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Amal Benzai, Xinzhe Shi, Fazia Derridj, Thierry Roisnel, Henri Doucet, et al.. Late-Stage Diversification of Imidazole-Based Pharmaceuticals through Pd-Catalyzed Regioselective C-H Bond Arylations. *Journal of Organic Chemistry*, 2019, 84 (20), pp.13135-13143. 10.1021/acs.joc.9b01469 . hal-02359968

HAL Id: hal-02359968

<https://univ-rennes.hal.science/hal-02359968>

Submitted on 26 Nov 2019

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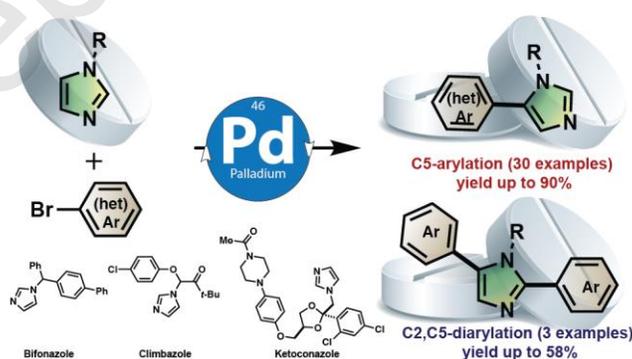
Late-Stage Diversification of Imidazole-Based Pharmaceuticals Through Pd-Catalyzed Regioselective C–H Bond Arylations

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Abstract: Palladium-catalyzed C–H bond arylation of imidazoles has been applied to pharmaceuticals such as Bifonazole, Climbazole and Prochloraz. In the presence of phosphine-free Pd(OAc)₂ catalyst, aryl bromides are efficiently coupled at the C5 position of the imidazole units which are widely decorated. Under these conditions, only C–H bond arylation reaction occurred without affecting the integrity of chemical structure of the imidazole-based pharmaceuticals. Moreover, with Bifonazole Pd-catalyzed C–H bond diarylation at C2 and C5 positions of imidazole unit has also been performed.



Introduction

Since the pioneering work by Ohta and co-workers at early 90's on Pd-catalyzed C–H bond arylation of heteroaromatics,¹ such catalytic methods have become a powerful methodology for the straightforward synthesis of heterobiphenyl products.² Besides the research to improve the regioselectivity of the C–H bond arylations,³ the functional group tolerance is an important issue to apply C–H bond arylation toward late-stage modifications of complex molecules.⁴ In 2010, Alberico, Lavilla and co-workers reported the post-modification of peptides *via* Pd-catalyzed C–H bond arylation of tryptophan residues (Figure 1a).⁵ In the presence of 10 equivalents of aryl iodides, several tryptophan derivatives were arylated at the C2 position of the indole ring. Such late-stage modifications of tryptophans by Pd-catalyzed C–H bond arylation have been applied for the preparation of macropeptides.⁶ Ackermann and co-workers have reported direct arylations of tryptophans using metal-free conditions⁷ or using a ruthenium catalyst.⁸ Itami, Wünsh and co-workers applied regiodivergent C–H bond arylation of spirocyclic thiophenes to modulate their affinity with σ_1 receptor surface (Figure 1b).⁹ However, only few methods for late-stage modification of pharmaceuticals have been reported in the literature.¹⁰ Imidazole ring is an important heterocycle present in many pharmaceuticals or agrochemicals. As examples, Bifonazole is an imidazole antifungal drug used in the form of an ointment; while Climbazole is prescribed for the treatment of human fungal skin infections such as dandruff and eczema. Ketoconazole is also an antifungal medication used to treat a number of fungal infections. During the past decade, Pd-catalyzed regioselective C–H bond arylation of imidazole ring using aryl bromides,¹¹ aryl chlorides,¹² or the successive arylations¹³ has been intensively studied by several research groups including ours.¹⁴ However, to the best of our knowledge, there is no applications of Pd-catalyzed C–H bond arylation of imidazole ring to the late-stage modification of imidazole-based pharmaceuticals. The late-stage diversification of structurally complex imidazoles is a very appealing method for drug discovery. Therefore, herein, we decided to survey the reactivity of several imidazole-based pharmaceuticals such as Bifonazole, Climbazole and Ketoconazole in Pd-catalyzed C–H bond arylation (Figure 1c).

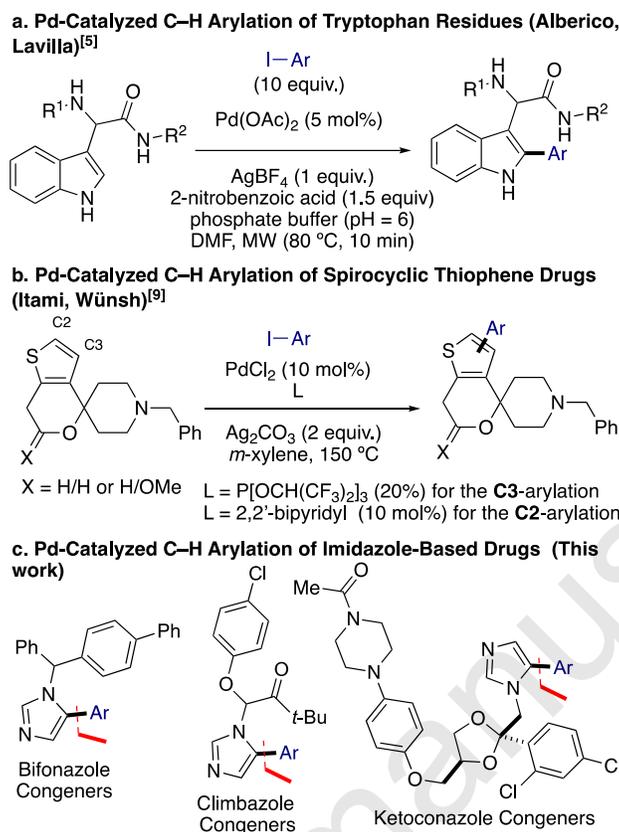
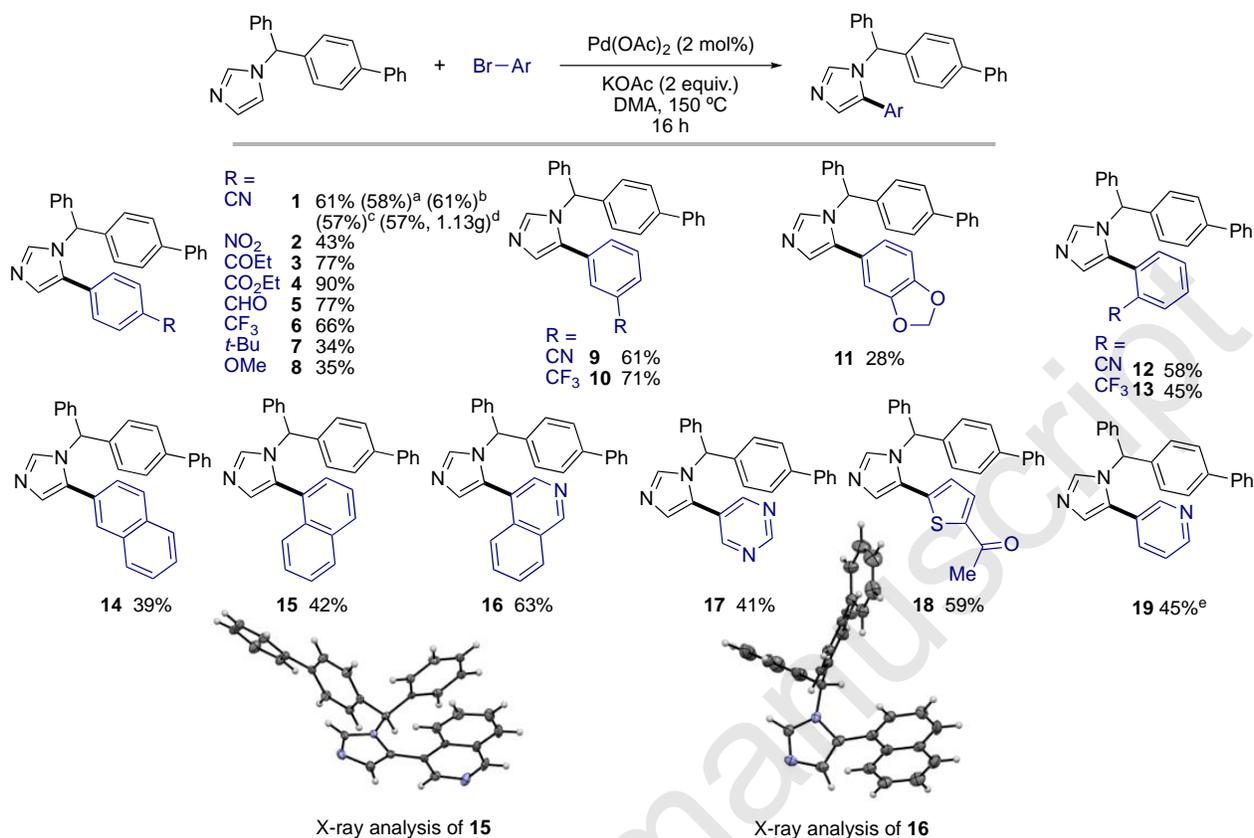


Figure 1. Palladium-Catalyzed Late-Stage C–H Bond Arylations of Pharmaceuticals Containing an Heteroaromatic Unit.

