key features of this synthetic protocol are the use of microwave-assisted mild reaction conditions, one-pot sequential pathway, broad substrate scope and green media, which make it feasible for the synthesis of fused polyheterocycles. Moreover, the synthetic manipulation proceeded well with heteroaromatic and aliphatic aldehydes also in good yields.

Introduction

Heterocyclic compounds are widely present in synthetic chemistry and natural products, contributing to 90% of marketed pharmacological drugs and agrochemicals.[1–3] In particular, fused N-heterocycles, also defined as polyheterocycles are reported to encompass a broad spectrum of biological activities due to the presence of specialised scaffolds. Some of our recent studies on various heterocyclic compounds proved that they have a potential role in the drug discovery and medicinal chemistry programme.[4–6] Designing simple, cost efficient, and green synthetic protocols for the formation of new C–N and C–C bonds in the synthesis of polyheterocyclic compounds[7–9] is of pharmacological importance, and plays a crucial role of torch bearer in the pharmaceutical industry. Medicinal chemists focus on reducing the risk of pollution and avoid the use of hazardous synthetic protocols. Amidst large number of heterocyclic compounds, imidazo[4,5-*c*]quinoline is considered as a "drug prejudice" and retains a broad class of pharmacological importance such as PI3K/PKB-pathway inhibitor[10] **(I)**, TNF-α inhibitor[11] **(II)**, and anticancer activity[12] **(III)**. Additionally, Imiquimod **(IV)** and Resiquimod **(V)** containing imidazo[4,5-*c*]quinolone moiety are marketed as immunomodulator drugs[13] as shown in Fig. 1.

Because of their wide-ranging bioactivities in pharmacological and biological investigations, the synthesis of imidazo[4,5-*c*]quinoline scaffolds is a challenging task. Based on this context, we previously developed a mosaic of imidazopyridine libraries using various strategies such as microwave assisted synthesis,[14] use of green solvents,[15] solvent free methods[16] and evaluated their biological importance. In the literature, the basic procedure followed for the synthesis of this scaffold included the formation of imidazopyridine from various substrates, conversion into its respective amine congener and subsequent cyclization to produce imidazo[4,5-*c*]quinoline. For the first time in 2007, Kundu *et al.* demonstrated the synthesis of imidazo[4,5-*c*]quinolines through the three step sequence involving the Hantzsch type cyclization, nitro group reduction and the Pictet–Spengler cyclization from 2-aminopyridine (Scheme 1A).[17] In 2014, Chouhan *et al.* reported the synthesis of imidazo[4,5-*c*]quinolines from imidazo[1,2-*a*]pyridine amines and substituted aldehydes and ketones in the presence of cyanuric chloride as catalyst and TBAB as additive in water (Scheme 1B).[18] Subsequently, in 2017, Atmakur *et al.* developed a one-pot protocol from 2-(imidazo[1,2-*a*]pyridin-2-yl)-aniline and aldehyde using I_2 in DMSO solvent (Scheme 1C).[19] In 2018, Kamal and his group reported a one-pot strategy for imidazo[4,5-*c*]quinolines from 2-(imidazo[1,2-*a*]pyridin-2-yl)aniline

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† Electronic supplementary information (ESI) available: Full spectroscopic data of all compounds, ^{1}H, ^{13}C NMR, HRMS, and IR spectra of compounds **3a–d**, **4a–d** and **6a–v** (PDF). See DOI: 10.1039/d0nj05835a

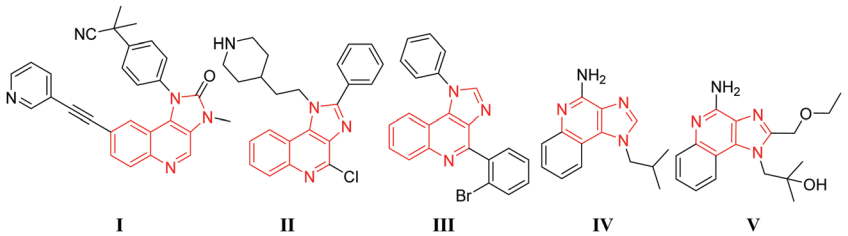
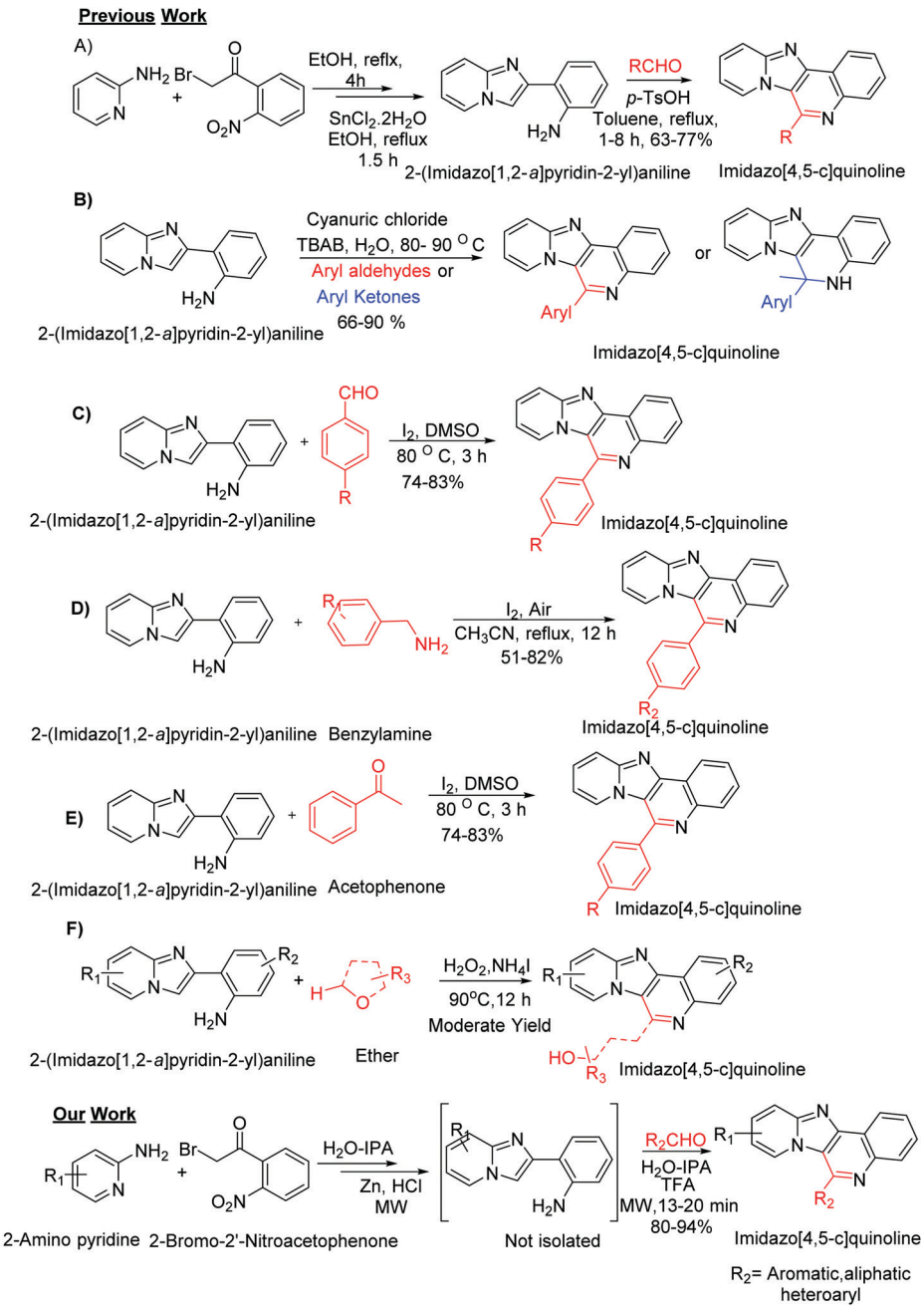
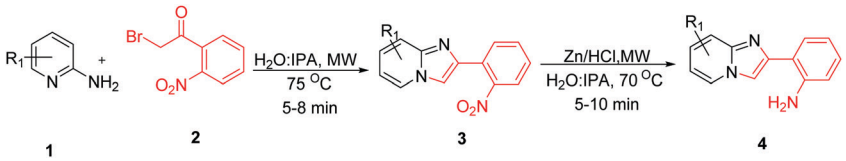


Fig. 1 Pharmacological Importance of Imidazo[4,5-*c*]quinoline.



