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Indium trifluoride: A highly efficient catalyst for the synthesis of fluorine-containing 2,4,5-trisubstituted imidazoles under solvent-free conditions

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ABSTRACT

A new green protocol has been developed for the synthesis of fluorine containing 2,4,5-trisubstituted imidazoles via one-pot, three-component condensation reaction of 4,4-difluorobenzil with aldehydes and ammonium acetate using reusable indium (III) fluoride (InF_3) as Lewis acid catalyst under solvent-free conditions. This protocol provides a novel and improved method for obtaining fluorine containing 2,4,5-trisubstituted imidazoles in terms of good yields with little catalyst loading.

1. Introduction

Fluorine-containing heterocycles are widely recognized as important organic molecules showing interesting biological activities with potential for applications in the medicinal and agricultural fields [1–5]. Particularly fluorine has played an important and historical role in the development of antipsychotic drugs [2]. Fluorine substitution is often used as a strategy to increase metabolic stability [3]. Introduction of fluorine-containing nitrogen heterocycles can bring about remarkable changes in the physical, chemical and biological properties [4,5] of drugs. Thus, fluorosubstituted nitrogen containing heterocycles possessing anticardiovascular diseases, DPP-IV inhibitory activity, herbicidal activity, anti-bacterial and anti-inflammatory activities [6–8] as well as efficacy in anticancer [9] and antagonists for paralyzing action of anti-diabetic activity [7]. Other beneficial properties related to fluorine substitution, such as increased blood brain barrier (BBB) permeability due to changes in lipophilicity or amine pK_a, are reasons that fluorinated drugs have been especially important in CNS active drugs [10]. Consequently, the development of novel synthetic methods for their synthesis has attracted sustained interest in organic synthesis. In recent years, a number of researches have been reported about the development of new methodologies for syntheses of various kinds of fluorine-containing heterocycles [11–13].

Imidazole and their derivatives, which usually possess diverse biological activities, play important roles as versatile building blocks for the synthesis of natural products and as therapeutic agents [14,15]. In particular, 2,4,5-trisubstituted imidazoles are biologically active and occur in structures of a number of anti-inflammatory [16], anti-allergic [17], analgesic [18] and glucagon receptor antagonism [19]. This core also has been utilized in diverse pharmaceutical applications such as anti-tumor [20] and anti-thrombotic [21] activities agents. Recently, some imidazole derivatives have been investigated for their piezochromism, photochromism and thermochromism properties, and the results reported suggest potential applications in molecular photonics and sensing [22]. Therefore, the synthesis of these imidazole derivatives has attracted much attention in organic synthesis.

In the last decade numerous methods have been developed for the synthesis of highly substituted imidazoles by using various catalytic systems including silica gel or Zeolite HY [23], silica gel/$NaHSO_4$ [24], molecular iodine [25], $K_5CoW_{12}O_{40}{\cdot}3H_2O$ [26], heteropolyacids [27], $HClO_4$–SiO_2 [28], $Yb(OTf)_3$ [29], L-proline [30], BF_3–SiO_2 [31], and silica-supported Wells–Dawson acid [32]. They can also be obtained by use of microwave irradiation [33] and refluxing in acetic acid [34], silica sulfuric acid [35], $NiCl_2{\cdot}6H_2O$/Al_2O_3 [36], $ZrCl_4$ [37], ionic liquids [38], CAN [39] and $Cu(NO_3)_2$·zeolite [40]. Moreover, the syntheses of these heterocyclic compounds have been usually carried out in polar solvents such as ethanol [27], methanol [30], acetic acid [34] and DMF [20] leading to complex isolation and recovery procedures. However, many of the methods reported above suffer from one or more disadvantages such as the use of expensive moisture sensitive

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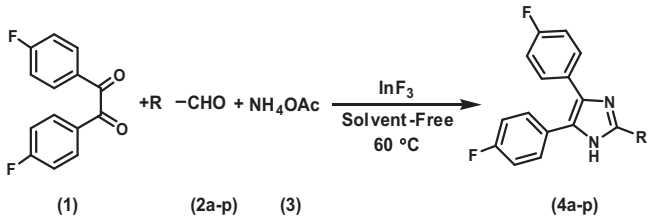


Scheme 1. Synthesis of fluorine containing 2,4,5-trisubstituted imidazoles catalyzed by InF_3 under solvent-free condition.

metallic reagents, longer reaction times, tedious separation procedures, and large amount of catalyst loadings which in turn results in the generation of huge amount of metal wastes into the environment. Hence, the development of clean safe, effective, economical, high yielding and mild environmental benign protocols is still desirable and is in demand.

