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Short communication

Synthesis and evaluation of new difluoromethyl azoles as antileishmanial agents

Sabrina B. Ferreira [a], Marilia S. Costa [b], Núbia Boechat [c], Rômulo J.S. Bezerra [d], Marcelo S. Genestra [d], Marilene M. Canto-Cavalheiro [d], Warner B. Kover [a], Vitor F. Ferreira [b,*]

[a] *Universidade Federal do Rio de Janeiro Departamento de Química Orgânica, Instituto de Química, Cidade Universitária, 21949-900 Rio de Janeiro, RJ, Brazil*
[b] *Universidade Federal Fluminense, Departamento de Química Orgânica, Instituto de Química, Outeiro de São João Baptista, CEP 24020-150 Niterói, RJ, Brazil*
[c] *Fundação Oswaldo Cruz, Instituto de Tecnologia em Fármacos, Departamento de Síntese Orgânica, Manguinhos, CEP 21041250 Rio de Janeiro, RJ, Brazil*
[d] *Fundação Oswaldo Cruz, Instituto Oswaldo Cruz, Departamento de Imunologia, Fiocruz, 21041-250 Rio de Janeiro, RJ, Brazil*

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Abstract

Several compounds of great pharmacological interest contain the triazole and imidazole rings. In order to find new drugs with antileishmanial activity we have synthesized and evaluated new imidazole and triazole compounds carrying either the carbaldehyde or the difluoromethylene functionalities against promastigote forms of *Leishmania amazonensis*. Among the compounds tested difluoromethylene azoles **4b** and **8f** have inhibited the parasite growth significantly. Our results show that the introduction of the difluoromethylene moieties has turned the inactive carbaldehydes into active antileishmanial compounds.

Keywords: Antileishmanial activity; Difluoromethylation; Imidazole; 1,2,3-Triazole

1. Introduction

Leishmaniasis is caused by several species of protozoan parasites transmitted by the bite of the female phlebotomine sand fly [1]. This disease is currently prevalent in four continents, being endemic in 88 countries, 72 of which are developing countries, threatening 350 millions worldwide [1]. Classified as an extremely neglected disease —leishmaniasis is still present as an additional difficulty in the long and inefficient treatment that is dependent on old and highly toxic drugs [2]. In addition, the development of the clinical resistance and the increase of co-infections leishmaniasis–AIDS, in some countries, have worried the authorities. Thus, the development of new, efficient, and safe drugs for the treatment of this disease is imperative [3,4].

Azole antifungal drugs have been used as antileishmanial agents since the 1980s [5]. Imidazole and triazole antifungals inhibit the growth of *Leishmania* amastigotes in culture systems by inhibiting the cytochrome P-450-mediated 14α-demethylation of lanosterol, blocking ergosterol synthesis, and causing accumulation of 14α-methyl sterols [6]. The pharmacological interest of the triazole [7] and imidazole [8] rings has been established and in order to find new drugs with antileishmanial activity we have synthesized and evaluated new imidazole and triazole compounds against promastigote forms of *Leishmania amazonensis*.

* Corresponding author. Tel.: +55 21 26292345; fax: +55 21 26292362.
E-mail address: cegvito@vm.uff.br (V.F. Ferreira).

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2. Chemistry

Different methods for synthesizing imidazole and 1,2,3-triazole are described in the literature [9,10]. The *N*-aryl-amidines (**1a**–**1l**) and 2-bromomalonaldehyde (**2**) were prepared and utilized as the starting materials for the synthesis of *N*-substitued-phenyl-imidazole-5-carbaldehyde (**3a**–**3l**) (Scheme 1). The synthesis of *N*-aryl-amidines [11] (**1a**–**1l**) was accomplished, in good yields, by condensation of commercial aromatic amines with acetonitrile in the presence of hydrogen chloride. The reaction time was dependent on substituent R_1 in aromatic ring (Table 1).

The 2-bromomalonaldehyde (**2**) was prepared, 90% yield, by the procedure described by Trofimenko [12]. The condensation reaction between **1a**–**1l** and **2** in isopropanol, using acetic acid and triethylamine as catalysts, leads exclusively to the formation of 5-carbaldehyde imidazole, which had it's structure confirmed by ^{1}H and ^{13}C NMR spectra. The target compounds **3a**–**3l** were obtained in 85–96% yield and fully characterized by ^{1}H NMR, ^{13}C NMR, IR and EI-MS spectroscopies.

The carbaldehyde moieties in **3a**–**3l** were readily converted into difluoromethyl groups for generating **4a**–**4l** (Scheme 1), by using *N*,*N*-diethylaminosulfur trifluoride (DAST) [13], with excellent yield (89–97%). The ^{1}H NMR spectra of **4a**–**4l** showed difluoromethylene (CHF_2) proton as a triplet at δ 6.42–6.51 ppm ($J_{HF} = 56.0$ Hz).

The 1,2,3-triazolic compounds **7a**–**7l** were prepared from diazomalonaldehyde (**5**) and aromatic amine hydrochlorides (**6a**–**6l**) (Scheme 2). Diazomalonaldehyde (**5**) was prepared by the procedure described by Arnold and co-workers [14]. The reaction of **5** with the appropriate aniline hydrochlorides (**6a**–**6l**), in aqueous solution, yielded *N*-substitued-phenyl-1,2,3-triazole-4-carbaldehyde (**7a**–**7l**) in good yields. The 4-difluoromethyl-1,2,3-triazoles (**8a**–**8l**) were obtained in 90–98% yields on reaction of **6a**–**6l** with DAST (Scheme 2).

The structures of compounds **7a**–**7l** and **8a**–**8l** were confirmed by Microanalysis, EI-MS, IR, ^{1}H NMR, ^{13}C NMR spectroscopy, X-ray diffraction [15,16] and for **8a**–**8l**, also by ^{19}F NMR spectroscopy. The ^{1}H NMR spectra of **7a**–**7l** showed carbaldehyde (CHO) proton as singlet at δ 10.21–10.24 ppm. Furthermore, the absence of this singlet and the presence of a triplet at δ 6.95–6.97 ppm ($J_{HF} = 55.5$ Hz) in the ^{1}H NMR spectra of **8a**–**8l** indicated the conversion of the carbaldehyde into the difluoromethyl (CHF_2) [17].