Scheme 1 Different synthetic approaches to pyrido fused imidazo[4,5-*c*]quinolones.



Scheme 2 Synthesis of 2-(imidazo[1,2-*a*]pyridin-2-yl)aniline congeners.

and benzylamine promoted by I_2 in CH_3CN solution (Scheme 1D).[20] The same group also reported the present scaffold from the reaction of 2-(imidazo[1,2-*a*]pyridin-2-yl)aniline with substituted acetophenone catalysed by molecular iodine (Scheme 1E).[21] Recently, Sun *et al.* developed the quinoline-fused imidazopyridines *via* cross dehydrogenative coupling reaction of ethers with imidazopyridines under metal-free conditions (Scheme 1F).[22]

Despite the significant progress made in imidazo[4,5-*c*]quinoline annulation, methodologies developed so far encompassed some disadvantages such as use of hazardous cyanuric chloride,[23] high boiling toxic solvents like DMSO, need of high temperature, longer reaction times, and tedious workup procedure. These drawbacks significantly restrict the use of imidazo[4,5-*c*]quinolines in pharmacological studies. These shortcomings could be addressed using an efficient one-pot sequential microwave assisted green synthetic approach.

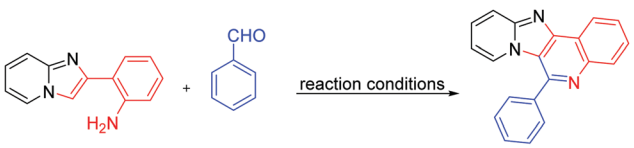
In continuation of our efforts to explore the potential application of synthesized bioactive compounds in our laboratory,[24–26] herein, we report an expeditious microwave assisted one-pot route to synthesize pyrido fused imidazo[4,5-*c*]quinolines and its derivatives *via* the Pictet–Spengler cyclization strategy. In 2011, Maiti *et al.* used the Pictet–Spengler cyclization strategy for the generation of biheterocyclic benzimidazole-pyrrolo[1,2-*a*]quinoxalines under microwave.[27] To the best of our knowledge, microwave assisted one-pot sequential pathway for the synthesis of imidazo[4,5-*c*]quinolines and its derivatives under green condition has not been reported yet. The synthetic approach shows a wide range of functional group tolerance, and the validity of the methodology has been investigated using various substituted 2-aminopyridines and substituted aromatic, heteroaromatic and aliphatic aldehydes resulting in excellent yields.

Results and discussions

To evaluate the feasibility of our proposed synthetic pathway, we first synthesized the precursor material, substituted 2-(imidazo[1,2-*a*]pyridin-2-yl)aniline **4** in 2 steps using our reported procedure (Scheme 2).[24] The first step involved the condensation of substituted 2-aminopyridine **1** with 2-bromo-2′-nitroacetophenone **2** under microwave irradiation resulting in the formation of substituted 2-(2-nitrophenyl)imidazo[1,2-*a*]pyridine **3**. The second step involved the reduction of the nitro group of compound **3** to its corresponding amine congeners **4** by using Zn dust/HCl in refluxing water medium, which took 45 min for completion. Surprisingly, the same NO_2 group reduction under microwave irradiation occurred in 5 min using H_2O-IPA medium to obtain the amine congeners **4**.

Next, we started our investigation of the Pictet–Spengler cyclization reaction by a benchmark reaction between 2-(imidazo[1,2-*a*]pyridin-2-yl)aniline **4a** and benzaldehyde **5a** as model substrates. The Pictet–Spengler cyclization is a two-step process, where an activated or unactivated aryl amine and carbonyl substrates first react to generate an imine intermediate followed by a 6-endo intramolecular cyclization to obtain the cyclized product. We carried out the optimization studies for the synthesis of our desired compound **6a** as shown in Table 1. Throughout the optimization studies, trifluoro acetic acid (TFA) was chosen as an acid catalyst in common. The compound **4a** when treated with benzaldehyde **5a** in the presence of trifluoro acetic acid (TFA) as an acid catalyst under neat condition for 6 h at room temperature did not yield any cyclized product **6a** (Table 1, entry 1). To our delight, when the temperature was increased to 70 °C, we obtained the desired product yield of 20% (Table 1, entry 2). Though the yield of the desired product was 20%, it motivated us to perform the reaction in polar aprotic solvents. Subsequently, we carried out the reaction in polar aprotic solvents like CH_3CN under refluxing conditions and DMSO at 85 °C, which did not significantly enhance the product yield (Table 1, entries 3 and 4). Next, we turned our attention to polar protic solvents such as ethanol. The product yield was enhanced to 60% when performing the cyclization reaction in ethanol under refluxing condition (Table 1 entry 5). Encouraged with this result, we examined the cyclization reaction in isopropanol solvent at a

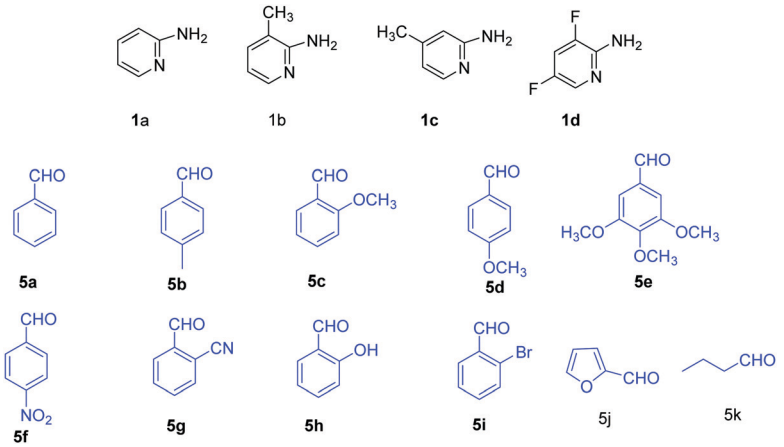
Table 1 Optimization of heterocyclization reaction conditions[a]



Entry	Solvent	Acid catalyst	Temperature	Time	Yield[c] (%)
1	Neat	CF_3COOH	rt	6 h	0
2	Neat	CF_3COOH	60 °C	6 h	20
3	CH_3CN	CF_3COOH	reflux	6 h	45
4	DMSO	CF_3COOH	80 °C	6 h	48
5	EtOH	CF_3COOH	80 °C	6 h	60
6	IPA	CF_3COOH	80 °C	6 h	70
7	H_2O-IPA	CF_3COOH	80 °C	6 h	75
8	H_2O-IPA	CF_3COOH	MW[b], 75 °C	13 min	91
9	H_2O-IPA	*p*-TSA	MW[b], 75 °C	13 min	50

[a] Reaction was performed using **4a** (1 mmol), **5a** (1.1 mmol), CF_3COOH (1 mmol). [b] Microwave reactions were carried out in Microwave Model No. CATA R (Catalyst systems, Pune) using power 280 Watt. [c] Yield of the isolated product.