It is evident from the recent literature that Indium (III) fluoride (InF_3) has invoked enormous interest as a green and potential Lewis acid catalyst to construct carbon–carbon and carbon–heteroatom bonds in various organic transformations [41–43]. Despite its great importance, only a few papers are reported on its catalytic application in organic synthesis [41–43]. In combination with the use of Lewis acid catalyst in organic transformations, solvent-free methodologies for the synthesis of organic compounds have attracted much interest because of their ease of experimental procedures as well as work-up, low cost, clean, efficient, environmentally benign, and high yielding processes. We therefore became interested in devising more general and green methods for the synthesis of fluorine containing 2,4,5-trisubstituted imidazoles derivatives.

Our literature survey at this stage revealed that there are no reports on the synthesis of fluorine containing 2,4,5-trisubstituted imidazoles under solvent-free at 60 °C mediated by InF_3. Our main target is to develop a green organic reaction methodology, which is relatively faster and cleaner than conventional reactions.

2. Results and discussion

As a part of our continuing studies in developing efficient synthetic methodologies [44,45] in organic preparations, we found that the synthesis of fluorine containing 2,4,5-trisubstituted imidazoles derivatives via a one-pot, three-component condensation reaction of 4,4-difluorobenzil (**1**) with aldehydes (**2a**–**p**) ammonium acetate (**3**) can be efficiently achieved without any solvent with the use of indium fluoride (InF_3) under mild conditions at 60 °C (Scheme 1). To optimize the reaction conditions, we first examined the reaction of 4,4-difluorobenzil (**1**, 1 mmol), 2-fluoro-4-methoxybenzaldehyde (**2d**, 1 mmol), and ammonium acetate (**3**, 2.2 mmol) at 60 °C without catalyst under solvent-free conditions in order to recognize the capability of the catalyst. The reaction did not proceed even after prolonged reaction time and no desired product was formed which supported the catalytic activity of InF_3. When the reaction was performed in the presence InF_3, it proceeded effectively to produce the desired product (**4d**) in high yields. Some other Lewis acid catalysts such as $GaCl_3$, TiO_2–SiO_2, $Cu(OSO_2CF_3)$–SiO_2, *p*-TSA polymer-supported, Li(OTf), $Zn(O_2CCH_3)_2$, and Nano Cu_2O exhibited moderate to good catalytic properties. In most of these cases comparative yields of the desired product were obtained. Following the InF_3-catalyzed procedure, the reported methods required expensive catalyst, toxic or organic solvents, strong acidic conditions, high catalyst loading, and long reaction times. These results clearly demonstrated that InF_3 is a more efficient catalyst for the synthesis of fluorine containing 2,4,5-trisubstituted imidazoles. The results are summarized in Table 1. Besides this, we observed that the concentration of the catalyst played a major role in catalyzing the condensation reaction for the synthesis of fluorine containing 2,4,5-trisubstituted imidazoles. Using a model reaction as described above and varying just the concentration of InF_3 from 2 mol% to 10 mol%, the yield of product was increased from 85% to 92%. This shows that 10 mol% of InF_3 is the suitable choice for the optimum reaction rate and yield of fluorine containing 2,4,5-trisubstituted imidazoles (Table 1, entries 9–11).

Table 1
Influence of different catalysts on the reaction of 4,4-difluorobenzil with 2-fluoro-4-methoxybenzaldehyde and ammonium acetate.[a]

Entry	Catalyst	Amount (mol%)	Time (min)	Yield[b] (%)
1	No Catalyst	–	500	Trace
2	$GaCl_3$		200	50
3	TiO_2-SiO_2		40	75
4	$Cu(OSO_2CF_3)$-SiO_2		60	76
5	*p*-TSA polymer-supported		180	55
6	Li(OTf)		120	60
7	$Zn(O_2CCH_3)_2$		130	70
8	Nano Cu_2O		90	65
9	InF_3	2	40	80
10	InF_3	5	25	85
11[c]	InF_3	10	20	92, 90, 88, 85

[a] Reaction conditions: 4,4-difluorobenzil (1 mmol), 2-fluoro-4-methoxybenzaldehyde (1 mmol) and ammonium acetate (2.2 mmol); temperature:60 °C.
[b] Isolated yields.
[c] Reusable catalyst.