Results and Discussion

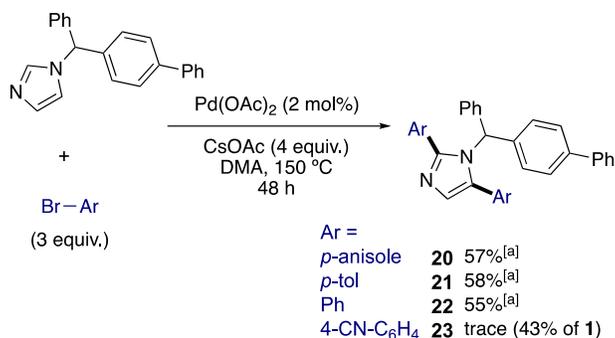
We started our investigations with the late-stage arylation of commercially available Bifonazole with 4-bromobenzonitrile as the coupling partner (Scheme 1). Using our previously optimized reaction conditions for C–H bond arylation of imidazole at C5 position [namely, 2 mol% Pd(OAc)₂ associated with KOAc as the base in DMA],^{14a} the C5-arylated Bifonazole derivative, the C5-arylated Bifonazole derivative, was isolated in 61% yield. The reaction was very regioselective as other C–H bonds were not arylated. Interestingly, under these reaction conditions, the benzhydryl function was not cleaved. The use of more sophisticated palladium catalysts such as PdCl(C₃H₅)(dppb) or base (PivOK) failed to improve the yield. A lower catalyst loading of 1 mol% Pd(OAc)₂ resulted in a lower yield in **1** of 57%. The reactions were carried out using 1.5 gram of Bifonazole with similar yields than on 1 mmol scale was obtained affording 1.13 g the 5-arylated product **1**. To evaluate the potential of this method for the one-step diversification of Bifonazole, we turned our attention to the

scope of aryl bromides. The reaction with aryl bromides substituted by electron withdrawing groups –such as nitro, propionyl, ethyl ester, formyl or trifluoromethyl– at *para*-position reacted smoothly to give a wide diversity of C5-arylated Bifonazole derivatives **2-6** in 43-70% yields. The aryl bromides substituted by an electron donating group, such as 1-bromo-4-(*tert*-butyl)benzene or 4-bromoanisole, can also be coupled with Bifonazole. However, the C5-arylated products **7** and **8** were isolated in lower yields due to a partial conversation of these less reactive aryl bromides. *Meta*-substituted aryl bromides efficiently underwent Pd-catalyzed C5–H bond arylation of Bifonazole. As examples, from 3-bromobenzonitrile and 3-bromobenzotrifluoride, **9** and **10** were obtained in 61% and 71% yield, respectively. Interestingly, this procedure also allowed to introduce a benzo[1,3]dioxolane, which is widely found in natural products, multitude of alkaloids as well as pharmaceutical drugs. The reaction is not very sensitive to the steric hindrance. Indeed, the reaction performed with 2-bromobenzonitrile or 2-bromobenzotrifluoride afforded the C5-arylated Bifonazole derivatives **12** and **13** in 58% and 45% yield, respectively. Naphthalene is an important chromophore which can be used as a suitable probe for biological investigations.¹⁵ The Bifonazole congeners **14** and **15** containing naphthyl units have been prepared in average yields from 2-, or 1-bromonaphthalene through Pd-catalyzed C5 direct arylation of the imidazole ring. Finally, heteroaryl bromides were evaluated. The reaction between Bifonazole and 4-bromoisoquinoline lead to the formation of the desired C5-heteroarylated imidazole **16** in 63% yield. The structures of **15** and **16** were also assigned by X-ray analysis. Moreover, 5-bromopyrimidine was coupled with Bifonazole to afford the product **17** in 40% yield. The reaction is not limited to the use of *N*-containing heteroaryl bromides as the reaction between Bifonazole and 2-acetyl-5-bromothiophene provided the 5-(thiophen-2-yl)-imidazole derivative **18** in 59% yield. Interestingly, heteroaryl chloride such as 3-chloropyridine can also be employed as aryl source for the C5 direct arylation of Bifonazole to afford the bis-heteroaryl product **19** in 45% yield.



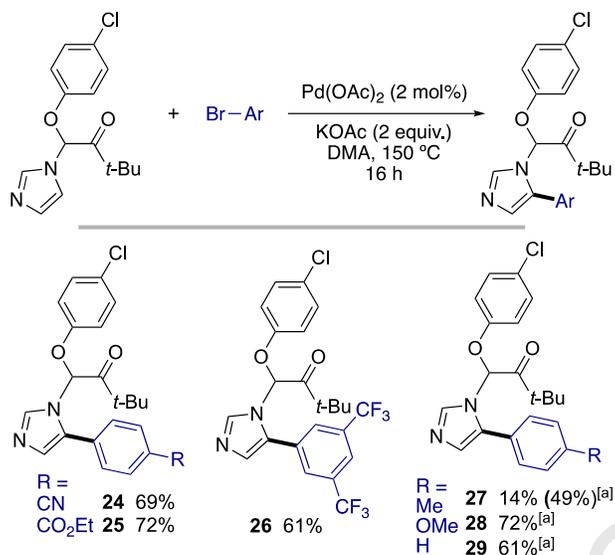
Scheme 1. Palladium-Catalyzed Late-Stage Arylations of Bifonazole at the C5-position of the Imidazolyl Unit. ^aUsing 2 mol% PdCl(C₃H₅)(dppb). ^bUsing PivOK as base. ^cUsing 1 mol% of Pd(OAc)₂. [c] Reaction performed with 3-chloropyridine. ^d Reaction performed using 1.5 g of Bifonazole

Based on our previous work on one-pot Pd(OAc)₂-catalyzed 2,5-diarylation of *N*-methyl imidazole,^{14b} we next also considered applying this transformation for the late-stage diversification of imidazole-based pharmaceuticals (Scheme 2). Using our previous optimized reaction conditions for the direct diarylation of imidazole derivatives, namely 2 mol% of Pd(OAc)₂ associated with 4 equivalents of CsOAc as strong base in DMA at 150 °C for 48 h, Bifonazole reacted with 4-bromotoluene to afford the C2,C5-diarylated imidazole **20** in 57% yield. Similar reactivities were observed with 4-bromoanisole and bromobenzene leading to the formation of C2,C5-diarylated Bifonazole congeners **21** and **22** in 58% and 55% yield, respectively. In all cases, we also observed the formation of C5-monoarylated product in the crude mixtures but in low yields (<10-15%). When the reaction is performed with 4-bromobenzonitrile, the diarylated product **23** is not formed and only monoarylated **1** is obtained in 43% yield. This reactivity trend –electron-rich aryl bromide favors the second arylation– has been previously observed with *N*-benzylimidazole.^{14b}



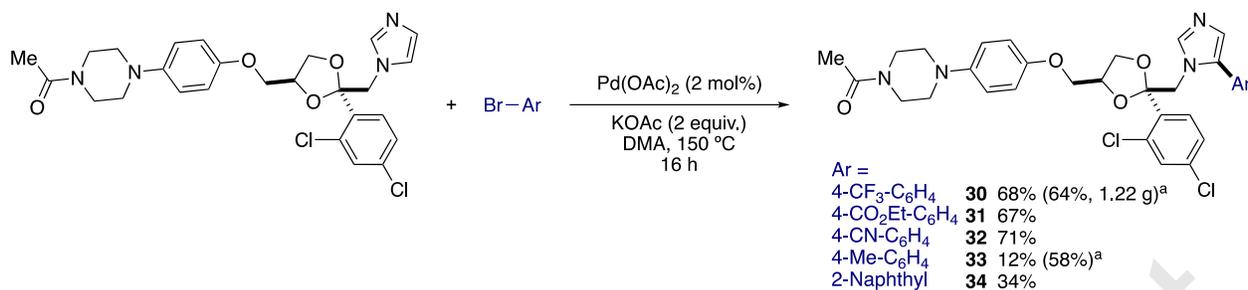
Scheme 2. Palladium-Catalyzed Late-Stage Diarylations of of Bifonazole at the C2 and C5-positions of the Imidazolyl Unit. [a] Formation of C5-monoarylated imidazole (10-15%).

