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Design, Synthesis, and Biological Evaluation of 1-[(Biarylmethyl)methylamino]-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ols as Potent Antifungal Agents: New Insights into Structure–Activity Relationships

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We recently reported the design and synthesis of azole antifungal agents with a focus on modifications to the side chain appended to the propanol group. Herein we have identified a series of new 1-[(biarylmethyl)methylamino] derivatives with broad-spectrum antifungal activities against the most prevalent human pathogenic fungi (*Candida* spp. and *Aspergillus fumigatus*). Compounds containing a flexible benzylamine moiety were clearly shown to yield the best antifungal activities, without the need for a hydrogen-bond acceptor substituent directly attached to the *para* position. We were also able to determine that selected compounds are able to overcome gene overexpression and point mutations that lead to reduced susceptibility or resistance against current treatments, such as fluconazole. As the minor differences observed with small structural modifications cannot be explain with only a three-dimensional model of CYP51, adequate physicochemical parameters must be evaluated in terms of antifungal potency, bioavailability, and toxicity. Therefore, structure–activity relationship studies such as these reveal new insights for the development of future antifungal therapies.

Introduction

Invasive fungal infections (IFIs) are a growing threat to human health. These infections have become increasingly common and predominantly occur in the context of aggressive immunosuppressive therapies, such as anticancer chemotherapy, organ transplants, or acquired immune deficiency syndrome (AIDS). The most prominent fungal pathogens affecting humans belong to *Candida* and *Aspergillus* species, and overall mortality for these infections remains at 40–80%.[1] Currently, the main classes of antifungal drugs for treatment of IFIs are polyenes, azoles, and echinocandins, which target components of either the fungal membrane or cell wall.[2] However, despite a larger therapeutic armamentarium, problems such as intrinsic or acquired antifungal resistance remain, which require researchers to develop new antifungal drugs with expanded effectiveness.[3]

Resistance to triazoles is the most serious concern, as these are commonly the antifungal agents used to treat *Candida* species. These drugs (fluconazole, voriconazole, itraconazole, and posaconazole) mainly target P450-dependent sterol 14α-demethylase (CYP51, Erg11), encoded by the *ERG11* gene, a key enzyme in fungal ergosterol biosynthesis.[4] Azole resistance in *C. albicans* has been associated with genetic alterations in the *ERG11* gene, leading to amino acid substitutions in the target enzyme CYP51 that reduce drug binding.[5–7] Resistance can also be the result of other mechanisms, such as overexpression of the *CDR1/2* and *MDR1* genes that encode drugs-efflux pumps,[8,9] development of pathways that bypass target enzymes,[10,11] and *ERG11* gene overexpression.[12]

Although CYP51 enzymes from *C. albicans* and *A. fumigatus* have recently been expressed in *Escherichia coli* and purified from the membrane fraction to investigate azole binding properties,[13,14] and numerous crystal structures of CYP51 from human and *Trypanosomatidae* in complex with azole antifungal inhibitors have been elucidated,[15,16] no experimental structural information from pathogenic fungi is yet available. This type of information is of fundamental importance to study azole binding interactions and to improve the characteristics of these compounds in a rational design approach. To date, only three-dimensional models of CYP51 from *C. albicans*, *A. fumigatus*, and *Cryptococcus neoformans* were constructed by homology modeling,[17–20] and the binding modes of antifungal agents were investigated. Of note, Sheng et al. constructed a pharmacophore model on the basis of the *C. albicans* enzyme and highlighted the importance of both Tyr118 and Ser378 for π–π stacking and hydrogen-bonding interactions in the stabili-

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zation of inhibitors.[21–24] Furthermore, Xiao et al. suggested a model for the binding of azoles with extended side chains in CYP51 from *C. albicans* and *A. fumigatus*. Specifically, itraconazole and posaconazole appear to be less affected by substitutions near the heme site than either fluconazole or voriconazole, which could be explained by tighter affinity and/or compensatory adjustments within the active site.[17]

In recent years, most of the work in azole optimization has been focused on modification of the side chain attached to the propanol group,[20,21,25,26] and we also reported the synthesis of multiple series of antifungal agents with varying degrees of antifungal activity against *C. albicans* and *A. fumigatus* strains.[27–31] Among our molecules, the recent series of 4-({2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl]-methylamino}methyl)benzenesulfonamides (**I**, Figure 1) yielded

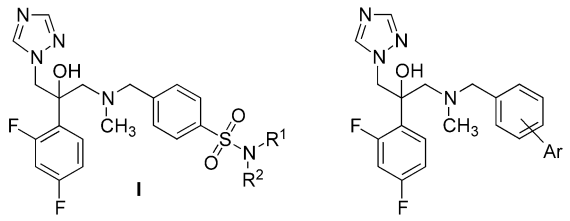


Figure 1. Lead structure **I** (left) reported in Reference [31] and general structures of synthesized compounds (right). For the structures of the aromatic moiety (Ar), see Table 1.

the most active compounds against *Candida* spp. and *A. fumigatus* strains, consistent with the pharmacophore model.[31] These compounds also demonstrated the capacity to overcome upregulation of *CDR* and *ERG11* genes and were able to maintain antifungal activity despite a recognized and critical CYP51 substitution in *C. albicans* isolates.

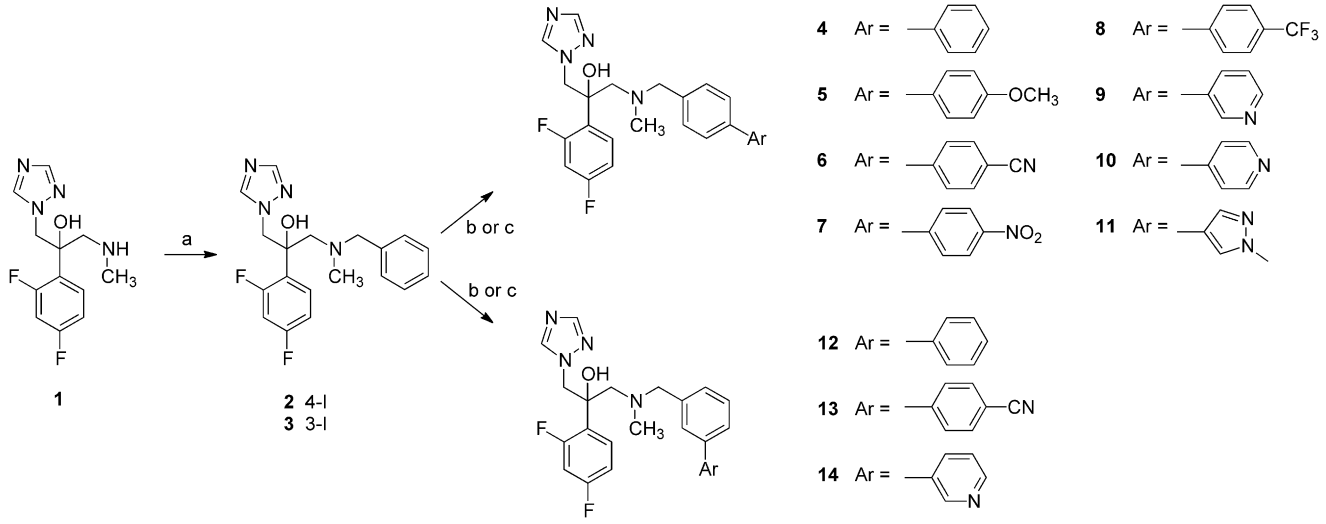
Taking into account that series with hydrogen-bond acceptors in the *para* position of a flexible benzyl group lead to broad-spectrum compounds, we decided to pursue new benzylamine derivatives with extended side chains, including additional aromatic rings (benzene, pyridine, or pyrazole) in the *meta* or *para* positions (Figure 1). With a diverse selection of "probe" substituents (methoxy, cyano, nitro, trifloromethyl, morpholine, *N*-methylpiperazine, and sulfonamides), this series has also provided new insights into structure–activity relationships (SAR).