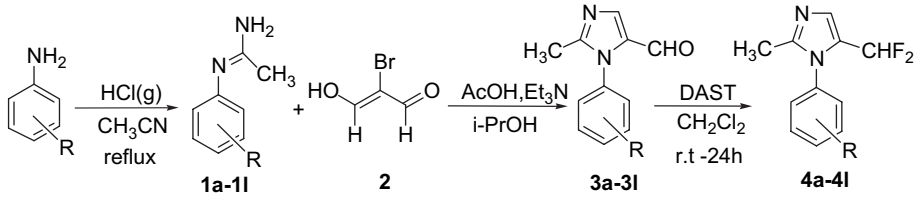
3. Activity assay against *L. amazonensis*

The in vitro efficacies of the synthesized compounds were performed on promastigotes of *L. amazonensis* (MHOM/BR/77/LTB0016). Parasites were maintained by animal passage and cryopreserved in liquid nitrogen. Promastigotes were cultured at 25 °C in Schneider's Insect Medium of pH 7.2 containing 10% (v/v) of heat-inactivated fetal bovine serum [18]. For the activity assay, the parasite culture was diluted with the fresh medium to a final concentration of 5×10^6 parasites/mL. The drugs were dissolved in dimethylsulfoxide (DMSO) and tested within a concentration range of 0.16–320 μg mL^{-1} (0.74–1493.33 μM). Drugs were added to a 96-well microtitre plate (up to 1.6% final DMSO concentration) and incubated at 26 °C for 24 h with the parasites in their metacyclic phase [19]. All the tests were carried out in triplicate and pentamidine was used as the reference drug. Results represent the mean values of three experiments and were expressed as IC_{50}, i.e., the concentration of a compound that caused a 50% reduction in survival/viability in comparison to identical cultures without the compounds. The procedure used to observe the drugs effects was the MTT reduction, using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide (MTT, Sigma, MO, USA) and the result could be read on an ELISA reader at 490 nm [20]. The percentage of inhibition was estimated and compared with the control. Antileishmanial activity was calculated as shown in Table 2. To ensure that the solvent had no effect on parasite growth a control test was performed with test medium and DMSO at the same dilution as used in the experiment.

4. Results and discussion

All the compounds were tested against the parasite; however, only the significant antileishmanial activities are reported in Table 2. Among them, the carbaldehyde **7f** and the difluormethylated azoles **4b** and **8f** showed IC_{50} below 3.0 μM (2.8, 1.7, and 2.6 μM, respectively). From these data, it is possible to argue if the introduction of the difluoromethyl (CHF_2) group in the azole rings may lead to compounds with any significant antileishmanial activity. In particular, the difluoromethyl imidazole **4b** (1.7 μM) is the only active imidazole compound in the series.

It is important to note that in vitro antituberculosis screening of **7a**–**7l** and **8a**–**8l** revealed an opposite trend between carbaldehyde and difluoromethyl groups. For the



R =**a**) H; **b**) 4-Cl; **c**) 4-Br; **d**) 4-F; **e**) 4-NO_2; **f**) 4-CF_3;**g**) 4-CN; **h**) 4-CH_3; **i**) 4-OCH_3; **j**) 2,6-F; **k**) 2-CH_3; **l**) 3-OCF_3

Scheme 1. Synthetic methods for the preparation of imidazole derivatives **3a**–**3l** and **4a**–**4l**.

Table 1
Reaction times and yields obtained in the preparation of *N*-aryl-amidines

Amidine	R_1	Time (h)	Yield (%)
1a	H	5.0	95
1b	4-Cl	6.5	96
1c	4-Br	6.5	95
1d	4-F	8.0	88
1e	4-NO_2	10.0	85
1f	4-CF_3	10.0	84
1g	4-CN	4.5	90
1h	4-CH_3	4.0	91
1i	4-OCH_3	4.0	90
1j	2,6-diF	20.0	83
1k	2-CH_3	4.5	87
1l	3-CF_3	6.0	88

mycobacterium the triazole-4-carbaldehylde derivatives were more effective than the 4-difluoromethyl derivatives (**8a–8l**) [17]. These results indicated that the positive effect of introducing fluorine atoms in these compounds is specific to their antileishmanial activity. The introduction of fluorine atom(s) may strongly modify the physical and chemical properties of a molecule and thus alter its biological activity [21]. Usually, incorporation of a fluorine atom increases lipophilicity thereby enhancing absorption of the biological membranes as well as favoring the docking with drug receptor(s).

Alvarez's group [22] verified that a possible mechanism of action of imidazolidinone compounds is related to inhibition of protein kinase C (PKC) family isoenzymes, which mediate a wide range of signal transduction pathways in many different cells lines, including leishmania [23]. Previous studies from our group verified the calcium independent-PKC activity in *L. amazonensis* promastigotes and some works describe that PKC plays a critical role in the invasion process [24]. Thus leishmania–PKC activity could be a relevant therapeutic target of these novel imidazole antileishmanial candidates.

5. Conclusion

In conclusion, the high in vitro leishmanicidal activity of **4b** and **8f** makes these compounds promising hits for the development of an effective therapeutic agent. However, additional tests with amastigote/macrophage in vitro models and in vivo (mouse) toxicity/mouse models need to be carried out in order prove the usefulness of this class of compounds.

6. Experimental protocols

Melting points were determined with a Buchi Model B-545 instrument and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer model 1420 FT-IR Spectrophotometer in KBr pellets. ^1H and ^{13}C NMR spectra were recorded on Bruker Advance 500 plus 400.00 and 500.00 MHz, employing tetramethylsilane as the internal reference at room temperature. ^{19}F NMR spectra were recorded on Bruker UltraShield plus 376.0 MHz, employing $CFCl_3$ as internal reference at room temperature. The chemical shifts (δ) are reported in ppm and the coupling constant (J) in Hz. Mass spectra were recorded on GC–MS (Hewlett Packard Model AT-6890N) auto sampler/direct injection (EI/CI). Reactions were routinely monitored by thin layer chromatography (TLC) on silica gel precoated F_{254} Merck plates. Microanalyses were performed on Perkin-Elmer Model 2400 instrument and all values were within ±0.4% of the calculated compositions. Compounds **7a–7l** and **8a–8l** were previously prepared by Ferreira and co-workers [17].

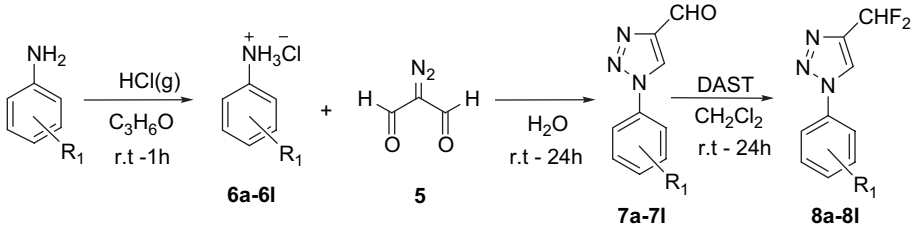
Chemicals obtained from commercial supplies were used without purification, unless otherwise stated.

6.1. Chemistry

6.1.1. General procedure for the preparation of *N*-aryl-amidines (*1a–1l*)

To a stirred solution of amine (10.75 mmol) in acetonitrile 42.91 mL (822.70 mmol) was bubbled hydrogen chloride. A precipitate was formed immediately. The resulting suspension was stirred at reflux and eventually becomes homogeneous. Thin layer chromatography was used to monitor the progress of the reaction. Upon complete reaction, the mixture was concentrated at reduced pressure and the residue partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The aqueous layer was washed (3×) with CH_2Cl_2, and the combined organic layers were dried over sodium sulfate, filtered, and the filtrate concentrated under reduced pressure. The following compounds were prepared according this general procedure.