Next, the effect of temperature was also evaluated for the model reaction. It was observed that fast reaction occurred on raising the temperature from 20 °C to 60 °C and the yield of desired product increased considerably. We were pleased to find that the reaction proceeded smoothly and almost complete conversion of reactants was observed at 60 °C to afford the desired product (**4a**) in 92% yield within 20 min (Table 2). However, at room temperature a lower yield of product was obtained even after longer reaction times. With the optimistic results in hand, we chose a variety of structurally diverse aromatic aldehydes to understand the scope and efficiency of the InF_3 promoted synthesis of fluorine containing 2,4,5-trisubstituted imidazoles.

It was observed that a wide variety of aldehydes (both aromatic and aliphatic) and 4,4-difluorobenzil (**1**) to establish the scope of this catalytic transformation (Table 3). A broad range of aromatic aldehydes bearing electron donating and electron withdrawing substituents underwent this one-pot, three-component cyclocondensation to furnish fluorine containing 2,4,5-trisubstituted imidazoles in high yields. Aliphatic aldehydes afforded the corresponding imidazoles in moderate yields. Various functional groups were found to be compatible under the reaction conditions. In general, the reactions were clean and no side products were detected. In all cases, the reactions proceeded efficiently at 60 °C in solvent-free and 10 mol% catalyst conditions.

The reusability of the catalyst was also examined in the synthesis of fluorine containing 2,4,5-trisubstituted imidazoles.

Table 2
Effect of temperature.[a]

Entry	Temperature (°C)	Time (min)	Yield[b] (%)
1	20	200	20
2	40	60	65
3	60	20	92

[a] Reaction conditions: 4,4-difluorobenzil (1 mmol), 2-fluoro-4-methoxybenzaldehyde (1 mmol) and ammonium acetate (2.2 mmol); different temperature.
[b] Isolated yields.

Table 3
Synthesis of fluorine containing 2,4,5-trisubstituted imidazoles.[a]

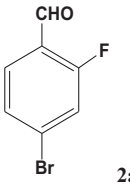
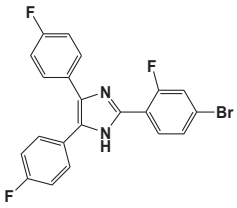
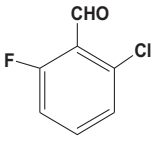
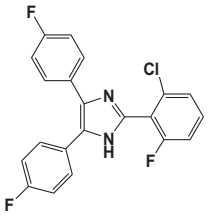
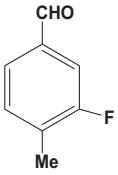
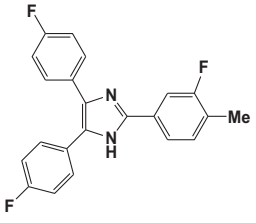
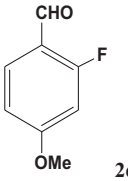
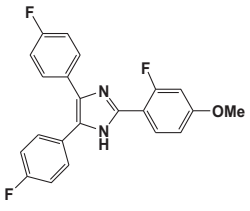
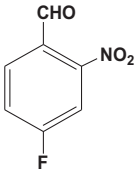
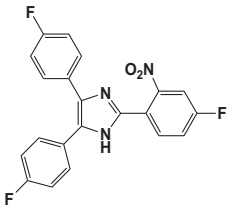
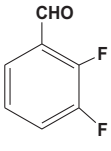
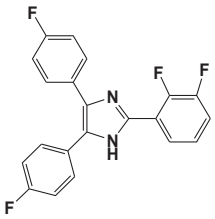
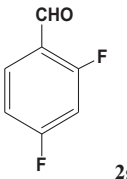
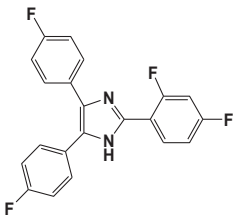
Entry	Aldehyde	Product	Time (min)	Yield[b] (%)	mp (°C)
1	 **2a**	 **4a**	22	91	150–152
2	 **2b**	 **4b**	25	90	156–158
3	 **2c**	 **4c**	20	92	232–234
4	 **2d**	 **4d**	20	92	250–252
5	 **2e**	 **4e**	26	89	175–177
6	 **2f**	 **4f**	24	88	192–194
7	 **2g**	 **4g**	24	90	210–212

Table 3 (*Continued*)