Results and Discussion

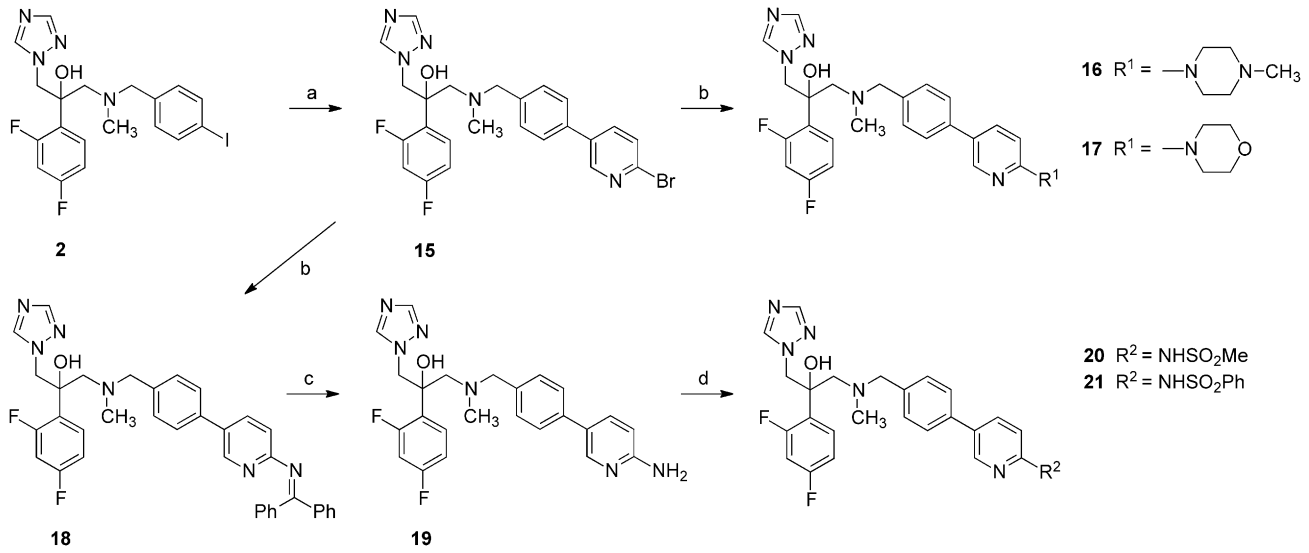
Chemistry

Synthesis of target compounds **4**–**14** began from derivative **1**,[29] which was combined with 4-iodobenzylbromide or 3-iodobenzylbromide in presence of Hunig's base to form intermediates **2** and **3** (Scheme 1). Suzuki cross-coupling with various *para*-substituted (hetero)arylboronic acids (or esters) afforded molecules **4**–**14**. Phenylboronic acid and 4-methoxyphenylboronic acid were coupled using standard reaction conditions, whereas introduction of aryls with electron-withdrawing substituents was performed using microwave irradiation.[32]

The synthetic route to target compounds **15**–**17** and **19**–**21** is outlined in Scheme 2. 2-Bromopyridine-5-boronic acid was prepared as described in the literature[33] and utilized in Suzuki cross-coupling with derivative **2** to afford derivative **15** in 60% yield.[34] Molecules **16** and **17** were obtained from **15** by optimization of Buchwald–Hartwig amination conditions with *N*-methylpiperazine or morpholine using $Pd_2(dba)_3$, *t*BuONa, and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) in toluene. Under the same conditions, benzophenone imine was coupled with **15** to afford intermediate **18**, which was deprotected with



Scheme 1. *Reagents and conditions*: a) 4-iodobenzylbromide or 3-iodobenzylbromide, *N*,*N*-diisopropylethylamine, CH_3CN, RT, 24 h, 54–92%; b) benzeneboronic acid or 4-methoxybenzeneboronic acid, $Pd(PPh_3)_4$, 2 M aq Na_2CO_3, EtOH, toluene, reflux, 3 h, 56–75%; c) boronic acid or boronic acid pinacol ester, $Pd(PPh_3)_4$, 2 M aq Na_2CO_3, CH_3CN, microwave 100 W, 120 °C, 10 min, 41–70%.



Scheme 2. *Reagents and conditions:* a) 2-bromopyridine-5-boronic acid, $Pd(PPh_3)_4$, 1 M aq Na_2CO_3, DMF, 90 °C, 2 h, 60%; b) amines or benzophenone imine, $Pd_2(dba)_3$, BINAP, *t*BuONa, toluene, 100 °C, 2 h, 70–82%; c) hydroxylamine hydrochloride, AcONa, MeOH, RT, 2 h, 82%; d) R^2SO_2Cl, pyridine, 55 °C, 2 h, 73–76%.

hydroxylamine hydrochloride to give amine **19** in good yield. Finally, reaction of **19** with methane- or benzenesulfonylchlorides in pyridine led to compounds **20** and **21**.

Antifungal activity

The in vitro antifungal activities of all compounds were evaluated against human pathogenic fungi (*C. albicans, C. krusei*, *C. glabrata*, *C. parapsilosis*, and *A. fumigatus*) and are summarized in Table 1. Minimum inhibitory concentration (MIC)values of fluconazole, voriconazole, and itraconazole are shown as reference compounds.

Regardless of the aromatic rings linked the benzylamine group or the size and nature of various substituents, all of the synthesized compounds displayed a high level of activity toward the *C. albicans* CA98001 strain, with MIC values ranging from 1.0 to 20 ng mL^{-1} and comparable to that of voriconazole. Significant broad-spectrum antifungal activity was also observed for the majority of these molecules against *C. krusei* CK8, *C. glabrata*, and *C. parapsilosis* strains, confirming their potential against *Candida* strains with low susceptibility or intrinsic resistance to fluconazole. Compounds **6** and **7**, with either a 4-cyano or a 4-nitrophenyl substituent, exhibited the most potent antifungal activity against the *C. krusei* CK506 strain (MIC values of 1.32 and 1.60 μg mL^{-1}, respectively). A majority of the compounds (**4**–**11** and **15**–**19**) exhibited promising biological results toward the *A. fumigatus* AF98003 strain, with MIC values ranging from 2.2 to 3.6 μg mL^{-1}, only five- to ninefold higher than that of itraconazole.

Compounds **12**–**14** are of particular interest, as compared to their immediate analogues **4**, **6**, and **9**. Overall, the introduction of aromatic substituents at the *para* versus the *meta* position of the benzylamine group yielded less active compounds, especially against *A. fumigatus*, *C. parapsilosis*, and *C. glabrata* strains. The biological activities against the *C. albicans* strain were less sensitive to these steric changes. Interestingly, the unsubstituted biphenyl molecule **4** (MIC < 0.001 ng mL^{-1}) was as active toward the *C. albicans* strain as compounds **5**–**8**, which have additional electron-donating or electron-withdrawing groups, suggesting that these substituents have only minor influence. Additionally, the biological results obtained for compounds **9**–**11**, which contain pyridine or pyrazole moieties, were comparable to those for derivative **4**, showing that the presence of such azaheterocycles is not necessary for potent antifungal activity against *C. albicans*.

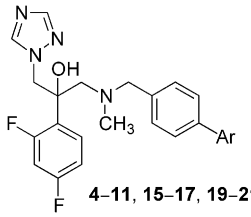
Sterol analysis

The mechanism of action for this series of azoles was investigated by studying inhibition of *C. albicans* CA98001 ergosterol biosynthesis following treatment with **6**, the most active compound. As shown in Table 2, 60% inhibition of ergosterol biosynthesis was obtained with a concentration of 4.59 ng mL^{-1}, near the MIC value (1.0 ng mL^{-1}), and lanosterol accumulation was observed. At a higher concentration (22.98 ng mL^{-1}), this effect was maximal with virtually undetectable production of ergosterol. Depletion of ergosterol and significant accumulation of 14-methyl-3,6-diol (a well-known toxic metabolite obtained from 14-methylfecosterol and catalyzed by the $\Delta^{5,6}$-desaturase encoded by the *ERG3* gene)[35] are typically the results of growth inhibition following azole treatment and confirm inhibition of the CYP51 enzyme.

