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Multi-targeted Imidazoles: Potential Therapeutic Leads for Alzheimer's and Other Neurodegenerative Diseases

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ABSTRACT: Alzheimer's disease (AD) is a complex, multifactorial disease in which different neuropathological mechanisms are likely involved, including those associated with pathological tau and A β species, as well as neuroinflammation. In this context, the development of single multi-targeted therapeutics directed against two or more disease mechanisms could be advantageous. Starting from a series of 1,5-diarylimidazoles with microtubule (MT)-stabilizing activity and structural similarities with known NSAIDs, we conducted structure-activity relationship studies that led to the identification of multi-targeted prototypes with activities as MT-stabilizing agents and/or inhibitors of the

1 cyclooxygenase (COX) and 5-lipoxygenase (5-LOX) pathways. Several examples are brain-penetrant
2 and exhibit balanced multi-targeted in vitro activity in the low μM range. As brain-penetrant MT-
3 stabilizing agents have proven effective against tau-mediated neurodegeneration in animal models, and
4 because COX- and 5-LOX-derived eicosanoids are thought to contribute to $\text{A}\beta$ plaque deposition, these
5 1,5-diarylimidazoles provide tools to explore novel multi-targeted strategies for AD and other
6 neurodegenerative diseases.
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20 **KEYWORDS:** polypharmacology, multi-targeted ligands, 1,5-diarylimidazoles, microtubule-stabilizing
21 agents, cyclooxygenase, lipoxygenase, Alzheimer's disease, tauopathies, neuroinflammation.
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28 **Introduction.** In Alzheimer's disease (AD), aggregated tau proteins and $\text{A}\beta$ peptides are thought to
29 participate in disease onset and progression. Moreover, other factors such as neuroinflammation and
30 oxidative stress are also believed to be intimately associated with the neurodegenerative process.
31 Although the precise relationship(s) linking these different neuropathological mechanisms remain the
32 focus of active research, it is clear that AD is a complex and multi-factorial disease. Thus far, $\text{A}\beta$
33 amyloidosis has been the target of choice in AD drug discovery, as most drug candidates have been
34 designed to modulate $\text{A}\beta$ homeostasis. However, in spite of generally strong preclinical data with such
35 therapeutic candidates, the outcomes of late stage AD clinical trials have thus far failed to demonstrate
36 clinical efficacy. These disappointing results raise the possibility that AD treatments may have to
37 interfere concurrently with more than one neuropathological mechanism to exert disease modifying
38 benefits. In this context, a single multi-targeted drug may have distinctive advantages in terms of
39 efficacy and safety over drug combination therapies.¹ As such, an increasing number of therapeutic
40 strategies that are based on polypharmacology have been proposed for AD.^{2,3}
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1 Over the past several years, our laboratories and others have demonstrated that brain-penetrant MT-
2 stabilizing agents have profoundly beneficial effects in animal models of tau pathology due to the ability
3 of these compounds to normalize hyperdynamic axonal MTs, restore axonal transport, reduce the
4 burden of tau pathology, and prevent cognitive impairments and neuron loss associated with tau
5 pathology.⁴⁻⁷ Furthermore, our recent work⁸ indicates that the binding of cyclooxygenase (COX)- and
6 lipoxigenase (5-LOX)-derived eicosanoids to their cognate receptors in neurons results in increased
7 production of amyloid precursor protein (APP) and A β peptides, adding to a body of literature⁹⁻²³
8 implicating inflammatory eicosanoids as key contributing factors to A β plaque deposition in AD. Thus,
9 a stabilization of axonal MTs, combined with a concurrent suppression of eicosanoid production, may
10 be considered as a multi-targeted therapeutic strategy that could attenuate both tau- and A β -mediated
11 neurodegeneration, as well as MT deficiencies²⁴ and/or neuroinflammation,²⁵⁻³¹ in AD. Moreover, this
12 approach may also provide benefit in other neurodegenerative tauopathies.

13 The rational design of multi-targeted compounds is challenging, especially when attempting to merge
14 multiple molecular frameworks and the corresponding underlying pharmacophores in a single small
15 molecule.³² However, a series of fungicidal diaryl-pyrazoles (*e.g.*, **1**, Figure 1) and -imidazoles (*e.g.*, **2**,
16 Figure 1) with known MT-stabilizing activity exhibit tricyclic structures similar to those found in known
17 non-steroidal anti-inflammatory drugs (NSAIDs), such as the potent COX-1 inhibitor³³ SC560 (**3**,
18 Figure 1) and to a lesser extent, the dual COX/5-LOX inhibitor³⁴ licofelone (**4**, Figure 1). Furthermore,
19 molecular docking studies indicated that selected representative examples of these MT-stabilizing
20 imidazoles could fit within the arachidonic acid binding site of COX-1 with a predicted binding energy
21 that is comparable (*i.e.*, within 2 kcal/mol) to that of **3** (see Figure 1 and Supporting Information). Thus,
22 although MT-stabilizing agents and NSAIDs are different classes of biologically active compounds that
23 interact with unrelated targets, the observed structural commonalities between these compounds
24 suggests that there may be significant degree of crosstalk between the different pharmacophores that
25 could be exploited to identify multi-targeted ligands. Toward this end, the synthesis and subsequent
26 evaluation of several closely related 1,5-diarylimidazole congeners led to the identification of specific

substitution patterns that are required to achieve different activity profiles in vitro. In particular, in addition to identifying compounds that act selectively as MT-stabilizers, and others that are selective inhibitors of the COX- and/or 5-LOX pathways with no effect on MTs, these studies led to the identification of a series of multi-targeted molecules that at low μM concentration can concurrently stabilize MTs and inhibit both COX- and 5-LOX derived eicosanoids in cell-based assays. Furthermore, several of these compounds were also confirmed to be brain-penetrant, indicating that molecules of this type may be considered as potential multi-targeted prototype structures for AD and related tauopathies.

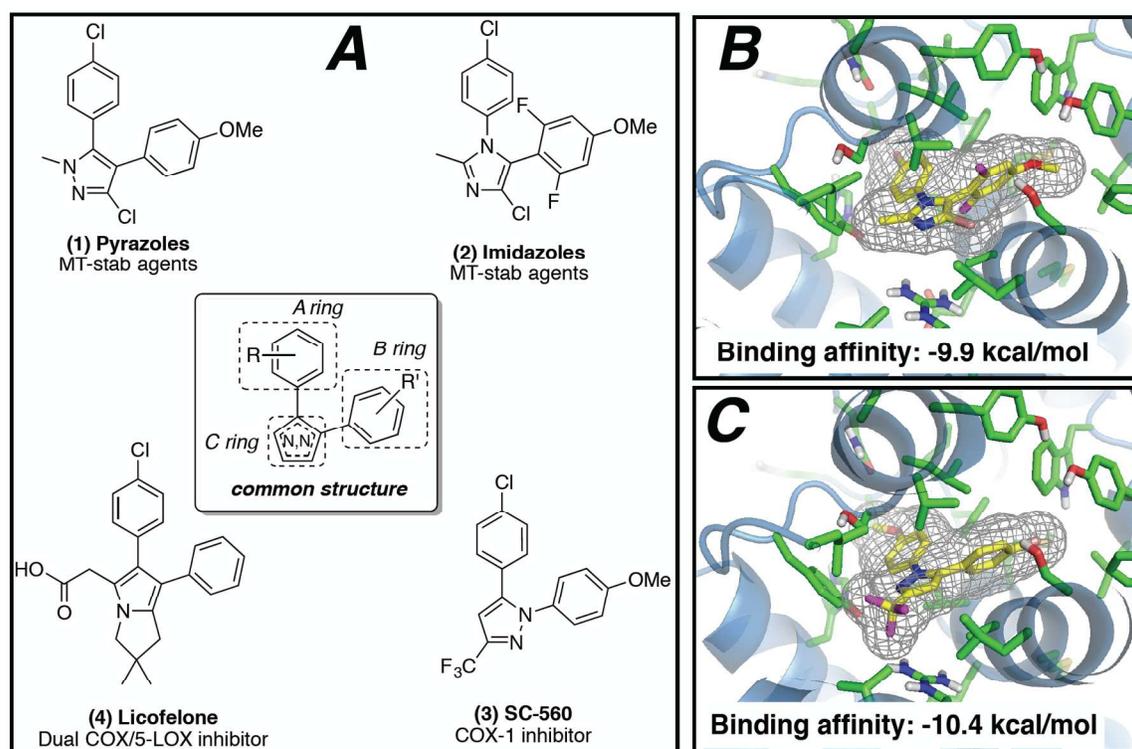


Figure 1. (A) Representative examples of fungicidal diaryl-pyrazoles (1) and -imidazoles (2) with reported MT-stabilizing activity, with known COX- (3) and dual COX/5-LOX (4) inhibitors; molecular docking of 2 (B) and 3 (C) within the arachidonic acid binding site of COX-1.

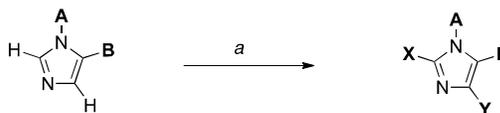
Results. Chemistry: As part of these studies, a library comprising 81 imidazoles has been synthesized, including 36 known compounds (*i.e.*, **2**, **25**, **29–31**, **35**, **36**, **38**, **43–46**, **51**, **54**, **55**, **57**, **58**, **61**, **62**, **64**, **65**, **67**, **68**, **70**, **71**, **73**, **74**, **83–86**, **88**, **92**, **94**, **95**, and **97**, Table 1), most with reported anti-fungal³⁵ or anti-microbial activity, as well as 45 new structures (*i.e.*, **26–28**, **32–34**, **37**, **39–42**, **47–50**, **52**, **53**, **56**, **59**, **60**, **63**, **66**, **69**, **72**, **75–82**, **87**, **89–91**, **93**, **96**, **98–104**, Table 1). In general, the synthesis of the 1,5-diarylimidazoles was conducted following the van Leusen imidazole synthesis.³⁶ Thus, after condensation of the appropriate aryl-amine and benzaldehyde, the resulting Schiff base (**5–24**, Scheme 1) was cyclized in the presence of toluenesulfonylmethyl isocyanide (TosMIC) to form the 1,5-diarylimidazole (**25–28**, **32**, **33**, **37–43**, **47–53**, Scheme 1). Further derivatizations of the imidazole ring included the introduction of small alkyl groups and/or halogens in position 2 and/or 4 (**29–31**, **34–36**, **44–46**, in Scheme 1, and **54–104** in Scheme 2). Imidazole derivatives bearing a methyl substituent at C4 were accessed by employing the appropriately *C* substituted TosMIC reagent during the cyclization step (**29**, **35**, **44**), while alkylated derivatives at C2 (*e.g.*, **34**, **86**) were obtained by treating the appropriate 1,5-diarylimidazole with LDA followed by addition of the desired alkyl iodide. Finally, halogenation of the imidazole ring was accomplished upon treatment with *N*-chlorosuccinimide. When the halogenation was carried out on imidazoles that were not substituted at C2 and C4, the reaction typically proceeded with the generation of separable mixtures of mono- and di-chlorinated imidazoles.



A = 4-chlorophenyl; **B** = 2,4,6-trifluorophenyl (**5**)
A = 4-methoxyphenyl; **B** = 2,4,6-trifluorophenyl (**6**)
A = 4-chlorophenyl; **B** = 2,6-difluoro-3-methylphenyl (**7**)
A = 4-chlorophenyl; **B** = 3-chloro-2,6-difluorophenyl (**8**)
A = 4-chlorophenyl; **B** = 3-bromo-2,6-difluorophenyl (**9**)
A = 4-chlorophenyl; **B** = 2,3,6-trifluorophenyl (**10**)
A = 4-chloro-3-fluorophenyl; **B** = 2,3,6-trifluorophenyl (**11**)
A = 6-chloropyridin-3-yl; **B** = 2,4,6-trifluorophenyl (**12**)
A = 4-chlorophenyl; **B** = 4-fluorophenyl (**13**)
A = 4-chloro-2-fluorophenyl; **B** = 2,6-difluorophenyl (**14**)
A = 4-chlorophenyl; **B** = 2,5-difluorophenyl (**15**)
A = 4-(trifluoromethoxy)phenyl; **B** = 2,6-difluorophenyl (**16**)
A = 4-chlorophenyl; **B** = 2,6-difluorophenyl (**17**)
A = 4-(trifluoromethoxy)phenyl; **B** = 2,3,6-trifluorophenyl (**18**)
A = 4-chlorophenyl; **B** = 2,6-difluoro-4-methylphenyl (**19**)
A = 4-chlorophenyl; **B** = 2,6-difluoro-3-methoxyphenyl (**20**)
A = 4-chlorophenyl; **B** = phenyl (**21**)
A = 4-chlorophenyl; **B** = 4-methoxyphenyl (**22**)
A = phenyl; **B** = 2,6-difluorophenyl (**23**)
A = 2-chlorophenyl; **B** = 2,6-difluorophenyl (**24**)

X = H; **Y** = H; **A** = 4-chlorophenyl; **B** = 2,4,6-trifluorophenyl (**25**)
X = H; **Y** = H; **A** = 4-methoxyphenyl; **B** = 2,4,6-trifluorophenyl (**26**)
X = H; **Y** = H; **A** = 4-chlorophenyl; **B** = 2,6-difluoro-3-methylphenyl (**27**)
X = H; **Y** = H; **A** = 4-chlorophenyl; **B** = 3-chloro-2,6-difluorophenyl (**28**)
X = H; **Y** = Me; **A** = 4-chlorophenyl; **B** = 3-chloro-2,6-difluorophenyl (**29**)
X = Cl; **Y** = Me; **A** = 4-chlorophenyl; **B** = 3-chloro-2,6-difluorophenyl (**30**) $\leftarrow d$
X = Me; **Y** = Me; **A** = 4-chlorophenyl; **B** = 3-chloro-2,6-difluorophenyl (**31**) $\leftarrow e$
X = H; **Y** = H; **A** = 4-chlorophenyl; **B** = 3-bromo-2,6-difluorophenyl (**32**)
X = H; **Y** = H; **A** = 4-chlorophenyl; **B** = 2,3,6-trifluorophenyl (**33**) $\leftarrow e$
X = Me; **Y** = H; **A** = 4-chlorophenyl; **B** = 2,3,6-trifluorophenyl (**34**) $\leftarrow e$
X = H; **Y** = Me; **A** = 4-chlorophenyl; **B** = 2,3,6-trifluorophenyl (**35**) $\leftarrow d$
X = Cl; **Y** = Me; **A** = 4-chlorophenyl; **B** = 2,3,6-trifluorophenyl (**36**) $\leftarrow d$
X = H; **Y** = H; **A** = 4-chloro-3-fluorophenyl; **B** = 2,3,6-trifluorophenyl (**37**)
X = H; **Y** = H; **A** = 6-chloropyridin-3-yl; **B** = 2,4,6-trifluorophenyl (**38**)
X = H; **Y** = H; **A** = 4-chlorophenyl; **B** = 4-fluorophenyl (**39**)
X = H; **Y** = H; **A** = 4-chloro-2-fluorophenyl; **B** = 2,6-difluorophenyl (**40**)
X = H; **Y** = H; **A** = 4-chlorophenyl; **B** = 2,5-difluorophenyl (**41**)
X = H; **Y** = H; **A** = 4-(trifluoromethoxy)phenyl; **B** = 2,6-difluorophenyl (**42**)
X = H; **Y** = H; **A** = 4-chlorophenyl; **B** = 2,6-difluorophenyl (**43**)
X = H; **Y** = Me; **A** = 4-chlorophenyl; **B** = 2,6-difluorophenyl (**44**) $\leftarrow d$
X = Cl; **Y** = Me; **A** = 4-chlorophenyl; **B** = 2,6-difluorophenyl (**45**) $\leftarrow e$
X = Me; **Y** = Me; **A** = 4-chlorophenyl; **B** = 2,6-difluorophenyl (**46**) $\leftarrow e$
X = H; **Y** = H; **A** = 4-(trifluoromethoxy)phenyl; **B** = 2,3,6-trifluorophenyl (**47**)
X = H; **Y** = H; **A** = 4-chlorophenyl; **B** = 2,6-difluoro-4-methylphenyl (**48**)
X = H; **Y** = H; **A** = 4-chlorophenyl; **B** = 2,6-difluoro-3-methoxyphenyl (**49**)
X = H; **Y** = H; **A** = 4-chlorophenyl; **B** = phenyl (**50**)
X = H; **Y** = H; **A** = 4-chlorophenyl; **B** = 4-methoxyphenyl (**51**)
X = H; **Y** = H; **A** = phenyl; **B** = 2,6-difluorophenyl (**52**)
X = H; **Y** = H; **A** = 2-chlorophenyl; **B** = 2,6-difluorophenyl (**53**)

Scheme 1. Reagents and reaction conditions: (a) Dean-Stark apparatus, toluene, 110 °C, 4 days, 99%;
 (b) 4 Å molecular sieves, Et₂O, 30 °C, 48 h, 99%; (c) appropriate TosMIC reagent, K₂CO₃, DMF/1,2-dimethoxyethane, 100 °C, 16 h, 7–90%; (d) *N*-chlorosuccinimide, CHCl₃, 60 °C, 16 h, 43–71%; (e) LDA, methyl iodide, THF, –20 °C to r.t., 1.5 h, 29–56%.



- X = H; Y = Cl; A = 4-chlorophenyl; B = 2,4,6-trifluorophenyl (54) ← b
 X = Me; Y = Cl; A = 4-chlorophenyl; B = 2,4,6-trifluorophenyl (55) ← c
 X = Me; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluoro-4-methoxyphenyl (2) ← c
 X = Cl; Y = H; A = 4-chlorophenyl; B = 2,4,6-trifluorophenyl (56)
 X = Cl; Y = Cl; A = 4-chlorophenyl; B = 2,4,6-trifluorophenyl (57) ← c
 X = Cl; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluoro-4-methoxyphenyl (58) ← c
 X = H; Y = Cl; A = 4-methoxyphenyl; B = 2,4,6-trifluorophenyl (59)
 X = Cl; Y = H; A = 4-methoxyphenyl; B = 2,4,6-trifluorophenyl (60)
 X = Cl; Y = Cl; A = 4-methoxyphenyl; B = 2,4,6-trifluorophenyl (61)
 X = H; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluoro-3-methylphenyl (62)
 X = Cl; Y = H; A = 4-chlorophenyl; B = 2,6-difluoro-3-methylphenyl (63)
 X = H; Y = Cl; A = 4-chlorophenyl; B = 3-chloro-2,6-difluorophenyl (64) ← b
 X = Me; Y = Cl; A = 4-chlorophenyl; B = 3-chloro-2,6-difluorophenyl (65) ← b
 X = Cl; Y = H; A = 4-chlorophenyl; B = 3-chloro-2,6-difluorophenyl (66)
 X = H; Y = Cl; A = 4-chlorophenyl; B = 3-bromo-2,6-difluorophenyl (67)
 X = H; Y = Cl; A = 4-chlorophenyl; B = 2,3,6-trifluorophenyl (68)
 X = Cl; Y = H; A = 4-chlorophenyl; B = 2,3,6-trifluorophenyl (69) ← b
 X = H; Y = Cl; A = 4-chloro-3-fluorophenyl; B = 2,3,6-trifluorophenyl (70) ← b
 X = Me; Y = Cl; A = 4-chloro-3-fluorophenyl; B = 2,3,6-trifluorophenyl (71) ← b
 X = Cl; Y = H; A = 4-chloro-3-fluorophenyl; B = 2,3,6-trifluorophenyl (72)
 X = H; Y = Cl; A = 6-chloropyridin-3-yl; B = 2,4,6-trifluorophenyl (73) ← b
 X = Me; Y = Cl; A = 6-chloropyridin-3-yl; B = 2,4,6-trifluorophenyl (74) ← b
 X = Cl; Y = H; A = 4-chlorophenyl; B = 4-fluorophenyl (75)
 X = H; Y = Cl; A = 4-chlorophenyl; B = 4-fluorophenyl (76)
 X = Cl; Y = H; A = 4-chloro-2-fluorophenyl; B = 2,6-difluorophenyl (77)
 X = H; Y = Cl; A = 4-chloro-2-fluorophenyl; B = 2,6-difluorophenyl (78)
 X = Cl; Y = H; A = 4-chlorophenyl; B = 2,5-difluorophenyl (79)
 X = H; Y = Cl; A = 4-chlorophenyl; B = 2,5-difluorophenyl (80)
 X = H; Y = Cl; A = 4-(trifluoromethoxy)phenyl; B = 2,6-difluorophenyl (81)
 X = Cl; Y = H; A = 4-(trifluoromethoxy)phenyl; B = 2,6-difluorophenyl (82)
 X = Cl; Y = Cl; A = 4-(trifluoromethoxy)phenyl; B = 2,6-difluorophenyl (83)
 X = H; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluorophenyl (84) ← b
 X = Me; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluorophenyl (85) ← b
 X = Et; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluorophenyl (86) ← d
 X = Cl; Y = H; A = 4-chlorophenyl; B = 2,6-difluorophenyl (87)
 X = Cl; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluorophenyl (88)
 X = H; Y = Cl; A = 4-(trifluoromethoxy)phenyl; B = 2,3,6-trifluorophenyl (89)
 X = Cl; Y = H; A = 4-(trifluoromethoxy)phenyl; B = 2,3,6-trifluorophenyl (90)
 X = Cl; Y = Cl; A = 4-(trifluoromethoxy)phenyl; B = 2,3,6-trifluorophenyl (91)
 X = H; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluoro-4-methylphenyl (92)
 X = Cl; Y = H; A = 4-chlorophenyl; B = 2,6-difluoro-4-methylphenyl (93)
 X = Cl; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluoro-4-methylphenyl (94)
 X = H; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluoro-3-methoxyphenyl (95)
 X = Cl; Y = H; A = 4-chlorophenyl; B = 2,6-difluoro-3-methoxyphenyl (96)
 X = Cl; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluoro-3-methoxyphenyl (97)
 X = H; Y = Cl; A = 4-chlorophenyl; B = phenyl (98)
 X = Cl; Y = H; A = 4-chlorophenyl; B = phenyl (99)
 X = Cl; Y = Cl; A = 4-chlorophenyl; B = phenyl (100)
 X = H; Y = Cl; A = 4-chlorophenyl; B = 4-methoxyphenyl (101)
 X = H; Y = Cl; A = 2-chlorophenyl; B = 2,6-difluorophenyl (102) ← a
 X = Cl; Y = H; A = 2-chlorophenyl; B = 2,6-difluorophenyl (103)
 X = Cl; Y = Cl; A = 2-chlorophenyl; B = 2,6-difluorophenyl (104) ← a

Scheme 2. Reagents and reaction conditions: (a) *N*-chlorosuccinimide, CHCl₃, 60 °C, 16 h, 9–77% for mono-halogenation at C4, 3–18% for mono-halogenation at C2, and 2–20% for di-halogenation at C2/C4; (b) LDA, methyl iodide, THF, –20 °C to r.t., 1.5 h, 2–48%; (c) NaOMe, MeOH, THF, r.t., 19 h, 33–97%; (d) LDA, ethyl iodide, THF, –20 °C to r.t., 1.5 h, 35%.

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Structure-activity relationships: The MT-stabilizing activity of test compounds was determined in QBI293 cells by monitoring compound-induced elevation in acetylated α -tubulin (AcTub),³⁷ which is a known marker of stable MTs.³⁸ Furthermore, as the MT-stabilizing imidazoles are believed to act on MTs in a manner similar to that described for the triazolopyrimidines,³⁵ and considering that certain triazolopyrimidines have been found to induce a proteasome-dependent degradation of α -tubulin,³⁹ the effect of compound treatment on total α -tubulin was also monitored. Evaluation of compound inhibition of the biosynthesis of COX- and 5-LOX-derived eicosanoids was conducted in a modified rat basophilic leukemia (RBL-1) cell assay that has previously been described⁴⁰ for the evaluation of 5-LOX and which we found can be used to assess both COX-derived prostaglandins (PGs) and 5-LOX-derived leukotrienes (LTs) formed in the presence or absence of test compounds.

