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Library construction of 1-(1*H*-imidazol-1-yl)-1,2-dihydroisoquinolines via three-component reaction of 2-alkynylbenzaldehyde, amine, and imidazole

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ABSTRACT

Parallel diversity-oriented synthesis of diverse 1-(1*H*-imidazol-1-yl)-1,2-dihydroisoquinolines via AgOTf-catalyzed three-component reaction of 2-alkynylbenzaldehyde, amine, and imidazole is described. This reaction works efficiently under mild conditions to generate a small library of imidazole-incorporated 1,2-dihydroisoquinolines.

1. Introduction

Parallel diversity-oriented synthesis has been recognized as a powerful and efficient tool for providing a large collection of small molecules in the field of combinatorial chemistry.[1] This strategy has a great impact on the drug discovery process currently. Among the scaffolds generated based on the approach, intense interest has been directed toward the design and synthesis of 1,2-dihydroisoquinolines,[2–4] which serves as a core structure in many natural alkaloids and pharmaceuticals with diverse biological and pharmacological activities.[5,6] On the other hands, the imidazole moiety is widely featured in many pharmacologically and biologically active compounds (including antivirals, antitumor, antifungals, etc.).[7] Thus, exploration for the efficient generation of highly functionalized imidazole-related compounds has drawn a great deal of attention from both medicinal and organic chemists.

As part of an ongoing program in our laboratory for natural product-like compounds generation,[8,9] we are interested in the methodology development for accessing 1,2-dihydroisoquinolines. Recently, we developed an efficient pathway to functionalized 1,2-dihydroisoquinolines starting from 2-alkynylbenzaldehydes.[10] Subsequent biological assay revealed that some of them showed promising result for PTP1B inhibition (Fig. 1). Protein tyrosine phosphatase 1B (PTP1B) has been demonstrated as a novel target for diabetes and obesity. Inhibition of PTP1B′s activity could improve the sensitivity of insulin signaling.[11] This biological result prompted us to consider to generate more novel 1,2-dihydroisoquinoline-based compounds for further screening. Encouraged by the importance of the imidazole skeleton, we conceived that the 1,2-dihydroisoquinoline with an imidazole substituent might be a choice for hit evaluation. Based on our previous reports[10] and the advancement of multi-component reactions,[12] we envisioned that three-component reaction of 2-alkynylbenzaldehyde, amine, and imidazole under suitable conditions would be a good device to afford the desired imidazole-derived 1,2-dihydroisoquinolines. Therefore, we started to investigate the methodology for the synthesis of imidazole-incorporated 1,2-dihydroisoquinolines.

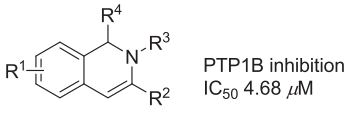

Fig. 1. 1,2-Dihydroisoquinoline scaffold.

2. Results and discussion

The initial studies were performed for three-component reaction of 2-alkynylbenzaldehyde **1a**, *p*-toluidine **2b**, and imidazole **3a** catalyzed by different Lewis acids in various solvents (Table 1).

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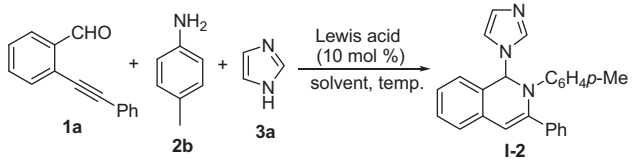
Table 1
Initial studies for three-component reaction of 2-alkynylbenzaldehyde **1a**, *p*-toluidine **2b**, and imidazole **3a**



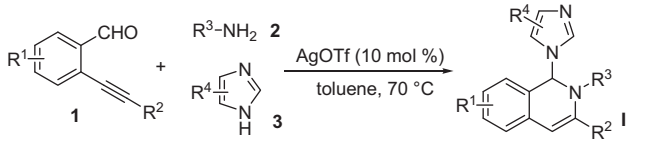
Entry	Lewis acid	Solvent	Temp (°C)	Yield[a] (%)
1	CuI	DCE	25	NR
2	AgOTf	DCE	25	NR
3	$PdCl_2$	DCE	25	NR
4	CuI	THF	25	NR
5	AgOTf	THF	25	NR
6	$PdCl_2$	THF	25	NR
7	CuI	DCE	50	Complex
8	AgOTf	DCE	50	27
9	$PdCl_2$	DCE	50	Trace
10	AgOTf	THF	50	43
11	AgOTf	MeCN	50	41
12	AgOTf	EtOH	50	27
13	AgOTf	Toluene	50	61
14	AgOTf	1,4-Dioxane	50	44
15	AgOTf	Toluene	70	80

[a] Isolated yield based on 2-alkynylbenzaldehyde **1a**.

Since Pd, Cu, and Ag salts have been demonstrated effectively for activation of triple bond,[10] the reaction was carried out in the presence of $PdCl_2$, CuI, or AgOTf (10 mol %) in dichloroethane at room temperature (Table 1, entries 1–3). However, no desired product was detected and only the intermediate *ortho*-alkynylaryl aldimine was observed. The same result was displayed when the reaction took place in THF (Table 1, entries 4–6). When the reaction occurred at 50 °C in dichloroethane, complex result was obtained when CuI was utilized as the catalyst (Table 1, entry 7). Gratifyingly, the corresponding product **I-2** was isolated in 27% yield when the reaction was catalyzed by AgOTf (Table 1, entry 8). Only a trace amount of product was formed when $PdCl_2$ was used as a catalyst (Table 1, entry 9). We further tested the AgOTf-catalyzed reaction in different solvents at 50 °C. It was found that the reaction worked the most efficiently in toluene, which furnished the 1,2-dihydroisoquinoline **I-2** in 61% yield (Table 1, entry 13). The result could be improved when the reaction occurred at 70 °C, with an isolated 80% yield (Table 1, entry 15). However, reducing the amount of catalyst resulted in lower reactivity (data not shown in Table 1).

With an expectation to generate a small library of imidazole-incorporated 1,2-dihydroisoquinolines **I**, we next investigate the scope of this three-component reaction of 2-alkynylbenzaldehyde **1**, amine **2**, and imidazole **3** under the optimized conditions [AgOTf (10 mol %), toluene, 70 °C]. This silver-catalyzed three-component reaction was shown to be effective for a number of substrates (Table 2). However, it seemed that the aniline was crucial for the transformation. No reaction took place when aliphatic amine, such as benzylic amine **2c** was used as a partner in the reaction of 2-alkynylbenzaldehyde **1a** with imidazole **3a**. Reaction of 2-alkynylbenzaldehyde **1a** with aniline, 5-methylimidazole **3b** proceeded smoothly as well under the standard conditions. Other 2-alkynylbenzaldehydes were examined meanwhile. As expected, the fluoro-substituted 2-alkynylbenzaldehyde **1b** reacted with various anilines and imidazole **3a** or **3b**, leading to the desired imidazole-incorporated 1,2-dihydroisoquinolines in moderate to good yield. No difference was observed when the phenyl group attached on the triple bond of 2-alkynylbenzaldehyde **1b** was changed to cyclopropyl (**1c**) or *n*-butyl group (**1d**). However, inferior results were obtained for the reaction of 2-alkynylbenzaldehyde **1e** with an electron-donating group attached on the aromatic ring, which might be due to the lower electrophilicity of intermediate *ortho*-alkynylaryl aldimine toward nucleophilic attack. We subsequently tested the reactions of 2-alkynylbenzaldehydes **1f**–**i**, anilines, and imidazole. All reactions worked well to provide the desired products in moderate to good yields.