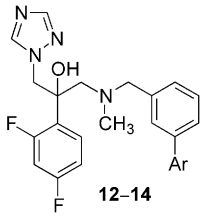
Biological evaluation against *C. albicans* isolates with reduced fluconazole susceptibility

The biological effects of these compounds were also investigated against two *C. albicans* strains with known mechanisms of resistance (DSY735 and CAAL-74).[31] Compounds **6** and **7** were selected for their broad-spectrum antifungal activity, with MIC values presented in Table 3. Both compounds exhibited high antifungal activities against these strains, with MIC values

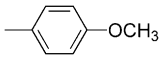
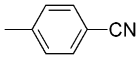
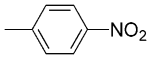
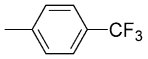
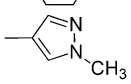
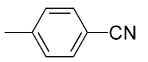
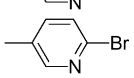
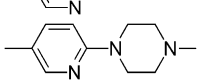
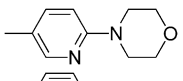
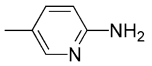
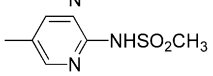
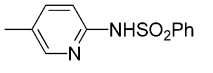
Table 1. In vitro antifungal activities of compounds **4–14**, **15–17**, and **19–21** against *Candida* spp. and *A. fumigatus* strains.



4–11, **15–17**, **19–21**



12–14

Compd	Ar	MIC values [μg mL^{-1}][a]						
		CA98001	CK506	CK8	CG468	CAPA1	CAPA2	AF98003
4		< 0.001	> 40	1.55 ± 0.06	0.154 ± 0.001	0.152 ± 0.035	0.143 ± 0.008	2.66 ± 0.13
5		0.001 ± 0.001	> 40	0.97 ± 0.25	0.156 ± 0.002	0.167 ± 0.014	0.110 ± 0.032	2.36 ± 0.05
6		0.001 ± 0.001	1.32 ± 0.02	0.193 ± 0.005	0.133 ± 0.009	0.092 ± 0.009	0.151 ± 0.030	2.76 ± 0.09
7		0.002 ± 0.001	1.60 ± 0.10	0.88 ± 0.09	0.158 ± 0.005	0.149 ± 0.014	0.134 ± 0.043	3.16 ± 0.05
8		< 0.001	2.40 ± 0.50	1.54 ± 0.08	1.52 ± 0.09	1.180 ± 0.151	1.11 ± 0.27	3.07 ± 0.15
9		0.013 ± 0.003	12.8 ± 0.7	1.9 ± 0.1	0.113 ± 0.004	0.875 ± 0.135	0.196 ± 0.078	2.96 ± 0.04
10		0.001 ± 0.001	13.8 ± 0.2	1.2 ± 0.1	0.122 ± 0.004	0.191 ± 0.037	0.218 ± 0.073	2.22 ± 0.04
11		0.008 ± 0.001	29.4 ± 5.0	8.7 ± 1.3	1.15 ± 0.13	1.263 ± 0.175	0.740 ± 0.019	2.89 ± 0.04
12		0.012 ± 0.001	35.8 ± 0.1	3.6 ± 1.2	0.786 ± 0.434	1.230 ± 0.035	1.53 ± 0.15	24.7 ± 0.9
13		0.002 ± 0.001	30.3 ± 2.4	0.16 ± 0.01	1.19 ± 0.14	0.873 ± 0.184	1.51 ± 0.11	20.2 ± 1.4
14		0.012 ± 0.002	> 40	14.3 ± 0.2	1.42 ± 0.01	9.42 ± 1.34	8.53 ± 1.17	> 40
15		0.002 ± 0.001	> 50	1.2 ± 0.1	0.139 ± 0.001	0.195 ± 0.001	0.118 ± 0.031	2.98 ± 0.05
16		0.020 ± 0.053	15.8 ± 0.8	1.54 ± 0.12	1.48 ± 0.04	0.080 ± 0.021	0.149 ± 0.011	3.62 ± 0.11
17		< 0.001	> 50	2.0 ± 0.1	11.3 ± 1.5	< 0.05	0.078 ± 0.026	2.92 ± 0.05
19		0.002 ± 0.001	15.3 ± 0.4	1.4 ± 0.1	0.401 ± 0.121	0.369 ± 0.203	0.203 ± 0.090	2.93 ± 0.09
20		0.010 ± 0.002	> 50	27.9 ± 4.1	12.7 ± 2.3	1.22 ± 0.20	2.71 ± 0.25	29.6 ± 1.1
21		0.002 ± 0.001	> 50	5.1 ± 1.6	1.91 ± 0.14	1.14 ± 0.12	1.35 ± 0.13	> 60
Fluconazole	–	0.036 ± 0.021	> 30	12.9 ± 0.9	7.7 ± 0.1	> 30	> 30	–
Voriconazole	–	0.005 ± 0.001	1.3 ± 0.3	0.24 ± 0.07	0.45 ± 0.04	0.95 ± 0.13	0.36 ± 0.01	0.15 ± 0.01
Itraconazole	–	–	–	–	–	–	–	0.42 ± 0.04

[a] Values represent the mean ± SD of experiments performed in triplicate; *C. albicans* (CA98001), *C. krusei* (CK506, CK8), *C. glabrata* (CG468), *C. parapsilosis* (CAPA1, CAPA2), and *A. fumigatus* (AF98003).

ranging from 22–91 ng mL^{-1}, implying that they are able to overcome overexpression of *CDR* and *ERG11* genes or specific point substitutions in the CYP51 enzyme which result in fluconazole resistance, as observed in the previously described benzenesulfonamide series (**I**, Figure 1).[31]

Molecular modeling

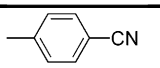
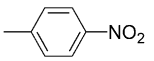
In an attempt to understand the observed SAR, we first performed docking of compounds **6** (MIC = 1.0 ng mL^{-1}) and **13** (MIC = 2.0 ng mL^{-1}) with our homology model of CYP51 from *C. albicans* (Figure 2 a).[30,36] Despite different side chain confor-

Table 2. Effect of compound **6** on sterol composition of *C. albicans* CA98001.

Sterols[a]	Control	**6** [ng mL^{-1}]	
		4.59	22.98
Lanosterol	6.0	27.6	14.5
Eburicol	3.4	21.8	7.9
Zymosterol	2.0	–	–
Episterol	3.7	–	–
14-Methylfecosterol	–	2.4	7.1
14-Methylepisterol	–	6.7	7.2
14-Methyl-3,6-diol	–	8.8	62.7
Ergosterol	84.7	32.7	0.7

[a] Sterols of interest were identified by mass spectrometry. The area under the curve (AUC) of each peak was used to calculate a ratio: [sterol AUC/sum of sterols AUC] × 100.

Table 3. In vitro antifungal activities of compounds **6** and **7** against *C. albicans* strains with reduced fluconazole susceptibility.

Compd	Ar	MIC [μg mL^{-1}][a]	
		DSY735	CAAL-74
6		0.073 ± 0.018	0.022 ± 0.004
7		0.086 ± 0.005	0.091 ± 0.023
Fluconazole	–	12.55	> 30

[a] Values represent the mean ± SD of experiments performed in triplicate.