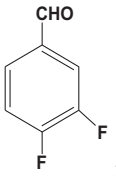
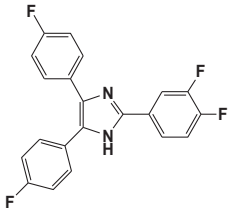
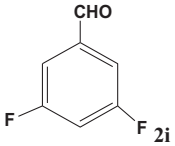
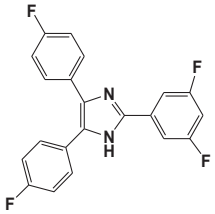
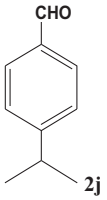
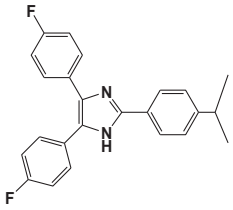
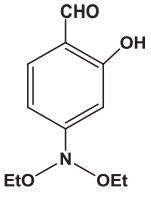
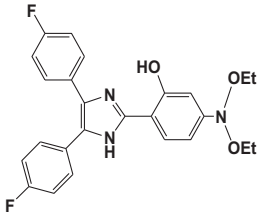
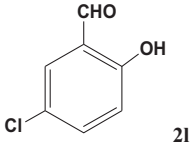
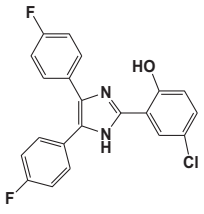
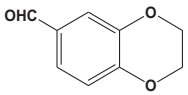
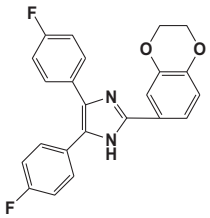
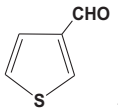
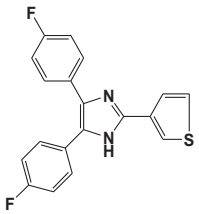
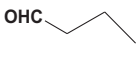
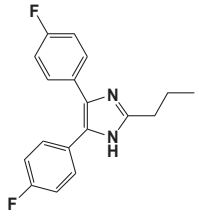
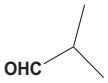
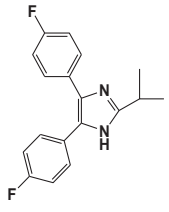
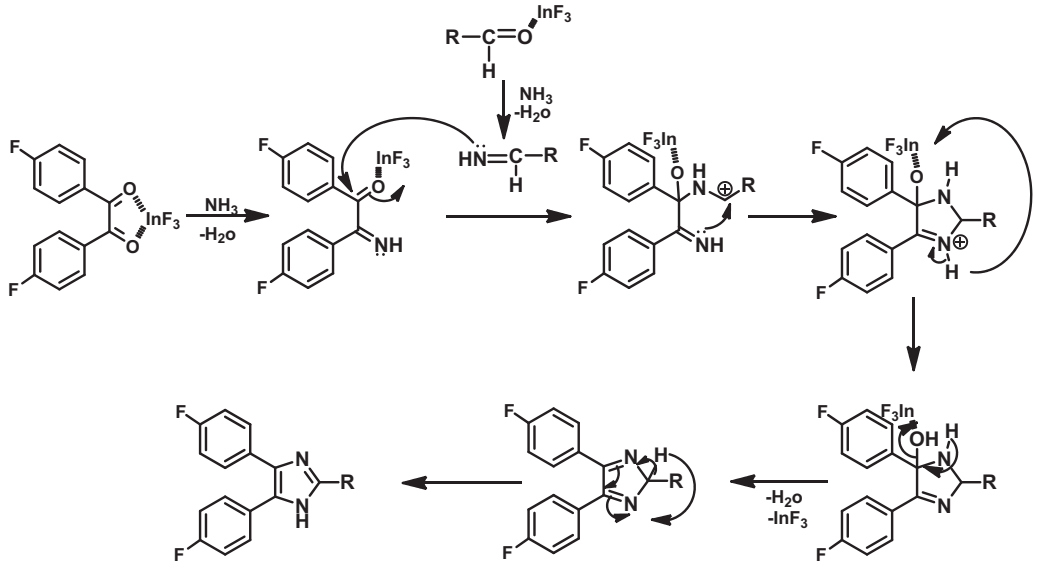
Entry	Aldehyde	Product	Time (min)	Yield[b] (%)	mp (°C)
8	 **2h**	 **4h**	26	91	238–240
9	 **2i**	 **4i**	23	90	282–284
10	 **2j**	 **4j**	22	92	214–216
11	 **2k**	 **4k**	29	88	150–152
12	 **2l**	 **4l**	28	87	220–222
13	 **2m**	 **4m**	25	92	216–218
14	 **2n**	 **4n**	26	90	247–249

Table 3 (*Continued*)

Entry	Aldehyde	Product	Time (min)	Yield[b] (%)	mp (°C)
15	 **2o**	 **4o**	35	84	160–162
16	 **2p**	 **4p**	40	80	198–200

[a] The 4,4-difluorobenzil (1 mmol), aldehydes (1 mmol) and ammonium acetate (2.2 mmol) using 10 mol% InF_3 in solvent-free at 60 °C.
[b] Isolated yields.