In the second part, we explored the reactivity of Climbazole in Pd-catalyzed late-stage diversification through regioselective C–H bond arylation (Scheme 3). The selective modification of this imidazole-based drug without affecting the integrity of the structure is more challenging owing to the presence of a reactive C–Cl chemical bond, an ether link (C–O bond) and a ketone function. In the presence of 2 mol% Pd(OAc)₂ with KOAc/DMA system, Climbazole was regioselectively arylated at the C5 position of the imidazole unit with 4-bromobenzonitrile to afford **24** in 69% yield. No degraded or coupling products resulting from the activation of C–Cl or C–O bonds were formed. A similar reactivity was obtained with ethyl 4-bromobenzoate to generate the C5-arylated Climbazole **25** in 72% yield. 1-Bromo-3,5-bis(trifluoromethyl)benzene was also found to be a suitable substrate for Pd-catalyzed C–H bond arylation affording the C5-arylated Climbazole **26** in 61% yield. The coupling with less reactive electron-rich 4-bromotoluene was more sluggish as the desired arylated imidazole **27** was obtained in only 14% yield. However, using the conditions for the diarylation (*i.e.*, 2 mol% of Pd(OAc)₂ associated with 4 equivalents of CsOAc as strong base in DMA at 150 °C for 48 h), the monoarylated Climbazole congener **27** was obtained in 49% yield without the formation of diarylated product. This reactivity is in line with our previous observations:^(10b) a bulky *N*-substituent prevents the second arylation at C2 position of the imidazolyl unit. Similar results were obtained with 4-bromoanisole and bromobenzene leading to the formation of the mono-arylated Climbazoles **28** and **29** in 72% and 61% yield, respectively.



Scheme 3. Palladium-Catalyzed Late-Stage Arylation of Climbazole at the C5-Position of the Imidazolyl Unit. [a] using 3 equivalents of ArBr, Cs₂CO₃ (4 equiv.).

To demonstrate the robustness of such late-stage diversification, we then focused to achieve Pd-catalyzed C–H bond arylation on larger imidazole-based pharmaceutical containing multiple reactive functions (Scheme 4). Hence, we selected Ketoconazole as substrate. Besides the C–Cl and ether bonds, this imidazole includes a piperazine unit, an acetamide function, and an acetal group. All these functionalities could potentially react with palladium species to inhibit the reaction or could undergo side-reactions. In the presence of 2 mol% Pd(OAc)₂ with KOAc/DMA system, the reaction between Ketoconazole and 4-bromobenzotrifluoride afforded the arylated product **30** in 68% yield, without affecting any other reactive functions. Again, the reaction was very regioselective as only the arylation product resulting from the cleavage of the C–H bond at C5 position of the imidazole unit was obtained. Gram-scale reaction was also evaluated using 1.5 g Ketoconazole and the arylated product **30** was obtained in 64% yield leading to 1.22 g of product. We then performed other late-stage diversifications of Ketoconazole by incorporating diverse aryl groups at C5 position of the imidazole unit. From ethyl 4-bromobenzoate and 4-bromobenzonitrile, the Ketoconazole congeners **31** and **32** were isolated in 67% and 71% yield, respectively. Again, the reaction with 4-bromotoluene was more sluggish, and required to use Cs₂CO₃ as base to give the arylated Ketoconazole **33** in good yield. The coupling reaction with 2-bromonaphthalene afforded the π -extended arylated Ketoconazole **34** in 43% yield.



Scheme 4. Palladium-Catalyzed Late-Stage Arylation of Ketoconazole at the C5-Position of the Imidazolyl Unit. [a] using 3 equivalents of ArBr, Cs₂CO₃ (4 equiv.).

Conclusion

In summary, we discovered that the system, Pd(OAc)₂ as the catalyst associated with KOAc as the base in DMA, can achieve the late-stage diversification of imidazole-based pharmaceuticals with a wide variety of aryl bromides. These post-modifications of imidazole-containing drugs are attractive for medical chemistry owing to: *i*) the reaction is very regioselective occurring only at the C5-position of the imidazole unit; *ii*) these conditions display broad functional group tolerance on both coupling partners; *iii*) no phosphine ligands are required, therefore no specific treatment to remove phosphine residue is needed before the evaluation of the biological activities. Moreover, in the case of Bifonazole, C–H bond diarylations at C2 and C5 positions of the imidazole unit can be carried out using 3 equivalents of aryl bromides and CsOAc as base. Overall, this method opens up the possibility of preparing new chemically modified imidazoles in one-step that is potentially useful in chemical biology, for instance to incorporate fluorescent probes linked by C–C bonds, or to tailor the biological or physical properties.

Experimental Section

All reactions were carried out under argon atmosphere with standard Schlenk techniques. DMA was purchased from Acros Organics and was not purified before use. ¹H and ¹³C NMR spectra were recorded on Bruker AV III 400 MHz NMR spectrometer equipped with BBFO probehead. Chemical shifts (δ) were reported in parts per million relative to residual chloroform (7.26 ppm for ¹H; 77.0 ppm for ¹³C), constants were reported in Hertz. ¹H NMR assignment abbreviations were the following: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), and multiplet (m). ¹³C NMR spectra

were recorded at 100 MHz on the same spectrometer and reported in ppm. All reagents were weighed and handled in air.

General Procedure for the Pd-catalyzed C5–H Arylation (A): To a 25 mL oven dried Schlenk tube imidazole derivatives (1 mmol), aryl bromides (1.5 mmol, 1.5 equiv.), KOAc (196 mg, 2 mmol, 2 equiv.), DMA (4 mL) and Pd(OAc)₂ (4.5 mg, 0.02 mmol, 2 mol%) were successively added. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and stirred at 150 °C (oil bath temperature) for 16 hours. After cooling the reaction at room temperature and concentration under reduced pressure, the crude mixture was purified by flash chromatography to afford the desired arylated products.

General Procedure for the Pd-catalyzed C2,C5–H Diarylation or C5–H Monoarylation (B): To a 25 mL oven dried Schlenk tube imidazole derivatives (0.5 mmol), aryl bromides (1.5 mmol, 3 equiv.), CsOAc (383 mg, 2 mmol, 2 equiv.), DMA (4 mL) and Pd(OAc)₂ (3.25 mg, 0.01 mmol, 2 mol%) were successively added. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and stirred at 150 °C (oil bath temperature) for 48 hours. After cooling the reaction at room temperature and concentration under reduced pressure, the crude mixture was purified by flash chromatography to afford the desired arylated products.

4-(1-([1,1'-Biphenyl]-4-yl(phenyl)methyl)-1H-imidazol-5-yl)benzotrile (1): Following the general procedure A using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1H-imidazole (310 mg, 1 mmol) and 4-bromobenzotrile (273 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **1** (251 mg, 61%) as a brown solid (Mp = 171-173 °C): ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.65 (d, *J* = 8.4 Hz, 2H), 7.62 – 7.58 (m, 4H), 7.52 – 7.45 (m, 3H), 7.39 (td, *J* = 2.0, 5.5, 6.1 Hz, 6H), 7.29 (s, 1H), 37.13 (d, *J* = 8.2 Hz, 2H), 7.12 – 7.08 (m, 2H), 6.54 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm). 141.5, 140.0, 139.2, 138.9, 137.8, 132.5, 129.8, 129.4, 129.1, 128.9, 128.6, 128.5, 128.0, 127.8, 127.7, 127.1, 118.5, 111.8, 63.2. Elemental analysis: calcd (%) for C₂₉H₂₁N₃ (411.51): C 84.64, H 5.14, N 10.21; found: C 84.91, H 5.29, N 10.36.