All compounds were initially screened at 1 and 10 μ M concentration in the QBI MT assay and at 10 μ M in the RBL-1 assay (Table 1). In this initial RBL-1 analysis, 5-LOX-derived LTB₄ and COX-derived PGD₂ and PGE₂, which co-eluted during LC/MS/MS, were quantified. Selected compounds (Table 2) exhibiting evidence of multi-targeted activity underwent further confirmatory studies in the RBL-1 assay, which included concentration-response testing, and further LC/MS/MS analyses using a refined protocol to individually detect and quantitate PGD₂ and PGE₂, as well as both LTB₄ and LTC₄. As the formation of each of these eicosanoids depends on separate enzymatic steps in the COX or 5-LOX pathways,⁴¹ concurrent analysis of all four of these eicosanoids provides a convenient and reliable method to evaluate the overall effect of test compounds on COX and 5-LOX pathways in a cellular milieu. Finally, several compounds in Table 2 were also assessed for their relative brain-to-plasma exposure levels after administration to mice.

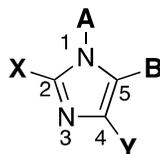
MT-stabilizing activity: Evaluation of compounds in the QBI MT assay revealed that out of 71 tested compounds, 48 examples exhibited activity on MTs as revealed by statistically significant changes in AcTub levels. Among MT-active compounds, 7 examples (*i.e.*, **2**, **58**, **65**, **71**, **85**, **86**, and **97**) were found to be active at 1 μ M compound concentration whereas the remaining 41 compounds were active only at 10 μ M. Consistent with the notion that the MT-stabilizing 1,5-diarylimidazoles may be acting on MTs

1 in a similar manner as the triazolopyrimidines,³⁵ the data presented in Table 1 reveal that like the latter
2 molecules, these imidazoles can be broadly divided into two subsets: one group of 15 entries, which
3 cause a significant reduction in total α -tubulin levels at doses typically required to induce an elevation in
4 AcTub (*i.e.*, **2**, **30**, **34**, **58**, **62**, **63**, **65**, **66**, **71**, **73**, **85**, **94–97**); and a second group of 33 compounds that
5 produce an elevation in AcTub at 1 or 10 μ M without decreasing α -tubulin level (**29**, **31**, **35**, **36**, **44–46**,
6 **54**, **55–57**, **59**, **60**, **64**, **67–70**, **72**, **74**, **78**, **82–84**, **86–88**, **90–93**, **102**, **104**). Also of interest, a comparison
7 of the activities of compounds in the AcTub assay at 1 and 10 μ M suggest that selected entries, such as
8 compounds **2**, **58**, and **71**, may exhibit a bell-shaped concentration-response relationship, and it is
9 possible that additional examples would show a similar concentration-response if tested at higher
10 concentrations. This phenomenon was observed in the case of the triazolopyrimidines that reduce α -
11 tubulin level, such as **108**.³⁹ Irrespective of whether or not test compounds cause a reduction in total α -
12 tubulin, the AcTub SAR emerging from the data shown in Table 1 appear to be in general agreement
13 with SAR from prior studies in which MT-stabilizing 1,5-diarylimidazoles were evaluated for anti-
14 fungal activity.³⁵ Thus, our results indicate that ring A is preferably a 4-chloro-phenyl, although
15 examples bearing other substituents in the *para*-position, such as a trifluoromethoxy (**83**), are also
16 active. Additional substitutions in the A ring, as in compound **77** and **78** in which a fluorine is present in
17 the *ortho*-position, appear to impact negatively MT interactions of the compound (*cf.*, **77** with **87**, and
18 **78** with **84**). With respect to the B ring, the degree and pattern of fluorination appear to be generally
19 important factors that determine the ability of these imidazoles to produce a significant elevation in the
20 marker of stable MTs in QBI293 cells. Whereas derivatives with either one or no fluorination in the B
21 ring (*i.e.*, **50**, **51**, **75**, **76**, **98–101**) were found to be essentially devoid of MT activity in our assay
22 conditions, other di- and tri-substituted congeners (*e.g.*, **54**, **68**, **84**) produced a significant increase in
23 AcTub. Furthermore, a comparison between the inactive difluorinated derivative **80** and the active di-
24 and tri-fluorinated compounds (*i.e.*, **54**, **68**, and **84**) suggests that the presence of two fluorine atoms in
25 the *ortho*-positions of ring B is required for MT activity. Finally, with respect to the imidazole ring (ring
26 C), our results indicate that 1,5-diarylimidazoles that are not substituted in positions 2 and 4 (*e.g.*, **25**,

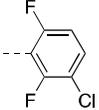
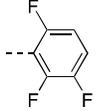
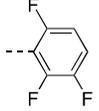
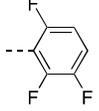
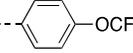
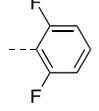
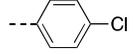
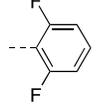
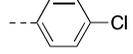
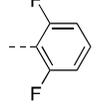
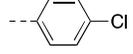
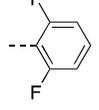
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26, 42, 43, 48, 49, 52 and 53) do not cause a detectable increase in AcTub, whereas tetrasubstituted imidazoles, including C2/C4 dihalogenated (*e.g.*, **88**) and dimethylated (*e.g.*, **46**) derivatives, as well as analogues bearing both a small alkyl- and a chloro-substituent in either C2 or C4 positions (*e.g.*, **85** and **45**), are generally more active than corresponding derivatives bearing a single substitution in either position 2 or 4 (*cf.*, **87**, **88**, and **44**, **46**). These results also suggest that MT activity does not strictly require a halogen in position 4 of the imidazole ring, as was required for optimal anti-fungal activity,³⁵ since congeners halogenated at C2 appear to retain comparable MT activity (*cf.*, **54**, **56** and **84**, **87**).

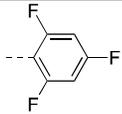
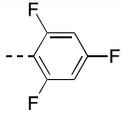
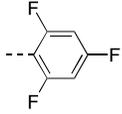
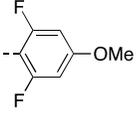
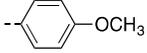
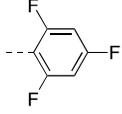
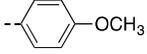
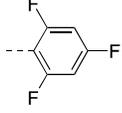
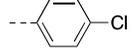
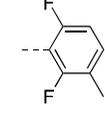
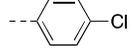
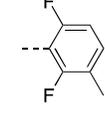
Table 1.

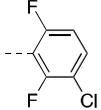
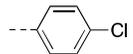
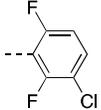
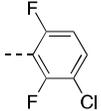
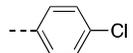
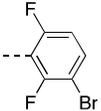
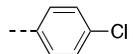
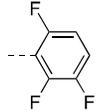
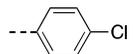
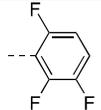
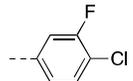
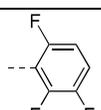
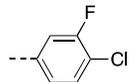
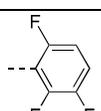


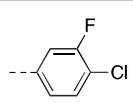
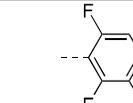
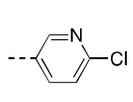
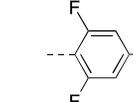
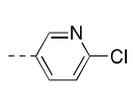
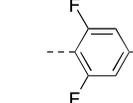
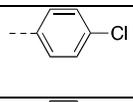
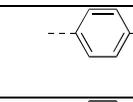
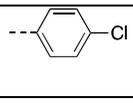
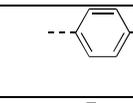
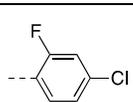
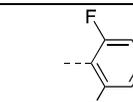
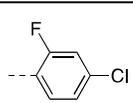
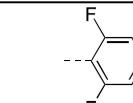
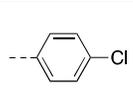
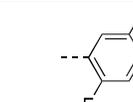
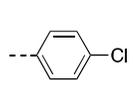
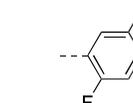
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2	Me	Cl			39	88	× 7.1 (1 μM)** × 2.9 (10 μM)**	× 0.6 (1 μM)** × 0.3 (10 μM)**
25	H	H			44	24	NS	NS
26	H	H			65	25	NS	NS
29	H	Me			59	71	× 3.5 (10 μM)**	NS
30	Cl	Me			<10	54	× 9.2 (10 μM)**	× 0.5 (10 μM)**

31	Me	Me			<10	51	× 14.2 (10 μM)**	NS
34	Me	H			49	45	× 4.7 (10 μM)**	× 0.9 (10 μM)**
35	H	Me			74	74	× 3.4 (10 μM)**	× 1.2 (1 μM)**
36	Cl	Me			<10	58	× 14.3 (10 μM)**	NS
42	H	H			38	55	NS	NS
43	H	H			15	46	NS	× 1.2 (1 μM)*
44	H	Me			72	44	× 1.6 (10 μM)**	NS
45	Cl	Me			<10	42	× 4.1 (10 μM)**	NS

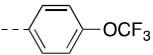
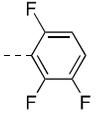
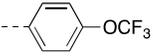
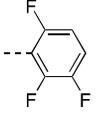
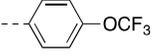
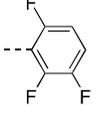
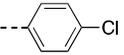
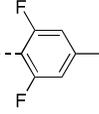
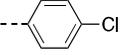
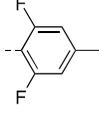
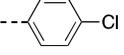
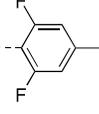
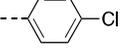
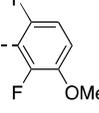
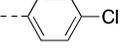
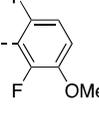
1 2 3 4 5 6 7	46	Me	Me			<10	40	× 8.3 (10 μM)**	× 1.2 (1 μM)*
8 9 10 11 12	47	H	H			31	52	NS	× 1.2 (10 μM)*
13 14 15 16	48	H	H			66	84	NS	NS
17 18 19 20 21	49	H	H			<10	78	NS	NS
22 23 24	50	H	H			40	16	NS	NS
25 26 27	51	H	H			94	<10	NS	NS
28 29 30 31 32	52	H	H			19	<10	NS	NS
33 34 35 36 37	53	H	H			24	<10	NS	NS
38 39 40 41 42	54	H	Cl			91	46	× 3.3 (10 μM)**	NS

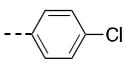
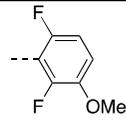
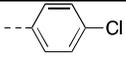
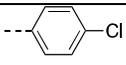
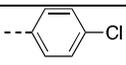
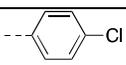
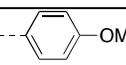
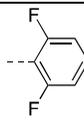
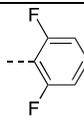
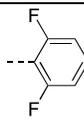
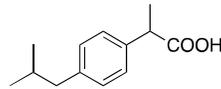
55	Me	Cl			<10	<10	× 5.7 (10μM)**	NS
56	Cl	H			34	61	× 3.1 (10 μM)**	NS
57	Cl	Cl			<10	48	× 4.2 (10 μM)**	NS
58	Cl	Cl			12	38	× 3.3 (1 μM)** × 2.5 (10 μM)**	× 0.6 (1 μM)** × 0.3 (10 μM)**
59	H	Cl			93	86	× 4.1 (10 μM)**	NS
60	Cl	H			85	75	× 3.4 (10 μM)**	NS
62	H	Cl			79	78	× 2.2 (10 μM)**	× 0.8 (10 μM)**
63	Cl	H			<10	69	× 2.3 (10 μM)**	× 0.8 (1 μM)** × 0.9 (10 μM)**

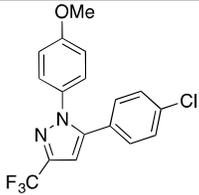
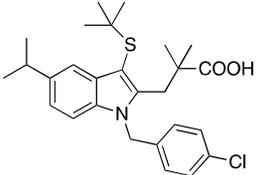
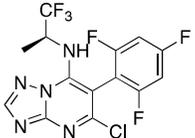
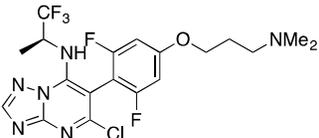
64	H	Cl			71	63	$\times 2.4$ (10 μM)**	NS
65	Me	Cl			34	84	$\times 1.7$ (1 μM)** $\times 9.7$ (10 μM)**	$\times 0.6$ (10 μM)**
66	Cl	H			<10	88	$\times 2.2$ (10 μM)**	$\times 0.8$ (10 μM)**
67	H	Cl			54	78	$\times 2.1$ (10 μM)**	NS
68	H	Cl			82	69	$\times 2.0$ (10 μM)**	NS
69	Cl	H			26	24	$\times 2.4$ (10 μM)**	NS
70	H	Cl			74	66	$\times 1.9$ (10 μM)**	NS
71	Me	Cl			<10	75	$\times 3.9$ (1 μM)** $\times 2.4$ (10 μM)**	$\times 0.8$ (1 μM)** $\times 0.7$ (10 μM)**

72	Cl	H			32	58	$\times 3.2$ (10 μM)**	NS
73	H	Cl			65	<10	$\times 1.9$ (10 μM)**	$\times 0.8$ (10 μM)**
74	Me	Cl			<10	26	$\times 4.4$ (10 μM)**	NS
75	Cl	H			87	57	NS	NS
76	H	Cl			85	59	NS	NS
77	Cl	H			<10	49	NS	NS
78	H	Cl			36	14	$\times 2.6$ (10 μM)**	NS
79	Cl	H			76	96	NS	NS
80	H	Cl			46	69	NS	NS

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89	H	Cl			54	85	NS	NS
90	Cl	H			58	80	× 3.4 (10 μM)**	NS
91	Cl	Cl			40	56	× 6.3 (10 μM)**	NS
92	H	Cl			90	75	× 3.6 (10 μM)**	NS
93	Cl	H			42	73	× 5.7 (10 μM)**	NS
94	Cl	Cl			<10	63	× 18.2 (10 μM)**	× 0.7 (10 μM)**
95	H	Cl			48	91	× 4.0 (10 μM)**	× 0.8 (10 μM)**
96	Cl	H			<10	68	× 8.2 (10 μM)**	× 0.6 (10 μM)**

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49	97	Cl	Cl			17	88	$\times 5.1 (1 \mu\text{M})^{**}$ $\times 10.1 (10 \mu\text{M})^{**}$	$\times 0.9 (1 \mu\text{M})^{**}$ $\times 0.4 (10 \mu\text{M})^{**}$
	98	H	Cl			94	71	NS	NS
	99	Cl	H			75	52	NS	$\times 1.2 (10 \mu\text{M})^{**}$
	100	Cl	Cl			14	<10	NS	NS
	101	H	Cl			95	<10	NS	NS
	102	H	Cl			44	56	$\times 3.5 (10 \mu\text{M})^{**}$	NS
	103	Cl	H			28	38	NS	NS
	104	Cl	Cl			66	21	$\times 3.8 (10 \mu\text{M})^{**}$	NS
	Ibuprofen (105)					95	<10	NS	NS

3		79 [§]	<10 [§]	NS	NS
MK866 (106) ⁴²		<10 [§]	70 [§]	ND	ND
Triazolopyrimidine (107)		ND	ND	× 2.5 (1 μM) [^] , × 4.9 (10 μM) [^]	NS
Triazolopyrimidine (108)		ND	ND	× 6.0 (1 μM) [^] , × 0.5 (10 μM) [^]	× 0.7 (1 μM), × 0.4 (10 μM)

^a Inhibition of COX pathway was determined by monitoring via LC/MS/MS analyses the combined production of COX-derived PGD₂ and PGE₂ in RBL-1 upon stimulation with arachidonic acid in the presence or absence of test compounds, with all samples run in at least triplicate; ^b Inhibition of 5-LOX pathway was determined by monitoring via LC/MS/MS analyses the production of 5-LOX-derived LTB₄ in RBL-1 upon stimulation with arachidonic acid in the presence or absence of test compounds, with all samples run in at least triplicate; ^c MT-stabilizing activity in QBI-293 cells was determined by monitoring via ELISA the relative changes in acetylated α-tubulin levels in response to 4-hour treatment with test compounds, with all samples run in at least triplicate; ^d

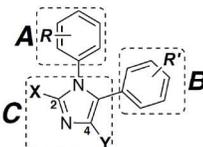
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2 Relative changes in total α -tubulin, as determined by tubulin ELISA, in response to compound treatment, with all samples run in at least triplicate; [§] compound
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4 tested at 10 nM; [^] previously published data;³⁹ * P < 0.05; ** P < 0.01 compared with vehicle (DMSO)-treated controls as determined using an two-tailed
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6 unpaired t-test; NS: not significant; ND: not determined.
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Inhibition of prostaglandin biosynthetic pathway: Evaluation of test compounds as potential inhibitors of COX-dependent formation of PGD₂/PGE₂ in RBL-1 cells revealed that optimal inhibition of PG synthesis is typically achieved when ring A is substituted in the *para*-position with either a chloride (*e.g.*, **54**) or methoxy group (*e.g.*, **59**). With respect to ring B, comparison of **54**, **68**, **76**, **79**, **84**, and **98** clearly suggests that the presence of fluorine substituents is not detrimental, nor necessary, for inhibition of PG production. Evaluation of the effect of different substitutions in the imidazole ring reveals that, with the possible exception of compound **104**, which shows a >50% inhibition in the PGD₂/PGE₂ assay, tetrasubstituted compounds (*e.g.*, **45**, **46**, **85**, **88**) are generally devoid of inhibitory activity against PG synthesis. Conversely, 1,5-diarylimidazole congeners with one substitution at either C2 or C4 are generally active, with the presence of a substituent at C4 being possibly preferred over the C2 position (*cf.*, **62** with **63**, **64** with **66**, **84** with **87**, and **92** with **93**). Among 1,5-diarylimidazoles that are not substituted at C2 and C4, although these compounds appear to be generally less active than the corresponding compounds bearing a substituent at C2 or C4, selected examples, such as **51**, have been identified that produce a near complete inhibition of the combined PGD₂/PGE₂ synthesis in the RBL-1 assay when tested at 10 μM.

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Inhibition of leukotriene biosynthetic pathway: Finally, evaluation of compound inhibitory activity in the LTB₄ assay revealed that whereas a number of substitutions in the *para*-position of ring A appeared to be well tolerated, the presence of a 2-chloro-pyridine (see **73** and **74**) prevented inhibition of LTB₄ synthesis. In addition, similarly to what was observed for the SAR of PGD₂/PGE₂ synthesis inhibition, the fluorination of the B ring did not impact activity, as both fluorinated (*e.g.*, **59**, **80** and **84**) and non-fluorinated (*e.g.*, **98**) congeners exhibit comparable inhibitory activity in the LTB₄ assay. However, in contrast to what was observed for inhibitory activity against PG synthesis, the choice of substituents at C2 and/or C4 of the imidazole ring did not play a critical role as examples of di- (*e.g.*, **47**), tri- (*e.g.*, **89** and **90**) and tetra-substituted (*e.g.*, **91**) imidazoles were found to exhibit comparable suppression of LTB₄ synthesis in RBL-1 cells at 10 μM.

1 Thus, in light of the observed elements of SAR for the three biological targets, the particular
2 substitution pattern decorating the 1,5-diarylimidazole scaffold can result in compounds with different
3 activity profiles, including multi-targeted activity on MTs and/or eicosanoid biosynthesis (Figure 2).
4 Selected representative examples of multi-targeted compounds were evaluated further to determine
5 the IC₅₀ values in the RBL-1 assays and brain penetration (see Figure 3 and Table 2). Moreover, the
6 compounds in Table 2 were also examined with improved LC/MS/MS methodologies for their ability
7 to inhibit the individual COX-derived products PGE₂ and PGD₂, as well as a second 5-LOX-derived
8 product, LTC₄ (see Supplemental Figure 1, Supporting Information). Finally, two example
9 compounds underwent full concentration-response analyses in the AcTub assay (see Supplemental
10 Figure 2, Supporting Information). Collectively, these studies confirmed that all Table 2 compounds
11 effectively inhibited both COX and 5-LOX biosynthetic pathways with multiple compounds
12 exhibiting balanced multi-targeted activity in the low μM range. Finally, consistent with the relatively
13 small size of these molecules, these compounds appeared to be generally brain-penetrant.
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Activities

		MT-stabilization	Inhibition COX pathway	Inhibition 5-LOX pathway
Structural features				
	ring A	<ul style="list-style-type: none"> * mono substituted phenyl in <i>para</i>-position typically preferred (especially Cl) 	<ul style="list-style-type: none"> * <i>para</i>-chlorophenyl most active 	<ul style="list-style-type: none"> * mono substituted phenyl in <i>para</i>-position (except -F) preferred * 2-chloro pyridine detrimental
	ring B	<ul style="list-style-type: none"> * degree of fluorination generally important * 2 fluorine atoms in <i>ortho</i> preferred 	<ul style="list-style-type: none"> * fluorination not necessary for activity 	
	ring C	<ul style="list-style-type: none"> * unsubstituted imidazoles in 2 and 4 positions generally inactive * halogen or small alkyl in position 2 or 4 lead to active derivatives * tetrasubstituted imidazoles most active 	<ul style="list-style-type: none"> * unsubstituted imidazoles in 2 and 4 positions are active * tetrasubstituted imidazoles inactive * for trisubstituted imidazoles, substituents in position 4 preferred over position 2 	<ul style="list-style-type: none"> * may be substituted or not in position 2 and/or 4

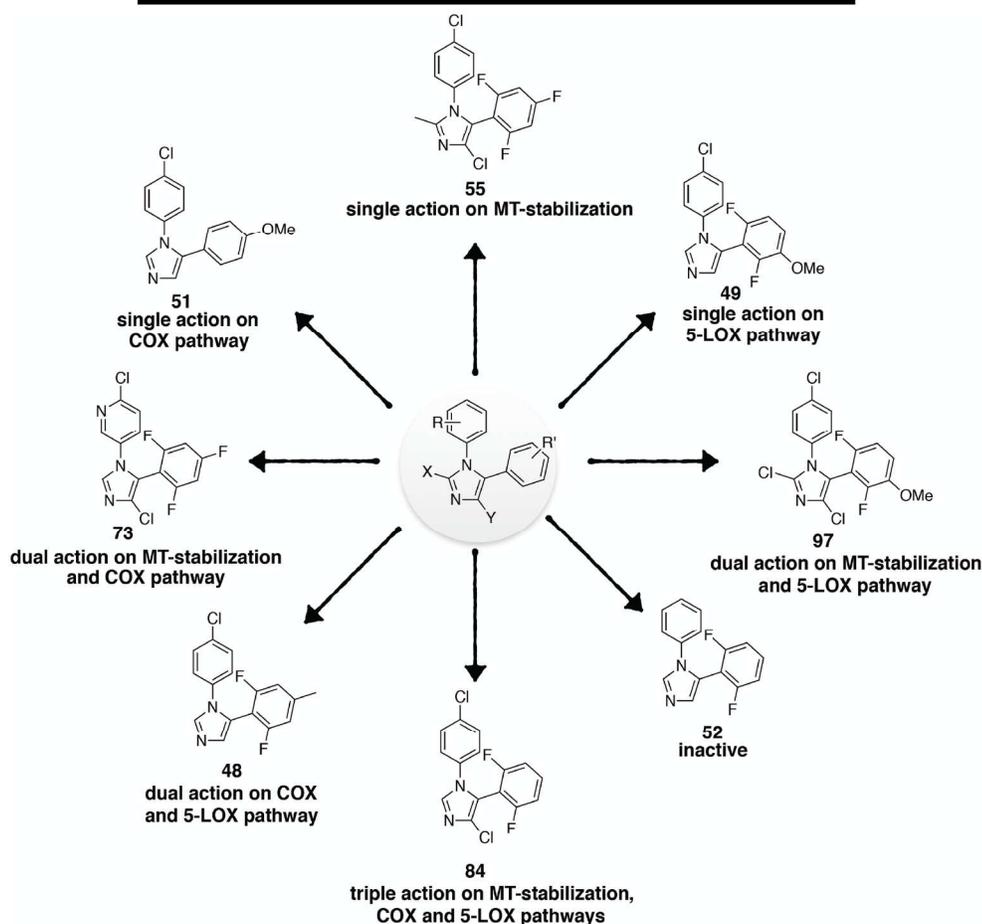
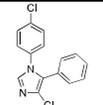


Figure 2. Summary of SARs (top) and representative structures exemplifying the different activity profiles exhibited by the 1,5-diarylimidazoles (bottom).