Table 2 Substrate scope of the reaction and physical properties of compound **6**



Entry	Product	Yield[a] (%)	LRMS[b]	H-Bond donor	H-Bond acceptor	*clog P*[c]
1	**6a**	91	295	0	3	5.35
2	**6b**	90	309	0	3	5.85
3	**6c**	90	325	0	4	4.80
4	**6d**	89	385	0	6	4.70
5	**6e**	92	340	1	6	5.09
6	**6f**	92	320	0	5	5.09
7	**6g**	82	311	1	4	4.78
8	**6h**	91	309	0	3	5.81
9	**6i**	92	339	0	4	5.29
10	**6j**	92	339	0	4	5.85
11	**6k**	90	399	0	6	5.26
12	**61**	94	354	1	6	5.59
13	**6m**	89	387	0	3	6.40
14	**6n**	89	309	0	3	5.85
15	**6o**	90	323	0	3	6.34
16	**6p**	90	339	0	4	5.85
17	**6q**	88	399	0	6	5.26
18	**6r**	92	387	0	3	6.41
19	**6s**	89	331	0	3	5.64
20	**6t**	88	361	0	4	5.64
21	**6u**	81	285	0	4	4.73
22	**6v**	80	261	0	3	4.81

[a] Isolated yields. [b] LRMS was recorded by GC-MS method. [c] Estimated *clog P* by ChemBioOffice 2010.

temperature of 80 °C, which surprisingly increased the yield to 70% (Table 1, entry 6).

Subsequently, using water as co-solvent (1 : 1 ratio) with isopropanol, the yield of the product **6**a was increased to 80% in just 6 h of reaction time at 80 °C (Table 1, entry 7). To our delight, 91% yield of product **6**a was achieved at 75 °C under microwave irradiation for 13 min (Table 2, entry 8), which established the supremacy of microwave irradiation in the Pictet–Spengler cyclization reaction. The use of *p*-TSA as an acid catalyst under microwave irradiation in the Pictet–Spengler cyclization reaction yielded the cyclized product **6a** in 50% yield (Table 1, entry 9).

The quantitative progress of product conversion was monitored by regular proton NMR spectroscopy. It has been found that the characteristic C_{11}–H_b proton of compound **3a** appeared at 8.0 ppm whereas the peak at 7.78 ppm corresponds to the C_3–Ha in spectrum A (Fig. 2).

In spectrum B, upon the reduction of NO_2 group in **3**a to the corresponding amine congeners **4a**, the chemical shift of the corresponding C_{11}–H_b proton shifted upfield to 7.55 ppm. Subsequent cyclization of compound **4a** with benzaldehyde **5a** to obtain compound **6a** was observed by the disappearance of the C_3–Ha proton along with the appearance of five aromatic protons of the benzaldehyde moiety in spectrum C.

After successfully executing the microwave-assisted reduction and acid catalyzed Pictet–Spengler reaction to obtain the pyrido fused imidazo[4,5-*c*]quinolines **6**, our next attempt was to obtain the desired scaffolds in a one-pot sequential manner. For this purpose, we performed one-pot sequential reaction where the reaction of substituted 2-aminopyridine **1** with 2-bromo-2′-nitroacetophenone **2** in H_2O-IPA medium under microwave irradiation resulted in the formation of substituted 2-(2-nitrophenyl)imidazo[1,2-*a*]pyridine **3**. Without isolating the intermediate product **3**, the same reaction mixtures were irradiated under microwave for another 5 min with the *in situ* addition of Zn dust/HCl to obtain desired amine congeners **4**, as shown in Scheme 3. After completion of the reaction, Zn was removed by centrifugation and substituted

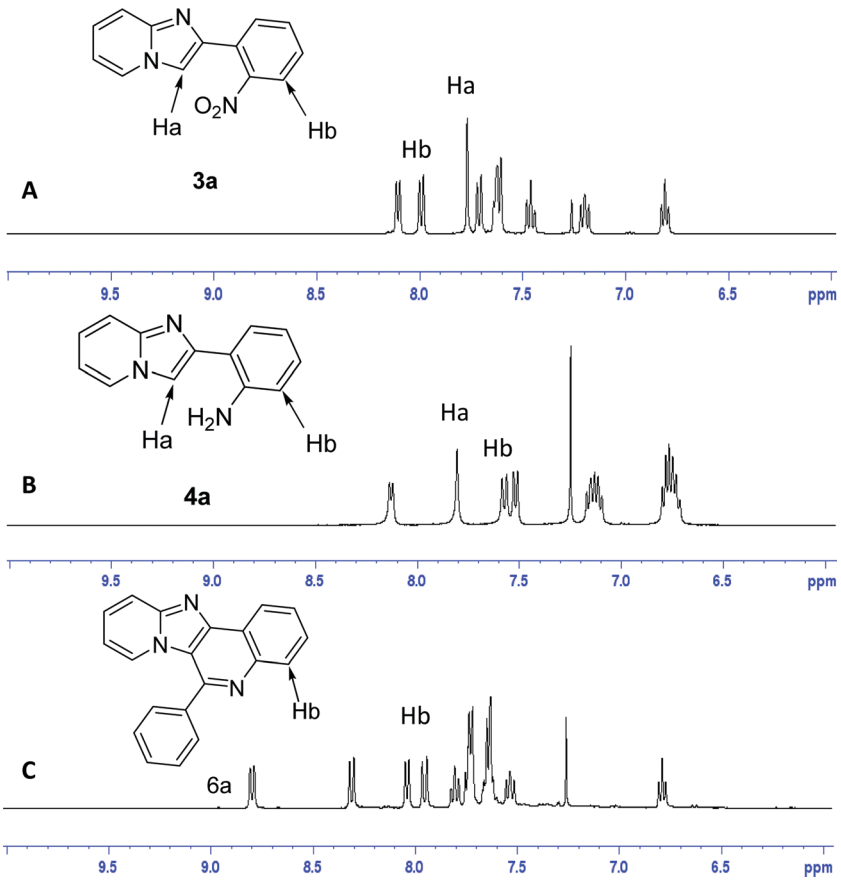
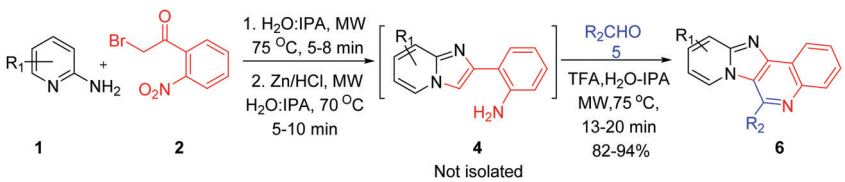