Table 2
Generation of diverse 1-(1*H*-imidazol-1-yl)-1,2-dihydroisoquinolines via AgOTf-catalyzed three-component reaction of 2-alkynylbenzaldehyde, amine, and imidazole



R^1, R^2	R^3	R^4	Yield[a] (%)
H, Ph (**1a**)	C_6H_5 (**2a**)	H (**3a**)	87 (**I-1**)
H, Ph (**1a**)	4-MeC_6H_4 (**2b**)	H (**3a**)	80 (**I-2**)
H, Ph (**1a**)	$C_6H_5CH_2$ (**2c**)	H (**3a**)	— (**I-3**)
H, Ph (**1a**)	4-FC_6H_4 (**2d**)	H (**3a**)	65 (**I-4**)
H, Ph (**1a**)	C_6H_5 (**2a**)	5-Me (**3b**)	67 (**I-5**)
5-F, Ph (**1b**)	C_6H_5 (**2a**)	H (**3a**)	76 (**I-6**)
5-F, Ph (**1b**)	4-MeC_6H_4 (**2b**)	H (**3a**)	78 (**I-7**)
5-F, Ph (**1b**)	4-FC_6H_4 (**2d**)	H (**3a**)	68 (**I-8**)
5-F, Ph (**1b**)	4-ClC_6H_4 (**2e**)	H (**3a**)	65 (**I-9**)
5-F, Ph (**1b**)	4-FC_6H_4 (**2d**)	5-Me (**3b**)	65 (**I-10**)
5-F, cyclopropyl (**1c**)	4-MeC_6H_4 (**2b**)	H (**3a**)	76 (**I-11**)
5-F, cyclopropyl (**1c**)	4-$MeOC_6H_4$ (**2f**)	H (**3a**)	65 (**I-12**)
5-F, cyclopropyl (**1c**)	C_6H_5 (**2a**)	H (**3a**)	67 (**I-13**)
5-F, cyclopropyl (**1c**)	4-FC_6H_4 (**2d**)	H (**3a**)	83 (**I-14**)
5-F, cyclopropyl (**1c**)	4-ClC_6H_4 (**2e**)	H (**3a**)	83 (**I-15**)
5-F, *n*-Bu (**1d**)	3-$NO_2C_6H_4$ (**2g**)	H (**3a**)	55 (**I-16**)
4,5-$(OMe)_2$, Ph (**1e**)	4-MeC_6H_4 (**2b**)	H (**3a**)	55 (**I-17**)
4,5-$(OMe)_2$, Ph (**1e**)	4-MeC_6H_4 (**2b**)	5-Me (**3b**)	41 (**I-18**)
5-Me, Ph (**1f**)	C_6H_5 (**2a**)	H (**3a**)	83 (**I-19**)
5-Me, Ph (**1f**)	4-MeC_6H_4 (**2b**)	H (**3a**)	87 (**I-20**)
5-Me, Ph (**1f**)	4-$MeOC_6H_4$ (**2f**)	H (**3a**)	89 (**I-21**)
5-Me, Ph (**1f**)	4-FC_6H_4 (**2d**)	H (**3a**)	80 (**I-22**)
5-Me, Ph (**1f**)	4-ClC_6H_4 (**2e**)	H (**3a**)	78 (**I-23**)
5-Me, Ph (**1f**)	C_6H_5 (**2a**)	5-Me (**3b**)	50 (**I-24**)
5-Me, Ph (**1f**)	4-MeC_6H_4 (**2b**)	5-Me (**3b**)	55 (**I-25**)
5-Me, Ph (**1f**)	4-$MeOC_6H_4$ (**2f**)	5-Me (**3b**)	56 (**I-26**)
5-Me, Ph (**1f**)	4-ClC_6H_4 (**2e**)	5-Me (**3b**)	52 (**I-27**)
H, cyclopropyl (**1g**)	C_6H_5 (**2a**)	H (**3a**)	60 (**I-28**)
H, cyclopropyl (**1g**)	4-MeC_6H_4 (**2b**)	H (**3a**)	62 (**I-29**)
H, cyclopropyl (**1g**)	4-$MeOC_6H_4$ (**2f**)	H (**3a**)	48 (**I-30**)
H, cyclopropyl (**1g**)	4-FC_6H_4 (**2d**)	H (**3a**)	55 (**I-31**)
H, cyclopropyl (**1g**)	4-ClC_6H_4 (**2e**)	H (**3a**)	65 (**I-32**)
H, cyclopropyl (**1g**)	4-MeC_6H_4 (**2b**)	5-Me (**3b**)	45 (**I-33**)
H, cyclopropyl (**1g**)	4-FC_6H_4 (**2d**)	5-Me (**3b**)	35 (**I-34**)
H, *n*-Bu (**1h**)	C_6H_5 (**2a**)	H (**3a**)	60 (**I-35**)
H, *n*-Bu (**1h**)	4-MeC_6H_4 (**2b**)	H (**3a**)	62 (**I-36**)
H, *n*-Bu (**1h**)	4-FC_6H_4 (**2d**)	H (**3a**)	47 (**I-37**)
H, *n*-Bu (**1h**)	4-ClC_6H_4 (**2e**)	H (**3a**)	56 (**I-38**)
4-OMe, Ph (**1i**)	C_6H_5 (**2a**)	H (**3a**)	73 (**I-39**)
4-OMe, Ph (**1i**)	4-MeC_6H_4 (**2b**)	H (**3a**)	76 (**I-40**)
4-OMe, Ph (**1i**)	4-$MeOC_6H_4$ (**2f**)	H (**3a**)	78 (**I-41**)
4-OMe, Ph (**1i**)	4-FC_6H_4 (**2d**)	H (**3a**)	69 (**I-42**)
4-OMe, Ph (**1i**)	4-ClC_6H_4 (**2e**)	H (**3a**)	66 (**I-43**)

[a] Isolated yield based on 2-alkynylbenzaldehyde **1**.

3. Conclusions

In conclusion, we have described a parallel diversity-oriented synthesis of diverse 1-(1*H*-imidazol-1-yl)-1,2-dihydroisoquinolines via AgOTf-catalyzed three-component reaction of 2-alkynylbenzaldehyde, amine, and imidazole. This reaction works efficiently under mild conditions to generate a small library of imidazole-incorporated 1,2-dihydroisoquinolines. Various 2-alkynylbenzaldehydes and anilines bearing electron-rich and electron-poor groups attached on the aromatic ring are suitable partners in the transformation. However, aliphatic amines are not workable as substrates in the reaction, which might be due to the stability issue

of intermediate *ortho*-alkynylaryl aldimines. The imidazole-derivatized 1,2-dihydroisoquinoline small library would be attractive and beneficial for the further biological screening.