Scheme 2. A plausible mechanism for the formation of fluorine containing 2,4,5-trisubstituted imidazoles catalyzed.

The catalyst was recovered after each run, washed three times with chloroform, dried in an oven at 100 °C, and tested for its activity in subsequent runs. It was found that the catalyst could be reused four times without the loss of activity (Table 1, 11). The structures of all the newly synthesized compounds were established by their ^1H, ^{13}C, ^{19}F & NMR and HRMS, ESI-MS analyses.

A mechanism for the catalytic activity of InF_3 in the synthesis of fluorine containing 2,4,5-trisubstituted imidazoles should be postulated as shown in Scheme 2. The InF_3 probably induces polarization of carbonyl group in aldehydes as well as in benzil. The nucleophilic attack of the nitrogen of ammonia obtained from ammonium acetate, on activated carbonyl, results the formation of aryl aldimine and α-iminokeone. Their subsequent reaction followed by intramolecular interaction leads to cyclization. Eventually to the formed intermediate dehydrates to give the fluorine containing 2,4,5-trisubstituted imidazoles (**4a**–**p**) in excellent yields.

3. Conclusion

In conclusion, we have developed a solvent-free reaction for the synthesis of fluorine containing 2,4,5-trisubstituted imidazoles via one-pot, three-component condensation reaction of 4,4-difluorobenzil with aldehydes and ammonium acetate, Indium fluoride as a novel, efficient, and recyclable catalyst. The salient features of this protocol are high product yields, shorter reaction time, solvent-free condition, low catalyst loading, and relatively mild acid catalyst with easy work-up procedure, which make this procedure quite simple, more convenient, and environmentally benign. Hopefully, our methodology could be a valid contribution to the existing processes in the field of fluorine containing 2,4,5-trisubstituted imidazoles synthesis.

4. Experimental

4.1. Method and apparatus

Chemicals were purchased from Aldrich and Alfaaesar Chemical Companies. NMR spectra were recorded in ppm in DMSO-d_6 on a JEOL JNM ECP 400 NMR instrument using TMS as internal standard. Mass spectra were recorded on a JEOL JMS-700 mass spectrometer. All melting points were determined using open capillaries on an Electrothermal-9100 (Japan) instrument.

4.2. Synthesis of fluorine containing 2,4,5-trisubstituted imidazoles

A mixture of 4,4-difluorobenzil (1 mmol), aldehydes (1 mmol), ammonium acetate (2.2 mmol) and InF_3 (10 mol%) was stirred at 60 °C under solvent-free condition for appropriate time (Table 3). The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was washed with chloroform and filtered to recover the catalyst. The filtrate was evaporated, and the crude product was recrystallized from ethanol to afford pure fluorine containing 2,4,5-trisubstituted imidazoles in good to excellent yields.

4.2.1. 2-(4-Bromo-2-fluorophenyl)-4,5-bis(4-fluorophenyl)-1H-imidazole (**4a**)

White solid; Mp: 150–152 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.2 (s, 1H), 8.05–8.01 (q, 4H), 7.96 (t, J = 8.2 Hz, 2H), 7.81 (dd, J = 2.5, 10.2 Hz 1H), 7.56–7.46 (m, 2H), 7.30 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.0 (C–F, d, ^1J = 244.5 Hz), 161.7 (C–F, d, ^1J = 242.0 Hz), 158.8 (d, J_{C-F} = 255.1 Hz), 145.4, 134.9, 133.1, 131.8, 130.2, 129.0, 125.4, 121.2, 120.2, 119.2, 116.6; ^{19}F NMR (376 MHz, DMSO-d_6): δ −109.92 (m, 2F), −113.73 (m, 1F); HRMS (ESI, m/z): calcd for $C_{21}H_{12}BrF_3N_2$ (M+H$^+$) 428.0136, found: 428.0140.