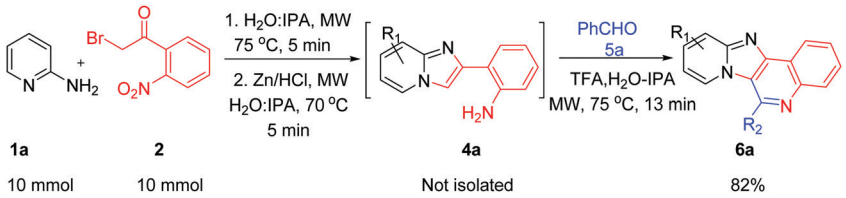
Fig. 2 Stepwise monitoring of pyrido fused imidazo[4,5-*c*]quinoline **6a** formation by ^{1}H NMR spectroscopy.

aldehydes along with trifluoroacetic acid were added to the same reaction mixtures and irradiated under microwave for a specified period of time. Upon successful completion of the reaction, the ^{1}H NMR spectrum of the synthesized compound indicated the formation of pure pyrido fused imidazo[4,5-*c*]quinolines **6** in excellent yield. It is interesting to note that the Pictet Spengler cyclization resulted in the formation of pyrido fused imidazo[4,5-*c*]quinolines **6** in 40% yield when only conc. HCl was used as an acid catalyst under desired reaction condition. With the one-pot sequential reaction conditions in hand, we next examined the substrate scope with respect to 2-aminopyridine **1a–d** and aldehydes **5a–k** (Scheme 3). We found that 2-aminopyridines **1** with electron donating groups and electron withdrawing groups at different positions gave corresponding products in very good yields. Aldehydes with electron withdrawing substituents such as **5f–g**, and **5i** produced the Pictet–Spengler cyclized products in less time with excellent yields whereas aldehydes with electron donating substituents or no substituents **5a–e, h** produced the pyrido fused imidazo[4,5-*c*]quinolines in good yields with slightly longer reaction times. The use of furfuraldehyde as heteroaromatic aldehyde and butyraldehyde resulted in pyrido fused imidazo[4,5-*c*]quinolines **6u–v** in good yield.

Upon completion of the reaction, the product was obtained by a simple workup procedure. The solvent was removed under reduced pressure and the reaction mixture was washed with sodium bicarbonate solution. The compounds were then purified by column chromatography and characterized by standard analytical techniques. The ^{1}H NMR spectrum of the synthesized compound indicated the formation of pure pyrido fused imidazo[4,5-*c*]-quinolines **6** in excellent yield, as depicted in Table 2. In addition, we have evaluated the drug likeliness of pyrido fused imidazo[4,5-*c*]-quinolines **6** by comparing it with Lipinski rules.[28–30] According to this rule, an ideal molecule should have a molecular weight



Scheme 3 Microwave-assisted one-pot sequential approach to substituted pyrido fused imidazo[4,5-*c*]quinolones **6** in green media.



Scheme 4 Gram-scale synthesis of 6-phenylpyrido[2′,1′:2,3]imidazo[4,5-*c*]quinoline **6a**.

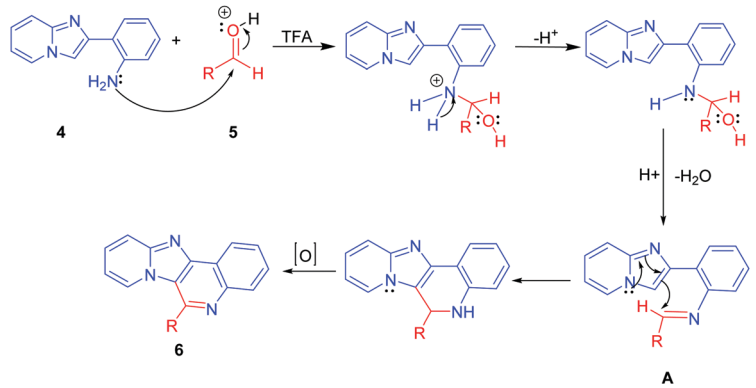


Fig. 3 Plausible mechanism for the formation of pyrido fused imidazo[4,5-*c*]quinoline **6**.

less than 500, *clog P* value, which defines the bioavailability and delivery issues should be less than 5, the number of hydrogen bond acceptors should not be more than 10, the number of hydrogen bond donors should not be more than 5. In addition to those, the molecule should not contain more than 10 rotatable bonds. However, for the design of a potential molecule as drug candidate, one Lipinski violation is allowed.

The scalability of the reaction was investigated on a gram scale with the reaction of 2-(imidazo[1,2-*a*]pyridin-2-yl)aniline **4a** and benzaldehyde **5a** under optimized reaction conditions that gave the corresponding product 6-phenylpyrido[2′,1′:2,3]imidazo[4,5-*c*]-quinoline **6a** in excellent yield (82%) without any significant loss in the optimized reaction yields (Scheme 4).

A plausible mechanistic pathway for the Pictet–Spengler annulation reaction is outlined in Fig. 3. Initially, carbonyl oxygen of aldehyde **5** is protonated by trifluoroacetic acid followed by the attack of the amine moiety of **4** on the electrophilic carbon atom to form the imine **A** with the removal of water. Finally after electron delocalization on N-atoms of imidazo[1,2-*a*]pyridine, the imine underwent cyclization and oxidative dehydrogenation under air to form the desired compound **6**.[17]

Conclusion

In a nutshell, we have proposed a one-pot sequential microwave assisted methodology for the synthesis of imidazo[4,5-*c*]quinoline derivatives **6** from substituted 2-aminopyridines **1** and 2-bromo-2′-nitroacetophenone **2** and aldehydes **5**. Compared with the literature protocols, the salient features of this method include the use of a green solvent, reduced reaction time, broad substrate scope and use of cheap reagents. Moreover, the outcome of waste from the reaction is minimum projecting it as a suitable methodology for the large-scale synthesis of pyrido fused imidazo[4,5-*c*]quinoline. Substrate versatility studies showed that this novel one-pot sequential process provided a facile route to access a class of tetracyclic heterocyclic compounds with varied structural diversity. Due to the presence of polyheterocycles, these compounds have varied biological importance. Conspicuously, the whole methodology combines condensation/amination/Pictet Spengler cyclization reactions in a one-pot sequential pathway to give complex compounds in a simple and practical manner. In this view, our protocol reduces the time drastically for a medicinal chemist and affords easy preparation of a molecule library for screening experiments and biological studies.

Experimental section

Procedure for the one-pot sequential synthesis of 6-phenylpyrido[2′,1′:2,3]imidazo[4,5-*c*]quinoline 6a

To a round bottom flask, a mixture of 2-aminopyridine **1a** (0.150 g, 1.6 mmol, 1.0 equiv.) and 2-bromo-2′-nitro acetophenone **2** (0.408 g, 1.6 mmol, 1.0 equiv.) were introduced in 5 mL of H_2O : IPA (1 : 1) solvent and the mixture was irradiated at 240 watts under microwave for 5 min at 75 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, conc. HCl (0.045 g, 1.26 mmol, 1.5 equiv.) was added to the mixture followed by zinc dust (0.163 g, 2.4 mmol, 3.0 equiv.) under vigorous stirring. The resulting reaction mixture was irradiated 70 °C under microwave for 5 min. After completion of the reaction as monitored by TLC, Zn dust was removed by centrifugation and to the same

reaction mixture benzaldehyde **5a** along with trifluoroacetic acid (0.081 g, 1.0 equiv., 0.7 mmol) were added. The same reaction mixture was irradiated at 280 watt for 13 minutes at 75 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed using a rotary evaporator and the resulting reaction mixture was neutralized with saturated sodium bicarbonate solution. Then, it was extracted with ethyl acetate (10 mL, thrice) and all the fractions of the organic layer were combined and dried over sodium sulphate. The combined filtrate was then evaporated to obtain a crude mixture. It was purified over silica gel (60–120 mesh) using 25% ethyl acetate in hexane solution to obtain pure 6-phenylpyrido[2′,1′:2,3]imidazo[4,5-*c*]quinoline **6a**.