1-([1,1'-Biphenyl]-4-yl(phenyl)methyl)-5-(4-nitrophenyl)-1H-imidazole (2): Following the general procedure **A** using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1H-imidazole (310 mg, 1 mmol) and 4-bromonitrobenzene (303 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **2** (185 mg, 43%) as a yellow solid (Mp = 151-153 °C): ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.23 (d, *J* = 8.8 Hz, 2H), 7.63 – 7.59 (m, 4H), 7.51 – 7.47 (m, 3H), 7.47 – 7.43 (m, 2H), 7.41 (dd, *J* = 1.5, 6.0 Hz, 4H), 7.33 (s, 1H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.13 – 7.08 (m, 2H), 6.57 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 147.3, 141.6, 140.0, 139.5, 138.8, 137.7, 136.4, 131.8, 129.4, 129.2, 128.9, 128.7, 128.5, 128.0, 127.8, 127.7, 127.1, 124.0, 63.3. Elemental analysis: calcd (%) for C₂₈H₂₁N₃O₂ (431.50): C 77.94, H 4.91, N 9.74; found: C 77.75, H 4.83, N 9.51.

1-(4-(1-([1,1'-Biphenyl]-4-yl(phenyl)methyl)-1H-imidazol-5-yl)phenyl)propan-1-one (3): Following the general procedure **A** using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1H-imidazole (310 mg, 1 mmol) and 4-bromopropiophenone (320 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 60-40) to afford the desired compound **3** (340 mg, 77%) as a white solid (Mp = 149-151 °C): ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.97 (d, *J* = 8.4 Hz, 2H), 7.63 – 7.57 (m, 4H), 7.50 – 7.44 (m, 3H), 7.41 – 7.36 (m, 6H), 7.28 – 7.26 (m, 1H), 7.17 – 7.09 (m, 4H), 6.60 (s, 1H), 3.01 (q, *J* = 7.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 200.1, 141.3, 140.1, 139.2, 138.8, 138.2, 136.2, 134.3, 132.9, 129.2, 129.0, 129.0, 128.9, 128.5, 128.5, 128.4, 128.1, 127.7, 127.6, 127.1, 63.0, 31.9, 8.2. Elemental analysis: calcd (%) for C₃₁H₂₆N₂O (442.56): C 84.13, H 5.92, N 65.33; found: C 82.89, H 5.98, N 6.58.

Ethyl 4-(1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1H-imidazol-5-yl)benzoate (4): Following the general procedure **A** using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1H-imidazole (310 mg, 1 mmol) and ethyl 4-bromobenzoate (343 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 60-40) to afford the desired compound **4** (412 mg, 90%) as a yellow solid (Mp = 143-145 °C): ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.05 (d, *J* = 8.3 Hz, 2H), 7.64 – 7.58 (m, 4H), 7.53 – 7.44 (m, 3H), 7.42 – 7.34 (m, 6H), 7.29 (s, 1H), 7.16 – 7.08 (m, 4H), 6.59 (s, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.42 (t,

$J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 166.1, 141.3, 140.1, 139.2, 138.7, 138.1, 134.2, 130.1, 129.9, 129.0, 128.9, 128.9, 128.5, 128.5, 128.1, 127.7, 127.6, 127.1, 63.0, 61.1, 14.3. Elemental analysis: calcd (%) for $\text{C}_{31}\text{H}_{26}\text{N}_2\text{O}_2$ (458.56): C 81.20, H 5.72, N 6.11; found: C 81.45, H 5.81, N 6.07.

4-([1,1'-Biphenyl]-4-yl(phenyl)methyl)-1H-imidazol-5-yl)benzaldehyde (5): Following the general procedure **A** using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1H-imidazole (310 mg, 1 mmol) and 4-bromobenzaldehyde (277 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 70-30) to afford the desired compound **5** (319 mg, 77%) as yellow solid (Mp = 167-168 °C): ^1H NMR (400 MHz, CDCl_3) δ (ppm) 10.03 (s, 1H), 7.88 (d, $J = 8.2$ Hz, 2H), 7.63 – 7.57 (m, 4H), 7.51 – 7.43 (m, 5H), 7.43 – 7.36 (m, 4H), 7.31 (s, 1H), 7.14 (d, $J = 8.2$ Hz, 2H), 7.13 – 7.08 (m, 2H), 6.60 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 191.5, 141.4, 140.1, 139.1, 139.0, 138.0, 135.9, 135.6, 132.7, 130.0, 129.6, 129.3, 129.1, 128.9, 128.5, 128.5, 128.1, 127.7, 127.6, 127.1, 63.1. Elemental analysis: calcd (%) for $\text{C}_{29}\text{H}_{22}\text{N}_2\text{O}$ (414.51): C 84.03, H 5.35, N 6.76; found: C 84.32, H 5.61, N 6.98.

1-([1,1'-Biphenyl]-4-yl(phenyl)methyl)-5-(4-(trifluoromethyl)phenyl)-1H-imidazole (6): Following the general procedure **A** using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1H-imidazole (310 mg, 1 mmol) and 4-bromobenzotrifluoride (338 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 60-40) to afford the desired compound **6** (300 mg, 66%) as yellow solid (Mp = 146-148 °C): ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.66 – 7.56 (m, 6H), 7.51 – 7.44 (m, 3H), 7.42 – 7.36 (m, 6H), 7.26 (s, 1H), 7.14 (d, $J = 8.2$ Hz, 2H), 7.13 – 7.09 (m, 2H), 6.54 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 141.4, 140.1, 139.1, 138.7, 138.1, 133.5, 132.5, 132.4, 130.2 (q, $J = 32.6$ Hz), 129.4, 129.2, 129.1, 128.9, 128.5, 128.1, 127.7, 127.6, 127.1, 125.7 (q, $J = 3.7$ Hz), 124.0 (q, $J = 272.1$ Hz), 63.0. Elemental analysis: calcd (%) for $\text{C}_{29}\text{H}_{21}\text{F}_3\text{N}_2$ (454.49): C 76.64, H 4.66, N 6.16; found: C 76.51, H 4.89, N 5.97.

1-([1,1'-Biphenyl]-4-yl(phenyl)methyl)-5-(4-(tert-butyl)phenyl)-1H-imidazole (7): Following the general procedure **A** using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1H-imidazole (310 mg, 1 mmol) and 1-bromo-4-*tert*-butylbenzene (320 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 70-30) to afford the desired compound **7** (151 mg, 34%) as yellow oil: ^1H NMR (400

MHz, CDCl₃) δ (ppm) 7.64 – 7.57 (m, 4H), 7.50 – 7.44 (m, 3H), 7.42 – 7.37 (m, 6H), 7.21 (d, J = 8.4 Hz, 2H), 7.19 – 7.15 (m, 2H), 7.14 – 7.10 (m, 3H), 6.59 (s, 1H), 1.35 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 151.3, 141.1, 140.3, 139.7, 138.7, 137.6, 129.0, 128.9, 128.9, 128.6, 128.2, 128.2, 127.9, 127.6, 127.5, 127.1, 126.7, 125.6, 62.5, 34.7, 31.3. Elemental analysis: calcd (%) for C₃₂H₃₀N₂ (442.61): C 86.84, H 6.83, N 6.33; found: C 86.97, H 6.61, N 6.18.

1-([1,1'-Biphenyl]-4-yl(phenyl)methyl)-5-(4-methoxyphenyl)-1H-imidazole (8): Following the general procedure **A** using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1H-imidazole (310 mg, 1 mmol) and 4-bromoanisole (281 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 70-30) to afford the desired compound **8** (146 mg, 34%) as yellow solid (Mp = 150-152 °C): ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.63 – 7.56 (m, 4H), 7.50 – 7.42 (m, 3H), 7.41 – 7.35 (m, 4H), 7.17 (d, J = 8.7 Hz, 2H), 7.15 – 7.08 (m, 5H), 6.90 (d, J = 8.7 Hz, 2H), 6.51 (s, 1H), 3.84 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 159.7, 141.0, 140.2, 139.6, 138.6, 137.4, 133.5, 130.9, 128.9, 128.9, 128.6, 128.2, 128.1, 127.7, 127.6, 127.5, 127.1, 122.0, 114.0, 62.5, 55.3. Elemental analysis: calcd (%) for C₂₉H₂₄N₂O (416.52): C 83.63, H 5.81, N 6.73; found: C 83.28, H 5.97, N 6.97.