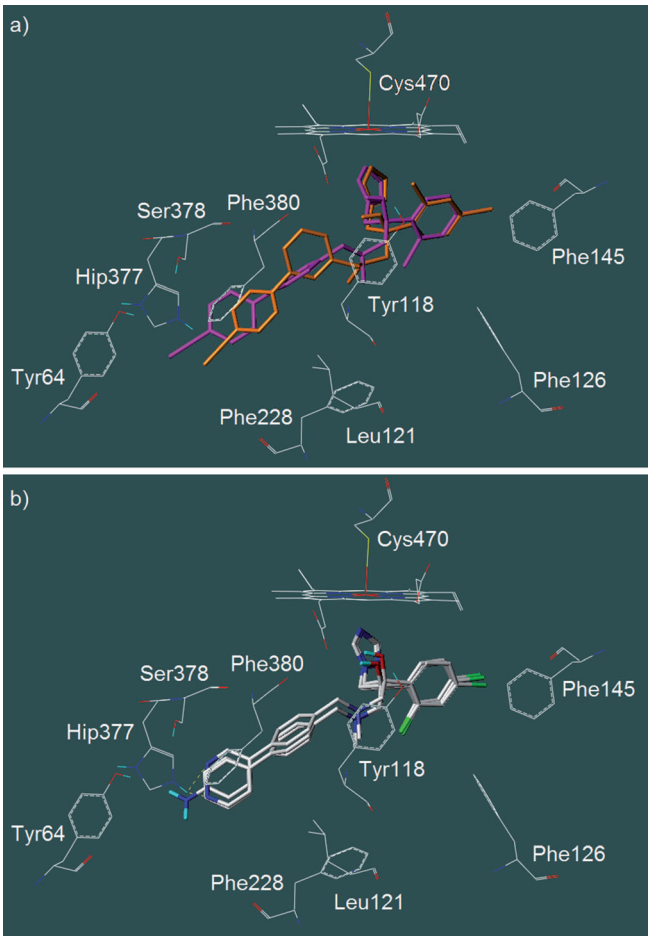


Figure 2. a) Predicted binding of compounds (*S*)-**6** (magenta) and (*S*)-**13** (orange) in the proposed active site pocket (channel 2) of CYP51 from *C. albicans*. Hip 377 is the protonated form of histidine residue. b) Predicted binding of compounds (*S*)-**4**, (*S*)-**10**, and (*S*)-**19** in the proposed active site pocket (channel 2) of CYP51 from *C. albicans*. Hydrogen bonds are indicated as yellow dotted lines.

mations, both compounds adopt a similar binding interaction with the enzyme. The benzonitrile groups are in close proximity to residues His 377, Tyr 64, and Phe 380 but not to Ser 378 (d > 5 Å), the amino acid conserved across the fungal CYP51 enzyme and proposed in the pharmacophore model to form a key hydrogen bonding interaction with inhibitors.[21]

The docking of representative molecules, such as the non-substituted biphenyl compound **4** or compounds **10** and **19**, which possess a terminal pyridin-4-yl or a 6-aminopyridin-3-yl group, respectively, should confirm that the binding of those azoles to the CYP51–*C. albicans* enzyme occurs mostly through hydrophobic interactions (Figure 2b). In fact, even if an additional hydrogen-bonding interaction seems possible between the imidazole side chain of His 377 and both nitrogen atoms in the 3- or 4-position of the pyridine ring, the fact that similar biological results are obtained for compound **4** (which does not have an electron-withdrawing substituent) clearly demonstrates the critical importance of key residue Tyr 118 and the class-specific residue Phe 380 in π–π stacking interactions with the bi(hetero)aryl groups of these antifungal agents. Interactions such as these contribute to improved stabilization of the inhibitors within the active site.

Conclusions

Among the several azoles synthesized in our laboratory, with a focus on modification of the side chain linked to the propanol group, this manuscript clearly confirms that compounds containing a flexible benzylamine moiety yielded the best results against *Candida* spp. and *A. fumigatus* strains, without the need for a hydrogen-bond acceptor substituent directly attached to the *para* position. Selected biaryl compounds **6** and **7**, with a 4-cyano or a 4-nitro substituent, are also able to overcome overexpression of *CDR* and *ERG11* genes in a *C. albicans* strain with reduced susceptibility to fluconazole and can maintain activity despite a known CYP51 point mutation from a fluconazole-resistant *C. albicans* strain. However, close attention must be paid to observed SAR based on MIC data in the absence of biological results regarding CYP51. Although all of the synthesized compounds exhibited excellent antifungal activity against *C. albicans*, minor differences observed with small structural modifications cannot be explained with a three-dimensional model of CYP51 alone. Adequate physicochemical parameters must be considered in terms of antifungal potency, bioavailability, and toxicity. In particular, the relatively high lipophilicity observed for these compounds (**6**, clog P = 3.77; **7**, clog P = 4.08; octanol–water partition coefficient calculated

using the Biobyte program: http://biobyte.com.index.html) is certainly of utmost importance for further development.

Experimental Section

Chemistry

General methods: Melting points were determined using an Electrothermal IA9300 digital melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC250 (250 MHz) or Bruker Avance 400 spectrometer (400 MHz). Chemical shifts are expressed as δ values (ppm) relative to tetramethylsilane (TMS) as an internal standard (s = singlet, d = doublet, t = triplet, q = quadruplet, sext = sextuplet, m = multiplet and b = broad). Coupling constants (*J*) are given in Hertz (Hz). IR spectra were obtained in KBr pellets using a Perkin–Elmer Paragon FTIR 1000 PC spectrometer. Only the most significant absorption bands have been reported. Electrospray ionization (ESI) mass spectrometric analysis was performed on a Waters Acquity UPLC System ZQ 2000 single quadrupole. All compounds tested displayed more than 96% purity. All reactions were monitored by thin-layer chromatography (TLC) using 0.2 mm silica gel plates 60F-254 (5735 Merck). Column chromatography was carried out using silica gel 60 (70–230 Mesh, ASTM, Merck). Chemicals and solvents used were commercially available. Focused microwave irradiations were carried out with a CEM Discover focused microwave reactor (300 W, 2455 MHz, monomode system).

2-(2,4-Difluorophenyl)-1-[(4-iodobenzyl)methylamino]-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (2): *N*-*N*-Diisopropylethylamine (774 μL, 4.47 mmol) was added to a stirred solution of **1** (1 g, 3.73 mmol) in CH_3CN (31 mL), followed by addition of 4-iodobenzylbromide (1.107 g, 3.73 mmol). The solution was stirred at RT for 24 h. The solvent was removed in vacuo, and the residue was partitioned between CH_2Cl_2 and H_2O. The organic layers were dried over anhyd Na_2SO_4 and concentrated in vacuo. The residue was purified using silica gel column chromatography (CH_2Cl_2 and CH_2Cl_2/EtOH, 98:2) to yield compound **2** as a white powder (1.67 g, 92%): R_f = 0.30 (CH_2Cl_2/EtOH, 98:2); mp: 98–99 °C; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 2.09 (s, 3H), 2.77 (d, 1H, J = 13.7 Hz), 3.04 (d, 1H, J = 13.7 Hz), 3.38 (d, 1H, J = 13.5 Hz), 3.55 (d, 1H, J = 13.5 Hz), 4.53 (d, 1H, J = 14.3 Hz), 4.58 (d, 1H, J = 14.3 Hz), 5.78 (s, 1H), 6.92 (d, 2H, J = 8.0 Hz), 6.99 (ddd, 1H, $J_{H-F} = J_{H-H}$ = 8.4 Hz, J_{H-H} = 2.4 Hz), 7.18 (ddd, 1H, $J_{H-F} = J'_{H-F}$ = 9.2 Hz, J_{H-H} = 2.4 Hz), 7.44 (ddd, 1H, J_{H-H} = 8.4 Hz, $J_{H-F} = J'_{H-F}$ = 6.8 Hz), 7.62 (d, 2H, J = 8.0 Hz), 7.78 (s, 1H), 8.31 ppm (s, 1H); IR (KBr): $\tilde{\nu}$ = 3451, 1613, 1495, 1272, 1127 cm^{-1}; MS (ESI) *m/z* (%): 485.0 (100) $[M+H]^+$.