Yield = 0.192 g, 91%; white solid; R_f = 0.63 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, J = 7.36 Hz, 1H), 8.30 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 6.96 Hz, 1H), 7.95 (d, J = 9.12 Hz, 1H), 7.80 (t, J = 7 Hz, 1H), 7.73 (t, J = 6.88 Hz, 3H), 7.65–7.61 (m, 3H), 7.53 (t, J = 7.12 Hz, 1H), 6.78 (t, J = 6.64 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 147.2, 146.3, 144.0, 137.2, 129.0, 128.6, 128.5, 128.3, 127.9, 127.7, 126.1, 125.6, 121.6, 120.4, 119.4, 117.0, 111.0; MS (GC-MS) 295; HRMS (EI, *m*/*z*) calcd for $C_{20}H_{13}N_3$: *m*/*z* 295.1109; Found: 295.1101; IR (cm^{-1}, KBr): 2916, 1600, 1427, 1365, 744.

6-(*p*-Tolyl)pyrido[2′,1′:2,3]imidazo[4,5-*c*]quinoline (6b)

Yield = 0.27 g, 90%; white solid; R_f = 0.61 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, J = 7.96 Hz, 1H), 8.29 (d, J = 8.08 Hz, 1H), 8.12 (d, J = 7 Hz, 1H), 7.92 (d, J = 9.16 Hz, 1H), 7.78 (t, J = 8.4 Hz, 1H), 7.71 (t, J = 8.08 Hz, 1H), 7.61 (d, J = 7.96 Hz, 2H), 7.52 (t, J = 5.56 Hz, 1H), 7.43 (d, J = 7.76 Hz, 2H), 6.78 (t, J = 6.92 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 148.4, 147.3, 145.0, 139.6, 135.4, 129.9, 129.5, 128.8, 128.6, 127.3, 126.5, 122.6, 121.4, 120.5, 118.0, 111.9, 21.5; MS (GC-MS) 309; HRMS (EI, *m*/*z*) calcd for $C_{21}H_{15}N_3$: *m*/*z* 309.1266; Found: 309.1263; IR (cm^{-1}, KBr): 3404, 1604, 1591, 1342, 758.

6-(2-Methoxyphenyl)pyrido[2′,1′:2,3]imidazo[4,5-*c*]quinoline (6c)

Yield = 0.29 g, 90%; white solid; R_f = 0.65 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, J = 7.96 Hz, 1H), 8.28 (d, J = 8 Hz, 1H), 8.16 (d, J = 7.04 Hz, 1H), 7.92 (d, J = 9.12 Hz, 1H), 7.78 (t, J = 8.4 Hz, 1H), 7.71 (d, J = 8.04 Hz, 1H), 7.66 (d, J = 7.42 Hz, 2H), 7.53 (t, J = 6.76 Hz, 1H), 7.15 (d, J = 8.72 Hz, 2H), 6.80 (d, J = 6.92 Hz, 1H) 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 149.6, 148.1, 147.4, 145.1, 130.1, 129.8, 129.5, 128.8, 127.2, 126.4, 122.6, 121.4, 120.6, 118.0, 114.7, 111.9, 55.5; MS (GC-MS) 325; HRMS (ESI, *m*/*z*) calcd for $C_{21}H_{16}N_3O$: *m*/*z* 326.1293; Found: 326.1453; IR (cm^{-1}, KBr): 2953, 1604,1502, 1361, 765.

6-(3,4,5-Trimethoxyphenyl)pyrido[2′,1′:2,3]imidazo[4,5-*c*]quinoline (6d)

Yield = 0.34 g, 89%; white solid; R_f = 0.61 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, J = 7.96 Hz, 1H), 8.30 (d, J = 8.24 Hz, 1H), 8.11 (d, J = 6.96 Hz, 1H), 7.94 (d, J = 9.12 Hz, 1H), 7.80 (t, J = 7.24 Hz, 1H), 7.73 (t, J = 7.6 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 6.91 (s, 2H), 6.85 (t, J = 6.84 Hz, 1H), 3.96 (s, 3H), 3.89 (6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 154.1, 149.7, 147.9, 147.4, 144.9, 138.9, 133.9, 130.1, 129.5, 129.0, 127.4, 126.7, 122.6, 121.5, 120.2, 118.0, 112.1, 105.5, 61.0, 60.4, 56.3; MS (GC-MS) 385; HRMS (ESI, *m*/*z*) calcd for $C_{23}H_{20}N_3O_3$: *m*/*z* 386.1505; Found: 386.1502; IR (cm^{-1}, KBr): 3030, 1735, 1598, 1381, 736.

6-(4-Nitrophenyl)pyrido[2′,1′:2,3]imidazo[4,5-*c*]quinoline (6e)

Yield = 0.31 g, 92%; white solid; R_f = 0.69 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, J = 9.04 Hz, 1H), 8.35 (d, J = 8.16 Hz, 1H), 8.21 (d, J = 7.88 Hz, 1H), 7.89 (t, J = 7.48 Hz, 2H), 7.84–7.74 (m, 3H), 7.67 (t, J = 7.92 Hz, 2H), 7.53 (t, J = 7.28 Hz, 1H), 6.78 (t, J = 6.72 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 148.1, 147.1, 144.8, 144.1, 134.3, 131.7, 130.7, 130.0, 129.5, 129.0, 127.1, 125.9, 125.2, 122.7, 121.8, 120.8, 118.3, 112.6; MS (GC-MS) 340; HRMS (ESI, *m*/*z*) calcd for $C_{20}H_{13}N_4O_2$: *m*/*z* 341.1039; Found: 341.1044; IR (cm^{-1}, KBr): 1620, 1560, 1319, 1483, 742.

2-(Pyrido[2′,1′:2,3]imidazo[4,5-*c*]quinolin-6-yl)benzonitrile (6f)

Yield = 0.29 g, 92%; white solid; R_f = 0.71 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, J = 7.92 Hz, 1H), 8.28 (d, J = 7.68 Hz, 1H), 8.21 (d, J = 8.48 Hz, 1H), 8.05 (d, J = 9.16 Hz, 1H), 7.99 (d, J = 5.08 Hz, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.44 Hz, 2H), 7.83 (t, J = 8.4 Hz, 1H), 7.76 (t, J = 4.01 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 145.7, 144.8, 142.5, 133.0, 132.2, 130.7, 130.5, 129.8, 129.5, 127.4, 126.7, 122.8, 121.3, 118.3, 118.2, 113.7, 112.8; MS (GC-MS) 320; HRMS (ESI, *m*/*z*) calcd for $C_{21}H_{12}N_4$: *m*/*z* 321.1140; Found: 321.1319; IR (cm^{-1}, KBr): 2920, 1620, 1514, 1485, 763.