4.2.2. 2-(2-Chloro-6-fluorophenyl)-4,5-bis(4-fluorophenyl)-1H-imidazole (**4b**)

White solid; Mp: 156–158 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.5 (s, 1H), 8.15–8.11 (m, 4H), 7.69–7.63 (q, 4H), 7.31–7.20 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.8 (C–F, d, ^1J = 244.3 Hz), 161.7 (C–F, d, ^1J = 242.5 Hz), 158.2 (d, J_{C-F} = 250.1 Hz), 148.0, 136.9, 134.6, 131.2, 129.8, 128.6, 125.1, 123.2, 122.1, 116.3, 112.3; ^{19}F NMR (376 MHz, DMSO-d_6): δ −109.96 (m, 2F), −112.27 (m, 1F); HRMS (ESI, m/z): calcd for $C_{21}H_{12}ClF_3N_2$ (M+H$^+$) 384.0641, found: 384.0637.

4.2.3. 2-(3-Fluoro-4-methylphenyl)-4,5-bis(4-fluorophenyl)-1H-imidazole (**4c**)

White solid; Mp: 232–234 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.7 (s, 1H), 8.02–7.96 (m, 4H), 7.80 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 8.2 Hz 1H), 7.24 (t, J = 8.0 Hz, 2H), 7.12–7.08 (m, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.0 (C–F, d, ^1J = 244.0 Hz), 162.5 (d, J_{C-F} = 249.7 Hz), 161.4 (C–F, d, ^1J = 242.0 Hz), 148.8, 136.9, 133.9, 131.2, 129.2, 128.2, 125.6, 124.6, 120.6, 118.2, 114.6, 13.9; ^{19}F NMR (376 MHz, DMSO-d_6): δ −114.51 (m, 2F), −118.17 (m, 1F); HRMS (ESI, m/z): calcd for $C_{22}H_{15}F_3N_2$ (M+H$^+$) 364.1187, found: 364.1189.

4.2.4. 2-(2-Fluoro-4-methoxyphenyl)-4,5-bis(4-fluorophenyl)-1H-imidazole (**4d**)

White solid; Mp: 250–252 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.0 (s, 1H), 8.14–8.10 (q, 4H), 7.90–782 (m, 2H), 7.69–7.20 (m, 3H), 6.76 (d, J = 8.0 Hz, 2H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.6 (C–F, d, ^1J = 244.0 Hz), 161.4 (C–F, d, ^1J = 242.0 Hz), 159.3 (d, J_{C-F} = 255.8 Hz), 158.2, 149.4, 136.2, 133.8, 131.2, 130.2, 129.8, 116.6, 112.7, 106.2, 102.2, 55.4; ^{19}F NMR (376 MHz, DMSO-d_6): δ −114.36 (m, 2F), −117.75 (m, 1F); HRMS (ESI, m/z): calcd for $C_{22}H_{15}F_3N_2O$ (M+H$^+$) 380.1136, found: 380.1138.

4.2.5. 2-(4-Fluoro-2-nitrophenyl)-4,5-bis(4-fluorophenyl)-1H-imidazole (**4e**)

White solid; Mp: 175–177 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.90 (s, 1H), 8.09–8.01 (m, 5H), 7.80 (t, J = 8.2 Hz, 2H), 7.54–7.45 (m, 2H), 7.35–730 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.8 (C–F, d, ^1J = 244.0 Hz), 161.5 (C–F, d, ^1J = 242.5 Hz), 160.2 (d, J_{C-F} = 248.5 Hz), 150.2, 149.2, 136.3, 133.2, 131.9, 130.7, 129.8, 125.5, 123.8, 118.2, 115.7; ^{19}F NMR (376 MHz, DMSO-d_6): δ −109.12 (m, 2F), −113.32 (m, 1F); HRMS (ESI, m/z): calcd for $C_{21}H_{12}F_3N_3O_2$ (M+H$^+$) 395.0882, found: 395.0870.

4.2.6. 2-(2,3-Difluorophenyl)-4,5-bis(4-fluorophenyl)-1H-imidazole (**4f**)

White solid; Mp: 192–194 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.01 (s, 1H), 8.09–8.01 (m, 4H), 7.80 (t, J = 8.0 Hz, 2H), 7.64 (t, J = 8.0 Hz, 1H) 7.50–7.42 (m, 2H), 7.33–722 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.2 (d, J_{C-F} = 255.1 Hz), 162.0 (C–F, d, ^1J = 244.0 Hz), 160.4 (C–F, d, ^1J = 243.0 Hz), 152.2, 148.2, 144.3, 132.4, 130.2, 129.8, 129.1, 128.0, 122.6, 117.3, 115.5; ^{19}F NMR (376 MHz, DMSO-d_6): δ −99.53 (m, 1F), −109.70 (m, 2F), −112.88 (m, 1F); HRMS (ESI, m/z): calcd for $C_{21}H_{12}F_4N_2$ (M+H$^+$) 368.0937, found: 368.0927.