2-(2,4-Difluorophenyl)-1-[(3-iodobenzyl)methylamino]-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (3): The synthetic procedure for compound **2** was used, beginning from **1** (1.0 g, 3.73 mmol) and 3-iodobenzylbromide (1.1 mg, 3.73 mmol), to yield compound **3** as a white powder (975 mg, 54%): R_f = 0.15 (CH_2Cl_2/EtOH, 98:2); mp: 85–86 °C; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 2.08 (s, 3H), 2.73 (d, 1H, J = 13.7 Hz), 3.10 (d, 1H, J = 13.7 Hz), 3.30 (d, 1H, J = 13.5 Hz), 3.61 (d, 1H, J = 13.5 Hz), 4.52 (d, 1H, J = 14.2 Hz), 4.57 (d, 1H, J = 14.2 Hz), 5.84 (s, 1H), 7.00 (ddd, 1H, $J_{H-F} = J_{H-H}$ = 8.4 Hz, J_{H-H} = 2.4 Hz), 7.04–7.12 (m, 2H), 7.19 (ddd, 1H, $J_{H-F} = J'_{H-F}$ = 9.2 Hz, J_{H-H} = 2.4 Hz), 7.29 (s, 1H), 7.46 (ddd, 1H, J_{H-H} = 8.4 Hz, $J_{H-F} = J'_{H-F}$ = 6.8 Hz), 7.57 (d, 1H, J = 7.6 Hz), 7.80 (s, 1H), 8.32 ppm (s, 1H); IR (KBr): $\tilde{\nu}$ = 3428, 3020, 1613, 1498, 1415, 1277, 1141 cm^{-1}; MS (ESI) *m/z* (%): 485.0 (100) $[M+H]^+$.

2-(2,4-Difluorophenyl)-1-[(biphenyl-4-ylmethyl)methylamino]-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (4): $Pd(PPh_3)_4$ (14 mg, 0.01 mmol) was added under argon to a stirred solution of **2** (200 mg, 0.41 mmol) in toluene (2 mL), and the solution was stirred at RT for 20 min. Benzeneboronic acid (60 mg, 0.50 mmol) in EtOH (0.1 mL) was added, followed by the addition of 2 M aq Na_2CO_3 (0.248 mL, 0.50 mmol). The resulting mixture was stirred at reflux for 3 h. The solvent was removed in vacuo, and the residue was partitioned between CH_2Cl_2 and H_2O. The organic layers were dried over anhyd Na_2SO_4 and concentrated in vacuo. The residue was purified using silica gel column chromatography (CH_2Cl_2 and CH_2Cl_2/EtOH, 99:1) to yield compound **4** as a white powder (120 mg, 67%): R_f = 0.10 (CH_2Cl_2/EtOH, 98:2); mp: 117–118 °C; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 2.13 (s, 3H), 2.82 (d, 1H, J = 13.2 Hz), 3.08 (d, 1H, J = 13.2 Hz), 3.48 (d, 1H, J = 13.6 Hz), 3.64 (d, 1H, J = 13.6 Hz), 4.55 (d, 1H, J = 14.0 Hz), 4.61 (d, 1H, J = 14.0 Hz), 5.80 (s, 1H), 7.01 (ddd, 1H, $J_{H-F} = J_{H-H}$ = 8.4 Hz, J_{H-H} = 2.4 Hz), 7.17–7.23 (m, 3H), 7.36–7.40 (m, 1H), 7.45–7.50 (m, 3H), 7.57 (d, 2H, J = 8.0 Hz), 7.67 (d, 2H, J = 8.0 Hz), 7.78 (s, 1H), 8.33 ppm (s, 1H); ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 43.8, 56.1, 62.4, 63.2, 75.2, 103.5, 110.3, 126.4, 126.5 (2C), 126.7 (2C), 127.4, 129.1 (2C), 129.3 (2C), 130.1, 138.4, 138.9, 140.2, 144.8, 150.6 ppm (CF not visible); IR (KBr): $\tilde{\nu}$ = 3450, 1614, 1495, 1267, 1132 cm^{-1}; MS (ESI) *m/z* (%): 435.5 (100) $[M+H]^+$; UPLC purity 99%.

2-(2,4-Difluorophenyl)-1-{[4-(4-methoxyphenyl)benzyl]methylamino}-3-(1*H*-,2,4-triazol-1-yl)propan-2-ol (5): The synthetic procedure for compound **4** was used, beginning from **2** (200 mg, 0.41 mmol) and 4-methoxybenzeneboronic acid (75 mg, 0.50 mmol) to yield compound **5** as a white powder (145 mg, 75%): R_f = 0.25 (CH_2Cl_2/EtOH 98:2); mp: 109–110 °C; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 2.12 (s, 3H), 2.81 (d, 1H, J = 13.6 Hz), 3.07 (d, 1H, J = 13.6 Hz), 3.46 (d, 1H, J = 13.2 Hz), 3.61 (d, 1H, J = 13.2 Hz), 3.82 (s, 3H), 4.55 (d, 1H, J = 14.4 Hz), 4.61 (d, 1H, J = 14.4 Hz), 5.79 (s, 1H), 6.99 (ddd, 1H, $J_{H-F} = J_{H-H}$ = 8.4 Hz, J_{H-H} = 2.4 Hz), 7.04 (d, 2H, J = 8.4 Hz), 7.16 (d, 2H, J = 8.0 Hz), 7.20 (ddd, 1H, $J_{H-F} = J'_{H-F}$ = 9.2 Hz, J_{H-H} = 2.4 Hz), 7.48 (ddd, 1H, J_{H-H} = 8.4 Hz, $J_{H-F} = J'_{H-F}$ = 6.8 Hz), 7.51 (d, 2H, J = 8.0 Hz), 7.61 (d, 2H, J = 8.4 Hz), 7.78 (s, 1H), 8.33 ppm (s, 1H); ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 43.7, 55.3, 56.1, 62.5, 63.2, 75.2, 103.9, 110.8, 114.5 (2C), 126.0 (2C), 126.4, 127.8 (2C), 129.3 (2C), 130.0, 132.5, 137.6, 138.6, 145.1, 150.6, 159.0 ppm (CF not visible); IR (KBr): $\tilde{\nu}$ = 3450, 1612, 1497, 1260, 1123 cm^{-1}; MS (ESI) *m/z* (%): 82.9 (35), 197.1 (24), 465.1 (100) $[M+H]^+$; UPLC purity 98%.

1-{[4-(4-Cyanophenyl)benzyl]methylamino}-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (6): To a 10 mL vial were added under argon **2** (200 mg, 0.41 mmol), 4-cyanobenzeneboronic acid (61 mg, 0.41 mmol), $Pd(PPh_3)_4$ (24 mg, 0.02 mmol), 2 M aq Na_2CO_3 (2 mL) and acetonitrile (2 mL). The resulting mixture was heated at 120 °C under microwave irradiation (100 W) for 10 min. The reaction mixture was cooled to RT and diluted with H_2O. Product was extracted with CH_2Cl_2, organic layers were dried over anhyd Na_2SO_4 and concentrated in vacuo. The residue was purified on silica gel column chromatography (CH_2Cl_2 and CH_2Cl_2/EtOH, 99:1) to yield compound **6** as a white powder (123 mg, 65%): R_f = 0.30 (CH_2Cl_2/EtOH, 98:2); mp: 132–134 °C; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 2.13 (s, 3H), 2.81 (d, 1H, J = 13.6 Hz), 3.09 (d, 1H, J = 13.6 Hz), 3.49 (d, 1H, J = 13.2 Hz), 3.66 (d, 1H, J = 13.2 Hz), 4.55 (d, 1H, J = 14.0 Hz), 4.61 (d, 1H, J = 14.0 Hz), 5.81 (s, 1H), 7.01 (ddd, 1H, $J_{H-F} = J_{H-H}$ = 8.4 Hz, J_{H-H} = 2.4 Hz), 7.20 (dd, 1H, $J_{H-F} = J'_{H-F}$ = 9.2 Hz), 7.24 (d, 2H, J = 8.0 Hz), 7.48 (ddd, 1H, J_{H-H} = 8.4 Hz, $J_{H-F} = J'_{H-F}$ = 6.8 Hz), 7.67 (d, 2H, J = 8.0 Hz), 7.79 (s, 1H), 7.90 (d, 2H, J = 7.6 Hz), 7.95 (d, 2H, J = 7.6 Hz), 8.32 ppm (s, 1H); ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 43.6, 55.9, 62.1, 63.0, 75.1, 103.7, 109.7, 110.5, 118.9, 126.7 (2C), 127.3 (2C), 128.0, 129.3 (2C), 130.0, 132.8

(2C), 136.7, 139.8, 144.4, 144.9, 150.4 ppm (CF not visible); IR (KBr): $\tilde{\nu}$ = 3451, 2360, 1615, 1503, 1272, 1108 cm^{-1}; MS (ESI) *m/z* (%): 460.1 (100) $[M+H]^+$; UPLC purity 98%.