4. Experimental section

4.1. General procedure for AgOTf-catalyzed three-component reactions of 2-alkynylbenzaldehyde 1, amine 2, and imidazole 3

Imidazole **3** (1.0 mmol, 2.0 equiv) and AgOTf (0.025 mmol, 5 mol%) were added to a mixture of 2-alkynylbenzaldehyde **1** (0.5 mmol) and amine **2** (0.5 mmol, 1.0 equiv) in toluene (2.0 mL). The reaction mixture was stirred at 70 °C vigorously until completion of the reaction. Subsequently, the mixture was diluted with ethyl acetate (5.0 mL), and quenched with water (5.0 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to provide the desired product **I**.

*4.1.1. 1-(1H-Imidazol-1-yl)-2,3-diphenyl-1,2-dihydroisoquinoline (**I-1**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (s, 1H), 6.48 (s, 1H), 6.54 (s, 1H), 6.79–6.82 (m, 1H), 7.07–7.11 (m, 4H), 7.14–7.16 (m, 6H), 7.22–7.23 (m, 2H), 7.45–7.48 (m, 2H), 7.52 (d, J=0.88 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.8, 111.2, 116.5, 121.9, 122.4, 124.3, 126.2, 126.4, 127.5, 127.7, 127.9, 128.3, 128.5, 130.5, 132.0, 135.0, 137.4, 140.1, 140.8, 146.9; HRMS calcd for $C_{24}H_{19}N_3$ (M^++H): 350.1657, found: 350.1663.

*4.1.2. 1-(1H-Imidazol-1-yl)-3-phenyl-2-p-tolyl-1,2-dihydroisoquinoline (**I-2**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3H), 6.07 (s, 1H), 6.46 (s, 1H), 6.54 (s, 1H), 6.86 (d, J=8.24 Hz, 2H), 6.96 (d, J=8.72 Hz, 2H), 7.11–7.15 (m, 6H), 7.21–7.22 (m, 2H), 7.46–7.50 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 62.1, 110.6, 116.6, 122.5, 124.2, 126.2, 126.3, 127.5, 127.6, 127.8, 128.2, 129.2, 130.1, 131.5, 132.0, 135.0, 137.5, 139.9, 141.0, 144.6; HRMS calcd for $C_{25}H_{21}N_3$ (M^++H): 364.1814, found: 364.1815.

*4.1.3. 2-(4-Fluorophenyl)-1-(1H-imidazol-1-yl)-3-phenyl-1,2-dihydroisoquinoline (**I-4**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (s, 1H), 6.45 (s, 1H), 6.51 (s, 1H), 6.75–6.80 (m, 2H), 7.07–7.10 (m, 2H), 7.16–7.18 (m, 5H), 7.25–7.26 (m, 2H), 7.44–7.46 (m, 2H), 7.57 (d, J=0.92 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.4, 110.6, 115.2 (d, $^2J_{CF}$=21.9 Hz), 116.0, 123.9 (d, $^3J_{CF}$=7.6 Hz), 124.3, 126.2, 126.4, 127.6, 127.7, 127.9, 128.3, 129.7, 130.2, 132.1, 135.1, 137.3, 140.8, 143.3 (d, $^4J_{CF}$=2.86 Hz), 158.1 (d, $^1J_{CF}$=220.5 Hz); HRMS calcd for $C_{24}H_{18}FN_3$ (M^++H): 368.1563, found: 368.1574.

*4.1.4. 1-(4-Methyl-1H-imidazol-1-yl)-2,3-diphenyl-1,2-dihydroisoquinoline (**I-5**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H), 6.28 (s, 1H), 6.49 (s, 1H), 6.61 (s, 1H), 6.84–6.88 (m, 1H), 7.08–7.13 (m, 5H), 7.19–7.23 (m, 6H), 7.29–7.31 (m, 2H), 7.43–7.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.7, 62.3, 110.2, 112.5, 112.8, 124.7, 126.7, 127.1, 127.8, 128.3, 128.4, 128.5, 128.6, 128.7, 129.1, 129.9, 131.6, 137.2, 142.0, 146.7, 148.6, 148.7; HRMS calcd for $C_{25}H_{21}N_3$ (M^++H): 364.1814, found: 364.1802.

*4.1.5. 7-Fluoro-1-(1H-imidazol-1-yl)-2,3-diphenyl-1,2-dihydroisoquinoline (**I-6**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (s, 1H), 6.46 (s, 1H), 6.56 (s, 1H), 6.82–6.84 (m, 1H), 6.90–6.98 (m, 2H), 7.09–7.10 (d, J=4.56 Hz, 4H), 7.14–7.22 (m, 5H), 7.45–7.47 (m, 2H), 7.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.0, 110.3, 113.3 (d, $^2J_{CF}$=21.9 Hz), 114.7 (d, $^2J_{CF}$=21.9 Hz), 122.0, 122.4, 125.8 (d, $^3J_{CF}$=7.6 Hz), 127.6, 128.0, 128.4, 128.5, 128.7, 132.7, 135.3, 137.5, 140.3, 147.0, 161.6 (d, $^1J_{CF}$=244.1 Hz); HRMS calcd for $C_{24}H_{18}FN_3$ (M^++H): 368.1563, found: 368.1543.

*4.1.6. 7-Fluoro-1-(1H-imidazol-1-yl)-3-phenyl-2-p-tolyl-1,2-dihydroisoquinoline (**I-7**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H), 6.05 (s, 1H), 6.44 (s, 1H), 6.56 (s, 1H), 6.87–6.99 (m, 6H), 7.14–7.17 (m, 4H), 7.45–7.47 (m, 2H), 7.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 62.1, 109.8, 113.2 (d, $^2J_{CF}$=21.9 Hz), 114.5 (d, $^2J_{CF}$=21.0 Hz), 116.0, 122.4, 125.5 (d, $^3J_{CF}$=8.6 Hz), 127.5, 127.8, 128.1, 128.2, 128.4 (d, $^4J_{CF}$=2.9 Hz), 129.2, 129.8, 131.6, 132.2 (d, $^3J_{CF}$=6.7 Hz), 135.2, 137.4, 140.4, 144.6, 161.5 (d, $^1J_{CF}$=244.1 Hz); HRMS calcd for $C_{25}H_{20}FN_3$ (M^++H): 382.1720, found: 382.1730.