Table 2. Further evaluation of test compounds with multi-targeted activity as MT-stabilizing agents and/or inhibitors of COX and 5-LOX pathways.

	Cpd#	Structure	PGD ₂ /E ₂ Inhibition IC ₅₀ (μM)	LTB ₄ Inhibition IC ₅₀ (μM)	Acetyl- Tubulin Assay	Brain (nM)	Plasma (nM)	B/P
Multi-targeted Compounds with Activity as MT-Stabilizing Agents and Inhibitors of COX and 5-LOX Pathways	29		12.1	13.4	× 3.5 (10 μM)	600 [^] ± 200	500 [^] ± 300	1.4 ± 0.3
	35		4.7	23.7	× 3.4 (10 μM)	400 [^] ± 200	200 [^] ± 100	1.9 ± 0.2
	59		2.4	9.7	× 4.1 (10 μM)	ND	ND	ND
	60		9.8	20.8	× 3.4 (10 μM)	210 [^] ± 90	210 [^] ± 80	0.9 ± 0.1
	64		2.2	9.5	× 2.4 (10 μM)	400 [#] ± 200	190 [#] ± 90	2.1 ± 0.5
	67		6.5	7.8	× 2.1 (10 μM)	240 [#] ± 100	260 [#] ± 90	0.9 [#] ± 0.2
	68		2.9	2.4	× 2.0 (10 μM)	700 [#] ± 500	300 [#] ± 200	2.8 ± 0.8
	70		4.6	6.0	× 1.9 (10 μM)	700 [#] ± 200	240 [#] ± 50	3.0 ± 1.0
	84		2.4	13.8	× 4.0 (10 μM)	700 [^] ± 400	400 [^] ± 200	1.9 ± 0.2
	87		15.0	10.7	× 4.8 (10 μM)	900 [#] ± 300	480 [#] ± 60	1.9 ± 0.4
92		1.8	11.7	× 3.6 (10 μM)	300 [^] ± 100	110 [^] ± 60	2.5 ± 0.1	

Dual Inhibitors of COX/5-LOX Pathways	79		2.2	2.5	Inactive	200 [^] ± 80	60 [^] ± 30	3.3 ± 0.1
	98		1.0	12.5	Inactive	200 [^] ± 60	80 [^] ± 20	2.4 ± 0.1

All concentration-response analyses were conducted at multiple concentrations with triplicate samples per concentration. # Study conducted after a 5 mg/kg i.p. injection of test compound; [^] Study conducted after a 2 mg/kg i.p. injection of test compound with drug concentrations adjusted proportionally upward to allow comparison to 5 mg/kg doses; ND: not determined. +/- errors represent standard deviations; all analyses were conducted with groups of 3 mice

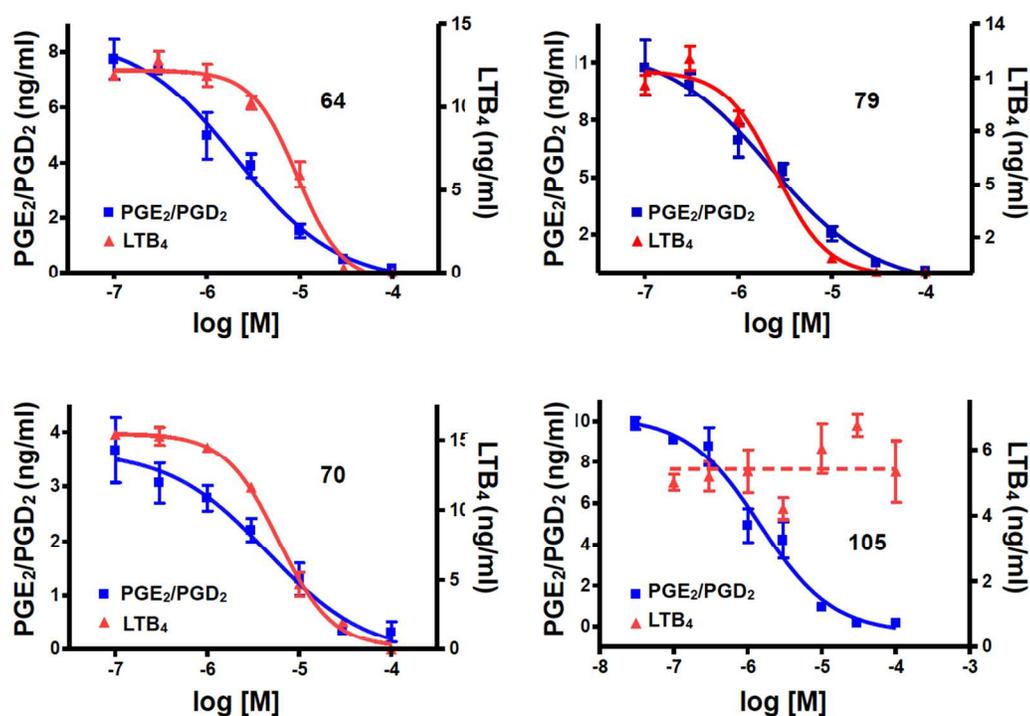


Figure 3. Representative dose-response curves in the RBL-1 cell assays. Samples were run in triplicate at each concentration, with the error bars representing standard error of the mean.

Discussion. Although selected cholinesterase inhibitors and a single NMDA receptor antagonist are approved for the treatment of AD, these provide only a modest and temporary symptomatic improvement in AD patients and thus far there have been no examples of disease-modifying drug candidates for AD with demonstrated efficacy in Phase III clinical trials.⁴³ This situation may be due, at

1 least in part, to the fact that several neuropathological mechanisms are likely to provide potentially
2 alternative or redundant pathways to drive/sustain the neurodegenerative process in AD. NSAIDs, for
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4 example, once attracted considerable attention as potential candidates for AD treatment due to
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6 promising results in a series of preclinical studies in animal models with A β plaque pathology,⁴⁴⁻⁴⁸
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8 coupled with compelling retrospective epidemiological data indicating that individuals who were on
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10 sustained regimens of COX-inhibiting NSAIDs had reduced AD risk.^{45, 49} A series of clinical trials with
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12 different COX inhibitors, however, yielded mostly disappointing results.^{45, 50-52} Although there may be
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14 multiple reasons for the lack of efficacy in these clinical trials, including issues with the particular
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16 candidate compounds used in the studies and/or trials that were conducted in patient populations with
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18 disease that was too advanced to respond to this therapeutic approach, or who had dementia that was not
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20 due to underlying AD pathology, another possible mechanistic explanation may be that even if
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22 substantial COX inhibition is achieved within the AD brain, this may not prevent the detrimental effects
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24 of inflammatory LTs. Indeed, different studies have now shown that these 5-LOX products are likely to
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26 contribute to A β plaque pathology,^{8, 18, 20, 21, 23} and there is evidence that blocking COX metabolism can
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28 lead to shunting of arachidonic acid to the 5-LOX pathway.⁵³⁻⁵⁵ Furthermore, it may be also argued that
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30 any potential benefit of lowering A β production and plaque pathology alone may be limited if tau
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32 pathology persists. Indeed, a recent retrospective analysis of several late-stage AD clinical trials,
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34 including the NSAIDs studies, concluded that candidate therapeutics affecting one target alone may not
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36 be likely to impact significantly disease progression,⁴³ suggesting that the evaluation and development
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38 of multi-targeted approaches for AD would be desirable.⁵⁶ However, although different examples of
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40 multi-targeted constructs have been proposed as experimental AD treatments, there have been only few
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42 reports⁵⁷ of molecules that exhibit polypharmacology against targets that are likely involved in tau and
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44 A β neuropathology.

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Prior studies suggested that axonal transport deficits associated with a loss of MTs and/or altered MT-
dynamics in the axon of neurons comprise a key neuropathological step of tauopathies and possibly
other neurodegenerative diseases.²⁴ As part of our ongoing efforts to develop brain-penetrant MT-

1 stabilizing agents as potential treatments for these diseases, we identified selected heterocyclic
2 compounds that are not derived from natural products, as exemplified here by triazolopyrimidine **107**⁵⁸
3 (Table 1), which exhibit a promising combination of MT-stabilizing activity and brain penetration.^{37, 39}
4
5 Among compound classes that are structurally and functionally related to the triazolopyrimidines are a
6 series of 1,5-diarylimidazoles.³⁵ Like the triazolopyrimidines, these imidazoles are found to promote
7 MT-polymerization in cell free assays and exhibit relatively potent and broad-spectrum fungicidal
8 activity.³⁵ Furthermore, considering that these tricyclic compounds exhibit structural similarities with
9 known NSAIDs, they may be considered as possible starting points in the development of small
10 molecules that could concurrently stabilize MTs and lower eicosanoid production. Given that MT
11 dynamics are believed to be affected in AD and other neurodegenerative disorders,^{24, 59} and considering
12 the involvement of both COX- and 5-LOX derived eicosanoids in AD and likely other
13 neurodegenerative diseases, a normalization of axonal MT dynamics, combined with a suppression of
14 eicosanoid production, may provide a potential multi-targeted strategy to mitigate concurrent disease
15 mechanisms in AD and other neurodegenerative conditions.
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36 Our multi-targeted structure-activity relationship (SAR) studies began with the observation that
37 selected examples from the previously reported fungicidal imidazoles,³⁵ such as **2**, exhibit evidence of
38 activity both as MT-stabilizing agents and inhibitors of eicosanoid biosynthesis *in vitro*, suggesting a
39 potentially significant overlap between the pharmacophore of these MT-stabilizing imidazoles and that
40 of NSAIDs, such as **3** (COX-1 inhibitor³³). Based on these initial findings, and taking into consideration
41 prior SAR studies³⁵ that defined a set of preferred substitutions on the imidazole ring that are generally
42 important for fungicidal activity, and thus presumably for MT-stabilizing activity, we focused on
43 evaluating whether changes in the substitution patterns of 1,5-diarylimidazoles may result in compounds
44 with improved and balanced multi-targeted activities. In particular, given that optimal broad-spectrum
45 fungicidal activity is typically achieved with tetrasubstituted imidazoles (*e.g.*, **2**) and other related
46 congeners that comprise a 4-chlorophenyl group at N1, a chlorine atom in position 4, and a di- or tri-
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1 fluorinated phenyl group in position 5, we focused primarily on evaluating (a) mono- and di-
2 substitutions in the A ring; (b) chloro- and/or alkyl-substitutions in positions 2 and/or 4 of the imidazole
3 ring; and (c) the effect of varying the degree and pattern of fluorination in the B ring. As shown in Table
4 1, these studies demonstrated that relatively small changes in the substitution pattern of 1,5-
5 diarylimidazoles can have profound effect in the activity profile of these molecules and ultimately led to
6 the identification of several compounds with MT-stabilizing activity and inhibitory activity against the
7 COX and/or 5-LOX pathways (see Table 2). Furthermore, with respect to the MT-stabilizing activity,
8 our studies suggest that like the triazolopyrimidines, MT-stabilizing 1,5-diarylimidazoles are likely to
9 affect MT structures in different ways depending on the particular substitution pattern. In the case of
10 triazolopyrimidines, it was suggested that congeners bearing an alkoxy side chain in the fluorinated
11 phenyl ring (e.g., **108**) typically produce an unusual cellular phenotype that is characterized by a bell-
12 shaped concentration-response relationship in the AcTub assay and proteasome-dependent degradation
13 of α -tubulin.³⁹ Interestingly, a similar type of observation is seen with the 1,5-diarylimidazoles, as all
14 MT-active compounds bearing an alkoxy substituent in ring B (i.e., **2**, **58**, **95–97**, Table 1) produce a
15 loss in α -tubulin at compound concentrations that are required to observe an increase in AcTub.
16 However, our results with the 1,5-diarylimidazoles clearly suggest that the substitution pattern of ring B
17 may not be the only determining factor in whether α -tubulin is affected, as other substitutions in the A
18 and C ring appear to play a role (e.g., compare **29** with **30**, and **54** with **73**, Table 1). As was noted for
19 the triazolopyrimidines,³⁹ compounds found to cause a reduction in total α -tubulin may not be desirable
20 for neurodegenerative diseases as this effect would be expected to ultimately compromise rather than
21 restore axonal MT function. Conversely, certain multi-targeted congeners, including examples listed in
22 Table 2 that do not appear to reduce total α -tubulin levels at concentrations that increase AcTub, may be
23 more promising candidates for tauopathy treatment. Further studies, however, will be necessary to
24 confirm that these compounds can produce beneficial effects in an animal model of tau pathology, as
25 observed previously with MT-stabilizing natural products like paclitaxel,⁶⁰ epothilone D, and
26 dictyostatin.⁴⁻⁷

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With respect to the ability of these compounds to act as inhibitors of the COX and/or 5-LOX pathways, although the IC₅₀ values in the COX biosynthetic pathway assay are much higher than the IC₅₀ of COX inhibitor **3** (*i.e.*, ~1 nM), the activity level displayed by these molecules is closely comparable to that of the over-the-counter drug, ibuprofen (**105**; Table 1 and Figure 3). Unlike **105** or **3**, however, these multi-targeted 1,5-diarylimidazoles (*e.g.*, **79**, see Table 2 and Figure 3) exhibit inhibition activity against the leukotriene biosynthetic pathway, while other derivatives (Table 2) are also capable of affecting MT stability in vitro, with several examples (*e.g.*, **68**, **70**, **87**) exhibiting relatively balanced multi-targeted activity. Moreover, an evaluation of the brain penetration of these molecules revealed that these multi-targeted prototypes are generally capable of reaching significant brain concentrations after peripheral administration, suggesting that compounds of this type may be appropriate for further evaluation in the context of CNS diseases. Taken together, these results indicate that these 1,5-diarylimidazoles comprise a promising scaffold for the evaluation of CNS-directed multi-targeted strategies that either focus on a concurrent inhibition of COX and 5-LOX biosynthetic pathways or on a combined stabilization of MTs and inhibition of eicosanoid production.

Conclusions. Starting from a series of 1,5-diarylimidazoles with reported MT-stabilizing activity and structural similarities with known NSAIDs, the SAR studies reported here led to the identification of a series of congeners that exhibit balanced low μM in vitro activity as MT-stabilizing agents and/or inhibitors of the COX and 5-LOX pathways. Given that prior preclinical studies demonstrated that MT stabilization in neurons is a promising therapeutic strategy to treat tau-mediated neurodegeneration, combined with the considerable body of evidence implicating eicosanoids in A β plaque pathology, the balanced polypharmacology and brain penetration displayed by these compounds suggest that these compounds are promising research tools as well as possible lead structures to investigate multi-targeted therapeutic approaches for AD.

Experimental Section

Materials and methods. All solvents were reagent grade. All reagents were purchased from Aldrich or Acros and used as received. Thin layer chromatography (TLC) was performed with 0.25 mm E. Merck pre-coated silica gel plates. Silica gel column chromatography was performed with silica gel 60 (particle size 0.040–0.062 mm) supplied by Silicycle and Sorbent Technologies. TLC spots were detected by viewing under a UV light. Melting points (Mp) were acquired on a Thomas-Hoover apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Jasco Model FT/IR-480 Plus spectrometer. Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a Bruker AMX-500 spectrometer. Chemical shifts were reported relative to solvents. High-resolution mass spectra were measured at the University of Pennsylvania Mass Spectrometry Center on either a VG Micromass 70/70H or VG ZAB-E spectrometer. Single-crystal X-ray structure determinations were performed at the University of Pennsylvania with an Enraf Nonius CAD-4 diffractometer. Analytical reverse-phase (Sunfire™ C18; 4.6×50 mm, 5 mL) high-performance liquid chromatography (HPLC) was performed with a Waters binary gradient module 2525 equipped with Waters 2996 PDA and Waters micromass ZQ. All samples were analyzed employing a linear gradient from 10% to 90% of CH_3CN in water over 8 min and flow rate of 1 mL/min, and unless otherwise stated, the purity level was >95%. Preparative reverse-phase HPLC purifications were performed on a Gilson instrument (*i.e.*, Gilson 333 pumps, a 215 liquid handler, 845Z injection module, and PDA detector) employing Waters SunFire™ preparative C_{18} OBD™ columns (5 μm 19×50 or 19×100 mm). Purifications were carried out employing a linear gradient from 10% to 90% of CH_3CN in water for 15 min with a flow rate of 20 mL/min. Unless otherwise stated, all final compounds were found to be >95% pure as determined by HPLC/MS and NMR.

General procedure A for the synthesis of imines: A solution of aniline (1 equiv) and benzaldehyde (1 equiv) in toluene (0.2 M) was heated at 110 °C in a Dean-Stark apparatus for 4 days. The reaction

1 mixture was then cooled and evaporated in vacuo to obtain the title compound, which was used in the
2 next step without further purification.
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5 *General procedure B for the synthesis of imines:* To a solution of a primary amine (1 equiv) in
6 anhydrous Et₂O (0.3 M) in the presence of molecular sieves (4 Å, 1.6 mm pellets, 7 g/mmol) was added
7 an aldehyde (1 equiv) according to the Taguchi's method. The mixture was heated and stirred at 30 °C
8 for 48 h. Molecular sieves were then removed by filtration and the solvent was evaporated in vacuo to
9 afford the desired imine in quantitative yields.
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17 *General procedure C for the synthesis of imidazoles:* To a solution of imine (1 equiv) in a mixture of
18 DMF (0.26 M) and 1,2-dimethoxyethane (0.32 M) were added toluenesulfonylmethyl isocyanide (1.5
19 equiv) and anhydrous K₂CO₃ (2.08 equiv). The reaction mixture was heated for 16 h at 100 °C, then
20 cooled to r.t., filtered, and evaporated in vacuo. The resulting material was adsorbed on Celite[®] 545 AW
21 and purified by silica gel column chromatography to obtain the desired compound.
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29 *General procedure D for the synthesis of 4-alkylated imidazoles:* To a solution of imine (1 equiv) in a
30 mixture of DMF (0.14 M) and 1,2-dimethoxyethane (0.17 M) were added 1-((1-isocyanoethyl)sulfonyl)-
31 4-methylbenzene (1.5 equiv) and anhydrous K₂CO₃ (2.08 equiv). The reaction mixture was heated for
32 16 h at 100 °C, then cooled to r.t., filtered through a pad of Celite[®] 545 AW, and evaporated in vacuo.
33 The resulting material was purified by silica gel column chromatography to obtain the desired
34 compound.
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43 *General procedure E for the mono and di-chlorination of 1,5-diarylimidazoles:* To a solution of
44 imidazole (1 equiv) in CHCl₃ (0.16 M) was added *N*-chlorosuccinimide (1.06 equiv). The reaction
45 mixture was heated at 60 °C for 16 h, then cooled to r.t. and diluted with EtOAc. The organic layer was
46 washed with brine (×3), dried over MgSO₄, filtered, and evaporated in vacuo. Purification via silica gel
47 column chromatography furnished the mono- and di-chlorinated imidazoles.
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55 *General procedure F for alkylation of 1,5-diarylimidazoles:* To a solution of diisopropylamine (1.5
56 equiv) in THF (0.3 M) at -20 °C was added *n*-BuLi (2.5 M in hexanes, 1.5 equiv), and the mixture was
57 stirred for 10 min. A solution of imidazole (1 equiv) in THF (0.15 M) was added, and after stirring for
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30 min, methyl iodide or ethyl iodide (3 equiv) was added. The mixture was stirred for 30 min at $-20\text{ }^{\circ}\text{C}$ and for 30 min at r.t.. H_2O was then added to the reaction mixture. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine ($\times 3$), dried over MgSO_4 , filtered, and concentrated in vacuo. Purification via silica gel column chromatography furnished the desired alkylated imidazoles.

4-Chloro-1-(4-chlorophenyl)-5-(2,6-difluoro-4-methoxyphenyl)-2-methyl-1*H*-imidazole (2)

To a solution of 4-chloro-1-(4-chlorophenyl)-2-methyl-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (0.004 g, 0.011 mmol) in THF (0.011 mL) at $0\text{ }^{\circ}\text{C}$ was added a 30% sodium methoxide solution in MeOH (0.007 mL). The reaction mixture was stirred for 19 h at r.t., then quenched with an aqueous ammonium chloride solution and extracted with EtOAc (3x). The combined organic layers were dried (MgSO_4), filtered, and concentrated in vacuo. The crude products were purified by preparative reverse-phase HPLC to obtain the title compound as a white solid (0.004 g, 0.011 mmol, 97% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.40 (d, $J = 8.5$ Hz, 2H), 7.11 (d, $J = 8.5$ Hz, 2H), 6.41 (d, $J = 9.1$ Hz, 2H), 3.78 (s, 3H), 2.41 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 163.04 (t, $J = 14.0$ Hz), 161.61 (dd, $J = 249.5$, 8.9 Hz), 145.57, 136.11, 133.46, 130.11, 129.90, 128.65, 128.38, 127.63, 117.32, 98.38 (d, $J = 28.0$ Hz), 96.57 (t, $J = 20.8$ Hz), 56.09, 13.37 ppm; IR (KBr) ν 2962, 2928, 2852, 1646, 1575, 1494, 1448, 1152 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{17}\text{H}_{13}\text{Cl}_2\text{F}_2\text{N}_2\text{O}$ [$\text{M} + \text{H}$] $^+$ 369.0373, found 369.0374.

(*E*)-*N*-(4-Chlorophenyl)-1-(2,4,6-trifluorophenyl)methanimine (5)

Following synthetic procedure A using 4-chloroaniline (0.829 g, 6.50 mmol) and 2,4,6-trifluorobenzaldehyde (1.04 g, 6.50 mmol), the title compound was obtained as a brown solid (1.75 g, 6.49 mmol, 99% yield). ^1H NMR (500 MHz, CDCl_3) δ 8.51 (s, 1H), 7.32 (app d, $J = 6.7$ Hz, 2H), 7.12 (app d, $J = 6.8$ Hz, 2H), 6.73 (m, 2H) ppm.

(*E*)-*N*-(4-Methoxyphenyl)-1-(2,4,6-trifluorophenyl)methanimine (6)

Following synthetic procedure A using 4-methoxyaniline (0.370 g, 3.00 mmol) and 2,4,6-trifluorobenzaldehyde (0.480 g, 3.00 mmol), the title compound was obtained as a brown solid (0.814 g,

3.07 mmol, 99% yield). ^1H NMR (500 MHz, CDCl_3) δ 8.59 (s, 1H), 7.25–7.22 (m, 2H), 6.97–6.90 (m, 2H), 6.81–6.72 (m, 2H), 3.84 (s, 3H) ppm.