3-(1-([1,1'-Biphenyl]-4-yl(phenyl)methyl)-1H-imidazol-5-yl)benzotrile (9): Following the general procedure **A** using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1H-imidazole (310 mg, 1 mmol) and 3-bromobenzotrile (273 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 60-60) to afford the desired compound **9** (251 mg, 61%) as a white solid (Mp = 135-137 °C): ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.67 – 7.62 (m, 1H), 7.62 – 7.58 (m, 4H), 7.53 (s, 1H), 7.50 – 7.44 (m, 5H), 7.44 – 7.35 (m, 4H), 7.24 (s, 1H), 7.13 (d, J = 8.2 Hz, 2H), 7.11 – 7.07 (m, 2H), 6.47 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 141.5, 140.0, 138.8, 137.7, 133.4, 132.6, 131.6, 131.5, 131.3, 129.5, 129.5, 129.1, 128.9, 128.7, 128.5, 128.0, 127.7, 127.7, 127.1, 118.2, 113.0, 63.2. Elemental analysis: calcd (%) for C₂₉H₂₁N₃ (411.51): C 84.64, H 5.14, N 10.21; found: C 84.57, H 5.34, N 10.21.

1-([1,1'-Biphenyl]-4-yl(phenyl)methyl)-5-(3-(trifluoromethyl)phenyl)-1H-imidazole (10): Following the general procedure **A** using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1H-imidazole (310 mg, 1 mmol) and

3-bromobenzotrifluoride (338 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 70-30) to afford the desired compound **10** (323 mg, 71%) as a white solid (Mp = 134-136 °C): ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.66 – 7.57 (m, 5H), 7.52 – 7.43 (m, 6H), 7.43 – 7.37 (m, 4H), 7.26 – 7.22 (m, 1H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.13 – 7.10 (m, 2H), 6.48 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 141.4, 140.2, 139.0, 138.5, 137.9, 132.5, 132.4, 131.1 (q, *J* = 32.7 Hz), 130.7, 129.2, 129.2, 129.0, 128.9, 128.5, 128.5, 128.1, 127.7, 127.7, 127.1, 126.1 (q, *J* = 3.8 Hz), 124.9 (q, *J* = 4.0 Hz), 123.8 (q, *J* = 272.3 Hz), 63.1. Elemental analysis: calcd (%) for C₂₉H₂₁F₃N₂ (454.49): C 76.64, H 4.66, N 6.16; found: C 76.56, H 4.41, N 6.19.

1-([1,1'-Biphenyl]-4-yl(phenyl)methyl)-5-(benzo[*d*][1,3]dioxol-5-yl)-1H-imidazole (11): Following the general procedure **A** using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1H-imidazole (310 mg, 1 mmol) and 5-bromobenzo[*d*][1,3]dioxole (302 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 70-30) to afford the desired compound **11** (121 mg, 28%) as yellow oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.64 – 7.55 (m, 4H), 7.51 – 7.44 (m, 2H), 7.43 – 7.37 (m, 5H), 7.16 – 7.08 (m, 5H), 6.83 – 6.78 (m, 1H), 6.75 – 6.70 (m, 2H), 6.53 (s, 1H), 6.00 (s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 147.8, 147.8, 141.2, 140.2, 139.4, 138.4, 137.5, 128.9, 128.9, 128.5, 128.3, 128.1, 128.1, 127.6, 127.5, 127.1, 123.5, 110.0, 108.5, 101.3, 62.6, 29.7. Elemental analysis: calcd (%) for C₂₉H₂₂N₂O₂ (430.51): C 80.91, H 5.15, N 6.51; found: C 81.23, H 4.89, N 6.89.

2-(1-([1,1'-Biphenyl]-4-yl(phenyl)methyl)-1H-imidazol-5-yl)benzotrifluoride (12): Following the general procedure **A** using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1H-imidazole (310 mg, 1 mmol) and 2-bromobenzotrifluoride (273 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 60-40) to afford the desired compound **12** (239 mg, 58%) as a brown solid (Mp = 181-183 °C): ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.74 (dd, *J* = 1.7, 7.2 Hz, 1H), 7.62 – 7.55 (m, 4H), 7.49 – 7.44 (m, 4H), 7.43 – 7.38 (m, 2H), 7.37 – 7.33 (m, 3H), 7.31 (s, 1H), 7.17 – 7.13 (m, 2H), 7.10 (s, 1H), 7.10 – 7.04 (m, 2H), 6.47 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 141.3, 140.1, 138.7, 138.3, 137.3, 133.6, 133.3, 132.4, 131.7, 130.8, 129.4, 128.9, 128.9, 128.9, 128.6, 128.5, 128.1, 127.7, 127.5, 127.1, 117.8,

114.0, 63.4. Elemental analysis: calcd (%) for C₂₉H₂₁N₃ (411.51): C 84.64, H 5.14, N 10.21; found: C 84.57, H 5.08, N 10.56.

1-([1,1'-Biphenyl]-4-yl(phenyl)methyl)-5-(2-(trifluoromethyl)phenyl)-1H-imidazole (13): Following the general procedure **A** using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1H-imidazole (310 mg, 1 mmol) and 2-bromobenzotrifluoride (338 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 60-40) to afford the desired compound **13** (205 mg, 45%) as a brown oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.92 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 7.7 Hz, 1H), 7.66 – 7.61 (m, 4H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.53 (d, *J* = 1.3 Hz, 1H), 7.51 – 7.35 (m, 7H), 7.28 – 7.20 (m, 4H), 7.18 (s, 1H), 6.63 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 141.4, 140.2, 138.9, 138.5, 137.9, 137.0, 133.6, 131.6, 131.6, 129.0, 128.9, 128.5, 128.5, 128.1, 127.6, 127.2, 127.1, 127.0, 126.9, 126.0 (q, *J* = 5.9 Hz), 124.4, (q, *J* = 273.5 Hz), 118.7 (q, *J* = 6.3 Hz), 65.1. Elemental analysis: calcd (%) for C₂₉H₂₁F₃N₂ (454.49): C 76.64, H 4.66, N 6.16; found: C 76.89, H 4.69, N 5.84.

1-([1,1'-Biphenyl]-4-yl(phenyl)methyl)-5-(naphthalen-2-yl)-1H-imidazole (14): Following the general procedure **A** using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1H-imidazole (310 mg, 1 mmol) and 2-bromonaphthalene (311 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 70-30) to afford the desired compound **14** (170 mg, 39%) as a white solid (Mp = 216-218 °C): ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.90 – 7.83 (m, 2H), 7.76 – 7.70 (m, 2H), 7.66 – 7.58 (m, 4H), 7.55 – 7.44 (m, 5H), 7.43 – 7.35 (m, 5H), 7.29 (s, 1H), 7.20 – 7.11 (m, 4H), 6.64 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 141.2, 140.2, 139.6, 138.5, 138.0, 133.8, 133.1, 132.8, 129.0, 128.9, 128.6, 128.5, 128.5, 128.3, 128.2, 128.1, 127.7, 127.6, 127.6, 127.1, 127.1, 127.0, 126.6, 62.8. Elemental analysis: calcd (%) for C₃₂H₂₄N₂ (436.56): C 88.04, H 5.54, N 6.42; found: C 88.27, H 5.61, N 6.51.

1-([1,1'-Biphenyl]-4-yl(phenyl)methyl)-5-(naphthalen-1-yl)-1H-imidazole (15): Following the general procedure **A** using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1H-imidazole (310 mg, 1 mmol) and 1-bromonaphthalene (311 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 60-40) to afford the desired compound **15** (183 mg, 42%) as a yellow oil: ¹H NMR (400

MHz, CDCl₃) δ (ppm) 7.97 – 7.87 (m, 2H), 7.76 (d, *J* = 9.2 Hz, 1H), 7.61 – 7.55 (m, 3H), 7.55 – 7.49 (m, 3H), 7.49 – 7.43 (m, 3H), 7.41 – 7.35 (m, 2H), 7.33 – 7.30 (m, 3H), 7.26 (s, 1H), 7.18 (d, *J* = 7.0 Hz, 1H), 7.08 – 6.94 (m, 4H), 6.14 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 140.9, 140.3, 137.4, 133.5, 133.3, 131.2, 129.8, 129.6, 129.4, 129.1, 128.8, 128.7, 128.6, 128.5, 128.3, 128.2, 127.6, 127.3, 127.1, 127.1, 127.0, 126.7, 126.2, 125.5, 125.1, 62.8. Elemental analysis: calcd (%) for C₃₂H₂₄N₂ (436.56): C 88.04, H 5.54, N 6.42; found: C 88.01, H 5.83, N 6.55.