2-(Pyrido[2′,1′:2,3]imidazo[4,5-*c*]quinolin-6-yl)phenol (6g)

Yield = 0.25 g, 82%; white solid; R_f = 0.71 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 5.52 Hz, 2H), 8.05 (d, J = 7.92 Hz, 1H), 7.92 (d, J = 9.12 Hz, 1H), 7.74 (t, J = 5.52 Hz, 1H), 7.68 (t, J = 8.08 Hz, 1H), 7.58 (t, J = 8.28 Hz, 2H), 7.45 (t, J = 6.7 Hz, 1H), 7.23 (d, J = 8.28 Hz, 1H), 7.08 (t, J = 7.56 Hz, 1H), 6.91 (t, J = 6.96 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1. 150.1. 146.9. 143.2. 131.9. 130.4. 129.5. 129.3. 128.0. 126.8. 122.8. 121.2. 120.7. 119.6. 118.8. 118.0. 112.0; MS (GC-MS) 311; HRMS (ESI, *m*/*z*) calcd for $C_{20}H_{14}N_3O$: *m*/*z* 312.1137; Found: 312.1139; IR (cm^{-1}, KBr): 3049, 1664, 1562, 1369, 765.

11-Methyl-6-phenylpyrido[2′,1′:2,3]imidazo[4,5-*c*]quinoline (6h)

Yield = 0.28 g, 91%; white solid; R_f = 0.73 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, J = 7.92 Hz, 1H), 8.30 (d, J = 8.24 Hz, 1H), 7.88 (d, J = 6.92 Hz, 1H), 7.78 (t, J = 7.2 Hz, 1H), 7.72 (d, J = 6.92, 3H), 7.62 (d, J = 6.88 Hz, 3H), 7.29 (d, J = 6.76 Hz, 1H), 6.66 (t, J = 6.92 Hz, 1H), 2.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 148.2, 147.1, 144.7, 138.2, 129.5, 129.3, 129.2, 128.8, 128.4, 128.0, 126.3, 124.9, 122.8, 121.6, 120.9, 111.9, 17.6; MS (GC-MS) 309; HRMS (EI, *m*/*z*) calcd for $C_{21}H_{15}N_3$: *m*/*z* 309.1266; found: 309.1263; IR (cm^{-1}, KBr): 1620, 1566, 1504, 1348, 729.

6-(2-Methoxyphenyl)-11-methylpyrido[2′,1′:2,3]imidazo[4,5-*c*]quinoline (6i)

Yield = 0.31 g, 92%; white solid; R_f = 0.68 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, J = 7.96 Hz, 1H), 8.33 (d, J = 8.16 Hz, 1H), 7.77 (t, J = 6.68 Hz, 2H), 7.70 (t, J = 7.72 Hz, 1H),

7.65 (d, J = 7.36 Hz, 1H), 7.58 (t, J = 8.08 Hz, 1H), 7.30 (d, J = 6.8 Hz, 1H), 7.23 (t, J = 7.44 Hz, 1H), 7.10 (d, J = 8.32 Hz, 1H), 6.68 (t, J = 6.92 Hz, 1H), 3.62 (s, 3H), 2.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 150.0, 146.5, 145.6, 131.3, 131.1, 129.3, 128.5, 128.2, 127.7, 126.3, 124.7, 122.8, 122.0, 121.8, 111.7, 111.0, 55.5, 17.6; MS (GC-MS) 339; HRMS (EI, m/z) calcd for $C_{22}H_{17}N_3O$: m/z 339.1372; found: 339.1370; IR (cm^{-1}, KBr): 2924, 1606, 1516, 1344, 804.

6-(4-Methoxyphenyl)-11-methylpyrido[2′,1′:2,3]imidazo[4,5-*c*]quinoline (6j)

Yield = 0.31 g, 92%; white solid; R_f = 0.63 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, J = 7.36 Hz, 1H), 8.32 (d, J = 8.12 Hz, 1H), 8.02 (d, J = 6.96 Hz, 1H), 7.76 (t, J = 7.12 Hz, 1H), 7.71 (d, J = 7.52 Hz, 1H), 7.67 (d, J = 8.56 Hz, 2H), 7.32 (d, J = 6.68 Hz, 1H), 7.15 (d, J = 8.56 Hz, 2H), 6.71 (t, J = 6.92 Hz, 1H), 3.94 (s, 3H), 2.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 148.0, 130.2, 129.1, 128.8, 128.5, 128.1, 126.3, 125.0, 122.8, 121.5, 121.0, 114.6, 111.9, 55.5, 17.6; MS (GC-MS) 339; HRMS (ESI, m/z) calcd for $C_{22}H_{18}N_3O$: m/z 340.1450; found: 340.1452; IR (cm^{-1}, KBr): 2841, 1641, 1581, 1355, 771.

11-Methyl-6-(3,4,5-trimethoxyphenyl)pyrido[2′,1′:2,3]imidazo[4,5-*c*]quinoline (6k)

Yield = 0.35 g, 90%; white solid; R_f = 0.74 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, J = 7.96 Hz, 1H), 8.34 (s, 1H), 7.98 (d, J = 6.88 Hz, 1H), 7.79 (t, J = 8.24 Hz, 1H), 7.72 (t, J = 7.96 Hz, 1H), 7.35 (d, J = 6.68 Hz, 1H), 6.91 (s, 2H), 6.75 (t, J = 6.92 Hz, 1H), 3.96 (s, 3H), 3.89 (s, 6H), 2.83 (3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 152.7, 144.0, 141.9, 133.3, 132.2, 129.2, 128.2, 126.8, 125.1, 124.5, 123.8, 122.9, 121.0, 120.7, 112.4, 105.7, 61.0, 56.3, 17.6; MS (GC-MS) 399; HRMS (EI, m/z) calcd for $C_{24}H_{21}N_3O_3$: m/z 399.1583; found: 399.1580; IR (cm^{-1}, KBr): 2916, 1641, 1354, 1581, 794.

11-Methyl-6-(4-nitrophenyl)pyrido[2′,1′:2,3]imidazo[4,5-*c*]quinoline (6l)

Yield = 0.33 g, 94%; white solid; R_f = 0.74 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, J = 7.96 Hz, 1H), 8.35 (d, J = 8.12 Hz, 1H), 8.20 (d, J = 8.04 Hz, 1H), 7.88 (t, J = 7.36 Hz, 1H), 7.82–7.72 (m, 3H), 7.67 (d, J = 7.32 Hz, 1H), 7.51 (d, J = 6.84 Hz, 1H), 7.31 (d, J = 6.76 Hz, 1H), 6.68 (t, J = 6.92 Hz, 1H), 3.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ150.1, 148.1, 146.8, 144.6, 134.2, 131.7, 130.6, 129.3, 128.8, 128.5, 128.4, 126.8, 125.2, 123.5, 122.9, 122.0, 112.5, 17.6; MS (GC-MS) 354; HRMS (EI, m/z) calcd for $C_{21}H_{14}N_4O_2$: m/z 354.1117; found: 354.1194; IR (cm^{-1}, KBr): 1649, 1591, 1363, 1176, 769.

6-(2-Bromophenyl)-11-methylpyrido[2′,1′:2,3]imidazo[4,5-*c*]quinoline (6m)

Yield = 0.34 g, 89%; white solid; R_f = 0.63 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, J = 7.68 Hz, 1H), 8.29 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 6.36 Hz, 1H), 7.76 (d, J = 7.52 Hz, 1H), 7.70–7.61 (m, 6H), 6.60 (s, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 147.8, 147.6, 144.9, 141.7, 138.2, 129.6, 129.4, 129.2, 128.8, 128.7, 126.4, 126.2, 122.6, 121.4, 120.3, 116.2, 114.8, 21.7; MS (GC-MS) 387; HRMS (ESI, m/z) calcd for $C_{21}H_{15}BrN_3$: m/z 388.0448; found: 388.0448; IR (cm^{-1}, KBr): 3385, 1676, 1502, 1363, 615.