(E)-N-(4-Chlorophenyl)-1-(2,6-difluoro-3-methylphenyl)methanimine (7)

Following synthetic procedure A using 4-chloro-aniline (0.383 g, 3 mmol) and 2,6-difluoro-3-methylbenzaldehyde (0.377 mL, 3 mmol), the title compound was obtained as a brown solid (0.781 g, 2.94 mmol, 98% yield). ^1H NMR (500 MHz, CDCl_3) δ 8.63 (s, 1H), 7.36 (app d, $J = 8.2$ Hz, 2H), 7.25 (app q, $J = 7.6$ Hz, 1H), 7.17 (app d, $J = 8.0$ Hz, 2H), 6.89 (app t, $J = 9.2$ Hz, 1H), 2.28 (s, 3H) ppm.

(E)-1-(3-Chloro-2,6-difluorophenyl)-N-(4-chlorophenyl)methanimine (8)

Following synthetic procedure A using 4-chloro-aniline (0.383 g, 3 mmol) and 3-chloro-2,6-difluorobenzaldehyde (0.530 g, 3 mmol), the title compound was obtained as a brown solid (0.850 g, 2.97 mmol, 99% yield). ^1H NMR (500 MHz, CDCl_3) δ 8.60 (s, 1H), 7.47 (td, $J = 8.4, 5.5$ Hz, 1H), 7.37 (app d, $J = 8.5$ Hz, 2H), 7.17 (app d, $J = 8.5$ Hz, 2H), 7.00–6.96 (m, 1H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 159.87 (dd, $J = 390.8, 5.6$ Hz), 157.80 (dd, $J = 393.2, 5.6$ Hz), 150.87, 150.42, 132.72 (d, $J = 10.3$ Hz), 132.65, 129.47, 122.29, 117.77 (dd, $J = 18.0, 3.9$ Hz), 115.03 (t, $J = 12.9$ Hz), 112.80 (dd, $J = 23.0, 4.4$ Hz) ppm.

(E)-1-(3-Bromo-2,6-difluorophenyl)-N-(4-chlorophenyl)methanimine (9)

Following synthetic procedure A using 4-chloro-aniline (0.383 g, 3 mmol) and 3-bromo-2,6-difluorobenzaldehyde (0.663 g, 3 mmol), the title compound was obtained as a brown solid (0.971 g, 2.94 mmol, 98% yield). ^1H NMR (500 MHz, CDCl_3) δ 8.59 (s, 1H), 7.61 (dd, $J = 14.2, 7.6$ Hz, 1H), 7.36 (app d, $J = 8.5$ Hz, 2H), 7.17 (app d, $J = 8.4$ Hz, 2H), 6.93 (t, $J = 9.2$ Hz, 1H) ppm.

(E)-N-(4-Chlorophenyl)-1-(2,3,6-trifluorophenyl)methanimine (10)

Following synthetic procedure A using 4-chloro-aniline (0.383 g, 3 mmol) and 2,3,6-trifluorobenzaldehyde (0.337 mL, 3 mmol), the title compound was obtained as a brown solid (0.778 g, 2.88 mmol, 96% yield). ^1H NMR (500 MHz, CDCl_3) δ 8.58 (s, 1H), 7.34 (app d, $J = 8.3$ Hz, 2H), 7.26–7.20 (m, 1H), 7.16 (app d, $J = 8.2$ Hz, 2H), 6.92 (app t, $J = 9.0$ Hz, 1H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 158.28, 156.26, 150.76, 150.19, 148.36–148.23 (m), 146.34 (dd, $J = 12.5, 3.6$ Hz), 132.51,

1 129.30, 122.18, 119.33 (dd, $J = 19.4, 10.4$ Hz), 115.07 (dd, $J = 14.2, 9.0$ Hz), 111.42 (dt, $J = 24.4, 5.3$
2 Hz) ppm.
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5 **(*E*)-*N*-(4-Chloro-3-fluorophenyl)-1-(2,3,6-trifluorophenyl)methanimine (11)**

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7 Following synthetic procedure A using 4-chloro-3-fluoroaniline (0.437 g, 3 mmol) and 2,3,6-
8 trifluorobenzaldehyde (0.337 mL, 3 mmol), the title compound was obtained as a brown solid (0.846 g,
9 2.94 mmol, 98% yield).
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14 **(*E*)-*N*-(6-Chloropyridin-3-yl)-1-(2,4,6-trifluorophenyl)methanimine (12)**

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16 Following synthetic procedure A using 6-chloropyridin-3-amine (0.385 g, 3 mmol) and 2,4,6-
17 trifluorobenzaldehyde (0.480 g, 3 mmol), the title compound was obtained as a brown solid (0.786 g,
18 2.90 mmol, 97% yield).
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24 **(*E*)-*N*-(4-Chlorophenyl)-1-(4-fluorophenyl)methanimine (13)**

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26 Following synthetic procedure A using 4-chloro-aniline (0.383 g, 3 mmol) and 4-fluorobenzaldehyde
27 (0.322 mL, 3 mmol), the title compound was obtained as a brown solid (0.687 g, 2.94 mmol, 98%
28 yield).
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34 **(*E*)-*N*-(4-Chloro-2-fluorophenyl)-1-(2,6-difluorophenyl)methanimine (14)**

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36 Following synthetic procedure A using 4-chloro-2-fluoroaniline (0.437 g, 3 mmol) and 2,6-
37 difluorobenzaldehyde (0.426 g, 3 mmol), the title compound was obtained as a brown solid (0.768 g,
38 2.85 mmol, 95% yield).
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43 **(*E*)-*N*-(4-Chlorophenyl)-1-(2,5-difluorophenyl)methanimine (15)**

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45 Following synthetic procedure A using 4-chloro-aniline (0.383 g, 3 mmol) and 2,5-
46 difluorobenzaldehyde (0.326 mL, 3 mmol), the title compound was obtained as a brown solid (0.698 g,
47 2.77 mmol, 93% yield). ^1H NMR (500 MHz, CDCl_3) δ 8.66 (s, 1H), 7.84 (dt, $J = 7.6, 4.2$ Hz, 1H), 7.35
48 (d, $J = 8.4$ Hz, 2H), 7.17 (d, $J = 8.4$ Hz, 2H), 7.14–7.06 (m, 2H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ
49 159.88, 157.92 (dd, $J = 7.7, 1.9$ Hz), 152.39 (d, $J = 1.2$ Hz), 149.67, 132.37, 131.65 (d, $J = 16.8$ Hz),
50 129.36, 129.11 (dd, $J = 51.2, 13.4$ Hz), 125.04 (dd, $J = 11.3, 7.8$ Hz), 122.40 (d, $J = 19.7$ Hz), 119.85
51 (dd, $J = 24.9, 9.0$ Hz), 117.27 (dd, $J = 24.0, 8.3$ Hz), 113.64 (dd, $J = 25.1, 2.9$ Hz) ppm.
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(E)-1-(2,6-Difluorophenyl)-N-(4-(trifluoromethoxy)phenyl)methanimine (16)

Following synthetic procedure A using 4-(trifluoromethoxy)aniline (0.531 g, 3.00 mmol) and 2,6-difluorobenzaldehyde (0.426 g, 3.00 mmol), the title compound was obtained as a brown liquid (1.034 g, 3.43 mmol, 99% yield). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.65 (s, 1H), 7.46–7.39 (m, 1H), 7.26–7.22 (m, 4H), 7.01 (t, $J = 8.6$ Hz, 2H) ppm.

(E)-N-(4-Chlorophenyl)-1-(2,6-difluorophenyl)methanimine (17)

Following synthetic procedure A using 4-chloroaniline (0.829 g, 6.50 mmol) and 2,6-difluorobenzaldehyde (0.924 g, 6.50 mmol) the title compound was obtained as a brown liquid (1.62 g, 6.45 mmol, 99% yield). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.64 (s, 1H), 7.46–7.40 (m, 1H), 7.40–7.34 (m, 2H), 7.20–7.14 (m, 2H), 7.04–6.96 (m, 2H) ppm.

(E)-N-(4-(Trifluoromethoxy)phenyl)-1-(2,3,6-trifluorophenyl)methanimine (18)

Following synthetic procedure A using 4-(trifluoromethoxy)aniline (0.531 g, 3.00 mmol) and 2,3,6-trifluorobenzaldehyde (0.480 g, 3.00 mmol), the title compound was obtained as a brown solid (1.08 g, 3.47 mmol, 99% yield). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.62 (s, 1H), 7.45–7.25 (m, 2H), 7.27–7.22 (m, 2H), 7.20–7.11 (m, 1H), 7.02–6.93 (m, 1H) ppm.

(E)-N-(4-Chlorophenyl)-1-(2,6-difluoro-4-methylphenyl)methanimine (19)

Following synthetic procedure A using 4-chloroaniline (0.157 g, 1.23 mmol) and 2,6-difluoro-4-methylbenzaldehyde (0.192 g, 3 mmol), the title compound was obtained as a brown solid (0.183 g, 0.69 mmol, 56% yield). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.59 (s, 1H), 7.36 (d, $J = 8.2$ Hz, 2H), 7.15 (d, $J = 8.2$ Hz, 2H), 6.82 (d, $J = 10.1$ Hz, 2H), 2.40 (s, 3H) ppm.

(E)-N-(4-Chlorophenyl)-1-(2,6-difluoro-3-methoxyphenyl)methanimine (20)

Following synthetic procedure A using 4-chloroaniline (0.383 g, 3.00 mmol) and 2,6-difluoro-3-methoxybenzaldehyde (0.468 g, 3.00 mmol), the title compound was obtained as a brown solid (0.745 g, 2.64 mmol, 88% yield). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.63 (s, 1H), 7.39–7.32 (m, 2H), 7.20–7.11 (m, 2H), 7.07–6.98 (m, 1H), 6.96–6.87 (m, 1H), 3.90 (s, 3H) ppm.

(E)-N-(4-Chlorophenyl)-1-phenylmethanimine (21)

1 Following synthetic procedure A using 4-chloroaniline (0.383 g, 3.00 mmol) and benzaldehyde
2 (0.318 g, 3.00 mmol), the title compound was obtained as a brown solid (0.702 g, 3.25 mmol, 99%
3 yield). ^1H NMR (500 MHz, CDCl_3) δ 8.44 (s, 1H), 7.96–7.87 (m, 2H), 7.57–7.45 (m, 3H), 7.36 (d, J =
4 8.3 Hz, 2H), 7.16 (d, J = 8.3 Hz, 2H) ppm.

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10 **(*E*)-*N*-(4-Chlorophenyl)-1-(4-methoxyphenyl)methanimine (22)**

11 Following synthetic procedure B using 4-chloroaniline (0.765 g, 6.00 mmol) and 4-
12 methoxybenzaldehyde (0.817 g, 6.00 mmol), the title compound was obtained as a yellow solid
13 (1.370 g, 5.58 mmol, 93% yield). ^1H NMR (500 MHz, CDCl_3) δ 8.35 (s, 1H), 7.84 (d, J = 8.4 Hz, 2H),
14 7.37–7.31 (m, 2H), 7.13 (d, J = 8.5 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 3.87 (s, 3H) ppm.

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21 **(*E*)-1-(2,6-Difluorophenyl)-*N*-phenylmethanimine (23)**

22 Following synthetic procedure B using aniline (0.559 g, 6.00 mmol) and 2,6-difluorobenzaldehyde
23 (0.853 g, 6.00 mmol), the title compound was obtained as a yellow liquid (0.637 g, 2.93 mmol, 49%
24 yield). ^1H NMR (500 MHz, CDCl_3) δ 8.65 (s, 1H), 7.44–7.34 (m, 3H), 7.26–7.19 (m, 3H), 7.02–6.95
25 (m, 2H) ppm.

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32 **(*E*)-*N*-(2-Chlorophenyl)-1-(2,6-difluorophenyl)methanimine (24)**

33 Following synthetic procedure B using 2-chloroaniline (0.765 g, 6.00 mmol) and 2,6-
34 difluorobenzaldehyde (0.853 g, 6.00 mmol), the title compound was obtained as a yellow liquid (1.41 g,
35 5.58 mmol, 93% yield). ^1H NMR (500 MHz, CDCl_3) δ 8.62 (s, 1H), 7.49–7.39 (m, 2H), 7.32–7.27 (m,
36 1H), 7.20–7.14 (m, 1H), 7.06–6.98 (m, 3H) ppm.

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44 **1-(4-Chlorophenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (25)**

45 Following synthetic procedure C using (*E*)-*N*-(4-chlorophenyl)-1-(2,4,6-trifluorophenyl)methanimine
46 (0.865 g, 3.21 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to
47 60:40) afforded the title compound as a white powder (0.429 g, 1.39 mmol, 43% yield). ^1H NMR
48 (500 MHz, CDCl_3) δ 7.98 (s, 1H), 7.39–7.36 (m, 2H), 7.35 (s, 1H), 7.13–7.10 (m, 2H), 6.71–6.65 (m,
49 2H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 163.14 (dt, J = 252.4, 15.3 Hz), 160.75 (ddd, J = 251.5, 14.9,
50 8.7 Hz), 138.95, 134.96, 134.41, 132.41, 129.76, 125.94, 119.16, 103.78 (td, J = 20.0, 4.6 Hz), 100.97–
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100.52 (m) ppm; IR (KBr) ν 3114, 3095, 3043, 2922, 1692, 1644, 1600, 1562, 1466, 1438, 1322, 1130 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_9\text{ClF}_3\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 309.0401, found 309.0339.

1-(4-Methoxyphenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (26)

Following synthetic procedure C using (*E*)-*N*-(4-methoxyphenyl)-1-(2,4,6-trifluorophenyl)methanimine (0.814 g, 3.07 mmol), purification by silica gel column chromatography (hexanes/EtOAc 60:40) afforded the title compound as an orange solid (0.065 g, 0.214 mmol, 7% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.76 (s, 1H), 7.25 (s, 1H), 7.09–7.04 (m, 2H), 6.88–6.83 (m, 2H), 6.66–6.59 (m, 2H), 3.79 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 163.05 (dt, $J = 251.4, 15.1$ Hz), 160.93 (ddd, $J = 251.1, 14.8, 8.6$ Hz), 159.50, 139.30, 131.76, 129.27, 126.21, 119.50, 114.58, 104.15 (td, $J = 20.4, 4.9$ Hz), 101.30–99.76 (m), 55.61 ppm; IR (KBr) ν 3102, 3008, 2935, 2840, 1689, 1644, 1599, 1564, 1515, 1489, 1465, 1439, 1301, 1250, 1172, 1123, 1033 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{16}\text{H}_{12}\text{F}_3\text{N}_2\text{O}$ [$\text{M} + \text{H}$] $^+$ 309.0902, found 309.0908.

1-(4-Chlorophenyl)-5-(2,6-difluoro-3-methylphenyl)-1*H*-imidazole (27)

Following synthetic procedure C using (*E*)-*N*-(4-chlorophenyl)-1-(2,6-difluoro-3-methylphenyl)methanimine (0.399 g, 1.5 mmol), purification by silica gel column chromatography (hexanes/EtOAc 80:20 to 20:80) afforded the title compound as a yellow solid (0.327 g, 1.07 mmol, 72% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.81 (s, 1H), 7.31 (t, $J = 7.6$ Hz, 3H), 7.15–7.08 (m, $J = 15.1, 7.5$ Hz, 3H), 6.75 (t, $J = 8.6$ Hz, 1H), 2.18 (s, 3H) ppm; MS (ES^+) calculated for $\text{C}_{16}\text{H}_{11}\text{ClF}_2\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 305.07, found 305.03.

5-(3-Chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole (28)

Following synthetic procedure C using (*E*)-1-(3-chloro-2,6-difluorophenyl)-*N*-(4-chlorophenyl)methanimine (0.429 g, 1.5 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 60:40) afforded the title compound as a white solid (0.298 g, 0.916 mmol, 61% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.77 (d, $J = 0.5$ Hz, 1H), 7.32–7.27 (m, 4H), 7.06–7.04 (m, 2H), 6.78 (td, $J = 8.7, 1.4$ Hz, 1H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 158.27 (dd, $J = 251.2, 4.4$ Hz), 155.38 (dd, $J = 252.0, 6.3$ Hz), 138.97, 134.65, 134.11, 132.45, 130.90, 130.83, 129.57, 125.53, 119.00,

1 116.96 (dd, $J = 18.6, 4.2$ Hz), 112.05 (dd, $J = 23.5, 4.1$ Hz), 108.51 (t, $J = 20.1$ Hz) ppm; MS (ES^+)
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3 calculated for $\text{C}_{15}\text{H}_9\text{Cl}_2\text{F}_2\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 325.01, found 324.93.

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5 **5-(3-Chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-4-methyl-1*H*-imidazole (29)**

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7 Following synthetic procedure D using (*E*)-1-(3-chloro-2,6-difluorophenyl)-*N*-(4-
8 chlorophenyl)methanimine (0.800 g, 2.80 mmol), purification by silica gel column chromatography
9 (hexanes/EtOAc 65:35) afforded the title compound as an orange solid (0.433 g, 1.28 mmol, 46% yield).
10
11 ^1H NMR (500 MHz, CDCl_3) δ 7.72 (s, 1H), 7.37 (ddd, $J = 9.0, 8.0, 5.6$ Hz, 1H), 7.34–7.27 (m, 2H),
12
13 7.08–7.01 (m, 2H), 6.84 (ddd, $J = 9.0, 8.2, 1.8$ Hz, 1H), 2.20 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl_3)
14
15 δ 158.82 (dd, $J = 250.6, 4.6$ Hz), 155.87 (dd, $J = 251.8, 6.6$ Hz), 140.71, 138.02, 135.11, 134.20, 131.25
16
17 (d, $J = 9.6$ Hz), 129.79, 125.77, 117.22 (dd, $J = 18.7, 4.2$ Hz), 115.41, 112.29 (dd, $J = 23.6, 4.3$ Hz),
18
19 109.12 (t, $J = 20.3$ Hz), 13.48 ppm; IR (KBr) ν 3077, 3036, 2960, 2925, 1625, 1568, 1498, 1477, 1453,
20
21 1352, 1282, 1269, 1218, 1091, 1003 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{16}\text{H}_{11}\text{Cl}_2\text{F}_2\text{N}_2$ [$\text{M} + \text{H}$] $^+$
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23 339.0267, found 339.0273.

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31 **2-Chloro-5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-4-methyl-1*H*-imidazole (30)**

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33 Following synthetic procedure E using 5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-4-methyl-
34
35 1*H*-imidazole (0.150 g, 0.442 mmol), purification by silica gel column chromatography
36 (hexanes/EtOAc 80:20) afforded the title compound as a white solid (0.071 g, 0.190 mmol, 43% yield).
37
38 ^1H NMR (500 MHz, CDCl_3) δ 7.39–7.31 (m, 3H), 7.14–7.06 (m, 2H), 6.86–6.75 (m, 1H), 2.17 (s, 3H)
39
40 ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 158.94 (dd, $J = 250.9, 4.3$ Hz), 156.02 (dd, $J = 252.1, 6.2$ Hz),
41
42 139.23, 135.37, 133.53 (d, $J = 11.2$ Hz), 131.74 (d, $J = 9.8$ Hz), 129.85, 129.61, 128.57, 117.71, 117.16
43
44 (dd, $J = 18.3, 3.5$ Hz), 112.23 (dd, $J = 23.6, 4.3$ Hz), 108.57 (t, $J = 20.1$ Hz), 13.43 ppm; IR (KBr) ν
45
46 3074, 2924, 2848, 1627, 1572, 1494, 1474, 1455, 1388, 1283, 1218, 1092, 1007 cm^{-1} ; HRMS (ES^+)
47
48 calculated for $\text{C}_{16}\text{H}_{10}\text{Cl}_3\text{F}_2\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 372.9878, found 372.9874.

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55 **5-(3-Chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-2,4-dimethyl-1*H*-imidazole (31)**

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57 Following synthetic procedure F using 5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-4-methyl-
58
59 1*H*-imidazole (0.050 g, 0.147 mmol), purification by silica gel column chromatography
60

(hexanes/EtOAc 60:40) afforded the title compound as a orange solid (0.029 g, 0.082 mmol, 56% yield).

^1H NMR (500 MHz, CDCl_3) δ 7.34–7.29 (m, 2H), 7.31–7.26 (m, 1H), 7.03 (d, $J = 8.4$ Hz, 2H), 6.82–6.74 (m, 1H), 2.29 (s, 3H), 2.14 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 158.99 (dd, $J = 249.9, 4.9$ Hz), 156.01 (dd, $J = 251.2, 6.6$ Hz), 146.28, 138.04, 135.07, 134.66, 130.99 (d, $J = 9.7$ Hz), 129.62, 128.34, 116.96 (dd, $J = 19.0, 3.9$ Hz), 115.69, 112.05 (dd, $J = 23.9, 4.3$ Hz), 109.60 (t, $J = 20.7$ Hz), 14.04, 13.13 ppm; IR (KBr) ν 3052, 2962, 2922, 2849, 1693, 1629, 1593, 1571, 1495, 1474, 1402, 1266, 1218, 1092, 1004 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{17}\text{H}_{13}\text{Cl}_2\text{F}_2\text{N}_2$ $[\text{M} + \text{H}]^+$ 353.0424, found 353.0413.

5-(3-Bromo-2,6-difluorophenyl)-1-(4-chlorophenyl)-1H-imidazole (32)

Following synthetic procedure C using (*E*)-1-(3-bromo-2,6-difluorophenyl)-*N*-(4-chlorophenyl)methanimine (0.495 g, 1.5 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 60:40) afforded the title compound as a yellow solid (0.450 g, 1.22 mmol, 82% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.83 (s, 1H), 7.53 (ddd, $J = 8.8, 7.7, 5.8$ Hz, 1H), 7.37–7.34 (m, 3H), 7.12–7.11 (m, 2H), 6.82 (td, $J = 8.7, 1.4$ Hz, 1H) ppm; MS (ES^+) calculated for $\text{C}_{15}\text{H}_9\text{BrClF}_2\text{N}_2$ $[\text{M} + \text{H}]^+$ 368.96, found 368.98.

1-(4-Chlorophenyl)-5-(2,3,6-trifluorophenyl)-1H-imidazole (33)

Following synthetic procedure C using (*E*)-*N*-(4-chlorophenyl)-1-(2,3,6-trifluorophenyl)methanimine (0.405 g, 1.5 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 60:40) afforded the title compound as a brown solid (0.350 g, 1.13 mmol, 76% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.80 (s, 1H), 7.34–7.31 (m, 3H), 7.15–7.11 (m, $J = 9.0, 5.0$ Hz, 1H), 7.09 (d, $J = 8.6$ Hz, 2H), 6.82–6.78 (m, 1H) ppm; MS (ES^+) calculated for $\text{C}_{15}\text{H}_8\text{ClF}_3\text{N}_2$ $[\text{M} + \text{H}]^+$ 309.04, found 309.18.

1-(4-Chlorophenyl)-2-methyl-5-(2,3,6-trifluorophenyl)-1H-imidazole (34)

To a solution of diisopropylamine (0.02 mL, 0.146 mmol, 1.5 equiv) in THF (0.3 M) at -20 °C was added *n*-BuLi (2.5M in hexanes, 0.06 mL, 0.146 mmol, 1.5 equiv), and the mixture was stirred for 10 min. A solution of 1-(4-chlorophenyl)-5-(2,3,6-trifluorophenyl)-1H-imidazole (0.030 g, 0.097 mmol, 1 equiv) in THF (1 mL) was added, and after stirring for 30 min, methyl iodide (0.009 mL, 0.146 mmol,

1.5 equiv) was added. The mixture was stirred for 30 min at $-20\text{ }^{\circ}\text{C}$ and for 30 min at r.t.. H_2O was added to the reaction mixture, the aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine ($\times 3$), dried over MgSO_4 , filtered, and concentrated. The mixture was purified by silica gel column chromatography (hexanes/EtOAc 65:35) afforded the title compound as a yellow solid (0.009 g, 0.028 mmol, 29% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.38–7.33 (m, 2H), 7.19 (s, 1H), 7.11–7.04 (m, 3H), 6.78–6.73 (m, 1H), 2.34 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 155.73 (dt, $J = 246.7, 3.2$ Hz), 148.24 (ddd, $J = 251.2, 14.2, 6.5$ Hz), 147.45, 147.13 (ddd, $J = 245.9, 13.2, 3.6$ Hz), 134.95, 134.80, 130.14, 129.73, 128.32, 125.88, 119.63, 117.77–117.37 (m), 110.88 (ddd, $J = 24.7, 6.9, 4.3$ Hz), 109.67 (dd, $J = 21.8, 16.1$ Hz), 14.24 ppm; IR (KBr) ν 3098, 3061, 2961, 2924, 2850, 1641, 1494, 1402, 1237, 1093 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{16}\text{H}_{11}\text{F}_3\text{N}_2\text{Cl}$ [$\text{M} + \text{H}$] $^+$ 323.0563, found 323.0568.