2-(2,4-Difluorophenyl)-1-{[4-(4-nitrophenyl)benzyl]methylamino}-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (7): The synthetic procedure for compound **6** was used, beginning from **2** (200 mg, 0.41 mmol) and 4-nitrobenzeneboronic acid (68 mg, 0.41 mmol), to yield compound **7** as a yellow powder (123 mg, 62%): R_f = 0.20 (CH_2Cl_2/EtOH, 99:1); mp: 125–126 °C; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 2.12 (s, 3H), 2.81 (d, 1H, J = 14.0 Hz), 3.10 (d, 1H, J = 14.0 Hz), 3.50 (d, 1H, J = 13.6 Hz), 3.68 (d, 1H, J = 13.6 Hz), 4.55 (d, 1H, J = 14.4 Hz), 4.61 (d, 1H, J = 14.4 Hz), 5.81 (s, 1H), 7.02 (ddd, 1H, J_{H-F} = J_{H-H} = 8.4 Hz, J_{H-H} = 2.4 Hz), 7.20 (m, 1H), 7.26 (d, 2H, J = 8.0 Hz), 7.48 (ddd, 1H, J_{H-H} = 8.4 Hz, J_{H-F} = J'_{H-F} = 6.8 Hz), 7.71 (d, 2H, J = 8.8 Hz), 7.79 (s, 1H), 7.99 (d, 2H, J = 8.8 Hz), 8.32 (s, 1H), 8.33 ppm (d, 2H, J = 8.8 Hz); ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 43.8, 56.1, 62.3, 63.2, 75.3, 104.1, 110.9, 124.3 (2C), 126.0, 127.1 (2C), 127.8 (2C), 129.5 (2C), 130.3, 137.3, 140.4, 145.1, 146.6, 148.3, 150.7 ppm (CF not visible); IR (KBr): $\tilde{\nu}$ = 3442, 1632, 1508,1496, 1338 cm^{-1}; MS (ESI) *m/z* (%): 480.1 (100) $[M+H]^+$; UPLC purity 96%.

1-{[4-(4-Trifluoromethylphenyl)benzyl]methylamino}-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (8): The synthetic procedure for compound **6** was used, beginning from **2** (200 mg, 0.41 mmol) and 4-trifluoromethylbenzeneboronic acid (78 mg, 0.41 mmol), to yield compound **8** as a white powder (135 mg, 65%): R_f = 0.20 (CH_2Cl_2/EtOH, 98:2); mp: 92–93 °C; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 2.13 (s, 3H), 2.81 (d, 1H, J = 13.9 Hz), 3.10 (d, 1H, J = 13.9 Hz), 3.49 (d, 1H, J = 13.1 Hz), 3.66 (d, 1H, J = 13.1 Hz), 4.55 (d, 1H, J = 13.8 Hz), 4.61 (d, 1H, J = 13.8 Hz), 5.81 (s, 1H), 7.01 (ddd, 1H, J_{H-F} = J_{H-H} = 8.4 Hz, J_{H-H} = 2.4 Hz), 7.18–7.25 (m, 3H), 7.47 (ddd, 1H, J_{H-H} = 8.4 Hz, J_{H-F} = J'_{H-F} = 6.8 Hz), 7.65 (d, 2H, J = 6.8 Hz), 7.79 (s, 1H), 7.83 (d, 2H, J = 7.2 Hz), 7.91 (d, 2H, J = 7.2 Hz), 8.33 ppm (s, 1H); ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 43.8, 56.1, 62.4, 63.2, 75.3, 103.9, 110.9, 125.8, 125.9 (2C), 126.4, 126.9 (2C), 127.5 (2C), 127.9, 129.5 (2C), 130.0, 137.3, 139.7, 144.1, 145.1, 150.7 ppm (CF not visible); IR (KBr): $\tilde{\nu}$ = 3452, 1626, 1497, 1123 cm^{-1}; MS (ESI) *m/z* (%): 503.1 (100) $[M+H]^+$; UPLC purity 98%.

2-(2,4-Difluorophenyl)-1-{[4-(pyridin-3-yl)benzyl]methylamino}-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (9): The synthetic procedure for compound **6** was used, beginning from **2** (200 mg, 0.41 mmol) and pyridine-3-boronic acid (51 mg, 0.41 mmol), to yield compound **9** as a white powder (73 mg, 41%): R_f = 0.05 (CH_2Cl_2/EtOH, 98:2); mp: 87–88 °C; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 2.09 (s, 3H), 2.77 (d, 1H, J = 14.0 Hz), 3.05 (d, 1H, J = 14.0 Hz), 3.45 (d, 1H, J = 13.2 Hz), 3.61 (d, 1H, J = 13.2 Hz), 4.51 (d, 1H, J = 14.0 Hz), 4.57 (d, 1H, J = 14.0 Hz), 5.77 (s, 1H), 6.97 (dd, 1H, J_{H-F} = J_{H-H} = 8.4 Hz), 7.15 (m, 1H), 7.19 (d, 2H, J = 7.6 Hz), 7.45 (m, 1H), 7.46 (m, 1H), 7.60 (d, 2H, J = 7.6 Hz), 7.75 (s, 1H), 8.04 (d, 1H, J = 7.2 Hz), 8.29 (s, 1H), 8.54 (m, 1H), 8.86 ppm (m, 1H); ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 43.8, 56.0, 62.4, 63.2, 75.3, 103.5, 110.3, 124.0, 126.7 (2C), 127.6, 129.5 (2C), 130.1, 134.1, 135.5, 135.8, 139.3, 145.1, 147.2, 148.5, 150.6 ppm (CF not visible); IR (KBr): $\tilde{\nu}$ = 3452, 1638, 1502, 1272, 1107 cm^{-1}; MS (ESI) *m/z* (%): 82.9 (100), 175.1 (3) 436.2 (5) $[M+H]^+$; UPLC purity 97%.

2-(2,4-Difluorophenyl)-1-{[4-(pyridin-4-yl)benzyl]methylamino}-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (10): The synthetic procedure for compound **6** was used, beginning from **2** (200 mg, 0.41 mmol) and pyridine-4-boronic acid pinacol ester (85 mg, 0.41 mmol), to yield compound **10** as a light brown powder (95 mg, 53%): R_f = 0.03 (CH_2Cl_2/EtOH, 98:2); mp: 104–105 °C; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 2.13 (s, 3H), 2.81 (d, 1H, J = 14.5 Hz), 3.10 (d, 1H, J = 14.5 Hz), 3.49 (d, 1H, J = 13.6 Hz), 3.67 (d, 1H, J = 13.6 Hz), 4.55 (d, 1H, J = 14.2 Hz), 4.61 (d, 1H, J = 14.2 Hz), 5.81 (s, 1H), 7.02 (dd, 1H, J_{H-F} = J_{H-H} = 8.4 Hz), 7.19 (ddd, 1H, J_{H-F} = J'_{H-F} = 9.2 Hz, J_{H-H} = 2.4 Hz), 7.25 (d, 2H, J = 8.4 Hz), 7.48 (ddd, 1H, J_{H-H} = 8.4 Hz, J_{H-F} = J'_{H-F} = 6.8 Hz), 7.72 (m, 4H), 7.79 (s, 1H), 8.33 (s, 1H), 8.65 ppm (d, 2H, J = 9.6 Hz); ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 43.8, 56.1, 62.4, 63.2, 75.4, 104.6, 111.0, 118.0 (2C), 126.7 (2C), 127.0, 129.5 (2C), 130.4, 135.8, 140.6, 145.1, 146.9, 150.4 (2C), 150.7 ppm (CF not visible); IR (KBr): $\tilde{\nu}$ = 3447, 1626, 1497, 1267, 1112 cm^{-1}; MS (ESI) *m/z* (%): 69.6 (18), 175.1 (100), 195.6 (33), 436.1 (58) $[M+H]^+$; UPLC purity 99%.