10-Methyl-6-phenylpyrido[2′,1′:2,3]imidazo[4,5-*c*]quinoline (6n)

Yield = 0.27 g, 89%; white solid; R_f = 0.71 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.3 (s, 1H), 8.77 (d, J = 7.96 Hz, 1H), 8.35 (d, J = 8.28 Hz, 1H), 7.95 (s, 1H), 7.84 (t, J = 7.32 Hz, 1H), 7.77 (d, J = 4.56 Hz, 1H), 7.67 (d, J = 7.32 Hz, 1H), 7.58 (t, J = 6.52 Hz, 1H), 6.83 (d, J = 6.96 Hz, 1H), 2.51, (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 146.2, 144.8, 142.4, 135.2, 133.3, 132.4, 131.4, 130.9, 128.8, 127.2, 126.1, 123.3, 122.5, 119.7, 119.6, 1175, 115.8, 22.1; MS (GC-MS) 309; HRMS (ESI, m/z) calcd for $C_{21}H_{16}N_3$: m/z 310.1344; Found: 310.1342; IR (cm^{-1}, KBr): 3053, 1568, 1622, 1361, 765.

10-Methyl-6-(p-tolyl)pyrido[2′,1′:2,3]imidazo[4,5-*c*]quinoline (6o)

Yield = 0.29 g, 90%; white solid; R_f = 0.61 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, J = 8.04 Hz, 1H), 8.54 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 7.12 Hz, 1H), 7.96 (t, J = 7.24 Hz, 1H), 7.91(s, 1H), 7.87 (t, J = 7.72 Hz, 1H), 7.69 (d, J = 7.96 Hz, 2H), 7.51 (d, J = 7.76 Hz, 2H), 6.91 (d, J = 7.04 Hz, 1H), 2.59 (3H), 2.54 (3H); ^{13}C NMR (100 MHz, $CDCl_3$) 155.0, 146.8, 144.5, 139.6, 138.4, 132.2, 130.5, 128.9, 128.6, 127.5, 126.7, 125.6, 123.4, 120.3, 119.4, 117.4, 116.7, 22.1, 21.7; MS (GC-MS) 323; HRMS (EI, m/z) calcd for $C_{22}H_{17}N_3$: m/z 323.1422; Found: 323.1420; IR (cm^{-1}, KBr): 3051, 2922, 1622, 1568, 819.

6-(4-Methoxyphenyl)-10-methylpyrido[2′,1′:2,3]imidazo[4,5-*c*]quinoline (6p)

Yield = 0.30 g, 90%; white solid; R_f = 0.61 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 8.04 Hz, 1H), 8.28 (d, J = 8.24 Hz, 1H), 8.01 (d, J = 7.12 Hz, 1H), 7.77 (t, J = 8.36 Hz, 1H), 7.70 (d, J = 7.92 Hz, 1H), 7.67 (d, J = 8.56 Hz, 3H), 7.15 (d, J = 8.64 Hz, 2H), 6.63 (d, J = 7.12 Hz, 1H), 3.94 (3H), 2.48 (3H); ^{13}C NMR (100 MHz, $CDCl_3$) 160.7, 150.4, 147.8, 147.6, 141.8, 130.2, 129.0, 128.9, 126.3, 122.6, 121.3, 120.4, 116.3, 114.8, 114.7, 55.5, 21.7 MS (GC-MS) 339; HRMS (ESI, m/z) calcd for $C_{22}H_{18}N_3O$: m/z 340.1450; Found: 340.1451; IR (cm^{-1}, KBr): 3059, 1656, 1593, 702.

10-Methyl-6-(3,4,5-trimethoxyphenyl)pyrido[2′,1′:2,3]imidazo[4,5-*c*]-quinoline (6q)

Yield = 0.35 g, 88%; white solid; R_f = 0.61 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, J = 7.56 Hz, 1H), 8.51 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 7.04 Hz, 1H), 7.94 (d, J = 7.36 Hz, 1H), 7.90 (d, J = 8.36 Hz, 1H), 7.84 (t, J = 7.4 Hz, 1H), 6.99 (s, 2H), 6.88 (d, J = 7.08 Hz, 1H), 3.99 (3H), 3.90 (6H), 2.58 (3H); ^{13}C NMR (100 MHz, $CDCl_3$) 154.3, 146.5, 145.5, 140.6, 131.6, 128.3, 126.8, 124.5, 123.2, 119.9, 117.1, 116.6, 106.0, 61.6, 56.5, 22.1 MS (GC-MS) 399; HRMS (ESI, m/z) calcd for $C_{24}H_{22}N_3O_3$: m/z 400.1661; Found: 400.1662; IR (cm^{-1}, KBr): 3061, 2852, 1687, 1595, 775.

6-(2-Bromophenyl)-10-methylpyrido[2′,1′:2,3]imidazo[4,5-*c*]quinoline (6r)

Yield = 0.35 g, 92%; white solid; R_f = 0.69 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, J = 7.96 Hz, 1H),

8.42 (d, J = 8.32 Hz, 1H), 8.01 (s, 1H), 7.91 (t, J = 7.32 Hz, 1H), 7.85 (d, J = 7.96 Hz, 2H), 7.73 (d, J = 7.32 Hz, 1H), 7.65 (t, J = 6.52 Hz, 2H), 7.58 (t, J = 7.64 Hz, 1H), 6.90 (d, J = 7 Hz, 1H), 2.57 (3H); ^{13}C NMR (100 MHz, $CDCl_3$) 152.2, 149.1, 148.5, 145.6, 142.6, 129.6, 129.4, 129.2, 128.8, 128.7, 127.4, 126.4, 126.2, 123.5, 122.5, 109.5, 24.3; MS (GC-MS) 387; HRMS (EI, m/z) calcd for $C_{21}H_{14}BrN_3$: m/z 387.0371; Found: 387.0369; IR (cm^{-1}, KBr): 3113, 1602, 1517, 1344, 520.

9,11-Difluoro-6-phenylpyrido[2′,1′:2,3]imidazo[4,5-*c*]quinoline (6s)

Yield = 0.29 g, 89%; white solid; R_f = 0.61 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 7.92 Hz, 1H), 8.32 (d, J = 8.16 Hz, 1H), 7.82 (t, J = 7.12 Hz, 2H), 7.76 (d, J = 7.44 Hz, 1H), 7.70 (s, 2H), 7.67 (d, J = 4.72 Hz, 3H), 7.22 (d, J = 8.16 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 161.3, 155.9, 154.5, 148.3, 143.7, 140.1, 130.2, 128.2, 126.4, 124.2, 123.6, 122.7, 114.9, 110.8, 106.2; MS (GC-MS) 331; HRMS (ESI, m/z) calcd for $C_{20}H_{12}F_2N_3$: m/z 332.0999; Found: 332.0997; IR (cm^{-1}, KBr): 3133, 1724, 1527, 184, 827.