1-(4-Chlorophenyl)-4-methyl-5-(2,3,6-trifluorophenyl)-1H-imidazole (35)

Following synthetic procedure D using (*E*)-*N*-(4-chlorophenyl)-1-(2,3,6-trifluorophenyl)methanimine (0.500 g, 1.85 mmol), purification by silica gel column chromatography (hexanes/EtOAc 60:40) afforded the title compound as an orange solid (0.190 g, 0.589 mmol, 32% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.72 (s, 1H), 7.33–7.29 (m, 2H), 7.15 (qd, $J = 9.1, 5.0$ Hz, 1H), 7.07–7.02 (m, 2H), 6.85–6.79 (m, 1H), 2.22 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 155.69 (dt, $J = 247.2, 3.4$ Hz), 148.15 (ddd, $J = 252.2, 14.3, 6.4$ Hz), 147.28 (ddd, $J = 246.6, 12.8, 4.1$ Hz), 140.74, 138.07, 135.11, 134.20, 129.79, 125.77, 117.83 (dd, $J = 19.4, 9.7$ Hz), 115.33 (d, $J = 2.3$ Hz), 111.14 (ddd, $J = 24.4, 6.9, 4.2$ Hz), 109.45 (dd, $J = 22.0, 16.2$ Hz), 13.48 ppm; IR (KBr) ν 3094, 2925, 1642, 1595, 1500, 1472, 1353, 1269, 1250, 1231, 1092, 1002, 973 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{16}\text{H}_{11}\text{ClF}_3\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 323.0563, found 323.0557.

2-Chloro-1-(4-chlorophenyl)-4-methyl-5-(2,3,6-trifluorophenyl)-1H-imidazole (36)

Following synthetic procedure E using 1-(4-chlorophenyl)-4-methyl-5-(2,3,6-trifluorophenyl)-1H-imidazole (0.100 g, 0.310 mmol), purification by silica gel column chromatography (hexanes/EtOAc 80:20) afforded the title compound as a white solid (0.079 g, 0.221 mmol, 71% yield). ^1H NMR

(500 MHz, CDCl₃) δ 7.36–7.31 (m, 2H), 7.17–7.07 (m, 3H), 6.82–6.76 (m, 1H), 2.17 (s, 3H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 155.82 (dt, J = 247.3, 2.9 Hz), 148.29 (ddd, J = 251.9, 14.1, 7.0 Hz), 147.12 (ddd, J = 246.7, 13.0, 3.9 Hz), 139.27, 135.37, 133.55 (d, J = 5.2 Hz), 129.85, 129.60, 128.57, 118.34 (dd, J = 19.3, 9.9 Hz), 117.60 (d, J = 2.3 Hz), 111.11 (ddd, J = 24.7, 6.9, 4.4 Hz), 108.90 (dd, J = 22.0, 16.2 Hz), 13.44 ppm; IR (KBr) ν 3052, 2983, 2918, 2849, 1494, 1448, 1265, 1236, 1092, 1001 cm⁻¹; HRMS (ES⁺) calculated for C₁₆H₁₀Cl₂F₃N₂ [M + H]⁺ 357.0173, found 357.0170.

1-(4-Chloro-3-fluorophenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (37)

Following synthetic procedure C using (*E*)-*N*-(4-chloro-3-fluorophenyl)-1-(2,3,6-trifluorophenyl)methanimine (0.431 g, 1.5 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 50:50) afforded the title compound as an orange solid (0.385 g, 1.18 mmol, 79% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.77 (s, 1H), 7.34 (t, J = 8.2 Hz, 1H), 7.27 (s, 1H), 7.09 (qd, J = 9.1, 5.0 Hz, 1H), 6.95 (dd, J = 9.1, 2.4 Hz, 1H), 6.87 (dd, J = 8.5, 1.0 Hz, 1H), 6.80–6.75 (m, 1H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 158.92, 156.92, 155.23 (dt, J = 247.6, 2.8 Hz), 147.79 (ddd, J = 252.4, 14.5, 6.4 Hz), 147.14 (ddd, J = 246.3, 13.0, 3.6 Hz), 139.06, 135.89 (d, J = 8.8 Hz), 132.81, 131.35, 121.36, 121.22, 120.81 (d, J = 3.8 Hz), 119.00 (d, J = 1.6 Hz), 117.76 (dd, J = 19.6, 9.6 Hz), 113.15, 112.96, 111.14 (dt, J = 24.5, 5.4 Hz), 108.61 (dd, J = 21.6, 15.7 Hz) ppm; MS (ES⁺) calculated for C₁₅H₈ClF₄N₂ [M + H]⁺ 327.03, found 327.14.

2-Chloro-5-(5-(2,4,6-trifluorophenyl)-1*H*-imidazol-1-yl)pyridine (38)

Following synthetic procedure C using (*E*)-*N*-(6-chloropyridin-3-yl)-1-(2,4,6-trifluorophenyl)methanimine (0.593 g, 2.2 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 60:40) afforded the title compound as an orange solid (0.304 g, 0.982 mmol, 45% yield). ¹H NMR (500 MHz, CDCl₃) δ 8.21 (s, 1H), 7.78 (s, 1H), 7.45 (ddd, J = 8.4, 2.5, 1.2 Hz, 1H), 7.35–7.33 (m, 1H), 7.28 (s, 1H), 6.66–6.63 (m, 2H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 163.30 (dt, J = 253.2, 15.2 Hz), 160.50 (ddd, J = 251.6, 14.8, 8.5 Hz), 151.19, 145.34, 138.80, 134.72, 132.82, 132.10, 124.96, 119.28, 102.94 (td, J = 19.9, 4.7 Hz), 101.23–100.79 (m) ppm; MS (ES⁺) calculated for C₁₄H₈ClF₃N₃ [M + H]⁺ 310.04, found 310.13.

1-(4-Chlorophenyl)-5-(4-fluorophenyl)-1*H*-imidazole (39)

Following synthetic procedure C using (*E*)-*N*-(4-chlorophenyl)-1-(4-fluorophenyl)methanimine (0.350 g, 1.5 mmol), purification by silica gel column chromatography (hexanes/EtOAc 90:10 to 60:40) afforded the title compound as a brown solid (0.260 g, 0.953 mmol, 64% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.67 (s, 1H), 7.39–7.36 (m, 2H), 7.22 (s, 1H), 7.12–7.08 (m, 4H), 7.00–6.96 (m, 2H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 162.48 (d, *J* = 248.1 Hz), 138.79, 135.13, 134.36, 132.22, 130.18 (d, *J* = 8.2 Hz), 129.92, 129.20, 126.92, 125.39 (d, *J* = 3.2 Hz), 115.85 (d, *J* = 21.8 Hz) ppm; MS (ES⁺) calculated for C₁₅H₁₁ClFN₂ [M + H]⁺ 273.06, found 273.25.

1-(4-Chloro-2-fluorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (40)

Following synthetic procedure C using (*E*)-*N*-(4-chloro-2-fluorophenyl)-1-(2,6-difluorophenyl)methanimine (0.539 g, 2 mmol), purification by silica gel column chromatography (hexanes/EtOAc 90:10 to 60:40) afforded the title compound as a yellow solid (0.351 g, 1.14 mmol, 57% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.77 (s, 1H), 7.35 (s, 1H), 7.31–7.27 (m, 1H), 7.21–7.19 (m, 1H), 7.15–7.10 (m, *J* = 6.6 Hz, 2H), 6.88 (quintet, *J* = 6.8 Hz, 2H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 160.46 (dd, *J* = 250.9, 5.9 Hz), 156.39 (d, *J* = 256.0 Hz), 139.44 (d, *J* = 1.1 Hz), 135.42 (d, *J* = 9.2 Hz), 131.92, 130.94 (t, *J* = 10.3 Hz), 128.57, 125.17, 125.14, 123.30 (d, *J* = 12.7 Hz), 120.88, 117.86, 117.67, 111.71 (dd, *J* = 20.5, 5.2 Hz), 106.96 (t, *J* = 19.5 Hz) ppm; MS (ES⁺) calculated for C₁₅H₉ClF₃N₂ [M + H]⁺ 309.04, found 309.12.

1-(4-Chlorophenyl)-5-(2,5-difluorophenyl)-1*H*-imidazole (41)

Following synthetic procedure C using (*E*)-*N*-(4-chlorophenyl)-1-(2,5-difluorophenyl)methanimine (0.378 g, 1.5 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 60:40) afforded the title compound as a yellow solid (0.392 g, 1.35 mmol, 90% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.72 (s, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.29 (s, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.09–7.07 (m, 2H), 6.86–6.83 (m, 1H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 158.35 (dd, *J* = 248.6, 7.2 Hz), 155.45 (d, *J* = 244.1 Hz), 139.09, 135.05, 134.29, 131.29, 129.80, 126.02, 118.66 (dd, *J* = 17.7, 8.8 Hz), 117.30

(dd, $J = 24.8, 3.1$ Hz), 117.18 (dd, $J = 24.8, 8.9$ Hz), 116.56 (dd, $J = 23.8, 8.3$ Hz) ppm; MS (ES^+) calculated for $\text{C}_{15}\text{H}_{10}\text{ClF}_2\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 291.05, found 291.04.

5-(2,6-Difluorophenyl)-1-(4-(trifluoromethoxy)phenyl)-1*H*-imidazole (42)

Following synthetic procedure C using (*E*)-1-(2,6-difluorophenyl)-*N*-(4-(trifluoromethoxy)phenyl)methanimine (1.03 g, 3.43 mmol), purification by silica gel column chromatography (hexanes/EtOAc 60:40) afforded the title compound as a white solid (0.644 g, 1.89 mmol, 55% yield). ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 8.20 (s, 1H), 7.54–7.47 (m, 1H), 7.45 (d, $J = 8.5$ Hz, 2H), 7.35 (d, $J = 8.5$ Hz, 2H), 7.32 (s, 1H), 7.15 (t, $J = 8.2$ Hz, 2H) ppm; ^{13}C NMR (126 MHz, $\text{DMSO-}d_6$) δ 159.54 (dd, $J = 248.4, 6.0$ Hz), 147.54–147.48 (m), 139.64, 135.08, 131.88, 131.76 (t, $J = 5.2$ Hz), 126.09, 122.12, 119.91 (q, $J = 256.9$ Hz), 118.93, 111.98 (dd, $J = 20.4, 5.1$ Hz), 106.56 (t, $J = 19.7$ Hz) ppm; IR (KBr) ν 3059, 2917, 2849, 1632, 1580, 1562, 1514, 1472, 1448, 1262, 1212, 1169 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{16}\text{H}_{10}\text{F}_5\text{N}_2\text{O}$ [$\text{M} + \text{H}$] $^+$ 341.0713, found 341.0714.

1-(4-Chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (43)

Following synthetic procedure C using (*E*)-*N*-(4-chlorophenyl)-1-(2,6-difluorophenyl)methanimine (1.62 g, 6.45 mmol), purification by silica gel column chromatography (hexanes/EtOAc 65:35) afforded the title compound as a yellow solid (1.18 g, 4.04 mmol, 63% yield). ^1H NMR (500 MHz, CDCl_3) δ 8.86 (s, 1H), 7.60 (s, 1H), 7.49–7.44 (m, 1H), 7.44–7.40 (m, 2H), 7.21–7.17 (m, 2H), 6.99–6.93 (m, 2H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 160.46 (dd, $J = 253.1, 5.2$ Hz), 136.99, 136.90, 133.44 (t, $J = 10.2$ Hz), 132.54, 130.41, 126.30, 123.71, 122.62, 112.21 (dd, $J = 20.4, 4.2$ Hz), 103.71 (t, $J = 19.4$ Hz) ppm; IR (KBr) ν 3104, 2919, 2851, 2612, 1987, 1680, 1590, 1536, 1491, 1469, 1414, 1348, 1148 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_{10}\text{ClF}_2\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 291.0501, found 291.0503.

1-(4-Chlorophenyl)-5-(2,6-difluorophenyl)-4-methyl-1*H*-imidazole (44)

Following synthetic procedure D using (*E*)-*N*-(4-chlorophenyl)-1-(2,6-difluorophenyl)methanimine (0.618 g, 2.46 mmol), purification by silica gel column chromatography (hexanes/EtOAc 65:35) afforded the title compound as an orange solid (0.292 g, 0.958 mmol, 39% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.72 (s, 1H), 7.36–7.28 (m, 1H), 7.32–7.25 (m, 2H), 7.08–7.01 (m, 2H), 6.93–6.83 (m, 2H),

2.21 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 160.61 (dd, $J = 250.3, 6.3$ Hz), 140.19, 137.61, 135.40, 133.91, 131.00 (t, $J = 10.2$ Hz), 129.63, 125.7, 116.13, 111.74 (dd, $J = 20.1, 5.3$ Hz), 107.53 (t, $J = 20.0$ Hz), 13.44 ppm; IR (KBr) ν 3105, 2921, 2851, 1692, 1630, 1590, 1569, 1498, 1479, 1461, 1274, 1235, 1091, 997 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{16}\text{H}_{12}\text{ClF}_2\text{N}_2$ $[\text{M} + \text{H}]^+$ 305.0657, found 305.0661.

2-Chloro-1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-4-methyl-1*H*-imidazole (45)

Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-4-methyl-1*H*-imidazole (0.150 g, 0.492 mmol), purification by silica gel column chromatography (hexanes/EtOAc 80:20) afforded the title compound as a yellow oil (0.079 g, 0.232 mmol, 47% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.31 (d, $J = 8.6$ Hz, 2H), 7.30–7.26 (m, 1H), 7.12–7.07 (m, 2H), 6.88–6.81 (m, 2H), 2.16 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 160.70 (dd, $J = 250.6, 6.0$ Hz), 138.71, 135.08, 133.82, 132.88, 131.46 (t, $J = 10.2$ Hz), 129.41, 128.60, 118.49, 111.65 (dd, $J = 20.6, 5.1$ Hz), 107.02 (t, $J = 19.8$ Hz), 13.37 ppm; IR (KBr) ν 3056, 2959, 2923, 2850, 1633, 1590, 1571, 1495, 1467, 1448, 1387, 1280, 1236, 1092, 998 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{16}\text{H}_{11}\text{Cl}_2\text{F}_2\text{N}_2$ $[\text{M} + \text{H}]^+$ 339.0267, found 339.0277.

1-(4-Chlorophenyl)-5-(2,6-difluorophenyl)-2,4-dimethyl-1*H*-imidazole (46)

Following synthetic procedure F using 1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-4-methyl-1*H*-imidazole (0.050 g, 0.164 mmol), purification by silica gel column chromatography (hexanes/EtOAc 65:35) afforded the title compound as a colorless liquid (0.025 g, 0.078 mmol, 48% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.31–7.27 (m, 2H), 7.25–7.18 (m, 1H), 7.06–7.01 (m, 2H), 6.81 (t, $J = 7.6$ Hz, 2H), 2.29 (s, 3H), 2.14 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 160.79 (dd, $J = 249.7, 6.3$ Hz), 145.79, 137.59, 135.43, 134.38, 130.69 (t, $J = 10.2$ Hz), 129.44, 128.40, 116.41, 111.49 (dd, $J = 20.3, 5.3$ Hz), 108.12 (t, $J = 20.1$ Hz), 14.09, 13.12 ppm; IR (KBr) ν 2958, 2923, 2851, 1633, 1594, 1572, 1495, 1464, 1403, 1274, 1235, 1092 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{17}\text{H}_{14}\text{ClF}_2\text{N}_2$ $[\text{M} + \text{H}]^+$ 319.0814, found 319.0807.

1-(4-(Trifluoromethoxy)phenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (47)

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Following synthetic procedure C using (*E*)-*N*-(4-(trifluoromethoxy)phenyl)-1-(2,3,6-trifluorophenyl)methanimine (1.08 g, 3.37 mmol), purification by silica gel column chromatography (hexanes/EtOAc 65:35) afforded the title compound as a brown solid (0.587 g, 1.64 mmol, 49% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.83 (s, 1H), 7.36 (s, 1H), 7.26–7.17 (m, 4H), 7.14 (qd, $J = 9.1, 4.9$ Hz, 1H), 6.86–6.77 (m, 1H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 155.51 (dt, $J = 247.8, 3.2$ Hz), 149.06–148.90 (m), 148.12 (ddd, $J = 261.9, 15.9, 9.2$ Hz), 147.33 (ddd, $J = 246.6, 12.7, 4.1$ Hz), 139.36, 134.80, 132.76, 126.15, 122.02, 120.40 (q, $J = 258.6$ Hz), 119.39, 117.84 (dd, $J = 19.1, 9.6$ Hz), 111.17 (ddd, $J = 24.6, 6.7, 4.2$ Hz), 109.03 (dd, $J = 21.9, 15.9$ Hz) ppm; IR (KBr) ν 3097, 2917, 2850, 1734, 1642, 1599, 1563, 1514, 1494, 1448, 1383, 1260, 1211, 1167, 1103, 1027, 1016, 994 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{16}\text{H}_9\text{F}_6\text{N}_2\text{O}$ [$\text{M} + \text{H}$] $^+$ 359.0619, found 359.0621.

1-(4-Chlorophenyl)-5-(2,6-difluoro-4-methylphenyl)-1*H*-imidazole (48)

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Following synthetic procedure C using (*E*)-*N*-(4-chlorophenyl)-1-(2,6-difluoro-4-methylphenyl)methanimine (0.183 g, 0.689 mmol), purification by silica gel column chromatography (hexanes/EtOAc 60:40) afforded the title compound as a yellow solid (0.127 g, 0.417 mmol, 61% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.76 (s, 1H), 7.31 (d, $J = 8.2$ Hz, 2H), 7.26 (s, 1H), 7.08 (d, $J = 8.3$ Hz, 2H), 6.67 (d, $J = 8.2$ Hz, 2H), 2.32 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 160.10 (dd, $J = 249.8, 7.0$ Hz), 142.34 (t, $J = 9.8$ Hz), 138.65, 135.27, 134.11, 132.11, 129.68, 125.88, 120.32, 112.32 (dd, $J = 19.8, 5.3$ Hz), 104.03 (t, $J = 19.8$ Hz), 21.58 ppm; IR (KBr) ν 3113, 3073, 3037, 2923, 2854, 1642, 1572, 1499, 1464, 1323, 1277, 1249, 1215, 1205, 1091 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{16}\text{H}_{12}\text{ClF}_2\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 305.0657, found 305.0658.

1-(4-Chlorophenyl)-5-(2,6-difluoro-3-methoxyphenyl)-1*H*-imidazole (49)

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Following synthetic procedure C using (*E*)-*N*-(4-chlorophenyl)-1-(2,6-difluoro-3-methoxyphenyl)methanimine (0.745 g, 2.64 mmol), purification by silica gel column chromatography (hexanes/EtOAc 60:40) afforded the title compound as a yellow solid (0.278 g, 0.867 mmol, 33% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.79 (s, 1H), 7.35–7.29 (m, 3H), 7.10 (d, $J = 8.1$ Hz, 2H), 6.94–6.85 (m, 1H), 6.79 (t, $J = 8.8$ Hz, 1H), 3.83 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 153.72 (dd, $J = 243.6,$

4.1 Hz), 149.74 (dd, $J = 250.3, 5.9$ Hz), 144.52 (dd, $J = 11.1, 3.0$ Hz), 138.92, 135.18, 134.20, 132.42, 129.73, 125.86, 120.12, 113.94 (dd, $J = 9.4, 2.9$ Hz), 110.40 (dd, $J = 23.1, 4.3$ Hz), 108.08 (dd, $J = 21.4, 16.8$ Hz), 56.86 ppm; IR (KBr) ν 3098, 2941, 2842, 1592, 1500, 1441, 1318, 1281, 1247, 1172, 1110, 1049 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{16}\text{H}_{12}\text{ClF}_2\text{N}_2\text{O}$ [$\text{M} + \text{H}$] $^+$ 321.0606, found 321.0606.

1-(4-Chlorophenyl)-5-phenyl-1*H*-imidazole (50)

Following synthetic procedure C using (*E*)-*N*-(4-chlorophenyl)-1-phenylmethanimine (0.702 g, 3.25 mmol), purification by silica gel column chromatography (hexanes/EtOAc 60:40) afforded the title compound as a orange solid (0.088 g, 0.345 mmol, 11% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.67 (s, 1H), 7.36 (d, $J = 8.0$ Hz, 2H), 7.30–7.26 (m, 4H), 7.16–7.09 (m, 4H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 138.80, 135.25, 134.08, 133.08, 129.77, 129.19, 129.15, 128.66, 128.28, 127.80, 126.84 ppm; IR (KBr) ν 3115, 3062, 2957, 2921, 2851, 1604, 1495, 1468, 1269, 1117, 1093 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_{12}\text{ClN}_2$ [$\text{M} + \text{H}$] $^+$ 255.0689, found 255.0690.

1-(4-Chlorophenyl)-5-(4-methoxyphenyl)-1*H*-imidazole (51)

Following synthetic procedure C using (*E*)-*N*-(4-chlorophenyl)-1-(4-methoxyphenyl)methanimine (0.100 g, 0.407 mmol), purification by silica gel column chromatography (hexanes/EtOAc 65:35) afforded the title compound as a orange solid (0.065 g, 0.228 mmol, 56% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.64 (s, 1H), 7.38–7.30 (m, 2H), 7.18 (s, 1H), 7.14–7.07 (m, 2H), 7.08–6.99 (m, 2H), 6.85–6.75 (m, 2H), 3.78 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 159.35, 138.30, 135.38, 134.01, 132.95, 129.74, 128.50, 126.88, 121.62, 114.17, 55.35 ppm; IR (KBr) ν 3118, 3046, 2960, 2916, 2836, 1614, 1557, 1497, 1466, 1297, 1271, 1250, 1178, 1113, 1093, 1063, 1030 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{16}\text{H}_{14}\text{ClN}_2\text{O}$ [$\text{M} + \text{H}$] $^+$ 285.0795, found 285.0798.

5-(2,6-Difluorophenyl)-1-phenyl-1*H*-imidazole (52)

Following synthetic procedure C using (*E*)-1-(2,6-difluorophenyl)-*N*-phenylmethanimine (0.600 g, 2.76 mmol), purification by silica gel column chromatography (hexanes/EtOAc 65:35) afforded the title compound as an orange solid (0.193 g, 0.753 mmol, 27% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.84 (s, 1H), 7.41–7.34 (m, 3H), 7.34 (s, 1H), 7.34–7.25 (m, 1H), 7.21–7.15 (m, 2H), 6.91–6.83 (m, 2H) ppm;

¹³C NMR (126 MHz, CDCl₃) δ 160.55 (dd, *J* = 250.5, 6.2 Hz), 138.99, 136.71, 132.15, 130.67 (t, *J* = 10.2 Hz), 129.46, 128.25, 124.59, 120.06, 111.61 (dd, *J* = 20.4, 5.0 Hz), 107.65 (t, *J* = 19.7 Hz) ppm; IR (KBr) ν 3103, 3070, 3045, 2916, 2848, 1631, 1597, 1563, 1498, 1470, 1447, 1278, 1255, 1236, 1216, 1116, 1077, 998 cm⁻¹; HRMS (ES⁺) calculated for C₁₅H₁₁F₂N₂ [M + H]⁺ 257.0890, found 257.0881.