4.2.7. 2-(2,4-Difluorophenyl)-4,5-bis(4-fluorophenyl)-1H-imidazole (**4g**)

White solid; Mp: 210–212 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.60 (s, 1H), 8.10–8.04 (q, 4H), 7.64 (t, J = 8.2 Hz, 2H), 7.57–7.40 (m, 2H), 7.46 (d, J = 8.2 Hz, 1H), 7.36 (t, J = 8.3 Hz, 1H), 7.12 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.5 (dd, J_{C-F} = 247.1, 9.2 Hz), 162.2 (C–F, d, ^1J = 244.0 Hz), 161.3 (C–F, d, ^1J = 242.0 Hz), 159.2 (dd, J_{C-F} = 251.1, 10.1 Hz), 147.0, 133.6, 132.2, 130.1, 129.6, 122.6, 119.2, 116.1, 112.2, 105.2; ^{19}F NMR (376 MHz, DMSO-d_6): δ −109.26 (m, 2F), −114.58 (m, 1F), −116.25 (m, 1F); MS (ESI): m/z 368 (M$^+$).

4.2.8. 2-(3,4-Difluorophenyl)-4,5-bis(4-fluorophenyl)-1H-imidazole (**4h**)

White solid; Mp: 238–240 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.01 (s, 1H), 8.07–8.02 (m, 4H), 7.70–7.46 (m, 5H), 7.34–7.29 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.7 (C–F, d, ^1J = 244.2 Hz), 161.2 (C–F, d, ^1J = 242.0 Hz), 150.2 (dd, J_{C-F} = 251.5, 9.2 Hz), 148.3, 145.5, 135.2, 133.2, 130.9, 129.8, 127.5, 125.2, 119.2, 117.5, 115.4; ^{19}F NMR (376 MHz, DMSO-d_6): δ −109.80 (m, 2F), −114.39 (m, 1F), −116.40 (m, 1F); MS (ESI): m/z 368 (M$^+$).

4.2.9. 2-(3,5-Difluorophenyl)-4,5-bis(4-fluorophenyl)-1H-imidazole (**4i**)

White solid; Mp: 340–342 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.90 (s, 1H), 8.01–7.96 (q, 4H), 7.74 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 8.2 Hz, 2H), 7.54 (t, J = 8.3 Hz, 1H), 7.29–7.25 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.8 (d, J_{C-F} = 255.1 Hz), 162.0 (C–F, d, ^1J = 244.7 Hz), 161.4 (C–F, d, ^1J = 241.0 Hz), 145.9, 137.1, 134.9, 130.2, 129.8, 128.1, 125.4, 115.6, 108.1; ^{19}F NMR (376 MHz, DMSO-d_6): δ −109.23 (m, 2F), −114.12 (m, 1F), −116.72 (m, 1F); MS (ESI): m/z 368 (M$^+$).

4.2.10. 4,5-Bis(4-fluorophenyl)-2-(4-isopropylphenyl)-1H-imidazole (**4j**)

White solid; Mp: 214–216 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.55 (s, 1H), 8.08 (d, J = 7.8 Hz, 4H), 7.59–7.47 (m, 2H), 7.35–7.29 (q, 4H), 7.16–7.03 (q, 2H), 3.03–2.96 (m, 1H), 1.25 (d, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.0 (C–F, d, ^1J = 244.0 Hz), 162.5 (C–F, d, ^1J = 242.0 Hz), 150.1, 145.3, 137.9, 134.2, 130.9, 129.8, 128.0, 124.2, 116.5, 39.0, 23.4, 20.7; ^{19}F NMR (376 MHz, DMSO-d_6): δ −112.67 (m, 2F); HRMS (ESI, m/z): calcd for $C_{24}H_{20}F_2N_2$ (M+H$^+$) 374.1595, found: 374.1580.