*4.1.7. 7-Fluoro-2-(4-fluorophenyl)-1-(1H-imidazol-1-yl)-3-phenyl-1,2-dihydroisoquinoline (**I-8**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (s, 1H), 6.46 (s, 1H), 6.51 (s, 1H), 6.78 (t, J=8.24, 2H), 6.90–6.99 (m, 2H), 7.05–7.08 (m, 2H), 7.15–7.22 (m, 4H), 7.43–7.46 (m, 2H), 7.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.2, 110.0, 113.2 (d, $^2J_{CF}$=22.9 Hz), 114.7 (d, $^2J_{CF}$=21.9 Hz), 115.3 (d, $^2J_{CF}$=22.9 Hz), 123.9 (d, $^3J_{CF}$=7.6 Hz), 125.7 (d, $^3J_{CF}$=8.6 Hz), 127.5, 128.0, 128.2, 128.3, 129.7, 131.9 (d, $^3J_{CF}$=7.6 Hz), 135.2, 137.0, 140.3, 140.5 (d, $^4J_{CF}$=3.8 Hz), 143.1 (d, $^4J_{CF}$=2.9 Hz), 158.3 (d, $^1J_{CF}$=240.3 Hz), 161.6 (d, $^1J_{CF}$=245.0 Hz); HRMS calcd for $C_{24}H_{17}F_2N_3$ (M^++H): 386.1469, found: 386.1458.

*4.1.8. 2-(4-Chlorophenyl)-7-fluoro-1-(1H-imidazol-1-yl)-3-phenyl-1,2-dihydroisoquinoline (**I-9**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (s, 1H), 6.46 (s, 1H), 6.47 (s, 1H), 6.88–6.97 (m, 2H), 7.02 (s, 4H), 7.15–7.20 (m, 5H), 7.41–7.43 (m, 2H), 7.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.0, 110.8, 113.3 (d, $^2J_{CF}$=21.9 Hz), 114.8 (d, $^2J_{CF}$=21.9 Hz), 115.7, 123.5, 126.0 (d, $^3J_{CF}$=8.6 Hz), 127.1, 127.5, 128.1, 128.2, 128.4 (d, $^4J_{CF}$=2.9 Hz), 128.5, 128.7, 132.6 (d, $^3J_{CF}$=6.7 Hz), 135.4, 137.1, 139.8, 140.6, 145.6, 161.7 (d, $^1J_{CF}$=245.0 Hz); HRMS calcd for $C_{24}H_{17}ClFN_3$ (M^++H): 402.1173, found: 402.1178.

*4.1.9. 7-Fluoro-2-(4-fluorophenyl)-1-(4-methyl-1H-imidazol-1-yl)-3-phenyl-1,2-dihydroisoquinoline (**I-10**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H), 6.13 (s, 1H), 6.45 (s, 1H), 6.61 (s, 1H), 6.77–6.82 (m, 2H), 6.93–7.08 (m, 4H), 7.21–7.28 (m, 5H), 7.40–7.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 62.4, 108.9, 113.6 (d, $^2J_{CF}$=21.9 Hz), 115.3 (d, $^2J_{CF}$=21.9 Hz), 115.4 (d, $^2J_{CF}$=21.9 Hz), 115.4, 124.2 (d, $^3J_{CF}$=7.6 Hz), 126.1 (d, $^3J_{CF}$=7.6 Hz), 127.6, 128.4 (d, $^3J_{CF}$=6.7 Hz), 128.5, 129.4, 130.3 (d, $^3J_{CF}$=6.7 Hz), 136.6, 141.3 (d, $^4J_{CF}$=1.9 Hz), 142.7 (d, $^4J_{CF}$=2.9 Hz), 147.8, 158.6 (d, $^1J_{CF}$=241.2 Hz), 161.9 (d, $^1J_{CF}$=246.0 Hz); HRMS calcd for $C_{25}H_{19}F_2N_3$ (M^++H): 400.1625, found: 400.1609.

*4.1.10. 3-Cyclopropyl-7-fluoro-1-(1H-imidazol-1-yl)-2-p-tolyl-1,2-dihydroisoquinoline (**I-11**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.56–0.64 (m, 3H), 0.72–0.78 (m, 1H), 1.30–1.38 (m, 1H), 2.29 (s, 3H), 5.62 (s, 1H), 5.79 (s, 1H), 6.63 (s, 1H), 6.70–6.85 (m, 2H), 6.92 (dd, J=5.5, 8.7 Hz, 1H), 7.06 (d, J=8.24 Hz, 2H), 7.17 (d, J=8.68 Hz, 2H), 7.46 (d, J=1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.7, 10.7, 13.9, 20.7, 62.0, 99.7, 112.8 (d, $^2J_{CF}$=21.9 Hz), 114.2 (d, $^2J_{CF}$=21.0 Hz), 123.7, 124.1 (d, $^3J_{CF}$=7.63 Hz), 128.5 (d, $^4J_{CF}$=2.9 Hz), 129.2, 130.6 (d, $^3J_{CF}$=6.7 Hz), 132.7, 135.9, 143.8, 144.6, 160.6 (d, $^1J_{CF}$=243.1 Hz); HRMS calcd for $C_{22}H_{20}FN_3$ (M^++H): 346.1720, found: 346.1726.

*4.1.11. 3-Cyclopropyl-7-fluoro-1-(1H-imidazol-1-yl)-2-(4-methoxyphenyl)-1,2-dihydroisoquinoline (**I-12**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.56–0.72 (m, 4H), 1.24–1.30 (m, 1H), 3.75 (s, 3H), 5.56 (s, 1H), 5.74 (s, 1H), 6.64 (s, 1H), 6.76–6.86 (m, 5H), 6.90–6.94 (m, 1H), 7.20–7.21 (m, 2H), 7.46 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.2, 10.5, 13.9, 55.4, 62.2, 98.4, 112.7 (d, $^2J_{CF}$=21.9 Hz), 113.7, 113.9, 114.2 (d, $^2J_{CF}$=21.9 Hz), 124.0 (d, $^3J_{CF}$=7.6 Hz), 125.9, 127.9, 128.7, 130.3 (d, $^3J_{CF}$=6.7 Hz), 135.0, 139.6, 145.1, 156.1, 160.6 (d, $^1J_{CF}$=242.2 Hz); HRMS calcd for $C_{22}H_{20}FN_3O$ (M^++H): 362.1669, found: 362.1673.

*4.1.12. 3-Cyclopropyl-7-fluoro-1-(1H-imidazol-1-yl)-2-phenyl-1,2-dihydroisoquinoline (**I-13**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57–0.66 (m, 3H), 0.75–0.81 (m, 1H), 1.34–1.41 (m, 1H), 5.67 (s, 1H), 5.85 (s, 1H), 6.61 (s, 1H), 6.80–6.82 (m, 1H), 6.86 (dd, J=2.76, 8.72 Hz, 1H),

6.95 (dd, J=5.52, 8.24 Hz, 1H), 7.00–7.02 (m, 1H), 7.24–7.32 (m, 5H), 7.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9, 10.8, 13.8, 61.8, 100.7, 112.8 (d, $^2J_{CF}$=21.9 Hz), 114.3 (d, $^2J_{CF}$=21.9 Hz), 122.9, 123.4, 124.3(d, $^3J_{CF}$=7.6 Hz), 128.4 (d, $^4J_{CF}$=1.9 Hz), 128.7, 130.9 (d, $^3J_{CF}$=6.7 Hz), 135.0, 144.3, 146.3, 160.7 (d, $^1J_{CF}$=242.2 Hz); HRMS calcd for $C_{21}H_{18}FN_3$ (M^++H): 332.1563, found: 332.1560.