1-(2-Chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (53)

Following synthetic procedure C using (*E*)-*N*-(2-chlorophenyl)-1-(2,6-difluorophenyl)methanimine (0.600 g, 2.38 mmol), purification by silica gel column chromatography (hexanes/EtOAc 65:35) afforded the title compound as a yellow solid (0.478 g, 1.64 mmol, 69% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.72 (s, 1H), 7.41–7.37 (m, 1H), 7.32–7.24 (m, 2H), 7.25–7.14 (m, 3H), 6.82–6.74 (m, 2H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 160.49 (dd, *J* = 250.9, 6.1 Hz), 139.5, 134.11, 131.55, 131.53, 130.68 (t, *J* = 10.2 Hz), 130.54, 130.13, 129.00, 127.44, 121.01, 111.52 (dd, *J* = 20.3, 5.0 Hz), 107.32 (t, *J* = 19.4 Hz) ppm; IR (KBr) ν 3104, 3062, 1632, 1587, 1566, 1491, 1467, 1444, 1275, 1235, 1213, 1110, 1089, 1045, 999 cm⁻¹; HRMS (ES⁺) calculated for C₁₅H₁₀ClF₂N₂ [M + H]⁺ 291.0501, found 291.0494.

4-Chloro-1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (54)

Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (0.400 g, 1.3 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 70:30) afforded the title compound as a white solid (0.305 g, 0.889 mmol, 69% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.68 (s, 1H), 7.36–7.33 (m, 2H), 7.09–7.07 (m, 2H), 6.71–6.65 (m, 2H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 163.93 (dt, *J* = 253.4, 15.3 Hz), 161.04 (ddd, *J* = 253.0, 15.1, 8.4 Hz), 136.90, 135.09, 134.44, 132.62, 129.98, 126.00, 115.23, 101.87 (td, *J* = 20.3, 4.8 Hz), 101.21–100.77 (m) ppm; IR (KBr) ν 3050, 2987, 2919, 2848, 1646, 1595, 1498, 1444, 1265, 1125, 1037, 908, 735 cm⁻¹; HRMS (ES⁺) calculated for C₁₅H₈Cl₂F₃N₂ [M + H]⁺ 343.0017, found 343.0008.

4-Chloro-1-(4-chlorophenyl)-2-methyl-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (55)

Following synthetic procedure F using 4-chloro-1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (0.100 g, 0.290 mmol), purification by silica gel column chromatography (hexanes/EtOAc

90:10 to 70:30) afforded the title compound as a white solid (9 mg, 9% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.81 (s, 1H), 7.37 (d, $J = 8.4$ Hz, 2H), 7.10 (d, $J = 8.4$ Hz, 2H), 6.66 (t, $J = 9.0$ Hz, 1H), 2.12 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 163.87 (dt, $J = 253.2, 15.3$ Hz, 1C), 161.27 (ddd, $J = 252.3, 15.1, 8.5$ Hz), 145.85, 135.65, 134.21, 130.25, 129.96, 128.37, 115.30, 102.36 (td, $J = 20.6, 4.2$ Hz), 101.05–100.60 (m), 14.02 ppm; IR (KBr) ν 2962, 2927, 2852, 1644, 1585, 1495, 1442, 1400, 1122, 1038, 999 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{16}\text{H}_{10}\text{Cl}_2\text{F}_3\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 357.0173, found 357.0171.

2-Chloro-1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1H-imidazole (56)

Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1H-imidazole (0.400 g, 1.3 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 70:30) afforded the title compound as a white solid (0.058 g, 0.169 mmol, 13% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.37–7.34 (m, 2H), 7.16 (s, 1H), 7.11 (d, $J = 8.6$ Hz, 2H), 6.64–6.58 (m, 2H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 163.54 (dt, $J = 253.0, 15.2$ Hz), 161.05 (ddd, $J = 251.8, 15.1, 8.4$ Hz), 135.66, 134.53, 133.38, 130.58, 129.69, 128.62, 121.59, 103.44 (td, $J = 20.1, 4.6$ Hz), 100.99–100.54 (m) ppm; IR (KBr) ν 3459, 1645, 1599, 1568, 1495, 1447, 1124, 1034 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_8\text{Cl}_2\text{F}_3\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 343.0017, found 343.0022.

2,4-Dichloro-1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1H-imidazole (57)

Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1H-imidazole (0.400 g, 1.3 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 70:30) afforded the title compound as a white solid (0.016 g, 0.042 mmol, 3% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.39–7.36 (m, 2H), 7.12 (d, $J = 8.6$ Hz, 2H), 6.69–6.63 (m, 2H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 164.23 (dt, $J = 254.2, 15.3$ Hz), 161.26 (ddd, $J = 253.1, 15.1, 8.3$ Hz), 136.22, 132.94, 132.88, 130.83, 129.91, 128.57, 117.68, 101.61 (td, $J = 20.2, 4.9$ Hz), 101.23–100.78 (m) ppm; IR (KBr) ν 3100, 3067, 2962, 2928, 2857, 1645, 1599, 1495, 1446, 1121, 1038, 998 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_7\text{Cl}_3\text{F}_3\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 376.9627, found 376.9627.

2,4-Dichloro-1-(4-chlorophenyl)-5-(2,6-difluoro-4-methoxyphenyl)-1H-imidazole (58)

To a solution of 2,4-dichloro-1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (0.032 g, 0.085 mmol) in THF (0.53 mL) at 0 °C was added a 30% sodium methoxide solution in MeOH (0.031 mL). The reaction mixture was stirred for 16 h at r.t., then quenched with an aqueous ammonium chloride solution and extracted with EtOAc (3x). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The crude products were purified by preparative reverse-phase HPLC to obtain the title compound as a white solid (0.011 g, 0.028 mmol, 33% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.38–7.35 (m, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.41 (q, *J* = 7.3 Hz, 2H), 3.78 (s, 3H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 162.97 (t, *J* = 14.0 Hz), 161.59 (dd, *J* = 249.7, 9.1 Hz), 135.90, 133.24, 132.20, 130.42, 129.75, 118.83, 101.00 (td, *J* = 26.4, 3.1 Hz), 98.46–98.24 (m), 97.03 (t, *J* = 20.6 Hz), 56.07 ppm; IR (KBr) ν 3390, 2965, 2924, 2848, 1644, 1574, 1495, 1445, 1384, 1352, 1150 cm⁻¹; HRMS (ES⁺) calculated for C₁₆H₁₀Cl₃F₂N₂O [M + H]⁺ 388.9827, found 388.9830.

4-Chloro-1-(4-methoxyphenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (59)

Following synthetic procedure E using 1-(4-methoxyphenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (0.086 g, 0.283 mmol), purification by silica gel column chromatography (hexanes/EtOAc 80:20) afforded the title compound as a yellow solid (0.043 g, 0.127 mmol, 45% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.76 (s, 1H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.88–6.82 (m, 2H), 6.71–6.61 (m, 2H), 3.79 (s, 3H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 163.80 (dt, *J* = 252.7, 15.1 Hz), 161.21 (ddd, *J* = 252.7, 15.3, 8.6 Hz), 159.90, 137.20, 131.91, 128.82, 126.27, 115.50, 114.71, 102.27 (td, *J* = 20.4, 4.7 Hz), 101.15–100.40 (m), 55.62 ppm; IR (KBr) ν 3149, 3047, 2983, 2941, 2916, 2838, 1644, 1595, 1564, 1517, 1468, 1439, 1249, 1179, 1128, 1028 cm⁻¹; HRMS (ES⁺) calculated for C₁₆H₁₁ClF₃N₂O [M + H]⁺ 339.0512, found 339.0481.

2-Chloro-1-(4-methoxyphenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (60)

Following synthetic procedure E using 1-(4-methoxyphenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (0.086 g, 0.283 mmol), purification by silica gel column chromatography (hexanes/EtOAc 80:20) afforded the title compound as a yellow solid (0.015 g, 0.044 mmol, 16% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.14 (s, 1H), 7.11–7.06 (m, 2H), 6.89–6.84 (m, 2H), 6.64–6.56 (m, 2H), 3.81 (s, 3H) ppm; ¹³C

1 NMR (126 MHz, CDCl₃) δ 163.34 (dt, $J = 252.7, 15.4$ Hz), 161.13 (ddd, $J = 251.5, 15.0, 8.5$ Hz),
2 160.07, 134.94, 130.16, 128.51, 127.52, 121.78, 114.42, 103.86 (td, $J = 20.3, 4.7$ Hz), 101.08–100.00
3 (m), 55.59 ppm; IR (KBr) ν 3053, 2962, 2917, 2847, 1645, 1596, 1570, 1514, 1485, 1448, 1253, 1171,
4 (m), 55.59 ppm; IR (KBr) ν 3053, 2962, 2917, 2847, 1645, 1596, 1570, 1514, 1485, 1448, 1253, 1171,
5 1124, 1035 cm⁻¹; HRMS (ES⁺) calculated for C₁₆H₁₁ClF₃N₂O [M + H]⁺ 339.0512, found 339.0499.
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9 **2,4-Dichloro-1-(4-methoxyphenyl)-5-(2,4,6-trifluorophenyl)-1H-imidazole (61)**

10 Following synthetic procedure E using 1-(4-methoxyphenyl)-5-(2,4,6-trifluorophenyl)-1H-imidazole
11 (0.086 g, 0.283 mmol), purification by silica gel column chromatography (hexanes/EtOAc 80:20)
12 afforded the title compound as a yellow solid (0.010 g, 0.027 mmol, 9% yield). ¹H NMR (500 MHz;
13 CDCl₃) δ 7.11–7.06 (m, 2H), 6.89–6.84 (m, 2H), 6.67–6.60 (m, 2H), 3.81 (s, 3H) ppm; ¹³C NMR (126
14 MHz, CDCl₃) δ 164.01 (dt, $J = 253.2, 15.2$ Hz), 161.30 (ddd, $J = 252.8, 14.8, 8.5$ Hz), 160.40, 133.20,
15 131.10, 130.15, 128.99, 128.46, 127.07, 117.87, 114.60, 101.95 (td, $J = 20.2, 4.6$ Hz), 101.36–100.34
16 (m), 55.63 ppm; IR (KBr) ν 2960, 2918, 2849, 1643, 1513, 1445, 1255, 1121, 1036 cm⁻¹; HRMS (ES⁺)
17 calculated for C₁₆H₁₀Cl₂F₃N₂O [M + H]⁺ 373.0122, found 373.0112.
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31 **4-Chloro-1-(4-chlorophenyl)-5-(2,6-difluoro-3-methylphenyl)-1H-imidazole (62)**

32 Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluoro-3-methylphenyl)-1H-
33 imidazole (0.326 g, 1.07 mmol), purification by silica gel column chromatography (hexanes/EtOAc
34 100:0 to 80:20) afforded the title compound as a beige solid (0.187 g, 0.551 mmol, 52% yield). ¹H NMR
35 (500 MHz, CDCl₃) δ 7.73 (s, 1H), 7.36–7.33 (m, 2H), 7.22 (q, $J = 7.5$ Hz, 1H), 7.14–7.11 (m, 2H), 6.81
36 (td, $J = 8.5, 0.9$ Hz, 1H), 2.22 (s, 3H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 158.49 (ddd, $J = 249.9, 12.8,$
37 5.7 Hz), 136.49, 134.57, 134.56, 133.20 (dd, $J = 9.5, 7.1$ Hz), 131.96, 129.69, 125.74, 121.03 (dd, $J =$
38 17.6, 3.8 Hz), 116.38, 110.95 (dd, $J = 21.2, 3.9$ Hz), 104.53 (t, $J = 20.1$ Hz), 14.10 (d, $J = 3.2$ Hz) ppm;
39 IR (KBr) ν 3121, 3096, 2924, 2852, 1497, 1482, 1265, 1093, 958 cm⁻¹; HRMS (ES⁺) calculated for
40 C₁₆H₁₁Cl₂F₂N₂ [M + H]⁺ 339.0267, found 339.0269.
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55 **2-Chloro-1-(4-chlorophenyl)-5-(2,6-difluoro-3-methylphenyl)-1H-imidazole (63)**

56 Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluoro-3-methylphenyl)-1H-
57 imidazole (0.326 g, 1.07 mmol), purification by silica gel column chromatography (hexanes/EtOAc
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100:0 to 80:20) afforded the title compound as a brown solid (0.030 g, 0.088 mmol, 8% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.35–7.32 (m, 2H), 7.16 (s, 1H), 7.14–7.08 (m, 3H), 6.71 (td, $J = 8.5, 1.1$ Hz, 1H), 2.15 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 158.66 (ddd, $J = 248.9, 13.9, 5.4$ Hz), 135.30, 134.12, 133.71, 132.66 (t, $J = 8.2$ Hz), 130.33, 129.48, 128.68, 123.01, 120.95 (dd, $J = 18.0, 4.0$ Hz), 110.88 (dd, $J = 21.7, 3.8$ Hz), 106.33 (t, $J = 20.1$ Hz), 14.27 (d, $J = 3.1$ Hz) ppm; IR (KBr) ν 3445, 2919, 2848, 1496, 1478, 1443, 1093, 1042 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{16}\text{H}_{11}\text{Cl}_2\text{F}_2\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 339.0267, found 339.0257.

4-Chloro-5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole (64)

Following synthetic procedure E using 5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole (0.280 g, 0.434 mmol, 0.861 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 80:20) afforded the title compound as a yellow solid (0.156 g, 0.434 mmol, 50% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.69 (s, 1H), 7.41 (td, $J = 8.6, 5.6$ Hz, 1H), 7.34–7.31 (m, 2H), 7.09–7.06 (m, 2H), 6.88–6.84 (m, 1H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 158.79 (dd, $J = 252.6, 4.4$ Hz), 155.89 (dd, $J = 253.6, 6.2$ Hz), 137.09, 135.05, 134.27, 132.65, 132.28 (d, $J = 9.6$ Hz), 129.97, 125.85, 117.26 (dd, $J = 18.4, 4.1$ Hz), 115.25, 112.37 (dd, $J = 23.3, 4.2$ Hz), 106.79 (t, $J = 20.1$ Hz) ppm; IR (KBr) ν 3121, 3104, 3075, 2932, 2848, 1558, 1497, 1472, 1453, 1267, 1092 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_8\text{Cl}_3\text{F}_2\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 358.9721, found 358.9724.

4-Chloro-5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-2-methyl-1*H*-imidazole (65)

Following synthetic procedure F using 4-chloro-5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole (0.078 g, 0.216 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 80:20) afforded the title compound as a brown solid (0.039 g, 0.104 mmol, 48% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.38–7.33 (m, 3H), 7.07 (d, $J = 8.6$ Hz, 2H), 6.83–6.79 (m, 1H), 2.30 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 159.02 (dd, $J = 251.5, 4.4$ Hz), 156.10 (dd, $J = 252.9, 6.3$ Hz), 146.08, 135.50, 134.14, 132.05 (d, $J = 9.6$ Hz), 130.54, 129.91, 128.29, 117.08 (dd, $J = 18.5, 4.1$ Hz), 115.24, 112.19 (dd, $J = 23.5, 4.4$ Hz), 107.42 (t, $J = 20.5$ Hz), 14.06 ppm; IR (KBr) ν

3100, 3071, 2928, 2848, 1558, 1495, 1465, 1399, 1495, 1465, 1399, 1338, 1287, 1242, 1219, 1092, 1011, 997 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{16}\text{H}_{10}\text{Cl}_3\text{F}_2\text{N}_2$ $[\text{M} + \text{H}]^+$ 372.9878, found 372.9864.

2-Chloro-5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole (66)

Following synthetic procedure E using 5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole (0.280 g, 0.861 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 80:20) afforded the title compound as a yellow solid (0.050 g, 0.139 mmol, 16% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.37–7.32 (m, 3H), 7.20 (s, 1H), 7.14–7.11 (m, 2H), 6.80 (td, $J = 8.6, 1.4$ Hz, 1H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 158.83 (dd, $J = 251.3, 4.1$ Hz), 155.97 (dd, $J = 252.5, 6.2$ Hz), 135.64, 134.85, 133.35, 131.78, 131.70, 130.88, 129.69, 128.57, 121.65, 117.22 (dd, $J = 18.6, 4.1$ Hz), 112.19 (dd, $J = 23.6, 4.3$ Hz), 108.44 (t, $J = 20.3$ Hz) ppm; IR (KBr) ν 3100, 3071, 2928, 2857, 1683, 1652, 1635, 1558, 1538, 1495 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_8\text{Cl}_3\text{F}_2\text{N}_2$ $[\text{M} + \text{H}]^+$ 358.9721, found 358.9717.

5-(3-Bromo-2,6-difluorophenyl)-4-chloro-1-(4-chlorophenyl)-1*H*-imidazole (67)

Following synthetic procedure E using 5-(3-bromo-2,6-difluorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole (0.452 g, 1.223 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 80:20) afforded the title compound as a brown solid (0.224 g, 0.554 mmol, 45% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.68 (s, 1H), 7.55 (ddd, $J = 8.9, 7.7, 5.8$ Hz, 1H), 7.33–7.31 (m, 2H), 7.08–7.06 (m, 2H), 6.83–6.79 (m, 1H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 159.51 (dd, $J = 252.8, 4.5$ Hz), 156.83 (dd, $J = 252.0, 6.2$ Hz), 137.04, 135.14, 135.07, 135.06 (d, $J = 1.3$ Hz), 135.06, 135.00, 134.23, 132.59, 129.93, 125.81, 115.25, 112.89 (dd, $J = 22.8, 4.2$ Hz, 1C), 106.70 (t, $J = 20.7$ Hz), 104.44 (dd, $J = 21.8, 4.3$ Hz) ppm; IR (KBr) ν 3092, 2915, 2848, 1558, 1497, 1471, 1327, 1267, 1216, 1090, 1015, 999, 959 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_8\text{BrCl}_2\text{F}_2\text{N}_2$ $[\text{M} + \text{H}]^+$ 402.9216, found 402.9217.

4-Chloro-1-(4-chlorophenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (68)

Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (0.406 g, 1.316 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 80:20) afforded the title compound as a beige solid (0.244 g, 0.711 mmol, 55% yield). ^1H NMR

(500 MHz, CDCl₃) δ 7.69 (s, 1H), 7.33–7.31 (m, 2H), 7.18 (qd, $J = 9.1, 5.0$ Hz, 1H), 7.09–7.07 (m, 2H), 6.85–6.80 (m, 1H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 155.66 (dt, $J = 248.9, 2.9$ Hz), 148.20 (ddd, $J = 253.9, 14.4, 6.4$ Hz), 147.08 (ddd, $J = 246.5, 12.7, 3.7$ Hz), 137.12, 135.02, 134.27, 132.63, 129.92, 125.83, 118.88 (dd, $J = 19.6, 9.5$ Hz), 115.11 (d, $J = 1.9$ Hz), 111.25 (ddd, $J = 24.1, 6.5, 4.4$ Hz), 107.09 (dd, $J = 21.5, 15.8$ Hz) ppm; IR (KBr) ν 3054, 2987, 2924, 2852, 1499, 1265, 739, 704 cm⁻¹; HRMS (ES⁺) calculated for C₁₅H₈Cl₂F₃N₂ [M + H]⁺ 343.0017, found 343.0005.

2-Chloro-1-(4-chlorophenyl)-5-(2,3,6-trifluorophenyl)-1H-imidazole (69)

Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,3,6-trifluorophenyl)-1H-imidazole (0.406 g, 1.316 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 80:20) afforded the title compound as a brown solid (0.220 g, 0.641 mmol, 5% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.36 (d, $J = 8.6$ Hz, 2H), 7.22 (s, 1H), 7.16–7.08 (m, 3H), 6.81–6.76 (m, 1H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 155.76 (dt, $J = 247.8, 3.0$ Hz), 148.33 (ddd, $J = 252.7, 14.5, 6.2$ Hz), 147.14 (ddd, $J = 246.7, 13.0, 3.7$ Hz), 135.73, 134.93, 133.32, 130.74, 130.06, 129.72, 128.59, 121.62, 118.53–118.29 (m), 111.11 (ddd, $J = 24.5, 6.5, 4.4$ Hz), 108.71 (dd, $J = 21.7, 15.9$ Hz) ppm; IR (KBr) ν 3092, 3058, 2924, 2857, 1496, 1461, 1433, 1318, 1235, 1094 cm⁻¹; HRMS (ES⁺) calculated for C₁₅H₈Cl₂F₃N₂ [M + H]⁺ 343.0017, found 343.0007.

4-Chloro-1-(4-chloro-3-fluorophenyl)-5-(2,3,6-trifluorophenyl)-1H-imidazole (70)

Following synthetic procedure E using 1-(4-chloro-3-fluorophenyl)-5-(2,3,6-trifluorophenyl)-1H-imidazole (0.370 g, 1.13 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 60:40) afforded the title compound as a yellow solid (0.126 g, 0.349 mmol, 31% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.72 (s, 1H), 7.40 (t, $J = 8.1$ Hz, 1H), 7.22 (qd, $J = 9.1, 5.0$ Hz, 1H), 6.99 (dd, $J = 8.8, 2.3$ Hz, 1H), 6.91 (dd, $J = 8.5, 1.0$ Hz, 1H), 6.89–6.84 (m, 1H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 158.05 (d, $J = 252.6$ Hz), 155.63 (dt, $J = 248.8, 2.8$ Hz), 148.20 (ddd, $J = 254.0, 14.4, 6.4$ Hz), 147.17 (ddd, $J = 246.9, 12.7, 3.7$ Hz), 137.11, 135.29 (d, $J = 8.7$ Hz), 133.06, 131.69, 122.28, 122.14, 121.01 (d, $J = 3.8$ Hz), 119.14 (dd, $J = 19.9, 9.7$ Hz), 115.09 (d, $J = 1.5$ Hz), 113.32 (d, $J = 24.0$ Hz), 111.42 (ddd, $J = 24.1, 6.6, 4.3$ Hz), 106.82 (dd, $J = 21.5, 15.9$ Hz) ppm; IR (KBr) ν 3126, 3096, 3058,

2915, 2848, 1497, 1266, 1225, 1197, 1004, 888, 863, 814, 738 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_7\text{Cl}_2\text{F}_4\text{N}_2$ $[\text{M} + \text{H}]^+$ 360.9922, found 360.9917.

4-Chloro-1-(4-chloro-3-fluorophenyl)-2-methyl-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (71)

Following synthetic procedure F using 4-chloro-1-(4-chloro-3-fluorophenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (0.100 g, 0.277 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 90:10) afforded the title compound as a white solid (0.014 g, 0.037 mmol, 13% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.43 (t, $J = 8.1$ Hz, 1H), 7.17 (qd, $J = 9.1, 5.0$ Hz, 1H), 6.99 (dd, $J = 8.8, 2.2$ Hz, 1H), 6.91 (d, $J = 8.5$ Hz, 1H), 6.84–6.80 (m, 1H), 2.33 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 158.00 (d, $J = 253.0$ Hz), 155.94 (dt, $J = 248.2, 3.0$ Hz), 148.48 (ddd, $J = 253.4, 14.4, 6.3$ Hz), 147.17 (ddd, $J = 244.4, 12.9, 3.8$ Hz), 146.11, 135.15 (d, $J = 8.6$ Hz), 131.59, 130.83, 123.69 (d, $J = 3.8$ Hz), 122.96 (d, $J = 17.4$ Hz), 118.97 (dd, $J = 19.6, 9.8$ Hz), 115.86 (d, $J = 23.1$ Hz), 115.23 (d, $J = 2.1$ Hz), 111.22 (ddd, $J = 24.3, 6.7, 4.3$ Hz), 107.44 (dd, $J = 21.9, 16.1$ Hz), 14.05 ppm; IR (KBr) ν 1493, 1435, 1394, 1249, 1234, 1222, 1077, 1058, 997 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{16}\text{H}_9\text{Cl}_2\text{F}_4\text{N}_2$ $[\text{M} + \text{H}]^+$ 375.0079, found 375.0070.