4.2.11. 2-(4,5-Bis(4-fluorophenyl)-1H-imidazol-2-yl)-5-(diethoxyamino)phenol (**4k**)

White solid; Mp: 150–152 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.95 (s, 1H), 9.50 (s, 1H), 8.09–8.06 (m, 4H), 7.80–7.25 (m, 7H), 3.61–3.55 (q, 4H), 1.08 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.3 (C–F, d, ^1J = 244.3 Hz), 161.4 (C–F, d,

^1J = 242.0 Hz), 153.6, 151.4, 147.2, 135.2, 131.5, 130.9, 129.6, 128.0, 126.7, 122.4, 119.5, 118.6, 116.5, 58.5, 14.5; ^{19}F NMR (376 MHz, DMSO-d_6): δ −112.17 (m, 2F); MS (ESI): m/z 451 (M^+).

*4.2.12. 2-(4,5-Bis(4-fluorophenyl)-1H-imidazol-2-yl)-4-chlorophenol (**4l**)*

White solid; Mp: 220–222 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.50 (s, 1H), 9.25 (s, 1H), 8.14–8.10 (m, 4H), 7.80–7.31 (m, 7H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.6 (C–F, d, ^1J = 243.5 Hz), 161.4 (C–F, d, ^1J = 241.8 Hz), 151.8, 148.8, 134.5, 132.5, 130.9, 129.6, 128.1, 126.4, 119.6, 115.8, 111.1; ^{19}F NMR (376 MHz, DMSO-d_6): δ −110.25 (m, 2F); HRMS (ESI, m/z): calcd for $C_{21}H_{13}ClF_2N_2O$ ($M+H^+$) 382.0684, found: 382.0697.

*4.2.13. 2-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-4,5-bis(4-fluorophenyl)-1H-imidazole (**4m**)*

White solid; Mp: 216–218 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.80 (s, 1H), 8.10–8.02 (m, 4H), 7.57–7.48 (m, 3H), 7.22 (t, J = 8.2 Hz, 2H), 6.95 (d, J = 8.2 Hz, 2H), 3.95 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.2 (C–F, d, ^1J = 244.0 Hz), 161.0 (C–F, d, ^1J = 242.1 Hz), 152.2, 145.2, 143.8, 134.2, 132.2, 129.8, 124.4, 122.8, 117.6, 113.8, 109.3, 64.2; ^{19}F NMR (376 MHz, DMSO-d_6): δ −110.21 (m, 2F); HRMS (ESI, m/z): calcd for $C_{23}H_{16}F_2N_2O_2$ ($M+H^+$) 390.118, found: 390.110.

*4.2.14. 4,5-Bis(4-fluorophenyl)-2-(thiophen-3-yl)-1H-imidazole (**4n**)*

White solid; Mp: 247–249 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.25 (s, 1H), 8.09–8.01 (q, 4H), 7.82–7.30 (m, 7H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.0 (C–F, d, ^1J = 244.5 Hz), 161.9 (C–F, d, ^1J = 241.9 Hz), 148.2, 137.8, 134.2, 132.9, 130.2, 129.8, 128.6, 127.8, 126.9, 117.8; ^{19}F NMR (376 MHz, DMSO-d_6): δ −110.53 (m, 2F); MS (ESI): m/z 338 (M^+).

*4.2.15. 4,5-Bis(4-fluorophenyl)-2-propyl-1H-imidazole (**4o**)*

White solid; Mp: 160–162 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.09 (s, 1H), 8.16–8.13 (m, 4H), 7.69–7.30 (m, 4H), 2.20–1.68 (m, 4H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.0 (C–F, d, ^1J = 244.0 Hz), 161.4 (C–F, d, ^1J = 242.0 Hz), 148.6, 133.2, 130.9, 130.0, 129.1, 117.5, 32.5, 21.2, 14.3; ^{19}F NMR (376 MHz, DMSO-d_6): δ −111.01 (m, 2F); MS (ESI): m/z 298 (M^+).

*4.2.16. 4,5-Bis(4-fluorophenyl)-2-isopropyl-1H-imidazole (**4p**)*

White solid; Mp: 198–200 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.80 (s, 1H), 8.10 (d, J = 8.2 Hz, 4H), 7.50–7.42 (m, 4H), 3.18–3.10 (m, 1H), 1.25(d, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.5 (C–F, d, ^1J = 244.8 Hz), 161.4 (C–F, d, ^1J = 241.9 Hz), 146.2, 133.5, 130.4, 129.7, 128.2, 115.5, 33.2, 21.3, 20.7; ^{19}F NMR (376 MHz, DMSO-d_6): δ −110.42 (m, 2F); HRMS (ESI, m/z): calcd for $C_{18}H_{16}F_2N_2$ ($M+H^+$) 298.1282, found: 298.1284.

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