*4.1.13. 3-Cyclopropyl-7-fluoro-2-(4-fluorophenyl)-1-(1H-imidazol-1-yl)-1,2-dihydroisoquinoline (**I-14**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.54–0.63 (m, 3H), 0.71–0.76 (m, 1H), 1.23–1.28 (m, 1H), 5.64 (s, 1H), 5.75 (s, 1H), 6.56 (s, 1H), 6.77–6.87 (m, 2H), 6.90–6.96 (m, 3H), 7.22–7.26 (m, 2H), 7.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.4, 10.7, 13.8, 62.2, 100.3, 112.8 (d, $^2J_{CF}$=21.9 Hz), 114.3 (d, $^2J_{CF}$=21.0 Hz), 115.3 (d, $^2J_{CF}$=21.9 Hz), 124.3 (d, $^3J_{CF}$=7.6 Hz), 125.4 (d, $^3J_{CF}$=7.6 Hz), 128.5 (d, $^4J_{CF}$=2.8 Hz), 130.6 (d, $^3J_{CF}$=7.6 Hz), 135.1, 142.5 (d, $^2J_{CF}$=1.9 Hz), 144.3, 159.1 (d, $^1J_{CF}$=241.2 Hz), 160.7 (d, $^1J_{CF}$=242.2 Hz); HRMS calcd for $C_{21}H_{17}F_2N_3$ (M^++H): 350.1469, found: 350.1464.

*4.1.14. 2-(4-Chlorophenyl)-3-cyclopropyl-7-fluoro-1-(1H-imidazol-1-yl)-1,2-dihydroisoquinoline (**I-15**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55–0.60 (m, 3H), 0.74–0.78 (m, 1H), 1.28–1.32 (m, 1H), 5.70 (s, 1H), 5.77 (s, 1H), 6.53 (s, 1H), 6.78 (dd, J=2.28, 8.72 Hz, 1H), 6.83–6.88 (m, 1H), 6.95 (dd, J=5.52, 8.72 Hz, 1H), 7.18–7.24 (m, 4H), 7.48 (d, J=0.92 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8, 10.8, 13.8, 61.9, 101.7, 112.8 (d, $^2J_{CF}$=21.9 Hz), 114.3 (d, $^2J_{CF}$=21.0 Hz), 124.4, 124.5, 127.9, 128.3 (d, $^4J_{CF}$=2.9 Hz), 128.6, 130.9 (d, $^3J_{CF}$=6.7 Hz), 135.1, 143.6, 144.9, 160.7 (d, $^1J_{CF}$=243.1 Hz); HRMS calcd for $C_{21}H_{17}ClFN_3$ (M^++H): 366.1173, found: 366.1165.

*4.1.15. 3-Butyl-7-fluoro-1-(1H-imidazol-1-yl)-2-(3-nitrophenyl)-1,2-dihydroisoquinoline (**I-16**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65 (t, J=7.32 Hz, 3H), 0.89–0.96 (m, 2H), 1.07–1.15 (m, 2H), 2.09–2.17 (m, 1H), 2.34–2.39 (m, 1H), 5.87 (s, 1H), 6.10 (s, 1H), 6.38 (s, 1H), 6.80 (dd, J=2.72, 8.68 Hz, 1H), 6.95 (td, J=2.32, 8.24 Hz, 1H), 7.10 (dd, J=5.52, 8.28 Hz, 1H), 7.45 (t, J=7.80 Hz, 1H), 7.63 (s, 1H), 7.77 (dd, J=1.4, 7.8 Hz, 1H), 7.84 (dd, J=2.28, 7.8 Hz, 1H), 8.08 (t, J=1.84 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 21.7, 29.9, 32.1, 61.7, 110.5, 112.9 (d, $^2J_{CF}$=21.9 Hz), 114.7 (d, $^2J_{CF}$=21.0 Hz), 116.0 (d, $^4J_{CF}$=2.9 Hz), 116.9, 117.1, 125.2 (d, $^3J_{CF}$=7.6 Hz), 128.1 (d, $^4J_{CF}$=2.9 Hz), 128.4, 129.6, 131.3 (d, $^3J_{CF}$=6.7 Hz), 135.2, 140.0 (d, $^4J_{CF}$=1.9 Hz), 147.2, 148.7, 155.5, 161.2 (d, $^1J_{CF}$=244.2 Hz); HRMS calcd for $C_{22}H_{21}FN_4O_2$ (M^++H): 393.1727, found: 393.1739.

*4.1.16. 1-(1H-Imidazol-1-yl)-6,7-dimethoxy-3-phenyl-2-p-tolyl-1,2-dihydroisoquinoline (**I-17**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H), 3.78 (s, 3H), 3.89 (s, 3H), 6.02 (s, 1H), 6.43 (s, 1H), 6.61(s, 1H), 6.70 (s, 1H), 6.79 (s, 1H), 6.90 (d, J=8.24 Hz, 2H), 6.99 (d, J=8.24 Hz, 2H), 7.12–7. 18 (m, 3H), 7.45–7.47 (m, 2H), 7.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 55.8, 55.9, 61.9, 107.4, 109.6, 110.6, 122.3, 122.9, 125.2, 127.3, 127.5, 128.2, 129.2, 131.2, 135.0, 137.6, 139.4, 144.8, 147.9, 148.4; HRMS calcd for $C_{27}H_{25}N_3O_2$ (M^++H): 424.2025, found: 424.2029.

*4.1.17. 6,7-Dimethoxy-1-(4-methyl-1H-imidazol-1-yl)-3-phenyl-2-p-tolyl-1,2-dihydroisoquinoline (**I-18**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.23 (s, 3H), 3.80 (s, 3H), 3.91 (s, 3H), 6.01 (s, 1H), 6.49 (s, 1H), 6.56 (s, 1H), 6.81 (s, 1H), 6.92 (s, 5H), 7.14–7.20 (m, 6H), 7.36 (s, 1H), 7.42–7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 29.7, 55.9, 56.0, 60.2, 107.4, 107.5, 109.3, 110.3, 122.3, 122.4, 124.8, 127.3, 127.8, 129.3, 131.8, 137.4, 140.8, 144.8; HRMS calcd for $C_{28}H_{27}N_3O_2$ (M^++H): 438.2182, found: 438.2186.