2-Chloro-1-(4-chloro-3-fluorophenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (72)

Following synthetic procedure E using 1-(4-chloro-3-fluorophenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (0.370 g, 1.13 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 60:40) afforded the title compound as a yellow solid (0.074 g, 0.205 mmol, 18% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.42 (t, $J = 8.1$ Hz, 1H), 7.21 (s, 1H), 7.14 (qd, $J = 9.0, 5.0$ Hz, 1H), 7.05 (dd, $J = 8.8, 2.3$ Hz, 1H), 6.94 (d, $J = 8.3$ Hz, 1H), 6.81 (tdd, $J = 8.7, 3.3, 1.9$ Hz, 1H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 157.84 (d, $J = 252.4$ Hz), 155.60 (dt, $J = 248.0, 2.9$ Hz), 148.19 (ddd, $J = 253.1, 14.6, 6.0$ Hz), 147.11 (ddd, $J = 247.0, 12.8, 3.6$ Hz), 134.77, 134.25 (d, $J = 8.6$ Hz), 131.23, 131.08, 123.87 (d, $J = 3.8$ Hz), 122.93, 122.79, 121.47 (d, $J = 1.3$ Hz), 118.53 (dd, $J = 19.2, 9.9$ Hz), 116.11 (d, $J = 23.5$ Hz), 111.23 (ddd, $J = 24.4, 6.5, 4.4$ Hz), 108.37 (dd, $J = 21.6, 15.9$ Hz) ppm; IR (KBr) ν 3094, 3058, 2932, 2860, 1587, 1494, 1459, 1426, 1313, 1238, 1074, 1009 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_7\text{Cl}_2\text{F}_4\text{N}_2$ $[\text{M} + \text{H}]^+$ 360.9922, found 360.9917.

2-Chloro-5-(4-chloro-5-(2,4,6-trifluorophenyl)-1*H*-imidazol-1-yl)pyridine (73)

Following synthetic procedure E using 2-chloro-5-(5-(2,4,6-trifluorophenyl)-1*H*-imidazol-1-yl)pyridine (0.304 g, 0.98 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 70:30) afforded the title compound as a brown solid (0.172 g, 0.500 mmol, 51% yield). ¹H NMR (500 MHz, CDCl₃) δ 8.24 (d, *J* = 2.7 Hz, 1H), 7.71 (s, 1H), 7.47 (dd, *J* = 8.4, 2.6 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 6.71 (t, *J* = 8.0 Hz, 2H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 164.22 (dt, *J* = 254.5, 15.2 Hz), 160.97 (ddd, *J* = 253.1, 15.1, 8.4 Hz), 151.97, 145.53, 136.91, 134.87, 133.36, 131.72, 125.18, 115.41, 101.48–101.04 (m) ppm; IR (KBr) ν 3100, 3058, 1646, 1599, 1575, 1558 cm⁻¹; HRMS (ES⁺) calculated for C₁₄H₇Cl₂F₃N₃ [M + H]⁺ 343.9969, found 343.9976.

2-Chloro-5-(4-chloro-2-methyl-5-(2,4,6-trifluorophenyl)-1*H*-imidazol-1-yl)pyridine (74)

Following synthetic procedure F using 2-chloro-5-(4-chloro-5-(2,4,6-trifluorophenyl)-1*H*-imidazol-1-yl)pyridine (0.120 g, 0.349 mmol), purification by reverse-phase HPLC afforded the title compound as a white solid (0.003 g, 0.008 mmol, 2% yield). ¹H NMR (500 MHz, CDCl₃) δ 8.24 (d, *J* = 2.6 Hz, 1H), 7.48 (dd, *J* = 8.4, 2.6 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 1H), 6.68 (t, *J* = 8.0 Hz, 2H), 2.38 (s, 3H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 164.28 (dt, *J* = 254.7, 15.4 Hz), 161.13 (ddd, *J* = 252.8, 15.0, 8.4 Hz), 152.78, 152.31, 147.82, 146.34, 145.63, 137.11, 134.97, 131.20, 130.32, 125.31, 115.88, 101.21 (td, *J* = 26.1, 3.8 Hz), 13.68 ppm; IR (KBr) ν 3067, 2962, 2924, 1733, 1683, 1646, 1558, 1539, 1506 cm⁻¹; HRMS (ES⁺) calculated for C₁₅H₉Cl₂F₃N₃ [M + H]⁺ 358.0126, found 358.0123.

2-Chloro-1-(4-chlorophenyl)-5-(4-fluorophenyl)-1*H*-imidazole (75)

Following synthetic procedure E using 1-(4-chlorophenyl)-5-(4-fluorophenyl)-1*H*-imidazole (0.124 g, 0.455 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 80:20) afforded the title compound as a yellow solid (0.009 g, 0.029 mmol, 7% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.58 (s, 1H), 7.37–7.31 (m, 4H), 7.20–7.19 (m, 2H), 7.06 (d, *J* = 8.0 Hz, 2H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 162.62 (d, *J* = 249.6 Hz), 135.75, 135.01, 134.79, 134.58, 131.70 (d, *J* = 8.3 Hz), 130.05, 129.94, 129.81, 128.65, 128.49, 127.38, 126.69, 126.66, 116.02, 115.84 ppm; IR (KBr) ν 3067,

2924, 2852, 1562, 1496 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_{10}\text{Cl}_2\text{FN}_2$ $[\text{M} + \text{H}]^+$ 307.0205, found 307.0210.

4-Chloro-1-(4-chlorophenyl)-5-(4-fluorophenyl)-1*H*-imidazole (76)

Following synthetic procedure E using 1-(4-chlorophenyl)-5-(4-fluorophenyl)-1*H*-imidazole (0.124 g, 0.455 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 80:20) afforded the title compound as a white solid (0.060 g, 0.195 mmol, 43% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.57 (s, 1H), 7.36–7.33 (m, 2H), 7.18–7.15 (m, 2H), 7.06–6.99 (m, 4H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 162.58 (d, $J = 249.6$ Hz), 135.74, 134.73 (d, $J = 3.7$ Hz), 131.66 (d, $J = 8.2$ Hz), 129.99, 129.33, 126.66, 126.23, 123.39 (d, $J = 3.4$ Hz), 115.96, 115.78 ppm; IR (KBr) ν 3117, 3062, 2962, 2916, 2848, 1683, 1652, 1599, 1575, 1558, 1497 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_{10}\text{Cl}_2\text{FN}_2$ $[\text{M} + \text{H}]^+$ 307.0205, found 307.0206.

2-Chloro-1-(4-chloro-2-fluorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (77)

Following synthetic procedure E using 1-(4-chloro-2-fluorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (0.351 g, 1.14 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 80:20) afforded the title compound as a yellow solid (0.025 g, 0.073 mmol, 6% yield). ^1H NMR (500 MHz; CDCl_3) δ 7.31–7.26 (m, 1H), 7.22 (s, 1H), 7.19 (d, $J = 9.3$ Hz, 1H), 7.15 (d, $J = 3.1$ Hz, 2H), 6.85 (t, $J = 7.6$ Hz, 2H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 160.60 (dd, $J = 251.4, 5.9$ Hz), 157.37 (d, $J = 257.9$ Hz), 136.78 (d, $J = 9.2$ Hz), 134.86, 131.52 (t, $J = 10.3$ Hz), 130.78, 130.32, 125.13, 125.10, 122.95, 121.74 (d, $J = 13.0$ Hz), 117.73 (d, $J = 23.1$ Hz), 111.69 (dd, $J = 20.5, 5.0$ Hz), 106.50 (t, $J = 19.5$ Hz) ppm; IR (KBr) ν 3104, 3071, 2936, 2860, 1683, 1652, 1634, 1587, 1558, 1538, 1505 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_8\text{Cl}_2\text{F}_3\text{N}_2$ $[\text{M} + \text{H}]^+$ 343.0017, found 343.0013.

4-Chloro-1-(4-chloro-2-fluorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (78)

Following synthetic procedure E using 1-(4-chloro-2-fluorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (0.351 g, 1.14 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 80:20) afforded the title compound as a yellow solid (0.126 g, 0.367 mmol, 32% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.65 (s, 1H), 7.38–7.33 (m, 1H), 7.19–7.17 (m, 1H), 7.13 (q, $J = 6.4$ Hz,

2H), 6.90 (t, $J = 7.8$ Hz, 2H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 160.74 (dd, $J = 252.5, 5.9$ Hz), 156.36 (d, $J = 256.9$ Hz), 137.49, 136.16 (d, $J = 9.2$ Hz), 132.18, 132.13 (t, $J = 10.1$ Hz), 128.61, 125.34 (d, $J = 3.7$ Hz), 122.69 (d, $J = 12.6$ Hz), 117.87 (d, $J = 22.8$ Hz), 116.88, 111.80 (dd, $J = 20.6, 4.5$ Hz), 105.04 (t, $J = 19.6$ Hz) ppm; IR (KBr) ν 3105, 2932, 1683, 1652, 1634, 1590, 1568, 1506 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_8\text{Cl}_2\text{F}_3\text{N}_2$ $[\text{M} + \text{H}]^+$ 343.0017, found 343.0018.

2-Chloro-1-(4-chlorophenyl)-5-(2,5-difluorophenyl)-1*H*-imidazole (79)

Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,5-difluorophenyl)-1*H*-imidazole (0.300 g, 1.03 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 50:50) afforded the title compound as a yellow solid (0.010 g, 0.031 mmol, 3% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.41–7.38 (m, 2H), 7.22 (s, 1H), 7.15–7.12 (m, 2H), 6.98–6.94 (m, 2H), 6.81–6.77 (m, 1H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 158.39 (dd, $J = 245.6, 4.0$ Hz), 155.71 (dd, $J = 247.1, 3.7$ Hz), 135.57, 134.62, 133.73, 129.79, 129.68 (d, $J = 2.8$ Hz), 128.87, 128.49, 118.43 (dd, $J = 16.0, 10.3$ Hz), 117.45–116.90 (m) ppm; IR (KBr) ν 3071, 2932, 2857, 1495 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_9\text{Cl}_2\text{F}_2\text{N}_2$ $[\text{M} + \text{H}]^+$ 325.0111, found 325.0110.

4-Chloro-1-(4-chlorophenyl)-5-(2,5-difluorophenyl)-1*H*-imidazole (80)

Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,5-difluorophenyl)-1*H*-imidazole (0.300 g, 1.03 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 50:50) afforded the title compound as a yellow solid (0.030 g, 0.092 mmol, 9% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.64 (s, 1H), 7.35–7.33 (m, 2H), 7.10–7.03 (m, 4H), 6.96 (td, $J = 8.8, 4.5$ Hz, 1H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 158.48 (dd, $J = 244.1, 2.0$ Hz), 155.77 (dd, $J = 246.1, 1.7$ Hz), 144.02, 136.41, 134.84, 134.79, 131.12, 129.97, 129.80, 129.45, 127.34, 125.83, 123.07, 121.05, 118.61 (dd, $J = 24.9, 2.7$ Hz), 117.94 (dd, $J = 24.0, 8.5$ Hz), 117.36 (dd, $J = 24.5, 8.9$ Hz), 116.91 (dd, $J = 18.1, 9.0$ Hz) ppm; IR (KBr) ν 3126, 3100, 3067, 2924, 2857, 1733, 1683, 1652, 1558, 1539, 1497 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_9\text{Cl}_2\text{F}_2\text{N}_2$ $[\text{M} + \text{H}]^+$ 325.0111, found 325.0095.

4-Chloro-5-(2,6-difluorophenyl)-1-(4-(trifluoromethoxy)phenyl)-1*H*-imidazole (81)

1 Following synthetic procedure E using 5-(2,6-difluorophenyl)-1-(4-(trifluoromethoxy)phenyl)-1*H*-
2 imidazole (0.400 g, 1.17 mmol), purification by silica gel column chromatography (hexanes/EtOAc
3 85:15) afforded the title compound as a white solid (0.192 g, 0.512 mmol, 44% yield). ¹H NMR
4 (500 MHz, CDCl₃) δ 7.70 (s, 1H), 7.43–7.33 (m, 1H), 7.24–7.16 (m, 4H), 6.91 (t, *J* = 7.8 Hz, 2H) ppm;
5 ¹³C NMR (126 MHz, CDCl₃) δ 160.71 (dd, *J* = 252.1, 6.0 Hz), 149.23–149.16 (m), 136.84, 134.52,
6 132.53, 132.20 (t, *J* = 10.2 Hz), 126.25, 122.01, 120.39 (q, *J* = 238.7 Hz), 116.18, 111.88 (dd, *J* = 20.5,
7 5.1 Hz), 105.32 (t, *J* = 19.7 Hz) ppm; IR (KBr) ν 3121, 3088, 1632, 1588, 1565, 1513, 1473, 1330,
8 1259, 1212, 1169, 1099 cm⁻¹; HRMS (ES⁺) calculated for C₁₆H₉ClF₅N₂O [M + H]⁺ 375.0324, found
9 375.0334.

22 **2-Chloro-5-(2,6-difluorophenyl)-1-(4-(trifluoromethoxy)phenyl)-1*H*-imidazole (82)**

23 Following synthetic procedure E using 5-(2,6-difluorophenyl)-1-(4-(trifluoromethoxy)phenyl)-1*H*-
24 imidazole (0.400 g, 1.17 mmol), purification by silica gel column chromatography (hexanes/EtOAc
25 85:15) afforded the title compound as a white solid (0.033 g, 0.088 mmol, 8% yield). ¹H NMR
26 (500 MHz, CDCl₃) δ 7.34–7.25 (m, 1H), 7.27–7.20 (m, 4H), 7.20 (s, 1H), 6.88–6.82 (m, 2H) ppm; ¹³C
27 NMR (126 MHz, CDCl₃) δ 160.59 (dd, *J* = 251.3, 5.8 Hz), 149.51–149.44 (m), 134.36, 133.35, 131.57
28 (t, *J* = 10.2 Hz), 130.53, 128.96, 122.52, 121.41, 120.39 (q, *J* = 259.6 Hz), 111.67 (dd, *J* = 21.2, 4.6 Hz),
29 106.84 (t, *J* = 19.5 Hz) ppm; IR (KBr) ν 3077, 2920, 2852, 1632, 1586, 1511, 1469, 1436, 1388, 1261,
30 1211, 1172, 1001 cm⁻¹; HRMS (ES⁺) calculated for C₁₆H₈ClF₅N₂NaO [M + Na]⁺ 397.0143, found
31 397.0149.

45 **2,4-Dichloro-5-(2,6-difluorophenyl)-1-(4-(trifluoromethoxy)phenyl)-1*H*-imidazole (83)**

46 Following synthetic procedure E using 5-(2,6-difluorophenyl)-1-(4-(trifluoromethoxy)phenyl)-1*H*-
47 imidazole (0.400 g, 1.17 mmol), purification by silica gel column chromatography (hexanes/EtOAc
48 85:15) afforded the title compound as a white solid (0.028 g, 0.068 mmol, 6% yield). ¹H NMR
49 (500 MHz, CDCl₃) δ 7.40–7.30 (m, 1H), 7.27–7.19 (m, 4H), 6.91–6.84 (m, 2H) ppm; ¹³C NMR
50 (126 MHz, CDCl₃) δ 160.74 (dd, *J* = 252.3, 5.6 Hz), 149.85–149.77 (m), 132.76, 132.65, 132.61 (t, *J* =
51 10.3 Hz), 130.50, 128.96, 121.54, 120.34 (q, *J* = 258.7 Hz), 118.60, 111.81 (dd, *J* = 21.0, 4.3 Hz),
52 53 54 55 56 57 58 59 60

104.93 (t, $J = 19.4$ Hz) ppm; IR (KBr) ν 3079, 2921, 2851, 1633, 1590, 1570, 1511, 1468, 1439, 1388, 1263, 1213, 1174 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{16}\text{H}_8\text{Cl}_2\text{F}_5\text{N}_2\text{O}$ [$\text{M} + \text{H}$] $^+$ 408.9934, found 408.9940.

4-Chloro-1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (84)

Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (0.400 g, 1.38 mmol), purification by silica gel column chromatography (hexanes/EtOAc 85:15) afforded the title compound as a white solid (0.265 g, 0.815 mmol, 59% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.69 (s, 1H), 7.41–7.35 (m, 1H), 7.33 (d, $J = 8.0$ Hz, 2H), 7.12–7.05 (m, 2H), 6.91 (t, $J = 7.9$ Hz, 2H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 160.67 (dd, $J = 252.0, 5.9$ Hz), 136.75, 134.89, 134.65, 132.40, 132.12 (t, $J = 10.1$ Hz), 129.91, 125.93, 116.10, 111.88 (dd, $J = 21.1, 4.3$ Hz), 105.36 (t, $J = 19.5$ Hz) ppm; IR (KBr) ν 3128, 2917, 2849, 1631, 1587, 1564, 1497, 1470, 1453, 1383, 1265, 1236, 1091, 998 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_9\text{Cl}_2\text{F}_2\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 325.0111, found 325.0122.

4-Chloro-1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-2-methyl-1*H*-imidazole (85)

Following synthetic procedure F using 4-chloro-1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (0.050 g, 0.154 mmol), purification by silica gel column chromatography (hexanes/EtOAc 80:20) afforded the title compound as a white solid (0.020 g, 0.059 mmol, 38% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.37–7.31 (m, 2H), 7.31–7.27 (m, 1H), 7.08 (d, $J = 8.6$ Hz, 2H), 6.89–6.82 (m, 2H), 2.31 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 160.83 (dd, $J = 250.5, 6.9$ Hz), 145.60, 135.23, 134.48, 131.79 (t, $J = 10.1$ Hz), 130.20, 129.75, 128.37, 116.02, 111.63 (dd, $J = 20.4, 4.8$ Hz), 105.96 (t, $J = 17.7$ Hz), 14.13 ppm; IR (KBr) ν 3064, 2960, 2921, 2850, 1634, 1576, 1494, 1467, 1402, 1278, 1238, 1093, 999 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{16}\text{H}_{11}\text{Cl}_2\text{F}_2\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 339.0267, found 339.0265.

4-Chloro-1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-2-ethyl-1*H*-imidazole (86)

Following synthetic procedure F using 4-chloro-1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (0.040 g, 0.123 mmol), purification by silica gel column chromatography (hexanes/EtOAc 85:15) afforded the title compound as a white solid (0.015 g, 0.042 mmol, 35% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.36–7.30 (m, 2H), 7.30–7.27 (m, 1H), 7.09 (d, $J = 8.5$ Hz, 2H), 6.87–6.81 (m,

2H), 2.58 (q, $J = 7.5$ Hz, 2H), 1.26 (t, $J = 7.4$ Hz, 3H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 160.87 (dd, $J = 251.5, 5.8$ Hz), 150.43, 135.27, 134.34, 131.77 (t, $J = 10.3$ Hz), 130.33, 129.71, 128.59, 115.90, 111.61 (dd, $J = 20.7, 5.4$ Hz), 105.96 (t, $J = 20.3$ Hz), 21.16, 12.21 ppm; IR (KBr) ν 3070, 2973, 2923, 2852, 1633, 1586, 1494, 1468, 1411, 1276, 1238, 1092, 1001 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{17}\text{H}_{13}\text{Cl}_2\text{F}_2\text{N}_2$ $[\text{M} + \text{H}]^+$ 353.0424, found 353.0429.

2-Chloro-1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (87)

Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (0.400 g, 1.38 mmol), purification by silica gel column chromatography (hexanes/EtOAc 85:15) afforded the title compound as a white solid (0.056 g, 0.172 mmol, 12% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.36–7.31 (m, 2H), 7.31–7.23 (m, 1H), 7.18 (s, 1H), 7.12 (d, $J = 8.2$ Hz, 2H), 6.84 (t, $J = 7.9$ Hz, 2H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 160.33 (dd, $J = 251.1, 5.8$ Hz), 135.10, 134.03, 133.32, 131.24 (t, $J = 10.3$ Hz), 130.21, 129.27, 128.36, 122.21, 111.39 (dd, $J = 20.4, 4.8$ Hz), 106.64 (t, $J = 19.5$ Hz) ppm; IR (KBr) ν 3098, 3063, 2919, 2847, 1632, 1585, 1564, 1495, 1468, 1434, 1384, 1315, 1276, 1235, 1092, 1001 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_8\text{Cl}_2\text{F}_2\text{N}_2\text{Na}$ $[\text{M} + \text{Na}]^+$ 346.9930, found 346.9933.

2,4-Dichloro-1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (88)

Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (0.400 g, 1.38 mmol), purification by silica gel column chromatography (hexanes/EtOAc 85:15) afforded the title compound as a white solid (0.026 g, 0.072 mmol, 5% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.39–7.30 (m, 3H), 7.13 (d, $J = 8.1$ Hz, 2H), 6.88 (t, $J = 8.0$ Hz, 2H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 160.75 (dd, $J = 252.3, 5.6$ Hz), 135.94, 133.03, 132.59, 132.54 (t, $J = 10.2$ Hz), 130.43, 129.75, 128.57, 118.55, 111.81 (dd, $J = 21.2, 4.2$ Hz), 105.00 (t, $J = 19.7$ Hz) ppm; IR (KBr) ν 2961, 2918, 2850, 1632, 1589, 1568, 1495, 1468, 1434, 1384, 1262, 1236, 1092, 1003 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_8\text{Cl}_3\text{F}_2\text{N}_2$ $[\text{M} + \text{H}]^+$ 358.9721, found 358.9725.

4-Chloro-1-(4-(trifluoromethoxy)phenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (89)

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Following synthetic procedure E using 1-(4-(trifluoromethoxy)phenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (0.500 g, 1.40 mmol), purification by silica gel column chromatography (hexanes/EtOAc 85:15) afforded the title compound as a yellow oil (0.198 g, 0.504 mmol, 36% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.72 (s, 1H), 7.25–7.17 (m, 5H), 6.88–6.82 (m, 1H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 155.78 (dt, *J* = 248.9, 3.1 Hz), 149.38 – 149.32 (m), 148.35 (ddd, *J* = 253.2, 14.1, 6.8 Hz), 147.23 (ddd, *J* = 247.2, 12.8, 3.7 Hz), 137.27, 134.21, 132.94, 126.29, 122.13, 120.36 (q, *J* = 258.7 Hz), 119.05 (dd, *J* = 19.2, 9.6 Hz), 115.30, 111.35 (ddd, *J* = 24.2, 6.8, 4.2 Hz), 107.15 (dd, *J* = 21.7, 15.8 Hz) ppm; IR (KBr) ν 3095, 2918, 2850, 1568, 1513, 1493, 1467, 1383, 1162, 1110, 999 cm⁻¹; HRMS (ES⁺) calculated for C₁₆H₇ClF₆N₂NaO [M + Na]⁺ 415.0049, found 415.0059.

2-Chloro-1-(4-(trifluoromethoxy)phenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (90)

Following synthetic procedure E using 1-(4-(trifluoromethoxy)phenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (0.500 g, 1.40 mmol), purification by silica gel column chromatography (hexanes/EtOAc 85:15) afforded the title compound as a yellow solid (0.047 g, 0.120 mmol, 9% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.29–7.24 (m, 5H), 7.16 (qd, *J* = 9.1, 5.0 Hz, 1H), 6.86–6.78 (m, 1H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 155.69 (dt, *J* = 248.0, 3.1 Hz), 149.67–149.59 (m), 148.28 (ddd, *J* = 252.4, 14.7, 5.9 Hz), 147.13 (ddd, *J* = 246.5, 12.4, 3.6 Hz), 134.96, 133.11, 130.95, 128.93, 121.59, 121.52, 120.37 (q, *J* = 258.7 Hz), 118.40 (dd, *J* = 19.2, 9.7 Hz), 111.10 (ddd, *J* = 24.3, 6.7, 4.1 Hz), 108.67 (dd, *J* = 21.8, 15.9 Hz) ppm; IR (KBr) ν 3081, 2920, 1511, 1493, 1460, 1433, 1387, 1260, 1211, 1172, 1113, 1018, 998 cm⁻¹; HRMS (ES⁺) calculated for C₁₆H₈ClF₆N₂O [M + H]⁺ 393.0229, found 393.0232.