*6.1.1.1. (1E/Z)-N-Phenylacetamidine (**1a**).* Obtained in 95% yield as white solid; mp 62–64 °C; IR (KBr) ν_{max} (cm^{-1}) 3441; 3310; 3197; 1643; 1445; ^1H NMR (500 MHz; $CDCl_3$/Me_4Si): δ 2.02 (s, 3H, CH_3); 4.26 (bs, 2H, NH_2); 6.86 (dd,



R_1 = **a**) 4-Cl; **b**) 4-Br; **c**) 4-CH_3; **d**) 4-OCH_3; **e**) 2,5-OCH_3; **f**) 3-Cl; **g**) 3,5-Cl; **h**) 3-CN; **i**) 4-CN; **j**) 4-NO_2; **k**) 2-OCH_3; **l**) 3,4-OCH_3

Scheme 2. Reaction conditions for the synthesis of 1,2,3-triazoles **7a–7l** and **8a–8l**.

Table 2
In vitro potency of azole compounds active over *L. amazonensis* promastigote forms

Azole compounds	$IC_{50} \pm$ S.D. (μM)[a]
4b	1.7 ± 0.4
7f	2.8 ± 0.0
8f	2.6 ± 0.43
Pentamidine[b]	0.46 ± 0.07

[a] Concentrations required to reduce the number of viable *L. amazonensis* promastigote forms by 50% as observed by the MTT reduction method [20]; S.D. = standard deviations ($n = 3$).
[b] Reference drug.

2H, $J = 4.0$ Hz); 7.29 (t, 2H, $J = 8.0$ Hz); 7.02 (ddd, 1H, $J = 8.0$ Hz); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 20.2 (CH_3); 121.8; 122.6; 129.1; 149.2; 156.0 ($H_2N-C{=}N$); EI-MS (*m/z*): 134 (M^+, 79%); 119 ($M^+ - 15$, 42%); 93 ($M^+ - 41$, 84%); 77 ($M^+ - 57$, 100%); 65 ($M^+ - 69$, 21%).

*6.1.1.2. (1E/Z)-N-(p-Chlorophenyl)acetamidine (**1b**).* Obtained in 96% yield as white solid; mp 116–117 °C; IR (KBr) ν_{max} (cm^{-1}) 3451; 3295; 3079; 1640; 1586; 1482; ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 1.99 (s, 3H, CH_3); 4.53 (bs, 2H, NH_2); 6.77 (d, 2H, $J = 8.0$ Hz); 7.24 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 21.59 (CH_3); 122.5; 121.1; 128.6; 144.6; 155.3 ($H_2N-C{=}N$); EI-MS (*m/z*): 168 (M^+, 68%); 153 ($M^+ - 15$, 38%); 127 ($M^+ - 41$, 100%); 111 ($M^+ - 57$, 54%); 75 ($M^+ - 93$, 42%).

*6.1.1.3. (1E/Z)-N-(p-Bromophenyl)acetamidine (**1c**).* Obtained in 95% yield as white solid; mp 207–208 °C; IR (KBr) ν_{max} (cm^{-1}) 3448; 3301; 3118; 1636; 1579; 1478; ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 1.97 (s, 3H, CH_3); 4.57 (bs, 2H, NH_2); 6.69 (d, 2H, $J = 8.0$ Hz); 7.35 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 21.7 (CH_3); 123.0; 114.7; 131.5; 148.1; 154.5 ($H_2N-C{=}N$); EI-MS (*m/z*): 212 (M^+, 74%); 197 ($M^+ - 15$, 32%); 171 ($M^+ - 41$, 100%); 155 ($M^+ - 57$, 42%); 92 ($M^+ - 120$, 30%).

*6.1.1.4. (1E/Z)-N-(p-Fluorophenyl)acetamidine (**1d**).* Obtained in 88% yield as white solid; mp 174–176 °C; IR (KBr) ν_{max} (cm^{-1}) 3452; 3316; 3065; 1658; 1615; 1498; ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 1.99 (s, 3H, CH_3); 4.53 (bs, 2H, NH_2); 6.77 (d, 2H, $J = 8.0$ Hz); 7.24 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 21.0 (CH_3); 128.6 (t, $J = 165.0$ Hz); 155.3 ($C_{Ar}-F$); 122.5 (t, $J = 156.0$ Hz); 147.5; 156.2 ($H_2N-C{=}N$); EI-MS (*m/z*): 152 (M^+, 70%); 137 ($M^+ - 15$, 40%); 111 ($M^+ - 41$, 100%); 95 ($M^+ - 57$, 84%); 83 ($M^+ - 69$, 18%).

*6.1.1.5. (1E/Z)-N-(p-Nitrophenyl)acetamidine (**1e**).* Obtained in 85% yield as yellow solid; mp 227–229 °C; IR (KBr) ν_{max} (cm^{-1}) 3411; 3330; 3146; 1661; 1578; 1484; 1402; ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 2.51 (s, 3H, CH_3); 4.80 (bs, 2H, NH_2); 7.62 (d, 2H, $J = 8.0$ Hz); 8.40 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 23.0 (CH_3); 122.9; 143.7 ($C_{Ar}-NO_2$); 126.0; 155.6; 150.2 ($H_2N-C{=}N$); EI-MS (*m/z*): 179 (M^+, 51%); 164 ($M^+ - 15$, 12.5%); 149 ($M^+ - 30$, 11.3%); 138 ($M^+ - 41$, 11.8%); 118 ($M^+ - 61$, 31%); 108 ($M^+ - 71$, 100%).

*6.1.1.6. (1E/Z)-N-(p-Trifluoromethylphenyl)acetamidine (**1f**).* Obtained in 84% yield as yellow solid; mp 115–117 °C; IR (KBr) ν_{max} (cm^{-1}) 3460; 3312; 3096; 1648; 1602; 1402; ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 2.03 (s, 3H, CH_3); 4.54 (bs, 2H, NH_2); 6.94 (d, 2H, $J = 8.0$ Hz); 7.53 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 22.8 (CH_3); 122.0; 125.0 ($C_{Ar}-CF_3$); 125.9; 155.5; e 155.0 ($H_2N-C{=}N$); 121.5–125.1 (d, CF_3, $J = 170.0$ Hz); EI-MS (*m/z*): 202 (M^+, 84.5%); 187 ($M^+ - 15$, 62%); 161 ($M^+ - 41$, 64%); 145 ($M^+ - 57$, 100%); 125 ($M^+ - 77$, 19%).

*6.1.1.7. (1E/Z)-N-(p-Cyanophenyl)acetamidine (**1g**).* Obtained in 90% yield as yellow solid; mp 97–98 °C; IR (KBr) ν_{max} (cm^{-1}) 3591; 3397; 3223; 1662; 1619; 1494; ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 2.20 (s, 3H, CH_3); 4.63 (bs, 2H, NH_2); 6.95 (d, 2H, $J = 8.0$ Hz); 7.67 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 22.8 (CH_3); 119.5 ($C_{Ar}-CN$); 122.7; 133.2 (CN); 133.7; 155.0; 160.1 ($H_2N-C{=}N$); EI-MS (*m/z*): 159 (M^+, 99%); 144 ($M^+ - 15$, 70%); 118 ($M^+ - 41$, 100%); 102 ($M^+ - 57$, 86%); 90 ($M^+ - 69$, 12%).