4-(1-([1,1'-Biphenyl]-4-yl(phenyl)methyl)-1H-imidazol-5-yl)isoquinoline (16): Following the general procedure **A** using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1H-imidazole (312 mg, 1 mmol) and 4-bromoisoquinoline (291 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 70-30) to afford the desired compound **16** (276 mg, 63%) as a brown oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 9.28 (s, 1H), 8.29 (s, 1H), 8.09 – 8.01 (m, 1H), 7.74 – 7.69 (m, 1H), 7.69 – 7.64 (m, 2H), 7.60 (s, 1H), 7.55 (d, *J* = 6.8 Hz, 2H), 7.50 (d, *J* = 7.0 Hz, 2H), 7.48 – 7.43 (m, 2H), 7.41 – 7.35 (m, 1H), 7.33 – 7.30 (m, 4H), 7.04 – 6.97 (m, 4H), 6.20 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 153.5, 145.1, 141.2, 140.2, 138.7, 137.6, 135.7, 131.1, 130.9, 129.1, 128.9, 128.8, 128.5, 128.4, 128.2, 128.0, 127.9, 127.6, 127.6, 127.5, 127.1, 127.1, 124.4, 121.1, 63.2. Elemental analysis: calcd (%) for C₃₁H₂₃N₃ (437.55): C 85.10, H 5.30, N 9.60; found: C 85.23, H 5.49, N 9.84.

5-(1-([1,1'-Biphenyl]-4-yl(phenyl)methyl)-1H-imidazol-5-yl)pyrimidine (17): Following the general procedure **A** using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1H-imidazole (312 mg, 1 mmol) and 5-bromopyrimidine (239 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **17** (159 mg, 41%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 9.13 (s, 1H), 8.58 (s, 2H), 7.55 (dd, *J* = 4.6, 7.8 Hz, 4H), 7.46 – 7.25 (m, 8H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.07 – 7.02 (m, 2H), 6.45 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 158.0, 156.3, 141.7, 139.9, 139.6, 138.4, 137.2, 130.6, 129.2, 128.9, 128.8, 128.5, 128.0, 127.8, 127.8, 127.1, 124.7, 63.5. Elemental analysis: calcd (%) for C₂₆H₂₀N₄ (388.47): C 80.39, H 5.19, N 14.42; found: C 80.58, H 5.25, N 14.21.

1-(5-(1-([1,1'-Biphenyl]-4-yl(phenyl)methyl)-1*H*-imidazol-5-yl)thiophen-2-yl)ethan-1-one (18):

Following the general procedure **A** using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1*H*-imidazole (312 mg, 1 mmol) and 2-acetyl-5-bromothiophene (308 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **18** (256 mg, 59%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.61 – 7.55 (m, 4H), 7.53 (d, *J* = 3.9 Hz, 1H), 7.47 – 7.32 (m, 8H), 7.15 – 7.06 (m, 4H), 6.84 (d, *J* = 3.9 Hz, 1H), 6.76 (s, 1H), 2.51 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 190.4, 144.3, 141.5, 140.1, 139.6, 138.8, 138.7, 137.7, 133.2, 132.8, 131.1, 129.1, 128.9, 128.7, 128.2, 127.8, 127.7, 127.2, 127.1, 126.0, 63.3, 26.7. Elemental analysis: calcd (%) for C₂₈H₂₂N₂OS (434.56): C 77.39, H 5.10, N 6.45; found: C 77.61, H 5.02, N 6.29.

3-(1-([1,1'-Biphenyl]-4-yl(phenyl)methyl)-1*H*-imidazol-5-yl)pyridine (19): Following the general procedure **A** using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1*H*-imidazole (312 mg, 1 mmol) and 3-chloropyridine (170 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 70-30) to afford the desired compound **19** (174 mg, 45%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.60 – 8.52 (m, 2H), 7.61 – 7.53 (m, 4H), 7.51 – 7.40 (m, 4H), 7.35 (p, *J* = 4.2, 5.1 Hz, 4H), 7.27 – 7.19 (m, 2H), 7.14 – 7.04 (m, 4H), 6.47 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 150.0, 149.5, 141.5, 140.2, 139.0, 138.8, 137.9, 136.6, 130.4, 129.6, 129.1, 129.0, 128.6, 128.6, 128.1, 127.8, 127.7, 127.2, 126.1, 123.4, 63.2. Elemental analysis: calcd (%) for C₂₇H₂₁N₃ (387.49): C 83.69, H 5.56, N 10.84; found: C 83.89, H 5.59, N 11.09.

1-([1,1'-Biphenyl]-4-yl(phenyl)methyl)-2,5-bis(4-methoxyphenyl)-1*H*-imidazole (20): Following the general procedure **B** using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1*H*-imidazole (155 mg, 0.5 mmol) and 4-bromoanisole (280 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **20** (149 mg, 57%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.61 (d, *J* = 6.9 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.50 – 7.44 (m, 5H), 7.42 – 7.33 (m, 4H), 7.13 (s, 1H), 7.12 – 7.08 (m, 5H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 8.9 Hz, 2H), 6.26 (s, 1H), 3.87 (s, 3H), 3.78 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 159.9, 158.2, 141.0, 140.3, 139.3, 138.4,

136.0, 132.5, 128.9, 128.9, 128.8, 128.6, 128.2, 128.2, 127.9, 127.6, 127.4, 127.1, 127.0, 114.4, 113.6, 62.6, 55.3, 55.2. Elemental analysis: calcd (%) for C₃₆H₃₀N₂O₂ (522.65): C 82.73, H 5.79, N 5.36; found: C 88.98, H 5.97, N 5.60.

1-([1,1'-Biphenyl]-4-yl(phenyl)methyl)-2,5-di-p-tolyl-1H-imidazole (21): Following the general procedure **B** using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1H-imidazole (155 mg, 0.5 mmol) and 4-bromotoluene (257 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **21** (142 mg, 58%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.61 (d, *J* = 7.3 Hz, 2H), 7.58 (d, *J* = 8.7 Hz, 2H), 7.50 – 7.45 (m, 3H), 7.44 – 7.40 (m, 2H), 7.40 – 7.35 (m, 4H), 7.19 (d, *J* = 7.9 Hz, 2H), 7.14 (s, 1H), 7.12 – 7.07 (m, 5H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.27 (s, 1H), 2.42 (s, 3H), 2.30 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 141.0, 140.3, 139.4, 138.7, 138.4, 138.0, 136.1, 135.8, 131.7, 131.0, 129.6, 128.9, 128.8, 128.8, 128.8, 128.6, 128.2, 127.7, 127.6, 127.4, 127.1, 126.3, 62.5, 21.4, 21.1. Elemental analysis: calcd (%) for C₃₆H₃₀N₂ (490.65): C 88.13, H 6.16, N 5.71; found: C 88.29, H 6.01, N 5.88.

1-([1,1'-Biphenyl]-4-yl(phenyl)methyl)-2,5-diphenyl-1H-imidazole (22): Following the general procedure **B** using 1-([1,1'-biphenyl]-4-yl(phenyl)methyl)-1H-imidazole (155 mg, 0.5 mmol) and bromobenzene (235 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **22** (127 mg, 55%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.64 – 7.57 (m, 4H), 7.53 (dd, *J* = 1.3, 7.1 Hz, 2H), 7.51 – 7.44 (m, 4H), 7.44 – 7.35 (m, 6H), 7.25 – 7.19 (m, 4H), 7.19 – 7.15 (m, 1H), 7.14 (d, *J* = 1.8 Hz, 1H), 7.13 – 7.08 (m, 3H), 6.29 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 141.1, 140.3, 139.2, 138.2, 138.1, 136.4, 134.4, 131.2, 130.7, 129.2, 128.9, 128.9, 128.9, 128.6, 128.3, 128.2, 128.1, 127.6, 127.5, 127.1, 126.5, 126.4, 62.7. Elemental analysis: calcd (%) for C₃₄H₂₆N₂ (462.59): C 88.28, H 5.67, N 6.06; found: C 88.47, H 5.29, N 6.19.