2,4-Dichloro-1-(4-(trifluoromethoxy)phenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (91)

Following synthetic procedure E using 1-(4-(trifluoromethoxy)phenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (0.500 g, 1.40 mmol), purification by silica gel column chromatography (hexanes/EtOAc 85:15) afforded the title compound as a yellow solid (0.010 g, 0.023 mmol, 2% yield). ¹H NMR (600 MHz, DMSO-*d*₆) δ 7.72 – 7.63 (m, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.53 – 7.48 (m, 2H), 7.27 – 7.21 (m, 1H). ppm; ¹³C NMR (151 MHz, DMSO-*d*₆) δ 155.16 (dt, *J* = 248.0, 3.1 Hz), 148.96 (q, *J* = 2.0 Hz), 147.29 (ddd, *J* = 252.1, 14.5, 6.2 Hz), 146.31 (ddd, *J* = 244.4, 12.4, 4.1 Hz), 133.01, 132.51, 129.62,

1 129.15, 122.11, 120.66 (dd, $J = 19.3, 9.7$ Hz), 119.87 (q, $J = 258.7$ Hz), 119.55, 112.27 (ddd, $J = 24.2,$
2 7.6, 4.4 Hz), 105.61 (dd, $J = 22.5, 16.2$ Hz) ppm; IR (KBr) ν 2919, 2850, 1642, 1383, 1247, 1179 cm^{-1} ;
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4 HRMS (ES⁺) calculated for C₁₆H₇Cl₂F₆N₂O [M + H]⁺ 426.9840, found 426.9850.

7 **4-Chloro-1-(4-chlorophenyl)-5-(2,6-difluoro-4-methylphenyl)-1H-imidazole (92)**

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9 Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluoro-4-methylphenyl)-1H-
10 imidazole (0.100 g, 0.328 mmol), purification by silica gel column chromatography (hexanes/EtOAc
11 85:15) afforded the title compound as a yellow solid (0.070 g, 0.206 mmol, 63% yield). ¹H NMR
12 (500 MHz, CDCl₃) δ 7.67 (s, 1H), 7.35–7.29 (m, 2H), 7.11–7.05 (m, 2H), 6.71 (d, $J = 8.4$ Hz, 2H), 2.35
13 (s, 3H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 160.37 (dd, $J = 251.2, 6.9$ Hz), 143.68 (t, $J = 9.9$ Hz),
14 136.56, 134.77, 134.75, 132.25, 129.86, 125.96, 116.31, 112.46 (dd, $J = 20.3, 4.9$ Hz), 102.16 (t, $J =$
15 19.8 Hz), 21.74 ppm; IR (KBr) ν 3064, 2922, 1644, 1568, 1496, 1412, 1321, 1265, 1205, 1086, 1037
16 cm^{-1} ; HRMS (ES⁺) calculated for C₁₆H₁₁Cl₂F₂N₂ [M + H]⁺ 339.0267, found 339.0259.

17 **2-Chloro-1-(4-chlorophenyl)-5-(2,6-difluoro-4-methylphenyl)-1H-imidazole (93)**

18
19 Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluoro-4-methylphenyl)-1H-
20 imidazole (0.100 g, 0.328 mmol), purification by silica gel column chromatography (hexanes/EtOAc
21 85:15) afforded the title compound as a yellow solid (0.009 g, 0.026 mmol, 8% yield). ¹H NMR
22 (500 MHz, CDCl₃) δ 7.38–7.31 (m, 2H), 7.18–7.10 (m, 3H), 6.65 (d, $J = 8.5$ Hz, 2H), 2.31 (s, 3H) ppm;
23 ¹³C NMR (126 MHz, CDCl₃) δ 160.30 (dd, $J = 250.0, 6.7$ Hz), 143.00 (t, $J = 9.9$ Hz), 135.27, 134.04,
24 133.66, 130.31, 129.52, 128.68, 122.73, 112.24 (dd, $J = 21.0, 4.4$ Hz), 103.73 (t, $J = 19.4$ Hz), 21.68
25 ppm; IR (KBr) ν 2918, 2850, 1644, 1494, 1440, 1383, 1315, 1205, 1094, 1039 cm^{-1} ; HRMS (ES⁺)
26 calculated for C₁₆H₁₁Cl₂F₂N₂ [M + H]⁺ 339.0267, found 339.0263.

27 **2,4-Dichloro-1-(4-chlorophenyl)-5-(2,6-difluoro-4-methylphenyl)-1H-imidazole (94)**

28
29 Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluoro-4-methylphenyl)-1H-
30 imidazole (0.100 g, 0.328 mmol), purification by silica gel column chromatography (hexanes/EtOAc
31 85:15) afforded the title compound as a yellow solid (0.024 g, 0.064 mmol, 20% yield). ¹H NMR
32 (500 MHz, CDCl₃) δ 7.35 (d, $J = 8.3$ Hz, 2H), 7.12 (d, $J = 8.3$ Hz, 2H), 6.68 (d, $J = 8.5$ Hz, 2H), 2.33 (s,
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3H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 160.45 (dd, $J = 251.3, 6.7$ Hz), 144.17 (t, $J = 9.9$ Hz), 135.85, 133.15, 132.32, 130.31, 129.72, 128.61, 118.80, 112.40 (dd, $J = 20.2, 4.1$ Hz), 101.84 (t, $J = 20.0$ Hz), 21.79 ppm; IR (KBr) ν 3065, 2924, 2853, 1645, 1573, 1493, 1436, 1385, 1324, 1263, 1237, 1206, 1093, 1040 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{16}\text{H}_{10}\text{Cl}_3\text{F}_2\text{N}_2$ $[\text{M} + \text{H}]^+$ 372.9878, found 372.9869.

4-Chloro-1-(4-chlorophenyl)-5-(2,6-difluoro-3-methoxyphenyl)-1H-imidazole (95)

Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluoro-3-methoxyphenyl)-1H-imidazole (0.132 g, 0.412 mmol), purification by silica gel column chromatography (hexanes/EtOAc 80:20) afforded the title compound as white foam (0.065 g, 0.183 mmol, 45% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.67 (s, 1H), 7.32 (d, $J = 8.7$ Hz, 2H), 7.09 (d, $J = 8.3$ Hz, 2H), 6.96 (td, $J = 9.2, 5.0$ Hz, 1H), 6.85–6.77 (m, 1H), 3.83 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 153.82 (dd, $J = 244.9, 3.7$ Hz), 149.93 (dd, $J = 251.9, 5.9$ Hz), 144.49 (dd, $J = 10.6, 2.7$ Hz), 136.77, 134.84, 134.59, 132.37, 129.88, 125.92, 116.10, 114.96 (dd, $J = 9.5, 2.1$ Hz), 110.52 (dd, $J = 22.6, 4.3$ Hz), 106.13 (dd, $J = 21.1, 16.7$ Hz), 56.81 ppm; IR (KBr) ν 3097, 2925, 2843, 1591, 1563, 1495, 1463, 1440, 1328, 1257, 1203, 1094, 1070 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{16}\text{H}_{11}\text{Cl}_2\text{F}_2\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 355.0217, found 355.0203.

2-Chloro-1-(4-chlorophenyl)-5-(2,6-difluoro-3-methoxyphenyl)-1H-imidazole (96)

Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluoro-3-methoxyphenyl)-1H-imidazole (0.132 g, 0.412 mmol), purification by silica gel column chromatography (hexanes/EtOAc 80:20) afforded the title compound as a yellow solid (0.015 g, 0.042 mmol, 10% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.38–7.31 (m, 2H), 7.18 (s, 1H), 7.16–7.11 (m, 2H), 6.88 (td, $J = 9.1, 5.0$ Hz, 1H), 6.80–6.72 (m, 1H), 3.82 (s, 3H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 153.85 (dd, $J = 243.6, 4.2$ Hz), 149.92 (dd, $J = 250.9, 5.9$ Hz), 144.38 (dd, $J = 11.0, 3.4$ Hz), 135.36, 134.38, 133.55, 130.48, 129.57, 128.66, 122.51, 114.40 (dd, $J = 9.5, 3.2$ Hz), 110.34 (dd, $J = 23.3, 4.4$ Hz), 107.70 (dd, $J = 21.2, 16.9$ Hz), 56.84 ppm; IR (KBr) ν 3096, 2923, 2849, 1590, 1493, 1459, 1438, 1383, 1318, 1244, 1175, 1123, 1093, 1058 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{16}\text{H}_{11}\text{Cl}_2\text{F}_2\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 355.0217, found 355.0219.

2,4-Dichloro-1-(4-chlorophenyl)-5-(2,6-difluoro-3-methoxyphenyl)-1H-imidazole (97)

Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluoro-3-methoxyphenyl)-1*H*-imidazole (0.132 g, 0.412 mmol), purification by silica gel column chromatography (hexanes/EtOAc 80:20) afforded the title compound as a yellow solid (0.009 g, 0.023 mmol, 6% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.37–7.34 (m, 2H), 7.15–7.12 (m, 2H), 6.94 (td, *J* = 9.2, 5.0 Hz, 1H), 6.81–6.77 (m, 1H), 3.83 (s, 3H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 153.94 (dd, *J* = 244.9, 4.0 Hz), 150.12 (dd, *J* = 252.5, 5.6 Hz), 144.45 (dd, *J* = 10.6, 3.4 Hz), 135.95, 133.06, 132.65, 130.49, 129.78, 128.61, 118.59, 115.43 (dd, *J* = 9.8, 3.0 Hz), 110.51 (dd, *J* = 22.8, 4.3 Hz), 105.84 (dd, *J* = 21.4, 16.8 Hz), 56.88 ppm; IR (KBr) ν 2921, 2850, 1639, 1494, 1440, 1384, 1331, 1251, 1090 cm⁻¹; HRMS (ES⁺) calculated for C₁₆H₁₀Cl₃F₂N₂O [M + H]⁺ 388.9827, found 388.9832.

4-Chloro-1-(4-chlorophenyl)-5-phenyl-1*H*-imidazole (98)

Following synthetic procedure E using 1-(4-chlorophenyl)-5-phenyl-1*H*-imidazole (0.070 g, 0.275 mmol), purification by silica gel column chromatography (hexanes/EtOAc 80:20) afforded the title compound as a yellow solid (0.061 g, 0.211 mmol, 77% yield). X-ray quality crystals were obtained by slow evaporation from a CH₂Cl₂/hexanes solution (see Supporting Information): mp (CH₂Cl₂/hexanes) 126–128°C. ¹H NMR (500 MHz, CDCl₃) δ 7.58 (s, 1H), 7.36–7.29 (m, 5H), 7.22–7.16 (m, 2H), 7.09–7.02 (m, 2H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 135.72, 134.91, 134.49, 129.89, 129.75, 129.24, 128.62, 128.44, 127.28, 127.09, 126.61 ppm; IR (KBr) ν 3121, 3096, 3034, 2917, 2849, 1607, 1558, 1497, 1483, 1467, 1413, 1329, 1259, 1199, 1090 cm⁻¹; HRMS (ES⁺) calculated for C₁₅H₁₁Cl₂N₂ [M + H]⁺ 289.0299, found 289.0300.

2-Chloro-1-(4-chlorophenyl)-5-phenyl-1*H*-imidazole (99)

Following synthetic procedure E using 1-(4-chlorophenyl)-5-phenyl-1*H*-imidazole (0.070 g, 0.275 mmol), purification by silica gel column chromatography (hexanes/EtOAc 80:20) afforded the title compound as a yellow solid (0.007 g, 0.025 mmol, 9% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.45–7.38 (m, 2H), 7.27–7.22 (m, 3H), 7.20–7.12 (m, 3H), 7.10–7.03 (m, 2H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 135.32, 134.09, 133.77, 129.85, 129.37, 128.95, 128.76, 128.12, 127.94, 127.21, 125.13 ppm;

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IR (KBr) ν 2956, 2918, 2850, 1487, 1457, 1432, 1383, 1307, 1256, 1146, 1146, 1093 cm^{-1} ; HRMS (ES⁺) calculated for C₁₅H₁₁Cl₂N₂ [M + H]⁺ 289.0299, found 289.0324.

2,4-Dichloro-1-(4-chlorophenyl)-5-phenyl-1*H*-imidazole (100)

Following synthetic procedure E using 1-(4-chlorophenyl)-5-phenyl-1*H*-imidazole (0.070 g, 0.275 mmol), purification by silica gel column chromatography (hexanes/EtOAc 80:20) afforded the title compound as a yellow solid (0.008 g, 0.024 mmol, 9% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.40–7.36 (m, 2H), 7.30–7.27 (m, 3H), 7.16–7.12 (m, 2H), 7.12–7.08 (m, 2H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 135.64, 133.57, 131.34, 129.89, 129.59, 129.21, 128.71, 128.65, 127.20, 127.05 ppm; IR (KBr) ν 2956, 2917, 2849, 1493, 1452, 1381, 1230, 1091 cm^{-1} ; HRMS (ES⁺) calculated for C₁₅H₁₀Cl₃N₂ [M + H]⁺ 322.9910, found 322.9906.

4-Chloro-1-(4-chlorophenyl)-5-(4-methoxyphenyl)-1*H*-imidazole (101)

Following synthetic procedure E using 1-(4-chlorophenyl)-5-(4-methoxyphenyl)-1*H*-imidazole (0.220 g, 0.773 mmol), purification by silica gel column chromatography (hexanes/EtOAc 80:20) afforded the title compound as a yellow solid (0.159 g, 0.498 mmol, 65% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.55 (s, 1H), 7.36–7.31 (m, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 7.06 (d, *J* = 7.9 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 2H), 3.79 (s, 3H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 159.66, 135.29, 135.02, 134.43, 131.15, 129.87, 128.71, 127.05, 126.64, 119.49, 114.17, 55.36 ppm; IR (KBr) ν 3116, 3004, 2960, 2836, 1713, 1614, 1556, 1497, 1467, 1290, 1253, 1179, 1087 cm^{-1} ; HRMS (ES⁺) calculated for C₁₆H₁₂Cl₂N₂NaO [M + Na]⁺ 341.0224, found 341.0229.

4-Chloro-1-(2-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (102)

Following synthetic procedure E using 1-(2-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (0.260 g, 0.894 mmol), purification by silica gel column chromatography (hexanes/EtOAc 75:25) afforded the title compound as a white solid (0.187 g, 0.575 mmol, 64% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.63 (s, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.36–7.29 (m, 2H), 7.29–7.26 (m, 2H), 6.85 (t, *J* = 8.6 Hz, 2H) ppm; ¹³C NMR (126 MHz, CDCl₃) δ 160.77 (dd, *J* = 252.5, 5.9 Hz), 137.58, 133.55, 131.88 (t, *J* = 10.2 Hz), 131.70, 131.67, 130.73, 130.61, 129.10, 127.60, 117.02, 111.64 (dd, *J* = 21.8, 3.6 Hz),

105.35 (t, $J = 19.5$ Hz) ppm; IR (KBr) ν 3129, 3052, 2988, 2922, 2846, 1633, 1589, 1568, 1492, 1471, 1455, 1266, 1238, 1003 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_9\text{Cl}_2\text{F}_2\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 325.0111, found 325.0111.

2-Chloro-1-(2-chlorophenyl)-5-(2,6-difluorophenyl)-1H-imidazole (103)

Following synthetic procedure E using 1-(2-chlorophenyl)-5-(2,6-difluorophenyl)-1H-imidazole (0.260 g, 0.894 mmol), purification by silica gel column chromatography (hexanes/EtOAc 75:25) afforded the title compound as a white solid (0.026 g, 0.080 mmol, 9% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.40 (d, $J = 8.0$ Hz, 1H), 7.36–7.27 (m, 3H), 7.25–7.16 (m, 2H), 6.79 (t, $J = 7.7$ Hz, 2H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 160.72 (dd, $J = 251.5, 5.8$ Hz), 134.75, 133.21, 132.81, 131.34 (t, $J = 10.2$ Hz), 131.06, 130.51, 130.44, 130.32, 127.44, 122.84, 111.53 (dd, $J = 20.6, 5.1$ Hz), 106.87 (t, $J = 19.5$ Hz) ppm; IR (KBr) ν 2916, 2852, 1633, 1587, 1487, 1468, 1435, 1383, 1313, 1277, 1235, 1000 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_9\text{Cl}_2\text{F}_2\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 325.0111, found 325.0119.

2,4-Dichloro-1-(2-chlorophenyl)-5-(2,6-difluorophenyl)-1H-imidazole (104)

Following synthetic procedure E using 4-chloro-1-(2-chlorophenyl)-5-(2,6-difluorophenyl)-1H-imidazole (0.060 g, 0.184 mmol), purification by silica gel column chromatography (hexanes/EtOAc 80:20) afforded the title compound as a white solid (0.047 g, 0.131 mmol, 71% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.44 (d, $J = 7.9$ Hz, 1H), 7.40–7.27 (m, 4H), 6.88 (t, $J = 8.5$ Hz, 1H), 6.82 (t, $J = 8.6$ Hz, 1H) ppm; ^{13}C NMR (126 MHz, CDCl_3) δ 161.07 (dd, $J = 254.4, 5.9$ Hz), 133.11, 133.08, 132.37 (t, $J = 11.2$ Hz), 131.53, 130.56, 130.39, 130.24, 130.22, 127.62, 118.89, 111.95 (dd, $J = 21.7, 3.5$ Hz), 111.41 (dd, $J = 21.8, 3.7$ Hz), 104.92 (t, $J = 19.8$ Hz) ppm; IR (KBr) ν 3073, 2918, 2853, 1633, 1588, 1487, 1466, 1439, 1384, 1278, 1237, 1002 cm^{-1} ; HRMS (ES^+) calculated for $\text{C}_{15}\text{H}_8\text{Cl}_3\text{F}_2\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 358.9721, found 358.9717.

Acetyl-Tubulin Assay

QBI-293 cells (ATCC, Manassas, VA, USA) were maintained in Dulbecco's Modified Eagle's Medium (Mediatech Inc, Manassas, VA, USA) containing 10% fetal bovine serum (FBS) (Atlanta Biologicals, Lawrenceville, GA, USA), 2 mM L-glutamine (Mediatech), 50 units/mL penicillin, and 50 $\mu\text{g}/\text{ml}$

1 streptomycin (1% penicillin/streptomycin; Thermo Fisher Scientific, Waltham, MA, USA). Cells were
2 maintained at 37 °C in a humidified atmosphere (5% CO₂) for all experiments. For compound testing,
3 cells were dissociated with trypsin/EDTA (Thermo Fisher Scientific) and plated at 6 x 10⁵ cells/well in
4 6-well plates. The medium was aspirated after overnight incubation and fresh medium containing
5 vehicle or test compound was added. After incubating for 4 h, cells were washed once with 1X
6 phosphate-buffered saline (PBS), pH 7.4 and then lysed in 200 µl RIPA buffer containing protease
7 inhibitor cocktail, 1 mM PMSF, and 1 µM TSA. Lysed cells were scraped into 1.5 mL Beckman
8 ultracentrifuge tubes (Beckman, Brea, CA, USA) and centrifuged at 100,000 x g for 30 min at 4 °C.
9 Following centrifugation, the supernatant from each sample was collected and analyzed for protein
10 content by BCA assay. The samples subsequently underwent analysis for acetyl-tubulin and α-tubulin
11 levels by ELISA, as previously described.³⁹

26 **RBL-1 Cell PG and LT Assay**

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30 Inhibition of PG and LT synthesis by test compounds was determined through the utilization of an
31 established RBL-1 cell assay.⁴⁰ Briefly, RBL-1 cells (ATCC) were maintained in RPMI 1640 medium
32 (Mediatech Inc., Manassas, VA) containing 10% fetal bovine serum (FBS) (Atlanta Biologicals,
33 Lawrenceville, GA), 1 mM L-glutamine (Mediatech), 50 U/mL penicillin, and 0.05 mg/mL
34 streptomycin (Thermo Fisher Scientific). For analysis of PG and LT production, RBL-1 cells were
35 plated at a density of 9 x 10⁵ cells/well in 24-well plates. After 2 h incubation at 37 °C, cells were added
36 with indicated concentrations of test compounds. Following 2 h incubation with test compounds, cells
37 were incubated with 12 µM calcium ionophore, A23187, for 15 min to induce arachidonic acid
38 production. Cell culture supernatants (200 µL/well) were then collected and treated with 600 µL MeOH
39 containing 0.01% BHT (Butylated Hydroxytoluene) to extract eicosanoids. After centrifugation, the
40 supernatant was dried with a vacuum centrifugation and redissolved in 200 µL 50% acetonitrile.
41 Enzyme products were quantified with an Acquity UPLC-TQ MS system (Waters Corporation, Milford,
42 MA). Injections (10 µL) were separated on an Acquity BEH C18, 1.7 µm, 2.1 x 50 mm column at 37 °C
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1 using a gradient from 5 to 95% acetonitrile with 10 mM ammonium formate over 2 minutes at
2 0.6 mL/min. Combined PGD₂+PGE₂, as well as LTB₄, were detected in negative ion mode using
3 compound specific collision induced mass transitions (PGD₂ and PGE₂: 351 > 315, LTB₄: 335 > 195).
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5 To separate the isomeric prostaglandins PGD₂ and PGE₂, a higher resolution gradient from 5 to 60%
6 acetonitrile over 3 minutes at 0.6 mL/min was used. The cysteinyl leukotriene LTC₄ was separated
7 using a gradient from 5 to 95% acetonitrile with 0.1% formic acid over 2 minutes at 0.6 mL/min. LTC₄
8 was detected using electrospray ionization in positive mode while monitoring for a compound specific
9 mass transition (626 > 189). Chromatograms are integrated and peak areas used to quantitate unknowns
10 against a curve of standards (Cayman Chemical, Ann Arbor, MI) from 1 to 50 ng/mL in 50%
11 acetonitrile.
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24 **Brain and Plasma Compound Determinations**

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27 All animal protocols were approved by the University of Pennsylvania Institutional Animal Care and
28 Use Committee (IACUC). Test compounds were administered to groups of three 2-5 month old CD-1 or
29 B6SJL mice, with both female and male mice used but not mixed within experimental groups. For
30 standard single time-point brain and plasma determinations, mice were injected i.p. with a single dose of
31 5 mg/kg compound dissolved in DMSO, or a dose of 2 mg/kg if two or three compounds were dosed
32 concurrently (cassette dosing). Compounds were quantified in plasma and brain homogenates as
33 previously described.³⁹
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46 AG044332-01), and the Marian S. Ware Alzheimer Program.
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50 **List of Nonstandard Abbreviations:** TosMIC = toluenesulfonylmethyl isocyanide; LDA = lithium
51 diisopropylamide; AcTub = acetylated α -tubulin.
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6 **Supporting Information Available:** NMR spectra of test compounds; X-ray crystal structures of
7 compound **98** (CCDC 1529316), Authors will release the atomic coordinates and experimental data
8 upon article publication; details for the docking studies; Analysis of Table 2 compounds for their ability
9 to reduce multiple COX and 5-LOX products; the SMILES string structures along the full data set in
10 tabular form (csv file format). This material is available free of charge via the Internet at
11 <http://pubs.acs.org>.
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GRAPHICAL ABSTRACT