*6.1.1.8. (1E/Z)-N-(p-Methylphenyl)acetamidine (**1h**).* Obtained in 91% yield as yellow solid; mp 199–203 °C; IR (KBr) ν_{max} (cm^{-1}) 3460; 3299; 3019; 1650; 1604; 1454; ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 2.00 (s, 3H, CH_3); 2.30 (s, 3H, CH_3); 4.54 (bs, 2H, NH_2); 6.65 (d, 2H, $J = 8.0$ Hz); 7.07 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 20.7 (CH_3); 22.4 (CH_3); 121.8; 129.7; 132.1; 146.4; 168.9 ($H_2N-C{=}N$); EI-MS (*m/z*): 148 (M^+, 80%); 133 ($M^+ - 15$, 38%); 106 ($M^+ - 42$, 100%);91 ($M^+ - 57$, 68%); 77 ($M^+ - 71$, 29%).

*6.1.1.9. (1E/Z)-N-(p-Methoxyphenyl)acetamidine (**1i**).* Obtained in 90% yield as yellow solid; mp 107–109 °C; IR (KBr) ν_{max} (cm^{-1}) 3458; 3323; 3182; 1644; 1465; 1441; ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 2.01 (s, 3H, CH_3); 3.77 (s, 3H, CH_3-O); 4.40 (bs, 2H, NH_2); 6.79 (d, 2H, $J = 8.0$ Hz); 6.85 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 21.0 (CH_3); 55.4 (CH_3-O); 114.6; 122.7; 142.6; 155.4; 163.5 ($H_2N-C{=}N$); EI-MS (*m/z*): 164 (M^+, 44%); 149 ($M^+ - 15$, 21%); 123 ($M^+ - 41$, 22%); 108 ($M^+ - 56$, 100%); 80 ($M^+ - 84$, 42%); 63 ($M^+ - 101$, 20%); 52 ($M^+ - 112$, 22%).

*6.1.1.10. (1E/Z)-N-(2,6-Difluorophenyl)acetamidine (**1j**).* Obtained in 83% yield as yellow solid; mp 179–182 °C; IR (KBr) ν_{max} (cm^{-1}) 3444; 3290; 3088; 1650; 1606; 1467; ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 1.98 (s, 6H, $2CH_3$); 5.35 (bs, 4H, $2NH_2$); 6.87–6.93 (m, 3H); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 17.3 (CH_3); 111.5 (dd, $C_{Ar}-F$, $J = 25.0$ Hz); 122.1 (t, $J = 2.1$ Hz); 122.9 (t, $J = 8.4$ Hz); 155.5 (ddd, $J = 210.2$ Hz); 161.1 ($H_2N-C{=}N$); EI-MS (*m/z*): 170 (M^+,

100%); 155 ($M^+ - 15$, 71%); 129 ($M^+ - 41$, 83%); 113 ($M^+ - 57$, 14.3%); 108 ($M^+ - 62$, 15%).

*6.1.1.11. (1E/Z)-N-(o-Methylphenyl)acetamidine (**1k**).* Obtained in 87% yield as colorless oil; IR (KBr) ν_{max} (cm^{-1}) 3456; 3328; 3103; 1647; 1482; 1439; ^1H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 2.01 (CH_3); 2.12 (s, 3H, CH_3); 3.59 (bs, 2H, NH_2); 6.75 (d, 1H, $J = 8.0$ Hz); 6.93 (d, 1H, $J = 8.0$ Hz); 7.10 (d, 1H, $J = 8.0$ Hz); 7.14 (t, 1H, $J = 8.0$ Hz); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 17.5 (CH_3); 21.4 (CH_3); 121.5; 122.9 (C_{Ar}–OCH_3); 126.9; 129.7; 130.6; 147.8; 161.0 (H_2N–C=N); EI-MS (*m/z*): 148 (M^+, 64%); 133 ($M^+ - 15$, 65%); 106 ($M^+ - 42$, 100%); 91 ($M^+ - 57$, 50%); 77 ($M^+ - 71$, 40%); 65 ($M^+ - 83$, 48%).

*6.1.1.12. (1E/Z)-N-(m-Trifluoromethylphenyl)acetamidine (**1l**).* Obtained in 88% yield as white solid; mp IR (KBr) ν_{max} (cm^{-1}) 3468; 3320; 3178; 1650; 1604; 1485; ^1H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 2.00 (s, 3H, CH_3); 4.51 (bs, 2H, NH_2); 7.02 (d, 1H, $J = 32.0$ Hz); 7.26 (d, 1H, $J = 4.0$ Hz); 7.39 (t, 1H, $J = 8.0$ Hz); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 22.8 (CH_3); 119.4; 118.7; 125.5 (CF_3, q, $J = 270.0$ Hz); 125.3; 129.8; 131.0 (m, C_{Ar}–CF_3); 150.1; 155.4 (H_2N–C=N); EI-MS (*m/z*): 202 (M^+, 70%); 187 ($M^+ - 15$, 50%); 161 ($M^+ - 41$, 72%); 145 ($M^+ - 57$, 100%); 125 ($M^+ - 77$, 15.5%); 95 ($M^+ - 107$, 22.5%).

*6.1.2. General procedure for the preparation of N-substitued-phenyl-imidazole-5-carbaldehydes (**3a–3l**)*

A mixture of isopropanol (102.07 mmol), corresponding amidine (**1a–1l**, 3.73 mmol), triethylamine (3.44 mmol) and acetic acid (3.92 mmol) was stirred for 5 min at room temperature. 2-Bromomalonaldehyde (**2**, 3.48 mmol) in isopropanol (14 mL) was added dropwise and the reaction mixture was heated for 1 h. The reaction mixture was stirred for 17 h at room temperature. The solvent was evaporated, water was added and mixture was washed with ether (3 × 10 mL). The washed organic layers were dried over sodium sulfate, filtered and the filtrate concentrated under reduced pressure. The following compounds were prepared according this general procedure.

*6.1.2.1. 2-Methyl-1-phenyl-1H-imidazole-5-carbaldehyde (**3a**).* Obtained in 90% yield as orange oil ($R_f = 0.6$; 9:1 $CHCl_3$/MeOH); IR (KBr) ν_{max} (cm^{-1}) 3131; 2853; 1674 (ν C=O); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 2.29 (s, 3H); 7.52 (t, 1H, $J = 3.6$ Hz); 7.26 (dd, 4H, $J = 5.2$ Hz and 3.6 Hz); 7.82 (s, 1H) and 9.56 (s, 1H; *H*C=O); ^{13}C NMR (100 MHz; $CDCl_3/Me_4Si$): δ 13.6; 120.7; 126.9; 129.4; 133.1; 135.7; 141.0; 152.4; 177.8 (H*C*=O); EI-MS (*m/z*): 186 (M^+, 100%); 157 ($M^+ - 29$, 17%); 116 ($M^+ - 70$, 98%); 108 ($M^+ - 78$, 40%); 89 ($M^+ - 97$, 46%); 77 ($M^+ - 109$, 57%).