4-(1-(1-(4-Chlorophenoxy)-3,3-dimethyl-2-oxobutyl)-1H-imidazol-5-yl)benzotrile (24): Following the general procedure **A** using 1-(4-chlorophenoxy)-1-(1H-imidazol-1-yl)-3,3-dimethylbutan-2-one (293 mg, 1 mmol) and 4-bromobenzotrile (273 mg, 1.5 mmol), the residue was purified by flash

chromatography on silica gel (CH₂Cl₂-MeOH, 95-5) to afford the desired compound **24** (271 mg, 69%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.86 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.9 Hz, 2H), 7.19 (s, 1H), 6.71 (d, *J* = 8.9 Hz, 2H), 6.36 (s, 1H), 1.19 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 203.8, 153.5, 138.8, 133.6, 132.7, 131.0, 130.1, 129.8, 129.7, 129.6, 118.4, 118.1, 112.6, 81.8, 43.9, 26.5. Elemental analysis: calcd (%) for C₂₂H₂₀ClN₃O₂ (393.87): C 67.09, H 5.12, N 10.67; found: C 67.23, H 5.29, N 10.54.

Ethyl 4-(1-(1-(4-chlorophenoxy)-3,3-dimethyl-2-oxobutyl)-1H-imidazol-5-yl)benzoate (25):

Following the general procedure **A** using 1-(4-chlorophenoxy)-1-(1H-imidazol-1-yl)-3,3-dimethylbutan-2-one (293 mg, 1 mmol) and ethyl 4-bromobenzoate (343 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (CH₂Cl₂-MeOH, 95-5) to afford the desired compound **25** (317 mg, 72%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.11 (d, *J* = 8.5 Hz, 2H), 7.86 (s, 1H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.9 Hz, 2H), 7.16 (s, 1H), 6.70 (d, *J* = 9.0 Hz, 2H), 6.41 (s, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.17 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 204.0, 165.9, 153.6, 138.3, 133.2, 131.8, 130.8, 130.2, 130.0, 129.4, 129.0, 118.3, 81.1, 61.4, 43.8, 26.5, 14.3. Elemental analysis: calcd (%) for C₂₄H₂₅ClN₂O₄ (440.92): C 65.38, H 5.72, N 6.35; found: C 65.21, H 5.56, N 6.31.

1-(5-(3,5-Bis(trifluoromethyl)phenyl)-1H-imidazol-1-yl)-1-(4-chlorophenoxy)-3,3-dimethylbutan-2-one (26): Following the general procedure **A** using 1-(4-chlorophenoxy)-1-(1H-imidazol-1-yl)-3,3-dimethylbutan-2-one (293 mg, 1 mmol) and 1-bromo-3,5-bis(trifluoromethyl)benzene (439 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (CH₂Cl₂-MeOH, 95-5) to afford the desired compound **26** (308 mg, 61%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.96 – 7.89 (m, 2H), 7.65 (s, 2H), 7.26 (d, *J* = 8.9 Hz, 2H), 7.22 (s, 1H), 6.71 (d, *J* = 8.9 Hz, 2H), 6.33 (s, 1H), 1.20 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 203.7, 153.3, 139.0, 132.40 (q, *J* = 33.8 Hz), 132.2, 131.9, 131.4, 130.2, 130.0, 129.3 (m), 122.8 (q, *J* = 272.1 Hz), 122.5 (m), 118.3, 82.2, 44.0, 26.4. Elemental analysis: calcd (%) for C₂₃H₁₉ClF₆N₂O₂ (504.86): C 54.72, H 3.79, N 5.55; found: C 54.41, H 3.78, N 5.49.

1-(4-Chlorophenoxy)-3,3-dimethyl-1-(5-(*p*-tolyl)-1H-imidazol-1-yl)butan-2-one (27): Following the general procedure **B** using 1-(4-chlorophenoxy)-1-(1*H*-imidazol-1-yl)-3,3-dimethylbutan-2-one (147 mg, 0.5 mmol) and 4-bromotoluene (256 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **27** (94 mg, 49%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.81 (s, 1H), 7.26 (d, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.12 – 7.05 (m, 3H), 6.70 (d, *J* = 9.0 Hz, 2H), 6.40 (s, 1H), 2.42 (s, 3H), 1.16 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 204.2, 153.8, 139.1, 137.2, 129.8, 129.7, 129.4, 129.0, 127.8, 125.7, 118.3, 118.3, 80.7, 43.8, 26.5, 21.3. Elemental analysis: calcd (%) for C₂₂H₂₃ClN₂O₂ (382.89): C 69.01, H 6.06, N 7.32; found: C 68.74, H 6.18, N 7.25.

1-(4-Chlorophenoxy)-1-(5-(4-methoxyphenyl)-1H-imidazol-1-yl)-3,3-dimethylbutan-2-one (28): Following the general procedure **B** using 1-(4-chlorophenoxy)-1-(1*H*-imidazol-1-yl)-3,3-dimethylbutan-2-one (147 mg, 0.5 mmol) and 4-bromoanisole (281 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **28** (144 mg, 72%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.80 (s, 1H), 7.22 (d, *J* = 8.9 Hz, 2H), 7.12 (d, *J* = 8.7 Hz, 2H), 7.04 (s, 1H), 6.96 (d, *J* = 8.7 Hz, 2H), 6.70 (d, *J* = 8.9 Hz, 2H), 6.37 (s, 1H), 3.87 (s, 3H), 1.15 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 204.2, 160.2, 153.8, 137.0, 130.9, 129.9, 129.1, 127.7, 120.8, 118.4, 118.3, 114.4, 80.7, 55.4, 43.8, 26.5. Elemental analysis: calcd (%) for C₂₂H₂₃ClN₂O₃ (398.89): C 66.24, H 5.81, N 7.02; found: C 66.57, H 5.98, N 7.11.

1-(4-Chlorophenoxy)-3,3-dimethyl-1-(5-phenyl-1H-imidazol-1-yl)butan-2-one (29) Following the general procedure **B** using 1-(4-chlorophenoxy)-1-(1*H*-imidazol-1-yl)-3,3-dimethylbutan-2-one (147 mg, 0.5 mmol) and bromobenzene (235 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **29** (112 mg, 61%) as yellow oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.82 (s, 1H), 7.48 – 7.40 (m, 3H), 7.25 – 7.17 (m, 4H), 7.09 (s, 1H), 6.69 (d, *J* = 8.9 Hz, 2H), 6.40 (s, 1H), 1.14 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) 204.1, 153.8, 129.9, 129.5, 129.2,

129.0, 129.0, 128.8, 128.1, 118.3, 80.9, 43.8, 26.5. Elemental analysis: calcd (%) for C₂₁H₂₁ClN₂O₂ (368.86): C 68.38, H 5.74, N 7.59; found: C 68.59, H 5.86, N 7.67.

(±)-Cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-((5-(4-(trifluoromethyl)phenyl)-1H-imidazol-1-

yl)methyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine (30): Following the general procedure **A** using

(±)-cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(imidazol-1-yl)methyl)-1,3-dioxolan-4-

yl]methoxy]phenyl]piperazine (530 mg, 1 mmol) and 4-bromobenzotrifluoride (338 mg, 1.5 mmol), the

residue was purified by flash chromatography on silica gel (CH₂Cl₂-MeOH, 95-5) to afford the desired

compound **30** (459 mg, 58%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.78 (s, 1H), 7.63 (d, *J*

= 8.1 Hz, 2H), 7.52 – 7.43 (m, 2H), 7.33 – 7.25 (m, 1H), 7.22 (dd, *J* = 2.1, 8.5 Hz, 1H), 7.08 – 6.96 (m, 2H),

6.90 (d, *J* = 8.6 Hz, 2H), 6.79 (td, *J* = 4.1, 9.0 Hz, 2H), 4.59 – 4.44 (m, 2H), 4.41 – 4.28 (m, 1H), 3.86 (q, *J*

= 6.7 Hz, 2H), 3.81 – 3.68 (m, 3H), 3.63 (t, *J* = 5.1 Hz, 2H), 3.52 (dd, *J* = 6.0, 9.7 Hz, 1H), 3.06 (dt, *J* = 5.1,

13.8 Hz, 4H), 2.15 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 169.0, 152.8, 145.8, 141.0, 135.9, 134.2,

134.6, 133.4, 133.1, 132.9, 129.9 (q, *J* = 32.6 Hz), 129.5, 128.3, 125.4 (d, *J* = 3.8 Hz), 124.1 (q, *J* = 270.2

Hz), 118.8, 115.3, 108.0, 74.8, 67.9, 67.1, 51.0, 50.7, 46.4, 41.5, 21.4. Elemental analysis: calcd (%) for

C₃₃H₃₁Cl₂F₃N₄O₄ (675.53): C 58.67, H 4.63, N 8.29; found: C 58.78, H 4.51, N 8.39.