9,11-Difluoro-6-(4-methoxyphenyl)pyrido[2′,1′:2,3]imidazo[4,5-*c*]-quinoline (6t)

Yield = 0.31 g, 88%; white solid; R_f = 0.59 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, J = 7.84 Hz, 1H), 8.35 (s, 1H), 7.99 (s, 1H), 7.83 (t, J = 7.16 Hz, 1H), 7.75 (t, J = 7.6 Hz, 2H), 7.67 (d, J = 7.84 Hz, 2H), 7.25(s, 1H), 7.18 (d, J = 7.92 Hz, 2H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 160.5, 158.0, 147.6, 134.1, 130.2, 129.6, 127.1, 122.7, 122.0, 121.4, 114.9, 111.4, 110.7, 55.5; MS (GC-MS) 361; HRMS (ESI, m/z) calcd for $C_{21}H_{14}F_2N_3O$: m/z 362.1105; Found: 362.1105; IR (cm^{-1}, KBr): 2937, 1616, 1433, 1080, 754.

6-(Furan-2-yl)pyrido[2′,1′:2,3]imidazo[4,5-*c*]quinolone (6u)

Yield = 0.227 g, 81%; white solid; R_f = 0.61 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 7.08 Hz, 1H), 8.68 (d, J = 8.04 Hz, 1H), 8.18 (d, J = 8.32 Hz, 1H), 7.84 (d, J = 9.12 Hz, 1H), 7.69 (d, J = 5.16 Hz, 2H), 7.62 (t, J = 7.6 Hz, 1H), 7.49 (t, J = 7.16 Hz, 1H), 7.20 (s, 1H), 6.88 (t, J = 6.84 Hz, 1H), 6.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 149.8, 147.8, 144.8, 143.5, 137.7, 130.1, 129.4, 129.0, 128.4, 126.8, 122.7, 121.6, 120.3, 117.8, 112.6, 112.5, 112.2; MS (GC-MS) 285.

6-Propylpyrido[2′,1′:2,3]imidazo[4,5-*c*]quinolone (6v)

Yield = 0.20 g, 80%; white solid; R_f = 0.59 (40%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70–8.64 (m, 2H), 8.21 (d, J = 7.92 Hz, 1H), 7.92 (d, J = 9.08 Hz, 1H), 7.70 (t, J = 7.2 Hz, 1H), 7.62 (d, J = 7.36 Hz, 1H), 7.57 (t, J = 8.4 Hz, 1H), 7.09 (t, J = 6.8 Hz, 1H), 3.45 (t, J = 7.8 Hz, 2H), 1.58–1.54 (m, 2H), 1.02 (t, J = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 149.7, 139.1, 129.8, 129.0, 127.4, 126.3, 123.6, 123.3, 122.6, 121.1, 118.3, 114.0, 113.1, 29.6, 20.9, 14.1; MS (GC-MS) 261.

Conflicts of interest

There are no conflicts of interest to declare.

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References

1 L. Zhang, X. M. Peng, G. L. V. Damu, R. X. Geng and C. H. Zhou, *Med. Res. Rev.*, 2014, **34**, 340–437.
2 A. T. Balaban, D. C. Oniciu and A. R. Katritzky, *Chem. Rev.*, 2004, **104**, 2777–2812.
3 N. R. Candeias, L. C. Branco, P. M. P. Gois, C. A. M. Afonso and A. F. Trindade, *Chem. Rev.*, 2009, **109**, 2703–2802.
4 R. N. Rao and K. Chanda, *Bioorg. Chem.*, 2020, **99**, 103801.
5 R. N. Rao, R. L. Panchangam, V. Manickam, M. M. Balamurali and K. Chanda, *ChemPlusChem*, 2020, **85**, 1800–1812.
6 R. D. Padmaja, M. M. Balamurali and K. Chanda, *J. Org. Chem.*, 2019, **84**, 11382–11390.
7 R. K. Kawade, D. B. Huple, R. J. Lin and R. S. Liu, *Chem. Commun.*, 2015, **51**, 6625–6628.
8 T. He, L. Yu, L. Zhang, L. Wang and M. Wang, *Org. Lett.*, 2011, **13**, 5016–5019.
9 Z. Xie, Y. Cai, H. Hu, C. Lin, J. Jiang, Z. Chen, L. Wang and Y. Pan, *Org. Lett.*, 2013, **15**, 4600–4603.
10 F. Stauffer, S. M. Maira, P. Furet and C. G. Echeverria, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 1027–1030.
11 T. Izumi, J. Sakaguchi, M. Takeshita, H. Tawara, K. Kato, H. Dose, T. Tsujino, Y. Watanabe and H. Kato, *Bioorg. Med. Chem.*, 2003, **11**, 2541–2550.
12 Y. Thigulla, M. Akula, P. Trivedi, B. Ghosh, M. Jha and A. Bhattacharya, *Org. Biomol. Chem.*, 2016, **14**, 876–883.
13 D. H. Dockrell and G. R. Kinghorn, *J. Antimicrob. Chemother.*, 2001, **48**, 751–755.
14 R. N. Rao, M. M. Balamurali, B. Maiti, R. Thakuria and K. Chanda, *ACS Comb. Sci.*, 2018, **20**, 164–171.
15 R. D. Padmaja, V. C. Devi, N. Mukku, K. Chanda and B. Maiti, *ACS Omega*, 2018, **3**, 4583–4590.
16 B. Maiti, K. Chanda, M. Selvaraju, C. C. Tseng and C. M. Sun, *ACS comb. Sci.*, 2013, **15**, 291–297.
17 S. Sharma, B. Saha, D. Sawant and B. Kundu, *J. Comb. Chem.*, 2007, **9**, 783–792.
18 A. K. Pandey, R. Sharma, A. Singh, S. Shukla, K. Srivastava, S. K. Puri, B. Kumar and P. M. S. Chauhan, *RSC Adv.*, 2014, **4**, 26757–26770.
19 A. Kale, C. Bingi, C. N. Ragi, P. Sripadi, R. P. Tadikamalla and K. Atmakur, *Synthesis*, 2017, 1603–1612.
20 S. Satish, P. Siddiq, N. Shaik, K. Hari, K. Bheeshma, A. Abdullah and A. Kamal, *Asian J. Org. Chem.*, 2017, **6**, 1830–1837.

21 S. M. Geeta, V. S. R. Ayanampudi, T. Yellaiah, S. Satish, S. Faria, K. N. Hari, S. Nagula and A. Kamal, *New J. Chem.*, 2018, **42**, 15820–15829.
22 L. Guifang, L. Jingyu, L. Ping and P. Sun, *J. Org. Chem.*, 2019, **84**, 16346–16354.
23 D. A. Probst, P. R. Hanson and D. A. Barda, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd, USA, 2004.
24 R. N. Rao, B. Maiti and K. Chanda, *ACS Comb. Sci.*, 2017, **19**, 199–221.
25 R. L. Panchangam, V. Manickam and K. Chanda, *ChemMedChem*, 2019, **14**, 262–271.
26 A. A. Saikia, R. N. Rao, B. Maiti, M. M. Balamurali and K. Chanda, *ACS Comb. Sci.*, 2020, **22**, 630–640.
27 B. Maiti and C. M. Sun, *New J. Chem.*, 2011, **35**, 1385–1396.
28 C. A. Lipinski, F. Lombardo, B. W. Dominy and P. J. Feeney, *Adv. Drug Delivery Rev.*, 1997, **23**, 3–25.
29 C. A. Lipinski, F. Lombardo, B. W. Dominy and P. J. Feeney, *Adv. Drug Delivery Rev.*, 2001, **46**, 3–26.
30 D. F. Veber, S. R. Johnson, H.-Y. Cheng, B. R. Smith, K. W. Ward and K. D. Kopple, *J. Med. Chem.*, 2002, **45**, 2615–2623.