*6.1.2.2. 1-(4-Chlorophenyl)-2-methyl-1H-imidazole-5-carbaldehyde (**3b**).* Obtained in 93% yield as orange oil ($R_f = 0.6$; 9:1 $CHCl_3$/MeOH); IR (KBr) ν_{max} (cm^{-1}) 3091; 3031; 2799; 2744; 1667 (ν C=O); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 2.29 (s, 3H,); 7.19 (d, 2H, $J = 8.0$ Hz); 7.49 (d, 2H, $J = 8.0$ Hz); 7.80 (s, 1H) and 9.59 (s, 1H, *H*C=O); ^{13}C NMR (100 MHz; $CDCl_3/Me_4Si$): δ 13.6; 128.2; 129.7; 132.9; 134.4; 135.5; 141.9; 152.5; 177.5 (H*C*=O); EI-MS (*m/z*): 220 (M^+, 64%); 191 ($M^+ - 29$, 10%); 185 ($M^+ - 35$, 15%); 150 ($M^+ - 70$, 100%); 123 ($M^+ - 97$, 22%).

*6.1.2.3. 1-(4-Bromophenyl)-2-methyl-1H-imidazole-5-carbaldehyde (**3c**).* Obtained in 91% yield as orange oil ($R_f = 0.6$; 9:1 $CHCl_3$/MeOH); IR (KBr) ν_{max} (cm^{-1}) 3087; 3030; 2812; 2742; 1667 (ν C=O); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 2.33 (s, 3H); 7.13 (d, 2H, $J = 10.0$ Hz); 7.67 (d, 2H, $J = 10.0$ Hz); 7.84 (s, 1H) and 9.60 (s, 1H, *H*C=O); ^{13}C NMR (100 MHz; $CDCl_3/Me_4Si$): δ 13.8 (CH_3); 123.3; 123.5; 128.4; 132.7; 134.7; 141.5; 151.2; 177.4 (H*C*=O); EI-MS (*m/z*): 264 (M^+, 59%); 196 ($M^+ - 68$, 78%); 185 ($M^+ - 79$, 22%); 156 ($M^+ - 108$, 100%); 115 ($M^+ - 149$, 76%).

*6.1.2.4. 1-(4-Fluorophenyl)-2-methyl-1H-imidazole-5-carbaldehyde (**3d**).* Obtained in 90% yield as orange oil ($R_f = 0.6$; 9:1 $CHCl_3$/MeOH); IR (KBr) ν_{max} (cm^{-1}) 3330; 3070; 2926; 2853; 1674 (ν C=O); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 2.32 (s, 3H); 7.40 (d, 2H, $J = 8.0$ Hz); 7.80 (d, 2H, $J = 8.0$ Hz); 7.84 (s, 1H) and 9.62 (s, 1H, *H*C=O); ^{13}C NMR (100 MHz; $CDCl_3/Me_4Si$): δ 32.9 (CH_3); 96.4; 147.6; 149.1; 152.0; 153.7; 154.8; 161.2; 175.5 (C_{Ar}–F) and 196.9 (H*C*=O); EI-MS (*m/z*): 204 (M^+, 77%); 175 ($M^+ - 29$, 13%); 134 ($M^+ - 70$, 100%); 108 ($M^+ - 96$, 39%); 95 ($M^+ - 109$, 31%).

*6.1.2.5. 2-Methyl-1-(4-nitrophenyl)-1H-imidazole-5-carbaldehyde (**3e**).* Obtained in 86% yield as orange oil ($R_f = 0.6$; 9:1 $CHCl_3$/MeOH); IR (KBr) ν_{max} (cm^{-1}) 3338; 3116; 2927; 2830; 1674 (ν C=O); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 2.31 (s, 3H); 7.43 (d, 2H, $J = 8.0$ Hz); 8.38 (d, 2H, $J = 8.0$ Hz); 7.83 (s, 1H) and 9.63 (s, 1H, *H*C=O); ^{13}C NMR (100 MHz; $CDCl_3/Me_4Si$): δ 12.9 (CH_3); 112.5; 124.1; 127.4; 132.1; 142.0; 147.3; 151.6; 176.7 (H*C*=O); EI-MS (*m/z*): 231 (M^+, 100%); 202 ($M^+ - 29$, 36.7%); 161 ($M^+ - 70$, 32.3%); 131 ($M^+ - 100$, 30.9%); 114 ($M^+ - 117$, 23.5%).

*6.1.2.6. 2-Methyl-1-(4-(trifluoromethyl)phenyl)-1H-imidazole-5-carbaldehyde (**3f**).* Obtained in 87% yield as orange oil ($R_f = 0.5$; 9:1 $CHCl_3$/MeOH); IR (KBr) ν_{max} (cm^{-1}) 3113; 3056; 2929; 2829; 1675 (ν C=O); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 2.32 (s, 3H); 7.40 (d, 2H, $J = 8.0$ Hz); 7.80 (d, 2H, $J = 8.0$ Hz); 7.84 (s, 1H) and 9.63 (s, 1H, *H*C=O); ^{13}C NMR (100 MHz; $CDCl_3/Me_4Si$): δ 14.2 (CH_3); 121.3; 127.2; 128.1; 132.1 (t, CF_3, $J = 49.0$ Hz); 133.4; 139.6; 142.7; 153.6; 178.0 (H*C*=O); EI-MS (*m/z*): 254 (M^+, 100%); 225 ($M^+ - 29$, 34%); 184 ($M^+ - 70$, 93%); 145 ($M^+ - 109$, 42%); 134 ($M^+ - 120$, 34%).

*6.1.2.7. 2-Methyl-1-(4-cyanophenyl)-1H-imidazole-5-carbaldehyde (**3g**).* Obtained in 90% yield as orange oil ($R_f = 0.6$; 9:1

$CHCl_3$/MeOH); IR (KBr) ν_{max} (cm^{-1}) 3366; 3217; 2924; 2850; 1675 (ν C=O); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 2.31 (s, 3H); 7.39 (d, 2H, $J = 8.0$ Hz); 7.83 (d, 2H, $J = 8.0$ Hz); 7.43 (s, 1H) and 9.63 (s, 1H, *H*C=O); ^{13}C NMR (100 MHz; $CDCl_3/Me_4Si$): δ 13.7 (CH_3); 100.3; 114.4; 117.6 (CN); 128.0; 133.2; 133.8; 142.6; 152.3; 177.4 (H*C*=O); EI-MS (*m/z*): 211 (M^+, 100%); 182 ($M^+ - 29$, 44%); 141 ($M^+ - 70$, 96%); 114 ($M^+ - 97$, 60%); 108 ($M^+ - 103$, 72%).

*6.1.2.8. 2-Methyl-1-p-tolyl-1H-imidazole-5-carbaldehyde (**3h**).* Obtained in 96% yield as orange oil ($R_f = 0.5$; 9:1 $CHCl_3$/MeOH); IR (KBr) ν_{max} (cm^{-1}) 3344; 3038; 2924; 2857; 1676 (ν C=O); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 2.26 (s, 3H); 2.30 (s, 3H, CH_3); 7.40 (d, 2H, $J = 8.0$ Hz); 7.79 (d, 2H, $J = 8.0$ Hz); 7.83 (s, 1H) and 9.65 (s, 1H, *H*C=O); ^{13}C NMR (100 MHz; $CDCl_3/Me_4Si$): δ 13.9 (CH_3); 29.7 (CH_3); 120.7; 126.7; 127.6; 132.8; 139.0; 142.3; 152.5; 177.5 (H*C*=O); EI-MS (*m/z*): 200 (M^+, 83%); 130 ($M^+ - 70$, 100%); 109 ($M^+ - 91$, 30%); 103 ($M^+ - 97$, 22%); 92 ($M^+ - 108$, 76%).