*4.1.18. 1-(1H-Imidazol-1-yl)-7-methyl-2,3-diphenyl-1,2-dihydroisoquinoline (**I-19**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 1H), 6.08 (s, 1H), 6.47 (s, 1H), 6.57 (s, 1H), 6.75–6.79 (m, 1H), 6.95 (s, 1H), 7.00–7.15 (m, 9H), 7.42–7.44 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 62.1, 111.3, 121.6, 122.1, 124.2, 126.8, 127.3, 127.6, 128.2, 128.3, 128.5, 129.3, 130.9, 135.0, 136.2, 137.6, 139.8, 147.1; HRMS calcd for $C_{25}H_{21}N_3$ (M^++H): 364.1814, found: 364.1830.

*4.1.19. 1-(1H-Imidazol-1-yl)-7-methyl-3-phenyl-2-p-tolyl-1,2-dihydroisoquinoline (**I-20**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.22 (s, 3H), 6.02 (s, 1H), 6.45 (s, 1H), 6.58 (s, 1H), 6.84 (d, J=8.68 Hz, 2H), 6.94 (d, J=8.24 Hz, 3H), 7.01 (d, J=8.24 Hz, 1H), 7.08–7.15 (m, 5H), 7.41–7.46 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 21.2, 62.4, 110.8, 116.3, 122.2, 124.1, 126.8, 127.4, 127.5, 128.1, 128.3, 129.1, 129.4, 130.6, 131.1, 135.0, 136.1, 137.7, 140.1, 144.8; HRMS calcd for $C_{26}H_{23}N_3$ (M^++H): 378.1970, found: 378.1963.

*4.1.20. 1-(1H-Imidazol-1-yl)-2-(4-methoxyphenyl)-7-methyl-3-phenyl-1,2-dihydroisoquinoline (**I-21**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 3.64 (s, 3H), 5.97 (s, 1H), 6.43 (s, 1H), 6.60–6.63 (m, 3H), 6.95 (s, 1H), 6.95–7.05 (m, 3H), 7.11–7.16 (m, 4H), 7.45–7.48 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 55.3, 62.7, 110.0, 113.9, 123.8, 124.1, 126.8, 127.5, 127.6, 128.2, 128.3, 129.4, 130.3, 134.9, 136.1, 137.7, 140.4, 140.9, 154.8; HRMS calcd for $C_{26}H_{23}N_3O$ (M^++H): 394.1919, found: 394.1911.

*4.1.21. 2-(4-Fluorophenyl)-1-(1H-imidazol-1-yl)-7-methyl-3-phenyl-1,2-dihydroisoquinoline (**I-22**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 5.98 (s, 1H), 6.46 (s, 1H), 6.53 (s, 1H), 6.74 (t, J=8.72 Hz, 2H), 6.95 (s, 1H), 7.01–7.06 (m, 3H), 7.11–7.15 (m, 4H), 7.41–7.48 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 62.5, 111.0, 115.1 (d, $^2J_{CF}$=21.9 Hz), 123.6 (d, $^3J_{CF}$=8.6 Hz), 124.3, 126.8, 127.4, 127.7, 128.2, 128.4, 129.3, 130.5, 135.0, 136.3, 137.4, 139.9, 143.4 (d, $^4J_{CF}$=1.9 Hz), 158.0 (d, $^1J_{CF}$=240.3 Hz); HRMS calcd for $C_{25}H_{20}FN_3$ (M^++H): 382.1720, found: 382.1715.

*4.1.22. 2-(4-Chlorophenyl)-1-(1H-imidazol-1-yl)-7-methyl-3-phenyl-1,2-dihydroisoquinoline (**I-23**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 6.02 (s, 1H), 6.48 (s, 1H), 6.52 (s, 1H), 6.96 (s, 1H), 7.00 (s, 4H), 7.04–7.06 (m, 1H), 7.12–7.15 (m, 4H), 7.40–7.42 (m, 2H), 7.49 (d, J=0.92 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 62.2, 111.7, 123.2, 124.4, 126.6, 126.8, 127.3, 127.8, 128.3, 128.5, 129.2, 130.8, 135.1, 136.5, 137.2, 139.4, 141.0, 145.7; HRMS calcd for $C_{25}H_{20}ClN_3$ (M^++H): 398.1424, found: 398.1426.

*4.1.23. 7-Methyl-1-(4-methyl-1H-imidazol-1-yl)-2,3-diphenyl-1,2-dihydroisoquinoline (**I-24**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.28 (s, 3H), 6.10 (s, 1H), 6.53 (s, 1H), 6.82–6.88 (m, 2H), 6.96–7.20 (m, 10H), 7.35 (s, 1H), 7.38–7.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 21.3, 60.2, 110.9, 122.1, 122.3, 124.4, 126.6, 127.4, 127.9, 128.3, 128.6, 128.9, 129.6, 130.6, 133.3, 136.9, 137.4, 141.4, 147.1; HRMS calcd for $C_{26}H_{23}N_3$ (M^++H): 378.1970, found: 378.1987.

*4.1.24. 7-Methyl-1-(4-methyl-1H-imidazol-1-yl)-3-phenyl-2-p-tolyl-1,2-dihydroisoquinoline (**I-25**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.22 (s, 3H), 2.27 (s, 3H), 6.03 (s, 1H), 6.50 (s, 1H), 6.82–6.90 (m, 5H), 7.04–7.07 (m, 1H), 7.12–7.20 (m, 5H), 7.35 (s, 1H), 7.40–7.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 20.6, 21.2, 60.4, 110.4, 122.5, 124.4, 126.7, 127.4, 127.9, 128.3, 128.6, 129.1, 129.2, 129.6, 129.8, 130.1, 131.8, 133.1, 136.8, 137.4, 141.6, 144.7; HRMS calcd for $C_{27}H_{25}N_3$ (M^++H): 393.2127, found: 393.2153.

*4.1.25. 2-(4-Methoxyphenyl)-7-methyl-1-(4-methyl-1H-imidazol-1-yl)-3-phenyl-1,2-dihydroisoquinoline (**I-26**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 3H), 2.27 (s, 3H), 3.65 (s, 3H), 5.97 (s, 1H), 6.46 (s, 1H), 6.62–6.64 (m, 2H), 6.85 (s, 1H), 6.92–6.95 (m, 2H), 7.06 (m, 1H), 7.14–7.20 (m, 4H), 7.35 (s, 1H), 7.39–7.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 21.3, 55.3, 60.7, 109.5, 113.9, 124.1, 124.3, 126.7, 127.6, 127.8, 127.9, 128.2, 128.5, 128.6, 129.1, 129.5, 129.9,

133.2, 136.7, 137.5, 140.8, 142.0, 155.2; HRMS calcd for $C_{27}H_{25}N_3O$ (M^++H): 408.2076, found: 408.2072.

*4.1.26. 2-(4-Chlorophenyl)-7-methyl-1-(4-methyl-1H-imidazol-1-yl)-3-phenyl-1,2-dihydroisoquinoline (**I-27**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.29 (s, 3H), 6.04 (s, 1H), 6.53 (s, 1H), 6.89 (s, 1H), 6.95–7.22 (m, 9H), 7.34 (s, 1H), 7.38–7.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5, 21.3, 60.6, 111.4, 123.3, 124.5, 126.7, 127.1, 127.4, 128.1, 128.4, 128.6, 128.7, 133.3, 137.1, 137.1, 140.9, 145.8; HRMS calcd for $C_{26}H_{22}ClN_3$ (M^++H): 412.1581, found: 412.1565.