(±)-Cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-((5-(4-(ethoxycarbonyl)phenyl)-1H-imidazol-1-

yl)methyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine (31): Following the general procedure **A** using

(±)-cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(imidazol-1-yl)methyl)-1,3-dioxolan-4-

yl]methoxy]phenyl]piperazine (530 mg, 1 mmol) and ethyl 4-bromobenzoate (343 mg, 1.5 mmol), the

residue was purified by flash chromatography on silica gel (CH₂Cl₂-MeOH, 95-5) to afford the desired

compound **31** (455 mg, 67%) as an orange solid (Mp = 141-143 °C): ¹H NMR (400 MHz, CDCl₃) δ (ppm)

8.06 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 1.1 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.31 (d, *J*

= 2.1 Hz, 1H), 7.22 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.05 (d, *J* = 1.1 Hz, 1H), 6.90 (d, *J* = 9.1 Hz, 2H), 6.78 (d, *J*

= 9.1 Hz, 2H), 4.57 (d, *J* = 14.9 Hz, 1H), 4.51 (d, *J* = 14.9 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.34 (t, *J* = 5.5

Hz, 1H), 3.90 – 3.75 (m, 4H), 3.71 (dd, *J* = 5.2, 9.6 Hz, 1H), 3.63 (t, *J* = 5.1 Hz, 2H), 3.46 (dd, *J* = 6.3, 9.6

Hz, 1H), 3.06 (dt, $J = 5.1, 13.4$ Hz, 4H), 2.15 (s, 3H), 1.44 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 171.1, 169.0, 166.3, 152.8, 145.7, 140.9, 135.9, 134.3, 133.1, 131.3, 129.7, 129.7, 129.5, 129.0, 128.1, 127.1, 118.8, 115.2, 108.1, 74.7, 67.8, 67.2, 61.1, 51.0, 50.7, 46.4, 41.5, 21.4, 14.4. Elemental analysis: calcd (%) for $\text{C}_{35}\text{H}_{36}\text{Cl}_2\text{N}_4\text{O}_6$ (679.59): C 61.86, H 5.34, N 8.24; found: C 62.07, H 5.59, N 8.07.

(±)-Cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-((5-(4-cyanophenyl)-1H-imidazol-1-yl)methyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine (32): Following the general procedure **A** using (±)-cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine (530 mg, 1 mmol) and 4-bromobenzonitrile (273 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (CH_2Cl_2 -MeOH, 95-5) to afford the desired compound **32** (449 mg, 71%) as a yellow oil: ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.80 (s, 1H), 7.66 (d, $J = 8.4$ Hz, 2H), 7.54 – 7.48 (m, 3H), 7.33 (d, $J = 2.1$ Hz, 1H), 7.25 (dd, $J = 2.1, 8.4$ Hz, 1H), 7.06 (s, 1H), 6.91 (d, $J = 9.4$ Hz, 2H), 6.78 (d, $J = 8.8$ Hz, 2H), 4.53 (t, $J = 14.2, 15.4$ Hz, 2H), 4.41 – 4.31 (m, 1H), 3.91 – 3.76 (m, 4H), 3.71 – 3.62 (m, 3H), 3.51 (dd, $J = 5.8, 9.7$ Hz, 1H), 3.15 – 3.03 (m, 4H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 169.0, 152.8, 145.8, 136.1, 134.5, 134.1, 133.0, 132.2, 131.3, 129.6, 129.5, 128.8, 127.3, 118.8, 118.6, 115.2, 111.4, 108.0, 74.8, 67.9, 67.1, 51.0, 50.7, 46.4, 41.5, 21.4. Elemental analysis: calcd (%) for $\text{C}_{33}\text{H}_{31}\text{Cl}_2\text{N}_5\text{O}_4$ (632.54): C 62.66, H 4.94, N 11.07; found: C 62.89, H 5.07, N 11.19.

(±)-Cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-((5-(*p*-tolyl)-1H-imidazol-1-yl)methyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine (33): Following the general procedure **B** using (±)-cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine (268 mg, 0.5 mmol) and 4-bromotoluene (256 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **33** (180 mg, 58%) as a yellow oil: ^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.15 (s, 1H), 7.52 (d, $J = 8.3$ Hz, 1H), 7.37 (d, $J = 9.2$ Hz, 1H), 7.33 (d, $J = 8.0$ Hz, 2H), 7.28 – 7.22 (m, 4H), 6.86 (d, $J = 8.9$ Hz, 2H), 6.72 (d, $J = 8.9$ Hz, 2H), 4.73 (q, $J = 4.5, 5.0$ Hz, 1H), 4.32 (s, 3H), 4.19 – 3.98 (m, 3H), 3.80 (t, $J = 5.2$ Hz, 2H), 3.64 (t, $J = 5.1$ Hz, 2H), 3.06 (dt, $J = 5.1, 11.1$ Hz, 4H), 2.45 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 169.0, 152.9, 145.9,

142.1, 138.0, 136.3, 134.1, 131.3, 129.7, 129.6, 128.6, 128.3, 128.3, 126.3, 125.5, 124.0, 118.7, 115.3, 105.4, 76.0, 67.6, 66.8, 51.1, 50.7, 46.4, 41.5, 29.7, 21.4. Elemental analysis: calcd (%) for C₃₃H₃₄Cl₂N₄O₄ (621.56): C 63.77 H 5.51 N 9.01; found: C 63.96, H 5.43, N 9.12.

(±)-Cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-((5-(2-naphthyl)-1H-imidazol-1-yl)methyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine (34): Following the general procedure A using 1-(4-(4(±)-cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine (530 mg, 1 mmol) and 2-bromonaphthalene (311 mg, 1.5 mmol), the residue was purified by flash chromatography on silica gel (CH₂Cl₂-MeOH, 95-5) to afford the desired compound **34** (282 mg, 43%) as an red oil: ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.85 – 7.81 (m, 2H), 7.80 (s, 1H), 7.57 – 7.52 (m, 2H), 7.50 – 7.43 (m, 2H), 7.21 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.17 (d, *J* = 2.1 Hz, 1H), 7.09 (s, 1H), 6.90 (d, *J* = 9.1 Hz, 2H), 6.80 (d, *J* = 9.1 Hz, 2H), 4.61 (s, 2H), 4.52 – 4.29 (m, 1H), 3.88 (d, *J* = 5.7 Hz, 2H), 3.83 – 3.74 (m, 3H), 3.68 – 3.59 (m, 2H), 3.53 (dd, *J* = 6.3, 9.7 Hz, 1H), 3.14 – 3.01 (m, 4H), 2.16 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) 169.0, 152.9, 145.7, 135.7, 134.4, 133.2, 132.7, 131.2, 129.5, 128.5, 128.1, 128.1, 127.7, 127.3, 127.2, 127.1, 126.4, 126.4, 118.8, 115.3, 108.2, 74.8, 67.9, 67.3, 51.1, 50.7, 46.4, 41.5, 21.4. Elemental analysis: calcd (%) for C₃₆H₃₄Cl₂N₄O₄ (657.59): C 65.75, H 5.21, N 8.52; found: C 65.82, H 5.07, N 8.82.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website. ¹H and ¹³C NMR spectra for all new compounds. CCDC 1916026 (**15**) and CCDC 1916027 (**16**)

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ACKNOWLEDGMENT

We thank the Algeria “Ministry of Higher Education and Scientific Research” for a fellowship to A. B and to the ANR (ANR-16-CE07-0001) for a grant to X.S.

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