*6.1.2.9. 1-(4-Methoxyphenyl)-2-methyl-1H-imidazole-5-carbaldehyde (**3i**).* Obtained in 94% yield as orange oil ($R_f = 0.4$; 9:1 $CHCl_3$/MeOH); IR (KBr) ν_{max} (cm^{-1}) 3111; 3056; 3005; 2935; 2838; 1675 (ν C=O); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 2.28 (s, 3H); 3.87 (s, 3H, OCH_3); 7.01 (d, 2H, $J = 8.0$ Hz); 7.16 (d, 2H, $J = 8.0$ Hz); 7.80 (s, 1H) and 9.55 (s, 1H, *H*C=O); ^{13}C NMR (100 MHz; $CDCl_3/Me_4Si$): δ 13.5 (CH_3); 55.5 (OCH_3); 114.7; 121.9; 128.2; 133.2; 140.9; 152.7; 160.1; 177.9 (H*C*=O); EI-MS (*m/z*): 216 (M^+, 68.3%); 146 ($M^+ - 70$, 54.8%); 131 ($M^+ - 85$, 10.5%); 108 ($M^+ - 108$, 100%); 77 ($M^+ - 139$, 9.9%).

*6.1.2.10. 1-(2,6-Difluorophenyl)-2-methyl-1H-imidazole-5-carbaldehyde (**3j**).* Obtained in 85% yield as orange oil ($R_f = 0.4$; 9:1 $CHCl_3$/MeOH); IR (KBr) ν_{max} (cm^{-1}) 3066; 2933; 2834; 1674 (ν C=O); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 2.31 (s, 3H, CH_3); 7.10 (t, 1H); 7.45–7.52 (m, 2H); 7.84 (s, 1H) and 9.65 (s, 1H, *H*C=O); ^{13}C NMR (100 MHz; $CDCl_3/Me_4Si$): δ 12.9 (CH_3); 112.2 (d, $J = 21.9$ Hz); 113.7 (t, C–F; $J = 13.5$ Hz); 131.1 (t, C–F, $J = 9.8$ Hz); 132.6; 142.4; 153.1; 157.9 (d, $J = 249.5$ Hz); 177.5 (H*C*=O); EI-MS (*m/z*): 222 (M^+, 66.5%); 193 ($M^+ - 29$, 18%); 152 ($M^+ - 70$, 100%); 125 ($M^+ - 97$, 16%); 108 ($M^+ - 114$, 40%).

*6.1.2.11. 1-(2-Methoxyphenyl)-2-methyl-1H-imidazole-5-carbaldehyde (**3k**).* Obtained in 94% yield as orange oil ($R_f = 0.4$; 9:1 $CHCl_3$/MeOH); IR (KBr) ν_{max} (cm^{-1}) 3053; 2930; 2854; 1677 (ν C=O); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 1.98 (s, 3H, CH_3); 2.20 (s, 3H, CH_3); 7.14 (d, 1H, $J = 8.0$ Hz); 7.31–7.44 (m, 3H); 7.84 (s, 1H) and 9.54 (s, 1H, *H*C=O); ^{13}C NMR (100 MHz; $CDCl_3/Me_4Si$): δ 13.3 (CH_3); 17.4 (CH_3); 116.6; 127.6; 129.8; 131.0; 132.8; 135.2; 141.0; 152.1; 177.7 (H*C*=O); EI-MS (*m/z*): 200 (M^+, 100%); 183 ($M^+ - 17$, 40%); 157 ($M^+ - 43$, 9%); 142 ($M^+ - 58$, 37.5%); 130 ($M^+ - 70$, 72.4%).

*6.1.2.12. 2-Methyl-1-(3-(trifluoromethyl)phenyl)-1H-imidazole-5-carbaldehyde (**3l**).* Obtained in 89% yield as orange oil ($R_f = 0.4$; 9:1 $CHCl_3$/MeOH); IR (KBr) ν_{max} (cm^{-1}) 3068; 2930; 2824; 1674 (ν C=O); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 2.31 (s, 3H); 7.47 (d, 1H, $J = 8.0$ Hz); 7.53 (s, 1H); 7.66 (t, 1H, $J = 8.0$ Hz); 7.79 (d, 1H, $J = 8.0$ Hz); 7.82 (s, 1H) and 9.61 (s, 1H, *H*C=O); ^{13}C NMR (100 MHz; $CDCl_3/Me_4Si$): δ 13.6 (CH_3); 117.4; 126.3; 129.8 (d, CF_3, $J = 41.8$ Hz); 130.5; 130.9; 131.7 (d, $J_{CF} = 32.8$ Hz); 136.4 (d, $J_{CF} = 23.3$ Hz); 134.3 (q, CF_3, $J = 197.8$ Hz); 142.1; 152.5; 177.5; EI-MS (*m/z*): 254 (M^+, 42%); 225 ($M^+ - 29$, 16%); 184 ($M^+ - 70$, 76%); 145 ($M^+ - 109$, 38%); 134 ($M^+ - 120$, 40%); 108 ($M^+ - 146$, 100%).

*6.1.3. General procedure for the preparation of N-substitued-phenyl-imidazole-5-difluoromethyl (**4a–4l**)*

A solution of a carbaldehyde derivative (7.5 mmol) in dichloromethane (15 mL) was added dropwise to DAST (2 equiv) at room temperature. The reaction mixture was stirred for 24 h at room temperature, poured onto a saturated sodium bicarbonate solution at 0 °C and extracted with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and the filtrate concentrated under reduced pressure. The solid residue was purified by column chromatography using chloroform as eluent. The following compounds were prepared according this general procedure.

*6.1.3.1. 5-(Difluoromethyl)-2-methyl-1-phenyl-1H-imidazole (**4a**).* Obtained in 92% yield as oil ($R_f = 0.5$; 7:3 ethyl acetate/hexane); IR (KBr) ν_{max} (cm^{-1}) 2926; 2851; 1422; 1265 (ν C–F); 1382 (δ_s CH_3); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 2.23 (s, 3H, CH_3); 6.42 (t, 1H, C*H*F_2, $J_{HF} = 56.0$ Hz); 7.28–7.30 (m, 5H); 7.51 (t, 1H, $J = 8.0$ Hz); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 13.4 (CH_3); 104.5 (t, *C*HF_2, $J_{CF} = 200.0$ Hz); 119.9; 127.5; 129.0; 129.5; 129.6; 141.0; 144.0; ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ –109.6 (2F, CHF_2); EI-MS (*m/z*): 208 (M^+, 100%); 189 ($M^+ - 19$, 6%); 166 ($M^+ - 42$, 15%); 148 ($M^+ - 60$, 17.5%); 147 ($M^+ - 61$, 57%).