*4.1.27. 3-Cyclopropyl-1-(1H-imidazol-1-yl)-2-phenyl-1,2-dihydroisoquinoline (**I-28**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.56–0.66 (m, 3H), 0.75–0.82 (m, 1H), 1.35–1.42 (m, 1H), 5.67 (s, 1H), 5.89 (s, 1H), 6.62 (s, 1H), 6.98–7.43 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.0, 10.9, 13.9, 61.9, 100.9, 122.7, 123.0, 123.5, 125.0, 125.8, 127.4, 128.6, 129.3, 132.1, 134.9, 145.0, 146.3; HRMS calcd for $C_{21}H_{19}N_3$ (M^++H): 314.1657, found: 314.1652.

*4.1.28. 3-Cyclopropyl-1-(1H-imidazol-1-yl)-2-p-tolyl-1,2-dihydroisoquinoline (**I-29**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.61–0.78 (m, 4H), 1.30–1.40 (m, 1H), 2.30 (s, 3H), 5.62 (s, 1H), 5.85 (s, 1H), 6.69 (s, 1H), 6.98–7.26 (m, 9H), 7.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.7, 10.9, 14.0, 20.8, 61.9, 99.8, 122.9, 124.0, 124.9, 125.8, 127.5, 129.2, 130.5, 132.2, 132.8, 143.9; HRMS calcd for $C_{22}H_{21}N_3$ (M^++H): 328.1814, found: 328.1819.

*4.1.29. 3-Cyclopropyl-1-(1H-imidazol-1-yl)-2-(4-methoxyphenyl)-1,2-dihydroisoquinoline (**I-30**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.58–0.76 (m, 4H), 1.26–1.28 (m, 1H), 3.78 (s, 3H), 5.56 (s, 1H), 5.78 (s, 1H), 6.66 (s, 1H), 6.81 (d, J=9.2 Hz, 2H), 6.95–7.04 (m, 4H), 7.13–7.17 (m, 1H), 7.23 (d, J=9.2 Hz, 2H), 7.44 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.3, 10.7, 14.0, 55.4, 98.5, 113.8, 122.8, 124.7, 125.8, 126.1, 127.4, 128.5, 132.4, 134.9, 145.8; HRMS calcd for $C_{22}H_{21}N_3O$ (M^++H): 344.1763, found: 344.1752.

*4.1.30. 3-Cyclopropyl-2-(4-fluorophenyl)-1-(1H-imidazol-1-yl)-1,2-dihydroisoquinoline (**I-31**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.59–0.79 (m, 4H), 1.24–1.30 (m, 1H), 5.65 (s, 1H), 5.80 (s, 1H), 6.57 (s, 1H), 6.93–7.05 (m, 6H), 7.14–7.18 (m, 1H), 7.25–7.29 (m, 2H), 7.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.5, 10.9, 13.9, 62.3, 100.4, 115.2 (d, $^2J_{CF}$=21.9 Hz), 123.0, 125.0, 125.5 (d, $^3J_{CF}$=7.6 Hz), 125.8, 127.5, 128.9, 132.2, 134.9, 142.5 (d, $^4J_{CF}$=2.9 Hz), 145.1, 159.1 (d, $^1J_{CF}$=241.2 Hz); HRMS calcd for $C_{21}H_{18}FN_3$ (M^++H): 332.1563, found: 332.1568.

*4.1.31. 2-(4-Chlorophenyl)-3-cyclopropyl-1-(1H-imidazol-1-yl)-1,2-dihydroisoquinoline (**I-32**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.60–0.79 (m, 4H), 1.25–1.33 (m, 1H), 5.71 (s, 1H), 5.82 (s, 1H), 6.52 (s, 1H), 7.00–7.24 (m, 9H), 7.45 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8, 11.0, 13.9, 62.1, 102.0, 123.2, 124.5, 125.2, 125.8, 127.6, 127.8, 128.6, 129.2, 131.9, 135.0, 144.3, 144.9; HRMS calcd for $C_{21}H_{18}ClN_3$ (M^++H): 348.1268, found: 348.1263.

*4.1.32. 3-Cyclopropyl-1-(4-methyl-1H-imidazol-1-yl)-2-p-tolyl-1,2-dihydroisoquinoline (**I-33**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.61–0.73 (m, 4H), 1.23–1.26 (m, 1H), 2.13 (s, 1H), 2.31 (s, 1H), 5.52 (s, 1H), 5.80 (s, 1H), 6.99–7.26 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.4, 10.4, 11.9, 14.1, 20.8, 60.0, 96.9, 116.4, 122.9, 125.0, 125.7, 127.6, 128.6, 129.3, 132.2, 133.1, 133.2, 134.3, 143.3, 147.4; HRMS calcd for $C_{23}H_{23}N_3$ (M^++H): 342.1970, found: 342.1956.

*4.1.33. 3-Cyclopropyl-2-(4-fluorophenyl)-1-(4-methyl-1H-imidazol-1-yl)-1,2-dihydroisoquinoline (**I-34**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.60–0.69 (m, 4H), 1.15–1.20 (m, 1H), 2.04 (s, 3H), 5.54 (s, 1H), 5.76 (s, 1H), 6.84–7.15 (m, 9H), 7.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.25, 10.0, 14.2, 20.6, 60.2, 97.5, 115.4 (d, $^2J_{CF}$=21.9 Hz), 123.1, 125.2, 125.8, 127.1, 127.7 (d, $^3J_{CF}$=8.6 Hz), 128.5 (d, $^3J_{CF}$=6.7 Hz), 129.4, 132.2, 133.3, 141.9, 147.0, 159.8 (d, $^1J_{CF}$=227.4 Hz); HRMS calcd for $C_{22}H_{20}FN_3$ (M^++H): 346.1720, found: 346.1729.

*4.1.34. 3-Butyl-1-(1H-imidazol-1-yl)-2-phenyl-1,2-dihydroisoquinoline (**I-35**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.69 (t, J=7.32 Hz, 3H), 0.96–1.08 (m, 2H), 1.20–1.30 (m, 2H), 2.08–2.15 (m, 1H), 2.36–2.45 (m, 1H), 5.85 (s, 1H), 5.97 (s, 1H), 6.51 (s, 1H), 7.01–7.30 (m, 10H), 7.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 21.9, 30.1, 32.5, 61.9, 107.7, 122.9, 123.2, 123.7, 125.3, 125.9, 127.5, 128.7, 132.2, 134.8, 142.8, 146.3; HRMS calcd for $C_{22}H_{23}N_3$ (M^++H): 330.1970, found: 330.1978.