2-(2,4-Difluorophenyl)-1-{[4-(1-methylpyrazol-4-yl)benzyl]methylamino}-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (11): The synthetic procedure for compound **6** was used, beginning from **2** (200 mg, 0.41 mmol) and 1-methylpyrazole-4-boronic acid pinacol ester (86 mg, 0.41 mmol) to yield compound **11** as a white powder (97 mg, 53%): R_f = 0.10 (CH_2Cl_2/EtOH, 98:2); mp: 84–85 °C; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 2.11 (s, 3H), 2.79 (d, 1H, J = 13.6 Hz), 3.05 (d, 1H, J = 13.6 Hz), 3.40 (d, 1H, J = 13.2 Hz), 3.56 (d, 1H, J = 13.2 Hz), 3.88 (s, 3H), 4.53 (d, 1H, J = 14.2 Hz), 4.59 (d, 1H, J = 14.2 Hz), 5.78 (s, 1H), 7.00 (dd, 1H, J_{H-F} = J_{H-H} = 8.4 Hz), 7.07 (d, 2H, J = 8.0 Hz), 7.19 (dd, 1H, J_{H-F} = J'_{H-F} = 9.2 Hz), 7.44–7.47 (m, 3H), 7.78 (s, 1H), 7.85 (s, 1H), 8.12 (s, 1H), 8.32 ppm (s, 1H); ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 38.8, 43.8, 56.1, 62.6, 63.1, 75.3, 103.0, 110.9, 122.0, 124.8 (2C), 126.5, 127.8, 129.3 (2C), 130.1, 131.4, 136.1, 136.7, 145.1, 150.6 ppm (CF not visible); IR (KBr): $\tilde{\nu}$ = 3448, 1630, 1497, 1272, 1133 cm^{-1}; MS (ESI) *m/z* (%): 82.9 (100), 171.1 (24), 439.1 (73) $[M+H]^+$; UPLC purity 98%.

2-(2,4-Difluorophenyl)-1-[(biphenyl-3-ylmethyl)methylamino]-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (12): Using the synthetic procedure used for compound **4** starting from **3** (200 mg, 0.41 mmol) and benzeneboronic acid (60 mg, 0.50 mmol) to yield compound **12** as a white powder (100 mg, 56%): R_f = 0.20 (CH_2Cl_2/EtOH, 98:2); mp: 74–75 °C; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 2.11 (s, 3H), 2.79 (d, 1H, J = 13.6 Hz), 3.16 (d, 1H, J = 13.6 Hz), 3.43 (d, 1H, J = 13.2 Hz), 3.72 (d, 1H, J = 13.2 Hz), 4.53 (d, 1H, J = 14.0 Hz), 4.58 (d, 1H, J = 14.0 Hz), 5.84 (s, 1H), 7.00 (ddd, 1H, J_{H-F} = J_{H-H} = 8.4 Hz, J_{H-H} = 2.4 Hz), 7.10 (d, 1H, J = 7.6 Hz), 7.17 (ddd, 1H, J_{H-F} = J'_{H-F} = 9.2 Hz, J_{H-H} = 2.4 Hz), 7.26 (s, 1H), 7.36 (dd, 1H, J = 7.6 Hz), 7.40 (d, 1H, J = 7.6 Hz), 7.34–7.60 (m, 6H), 7.79 (s, 1H), 8.32 ppm (s, 1H); ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 43.7, 56.2, 62.6 63.3, 75.5, 103.8, 110.8, 125.4, 126.4, 126.8 (2C), 126.9, 127.5, 127.9, 128.8, 129.0 (2C), 130.1, 140.0, 140.1, 140.3, 145.1, 150.6, 158.9, 161.6 ppm; IR (KBr): $\tilde{\nu}$ = 3446, 1618, 1501, 1267, 1133 cm^{-1}; MS (ESI) *m/z* (%): 435.2 (100) $[M+H]^+$; UPLC purity 100%.

1-{[3-(4-Cyanophenyl)benzyl]methylamino}2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (13): The synthetic procedure for compound **6** was used, beginning from **3** (200 mg, 0.41 mmol) and 4-cyanobenzeneboronic acid (61 mg, 0.41 mmol) to yield compound **13** as a white powder (135 mg, 70%): R_f = 0.20 (CH_2Cl_2/EtOH, 98:2); mp: 45–46 °C; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 2.12 (s, 3H), 2.78 (d, 1H, J = 13.6 Hz), 3.16 (d, 1H, J = 13.6 Hz), 3.44 (d, 1H, J = 13.4 Hz), 3.73 (d, 1H, J = 13.4 Hz), 4.52 (d, 1H, J = 14.1 Hz), 4.58 (d, 1H, J = 14.1 Hz), 5.85 (s, 1H), 7.00 (m, 1H), 7.14–7.19 (m, 2H), 7.31 (s, 1H), 7.41 (t, 1H, J = 7.6 Hz), 7.48 (m, 1H), 7.60 (d, 1H, J = 7.6 Hz), 7.78–7.80 (m, 3H), 7.95 (d, 2H, J = 8.0 Hz), 8.32 ppm (s, 1H); ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 43.8, 56.2, 62.4, 63.2, 75.5, 103.9, 110.1, 110.8, 119.1, 125.7, 126.4, 127.2, 127.7 (2C), 129.0, 129.1, 130.0, 133.0 (2C), 138.2, 140.4, 144.8, 145.1, 150.6, 159.2, 161.8 ppm; IR (KBr): $\tilde{\nu}$ = 3457, 2216, 1618, 1497, 1272,

1133 cm^{-1}; MS (ESI) *m/z* (%): 460.2 (100) $[M+H]^+$; UPLC purity 100%.

2-(2,4-Difluorophenyl)-1-{[3-(pyridin-3-yl)benzyl]methylamino}-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (14): The synthetic procedure for compound **6** was used, beginning from **3** (200 mg, 0.41 mmol) and pyridine-3-boronic acid (51 mg, 0.41 mmol), to yield compound **14** as a colorless oil (100 mg, 56%): R_f=0.45 (CH_2Cl_2/EtOH, 95:5); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.07 (s, 3H), 2.74 (d, 1H, J=13.6 Hz), 3.09 (d, 1H, J=13.6 Hz), 3.41 (d, 1H, J=13.6 Hz), 3.67 (d, 1H, J=13.6 Hz), 4.48 (d, 1H, J=14.0 Hz), 4.53 (d, 1H, J=14.0 Hz), 5.79 (s, 1H), 6.94 (ddd, 1H, $J_{H-F}=J_{H-H}$=8.4 Hz, J_{H-H}=2.4 Hz), 7.08–7.12 (m, 2H), 7.29 (s, 1H), 7.35 (t, 1H, J=7.6 Hz), 7.40–7.49 (m, 2H), 7.54 (d, 1H, J=7.6 Hz), 7.73 (s, 1H), 7.93 (dd, 1H, J=7.6 Hz, J=1.2 Hz), 8.27 (s, 1H), 8.56 (d, 1H, J=7.6 Hz), 8.80 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=43.8, 56.2, 62.5, 63.2, 75.4, 103.8, 110.7, 124.0, 125.6, 126.4, 127.1, 128.5, 129.0, 130.0, 134.2, 135.7, 137.1, 140.3, 145.1, 147.8, 148.6, 150.6, 159.1, 161.8 ppm; IR (NaCl): $\tilde{\nu}$=3411, 1610, 1497, 1456, 1272, 1133 cm^{-1}; MS (ESI) *m/z* (%): 69.9 (30), 175.2 (36), 195.7 (100), 239.2 (46), 436.2 (69) $[M+H]^+$; UPLC purity 98%.