*6.1.3.2. 1-(4-Chlorophenyl)-5-(difluoromethyl)-2-methyl-1H-imidazole (**4b**).* Obtained in 95% yield as oil ($R_f = 0.5$; 7:3 ethyl acetate/hexane); IR (KBr) ν_{max} (cm^{-1}) 3095; 2984; 2929; 1425; 1497 (ν C–F); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 2.23 (s, 3H, CH_3); 6.46 (t, 1H, C*H*F_2, $J_{HF} = 52.0$ Hz); 7.50 (d, 2H, $J = 8.0$ Hz); 7.29 (t, 1H, $J = 4.0$ Hz); 7.25 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 13.6 (CH_3); 109.0 (t, CHF_2, $J_{CF} = 232.3$ Hz); 126.5 (t, $J_{CF} = 26.6$ Hz); 128.8; 129.4 (t, $J_{CF} = 5.7$ Hz); 129.9; 134.0; 135.8; 148.7; ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ –109.2 (2F, CHF_2); EI-MS (*m/z*): 242 (M^+, 100%); 223

($M^+ - 19$, 12%); 215 ($M^+ - 27$, 14%); 200 ($M^+ - 42$, 13%); 181 ($M^+ - 61$, 42%).

*6.1.3.3. 1-(4-Bromophenyl)-5-(difluoromethyl)-2-methyl-1H-imidazole (**4c**).* Obtained in 94% yield as oil ($R_f = 0.5$; 7:3 ethyl acetate/hexane); IR (KBr) ν_{max} (cm^{-1}) 3035; 1422; 1495 (ν C–F); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 2.29 (s, 3H, CH_3); 6.45 (t, 1H, CHF_2, $J = 56.0$ Hz); 7.66 (d, 2H, $J = 12.0$ Hz); 7.29 (t, 1H, $J = 4.0$ Hz); 7.18 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 13.4 (CH_3); 109.0 (t, CHF_2, $J_{CF} = 232.2$ Hz); 123.8; 126.5 (t, $J_{CF} = 35.0$ Hz); 129.1; 129.7 (t, $J_{CF} = 10.0$ Hz); 132.9; 134.6; 148.6; ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ −109.0 (2F, CHF_2); EI-MS (*m/z*): 286 (M^+, 100%); 225 ($M^+ - 61$, 22%); 194 ($M^+ - 92$, 44%); 180 ($M^+ - 106$, 69%).

*6.1.3.4. 5-(Difluoromethyl)-1-(4-fluorophenyl)-2-methyl-1H-imidazole (**4d**).* Obtained in 95% yield as oil ($R_f = 0.6$; 7:3 ethyl acetate/hexane); IR (KBr) ν_{max} (cm^{-1}) 3078; 3390; 2927; 1430; 1513 (ν C–F); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 2.25 (s, 3H, CH_3); 6.46 (t, 1H, CHF_2, $J = 56.0$ Hz); 7.22 (t, 2H, $J = 8.0$ Hz); 7.30 (d, 3H, $J = 8.0$ Hz); 7.31 (d, $J = 4.0$ Hz); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 13.1 (CH_3); 99.0 (t, CHF_2, $J_{CF} = 250.0$ Hz); 108.0; 113.0; 116.8 (d, $J_{CF} = 23.0$ Hz); 129.4 (d, $J_{CF} = 8.7$ Hz); 140.0; 150.0; 164.5 (d, $J_{CF} = 69.6$ Hz); ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ −109.7 (2F, CHF_2); −110.2 (1F); EI-MS (*m/z*): 226 (M^+, 100%); 207 ($M^+ - 19$, 15%); 184 ($M^+ - 42$, 18%); 165 ($M^+ - 61$, 57%); 134 ($M^+ - 92$, 74%).

*6.1.3.5. 5-(Difluoromethyl)-2-methyl-1-(4-nitrophenyl)-1H-imidazole (**4e**).* Obtained in 90% yield as oil ($R_f = 0.5$; 7:3 ethyl acetate/hexane); IR (KBr) ν_{max} (cm^{-1}) 3116; 2920; 2850; 1422; 1500 (ν C–F); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 2.24 (s, 3H, CH_3); 6.51 (t, 1H, CHF_2, $J = 52.0$ Hz); 7.29 (t, 1H, $J = 4.0$ Hz); 7.52(d, 2H, $J = 8.0$ Hz); 8.37 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 14.0 (CH_3); 109.5 (t, CHF_2, $J_{CF} = 232.5$ Hz); 125.5; 126.9 (t, $J_{CF} = 25.5$ Hz); 129.3; 131.1 (t, $J_{CF} = 6.0$ Hz); 141.7; 148.7; 149.1; ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ −108.5 (2F, CHF_2); EI-MS (*m/z*): 253 (M^+, 100%); 234 ($M^+ - 19$, 8%); 182 ($M^+ - 71$, 12%); 166 ($M^+ - 87$, 36%); 131 ($M^+ - 122$, 12%).

*6.1.3.6. 5-(Difluoromethyl)-2-methyl-1-(4-(trifluoromethyl)-phenyl)-1H-imidazole (**4f**).* Obtained in 93% yield as oil ($R_f = 0.5$; 7:3 ethyl acetate/hexane); IR (KBr) ν_{max} (cm^{-1}) 2930; 1425; 1324 (ν C–F); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 2.25 (s, 3H, CH_3); 6.49 (t, 1H, CHF_2, $J = 52.0$ Hz); 7.33 (t, 1H, $J = 4.0$ Hz); 7.81 (d, 2H, $J = 8.0$ Hz); 7.47 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 13.4 (CH_3); 108.9 (t, CHF_2, $J_{CF} = 232.5$ Hz); 124.3 (q, CF_3, $J_{CF} = 270.7$ Hz); 126.8; 127.6 (q, $J_{CF} = 10.0$ Hz); 128.2; 129.8 (t, $J_{CF} = 5.9$ Hz); 131.9 (t, $J_{CF} = 32.8$ Hz); 138.6; 148.6; ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ −62.7 (3F, CF_3); −108.9 (2F, CHF_2); EI-MS (*m/z*): 276 (M^+, 100%); 257 ($M^+ - 19$, 30%); 235 ($M^+ - 41$, 25%); 215 ($M^+ - 61$, 48%); 184 ($M^+ - 92$, 58%).

*6.1.3.7. 4-(5-(Difluoromethyl)-2-methyl-1H-imidazol-1-yl)benzonitrile (**4g**).* Obtained in 95% yield as oil ($R_f = 0.5$; 7:3 ethyl acetate/hexane); IR (KBr) ν_{max} (cm^{-1}) 3368; 2924 (ν C–H_{Ar}); 1423 (δ_a CH_3); 1508 (ν C–F); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 2.25 (s, 3H, CH_3); 6.51 (t, 1H, CHF_2, $J = 56.0$ Hz); 7.31 (t, 1H, $J = 4.0$ Hz); 7.46 (d, 2H, $J = 8.0$ Hz); 7.84 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 13.5 (CH_3); 108.9 (t, CHF_2, $J_{CF} = 232.4$ Hz); 114.4; 117.5 (CN); 126.4 (t, $J_{CF} = 25.0$ Hz); 128.6; 130.5 (t, $J_{CF} = 6.5$ Hz); 133.5; 139.6; 148.5; ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ −108.2 (2F, CHF_2); EI-MS (*m/z*): 233 (M^+, 100%); 214 ($M^+ - 19$, 7%); 192 ($M^+ - 41$, 22.2%); 182 ($M^+ - 51$, 7%); 172 ($M^+ - 61$, 23%).