*4.1.35. 3-Butyl-1-(1H-imidazol-1-yl)-2-p-tolyl-1,2-dihydroisoquinoline (**I-36**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70 (t, J=6.88 Hz, 3H), 1.00–1.07 (m, 2H), 1.21–1.28 (m, 2H), 2.07–2.13 (m, 2H), 2.30 (s, 3H), 5.79 (s, 1H), 5.91 (s, 1H), 6.55 (s, 1H), 6.98–7.18 (m, 9H), 7.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 20.8, 21.9, 30.1, 32.6, 59.9, 106.6, 123.0, 124.0, 125.1, 125.9, 127.4, 129.3, 132.3, 134.7, 143.3, 143.9; HRMS calcd for $C_{23}H_{25}N_3$ (M^++H): 344.2127, found: 344.2127.

*4.1.36. 3-Butyl-2-(4-fluorophenyl)-1-(1H-imidazol-1-yl)-1,2-dihydroisoquinoline (**I-37**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.69 (t, J=7.36 Hz, 3H), 0.94–1.00 (m, 2H), 1.16–1.22 (m, 2H), 2.04–2.12 (m, 1H), 2.28–2.36 (m, 1H), 5.76 (s, 1H), 5.93 (s, 1H), 6.93–7.22 (m, 9H), 7.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 21.8, 30.0, 32.5, 62.2, 107.1, 115.4 (d, $^2J_{CF}$=22.9 Hz), 123.2, 125.3, 125.6 (d, $^3J_{CF}$=8.6 Hz), 125.9, 127.5, 128.7, 132.2, 134.8, 142.5, 142.8, 159.1 (d, $^1J_{CF}$=241.2 Hz); HRMS calcd for $C_{22}H_{22}FN_3$ (M^++H): 348.1876, found: 348.1875.

*4.1.37. 3-Butyl-2-(4-chlorophenyl)-1-(1H-imidazol-1-yl)-1,2-dihydroisoquinoline (**I-38**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.68 (t, J=7.36 Hz, 3H), 0.94–1.02 (m, 2H), 1.14–1.20 (m, 2H), 2.07–2.11 (m, 1H), 2.35–2.39 (m, 1H), 5.80 (s, 1H), 6.99 (s, 1H), 6.44 (s, 1H), 7.02–7.10 (m, 4H), 7.18–7.26 (m, 6H), 7.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 21.8, 30.0, 32.4, 62.0, 108.6, 123.3, 124.6, 124.7, 125.5, 127.6, 127.9, 128.7, 129.0, 132.1, 134.8, 142.1, 144.9; HRMS calcd for $C_{22}H_{22}ClN_3$ (M^++H): 364.1581, found: 364.1592.

*4.1.38. 1-(1H-Imidazol-1-yl)-6-methoxy-2,3-diphenyl-1,2-dihydroisoquinoline (**I-39**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 6.08 (s, 1H), 6.40 (s, 1H), 6.54 (s, 1H), 6.68–6.70 (m, 1H), 6.77–6.80 (m, 2H), 7.04–7.13 (m, 9H), 7.43–7.48 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 61.6, 109.0, 110.9, 112.1, 121.7, 122.3, 123.4, 127.0, 127.5, 127.9, 128.2, 128.5, 133.2, 135.1, 137.5, 141.2, 147.0, 159.1; HRMS calcd for $C_{25}H_{21}N_3O$ (M^++H): 380.1763, found: 380.1749.

*4.1.39. 1-(1H-Imidazol-1-yl)-6-methoxy-3-phenyl-2-p-tolyl-1,2-dihydroisoquinoline (**I-40**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3H), 3.78 (s, 3H), 6.03 (s, 1H), 6.38 (s, 1H), 6.57 (s, 1H), 6.67–6.70 (m, 1H), 6.77 (d, J=2.32 Hz, 1H), 6.87 (d, J=8.28 Hz, 2H), 6.98 (d, J=8.28 Hz, 2H), 7.05 (d, J=8.24 Hz, 1H), 7.11–7.15 (m, 3H), 7.44–7.48 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 55.2, 61.9, 108.9, 110.4, 112.0, 122.4, 123.2, 127.1, 127.6, 127.8, 128.2, 129.1, 131.3, 133.3, 135.0, 137.6, 141.5, 144.7; HRMS calcd for $C_{26}H_{23}N_3O$ (M^++H): 394.1919, found: 394.1938.

*4.1.40. 1-(1H-Imidazol-1-yl)-6-methoxy-2-(4-methoxyphenyl)-3-phenyl-1,2-dihydroisoquinoline (**I-41**).* ^{1}H NMR (400 MHz, $CDCl_3$)

δ 3.64 (s, 3H), 3.79 (s, 3H), 5.97 (s, 1H), 6.36 (s, 1H), 6.58 (s, 1H), 6.61–6.63 (m, 2H), 6.68–6.71 (m, 1H), 6.77 (d, J=2.28 Hz, 1H), 7.02–7.15 (m, 7H), 7.45–7.49 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 55.3, 62.2, 108.8, 109.7, 112.0, 113.8, 122.8, 124.0, 127.1, 127.7, 127.8, 128.2, 133.4, 135.0, 137.6, 140.8, 141.7, 154.9, 159.1; HRMS calcd for $C_{26}H_{23}N_3O_2$ (M^++H): 410.1869, found: 410.1851.

*4.1.41. 2-(4-Fluorophenyl)-1-(1H-imidazol-1-yl)-6-methoxy-3-phenyl-1,2-dihydroisoquinoline (**I-42**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 5.99 (s, 1H), 6.39 (s, 1H), 6.52 (s, 1H), 6.70–6.79 (m, 4H), 7.05–7.08 (m, 4H), 7.14–7.16 (m, 3H), 7.42–7.44 (m, 2H), 7.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 62.0, 109.0, 110.6, 112.2, 115.1 (d, $^2J_{CF}$=21.9 Hz), 123.0, 123.9 (d, $^3J_{CF}$=7.6 Hz), 127.1, 127.7, 127.9, 128.2, 133.2, 135.1, 137.3, 141.3, 143.3 (d, $^4J_{CF}$=2.9 Hz), 159.2, 158.2 (d, $^1J_{CF}$=239.3 Hz); HRMS calcd for $C_{25}H_{20}FN_3O$ (M^++H): 398.1669, found: 398.1672.

*4.1.42. 2-(4-Chlorophenyl)-1-(1H-imidazol-1-yl)-6-methoxy-3-phenyl-1,2-dihydroisoquinoline (**I-43**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.02 (s, 1H), 6.42 (s, 1H), 6.50 (s, 1H), 6.71–6.74 (m, 1H), 6.79 (d, J=2.28 Hz, 1H), 7.03 (s, 5H), 7.14–7.17 (m, 3H), 7.40–7.43 (m, 2H), 7.53 (d, J=0.88 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 61.6, 109.1, 111.3, 112.3, 123.3, 123.4, 126.7, 127.0, 127.6, 128.0, 128.3, 128.5, 133.1, 135.1, 137.2, 140.7, 145.6, 159.2; HRMS calcd for $C_{25}H_{20}ClN_3O$ (M^++H): 414.1373, found: 414.1365.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.01.048.

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