*6.1.3.8. 5-(Difluoromethyl)-2-methyl-1-p-tolyl-1H-imidazole (**4h**).* Obtained in 96% yield as oil ($R_f = 0.4$; 7:3 ethyl acetate/hexane); IR (KBr) ν_{max} (cm^{-1}) 3052; 1423; 1265 (ν C–F); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 2.26 (s, 3H, CH_3); 2.44 (s, 3H, CH_3); 6.43 (t, 1H, CHF_2, $J = 52.0$ Hz); 7.18 (d, 2H, $J = 8.0$ Hz); 7.31 (d, 2H, $J = 8.0$ Hz); 7.35 (sl, 1H); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 13.1 (CH_3); 21.2 (CH_3); 109.1 (t, CHF_2, $J = 250.0$ Hz); 126.7 (t, $J_{CF} = 20.0$ Hz); 127.1; 128.0; 130.3; 132.4; 140.0; 148.5; ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ −110.1 (2F, CHF_2); EI-MS (*m/z*): 222 (M^+, 100%); 195 ($M^+ - 27$, 17%); 194 ($M^+ - 28$, 11%); 180 ($M^+ - 42$, 22%); 161 ($M^+ - 61$, 8%).

*6.1.3.9. 5-(Difluoromethyl)-1-(4-methoxyphenyl)-2-methyl-1H-imidazole (**4i**).* Obtained in 97% yield as oil ($R_f = 0.5$; 7:3 ethyl acetate/hexane); IR (KBr) ν_{max} (cm^{-1}) 3412; 2982 (ν C–H_{ar}); 1458 (δ_a CH_3); 1114 (ν C–F); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 2.35 (s, 3H, CH_3); 3.86 (s, 3H, OCH_3); 6.50 (t, 1H, CHF_2, $J = 52.0$ Hz); 7.03 (d, 2H, $J = 8.0$ Hz); 7.28 (d, 2H, $J = 8.0$ Hz); 7.53 (sl, 1H); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 12.4 (CH_3); 55.6 (OCH_3); 108.4 (t, CHF_2, $J = 233.2$ Hz); 115.0; 125.1; 126.3; 127.3 (t, $J_{CF} = 27.7$ Hz); 128.5; 148.6; 160.8; ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ −111.7 (2F, CHF_2); EI-MS (*m/z*): 238 (M^+, 100%); 211 ($M^+ - 27$, 21%); 196 ($M^+ - 42$, 15.5%); 187 ($M^+ - 51$, 18%); 170 ($M^+ - 68$, 43%).

*6.1.3.10. 5-(Difluoromethyl)-1-(2,6-difluorophenyl)-2-methyl-1H-imidazole (**4j**).* Obtained in 89% yield as oil ($R_f = 0.4$; 7:3 ethyl acetate/hexane); IR (KBr) ν_{max} (cm^{-1}) 3391; 2925; 1417 (δ_a CH_3); 1514 (ν C–F); ^1H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 2.24 (s, 3H, CH_3); 6.54 (t, 1H, CHF_2, $J_{HF} = 52.0$ Hz); 7.12 (dd, 1H, $J_{HF} = 8.0$ Hz); 7.36 (t, 1H, $J = 4.0$ Hz); 7.48–7.54 (m, 2H); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 12.6 (CH_3); 108.7 (t, CHF_2, $J_{CF} = 233.0$ Hz); 112.3 (dd, $J_{CF} = 23.0$ Hz); 112.9 (t, $J_{CF} = 17.9$ Hz); 126.4 (t, $J_{CF} = 22.7$ Hz); 129.9 (t, $J_{CF} = 6.3$ Hz); 131.8 (t, $J = 9.3$ Hz); 149.5; 158.4 (d, $J_{CF} = 254.6$ Hz); ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ −112.4 (2F, CHF_2); −117.5 (2F); EI-MS

(*m/z*): 244 (M^+, 100%); 225 ($M^+ - 19$, 17%); 217 ($M^+ - 27$, 8.5%); 193 ($M^+ - 51$, 22%); 183 ($M^+ - 61$, 8%).

*6.1.3.11. 5-(Difluoromethyl)-2-methyl-1-o-tolyl-1H-imidazole (**4k**).* Obtained in 94% yield as oil ($R_f = 0.4$; 7:3 ethyl acetate/hexane); IR (KBr) ν_{max} (cm^{-1}) 3400; 2925; 2852; 1420 (δ_a CH_3); 1159 (ν C–F); ^1H NMR (400 MHz; $CDCl_3$/Me_4Si): δ 2.01 (s, 3H, CH_3); 2.18 (s, 3H, CH_3); 6.41 (t, 1H, CHF_2, $J_{HF} = 56.0$ Hz); 7.23 (d, 1H, $J = 4.0$ Hz); 7.32–7.44 (m, 4H); ^{13}C NMR (125 MHz; $CDCl_3$/Me_4Si): δ 12.6 (CH_3); 16.9 (CH_3); 108.8 (t, CHF_2, $J_{CF} = 232.5$ Hz); 126.2 (t, $J_{CF} = 26.9$ Hz); 127.2; 128.0; 129.8; 130.3; 131.3; 133.9; 136.0; 148.4; ^{19}F NMR (376.0 MHz, $CDCl_3$/$CFCl_3$): δ −110.1 (2F, CHF_2) EI-MS (*m/z*): 222 (M^+, 100%); 207 ($M^+ - 15$, 16%); 195 ($M^+ - 27$, 16%); 171 ($M^+ - 51$, 30%).

*6.1.3.12. 5-(Difluoromethyl)-2-methyl-1-(3-(trifluoromethyl)-phenyl)-1H-imidazole (**4l**).* Obtained in 92% yield as oil ($R_f = 0.5$; 7:3 ethyl acetate/hexane); IR (KBr) ν_{max} (cm^{-1}) 3400; 2985; 1458 (δ_a CH_3); 1130 (ν C–F); ^1H NMR (400 MHz; $CDCl_3$/Me_4Si): δ 2.25 (s, 3H, CH_3); 6.49 (t, 1H, CHF_2 $J_{HF} = 52.0$ Hz); 7.32 (t, 1H, $J = 4.0$ Hz); 7.53 (d, 1H, $J = 8.0$ Hz); 7.60 (s, 1H, CH3); 7.68 (t, 1H, $J = 8.0$ Hz); 7.81 (t, 1H, $J = 8.0$ and 4.0 Hz); ^{13}C NMR (125 MHz; $CDCl_3$/Me_4Si): 13.4 (CH_3); 108.9 (t, CHF_2, $J_{CF} = 232.5$ Hz); 124.6 (d, $J = 5.8$ Hz); 123.5 (q, CF_3, $J = 270.2$ Hz); 126.3 (t, $J_{CF} = 25.3$ Hz); 129.8 (t, $J_{CF} = 5.5$ Hz); 130.6; 131.0; 132.3 (d, $J_{CF} = 33.4$ Hz); 142.1; 148.7; ^{19}F NMR (376.0 MHz, $CDCl_3$/$CFCl_3$): −109.0 (2F, CHF_2); −62.7 (3F, CF_3); EI-MS (*m/z*): 276 (M^+, 100%); 257 ($M^+ - 19$, 22.5%); 235 ($M^+ - 41$, 32%); 215 ($M^+ - 61$, 56%); 184 ($M^+ - 92$, 58%).

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