1-{[4-(6-Bromopyridin-3-yl)benzyl]methylamino}-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (15): $Pd(PPh_3)_4$ (378 mg, 0.33 mmol) was added under argon to a stirred solution of **2** (2.29 g, 4.73 mmol) in DMF (67 mL), and the solution was stirred at RT for 20 min. 2-Bromopyridine-5-boronic acid (1.5 g, 7.43 mmol) was added, followed by the addition of 1 M aq Na_2CO_3 (23.7 mL, 23.70 mmol). The resulting mixture was heated at 90 °C for 2 h, then cooled to RT and diluted with H_2O. The product was extracted with EtOAc, and the organic layers were dried over anhyd Na_2SO_4 and concentrated in vacuo. The residue was purified using silica gel column chromatography (CH_2Cl_2 and CH_2Cl_2/EtOH, 99:1) to yield compound **15** as a white powder (1.467 g, 60%): R_f= 0.25 (CH_2Cl_2/EtOH, 98:2); mp: 127–128 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.12 (s, 3H), 2.80 (d, 1H, J=13.5 Hz), 3.10 (d, 1H, J=13.5 Hz), 3.48 (d, 1H, J=13.5 Hz), 3.64 (d, 1H, J=13.5 Hz), 4.55 (d, 1H, J=14.3 Hz), 4.60 (d, 1H, J=14.3 Hz), 5.81 (s, 1H), 7.02 (dd, 1H, $J_{H-F}=J_{H-H}$=8.8 Hz), 7.19 (m, 1H), 7.23 (d, 2H, J=8.0 Hz), 7.49 (ddd, 1H, J_{H-H}=8.8 Hz, $J_{H-F}=J'_{H-F}$=6.8 Hz), 7.65 (d, 2H, J=8.0 Hz), 7.75 (d, 1H, J=8.4 Hz), 7.79 (s, 1H), 8.07 (dd, 1H, J=8.4 Hz, J=2.0 Hz), 8.33 (s, 1H), 8.73 ppm (d, 1H, J=2.0 Hz); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=43.8, 46.5, 62.3, 62.9, 75.3, 103.5, 110.4, 126.7 (2C), 128.0, 128.2, 129.5 (2C), 130.0, 134.3, 135.3, 137.0, 137.6, 139.8, 145.1, 148.4, 150.7, 154.9, 157.8 ppm; IR (KBr): $\tilde{\nu}$= 3484, 1641, 1497, 1272, 1082 cm^{-1}; MS (ESI) *m/z* (%): 514.0 (47), 516.0 (50) $[M+H]^+$; UPLC purity 97%.

2-(2,4-Difluorophenyl)-1-({4-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]benzyl}methylamino)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (16): Compound **15** (150 mg, 0.29 mmol), $Pd_2(dba)_3$ (5.4 mg, 0.006 mmol), (±)-BINAP (7.3 mg, 0.012 mmol), *t*BuONa (39 mg, 0.41 mmol), *N*-methylpiperazine (38 μL, 0.35 mmol) and toluene (2.6 mL) were added to a 10 mL vial under argon. The resulting mixture was heated at 100 °C for 2 h. The reaction mixture was cooled to RT and diluted with H_2O. The product was extracted with CH_2Cl_2, and the organic layers were dried over anhyd Na_2SO_4 and concentrated in vacuo. The residue was purified using silica gel column chromatography (CH_2Cl_2 and CH_2Cl_2/EtOH, 99:1) to yield compound **16** as a white powder (128 mg, 82%): R_f=0.45 (CH_2Cl_2/EtOH, 90:10); mp: 112–113 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ= 2.12 (s, 3H), 2.27 (s, 3H), 2.45 (s, 4H), 2.81 (d, 1H, J=13.6 Hz), 3.08 (d, 1H, J=13.6 Hz), 3.45 (d, 1H, J=14.4 Hz), 3.56 (s, 4H), 3.61 (d, 1H, J=14.4 Hz), 4.55 (d, 1H, J=14.8 Hz), 4.60 (d, 1H, J=14.8 Hz), 5.80 (s, 1H), 6.93 (d, 1H, J=8.8 Hz), 7.01 (ddd, 1H, $J_{H-F}=J_{H-H}$= 8.4 Hz), 7.16 (d, 2H, J=8.0 Hz), 7.20 (m, 1H), 7.47 (m, 1H), 7.52 (d, 2H, J=8.0 Hz), 7.78 (s, 1H), 7.86 (dd, 1H, J=8.8 Hz, J=1.6 Hz), 8.33 (s, 1H), 8.46 ppm (d, 1H, J=1.6 Hz); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=43.7, 44.8 (2C), 46.0, 54.5 (2C), 55.2, 62.5, 63.1, 75.2, 101.5, 107.2, 111.3, 124.5, 125.5 (2C), 126.4, 129.4 (2C), 129.0, 135.8, 136.3, 137.5, 145.1, 145.5, 150.6, 158.4 ppm (CF not visible); IR (KBr): $\tilde{\nu}$=3445, 1622, 1492, 1246, 1133 cm^{-1}; MS (ESI) *m/z* (%): 195.6 (50), 224.1(85), 244.6 (50), 267.7 (100), 288.2 (54), 534.2 (16) $[M+H]^+$; UPLC purity 98%.

2-(2,4-Difluorophenyl)-1-{[4-(6-morpholin-4-ylpyridin-3-yl)benzyl]methylamino}-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (17): The synthetic procedure for compound **16** was used, beginning from **15** (150 mg, 0.29 mmol) and morpholine (30 μL, 0.35 mmol), to yield compound **17** as a yellow powder (110 mg, 72%): R_f=0.30 (CH_2Cl_2/EtOH, 90:10); mp: 150–151 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.12 (s, 3H), 2.81 (d, 1H, J=13.6 Hz), 3.08 (d, 1H, J=13.6 Hz), 3.45 (d, 1H, J=13.2 Hz), 3.52 (t, 4H, J=4.4 Hz), 3.61 (d, 1H, J=13.2 Hz), 3.75 (t, 4H, J=4.0 Hz), 4.55 (d, 1H, J=14.0 Hz), 4.60 (d, 1H, J=14.0 Hz), 5.79 (s, 1H), 6.94 (d, 1H, J=8.4 Hz), 7.01 (ddd, 1H, $J_{H-F}=J_{H-H}$=8.4 Hz), 7.16 (d, 2H, J=8.0 Hz), 7.20 (dd, 1H, $J_{H-F}=J'_{H-F}$=9.6 Hz), 7.47 (m, 1H), 7.53 (d, 2H, J=8.0 Hz), 7.78 (s, 1H), 7.89 (dd, 1H, J=8.4 Hz, J=1.6 Hz), 8.33 (s, 1H), 8.48 ppm (d, 1H, J=1.6 Hz); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=43.7, 45.3 (2C), 56.4, 62.5, 63.4, 66.1 (2C), 75.3, 104.1, 107.1, 110.8, 124.5, 125.5 (2C), 127.0, 129.4 (2C), 130.3, 134.3, 135.3, 137.0, 145.1, 145.5, 150.6, 158.4 ppm (CF not visible); IR (KBr): $\tilde{\nu}$=3453, 1626, 1482, 1231, 1108 cm^{-1}; MS (ESI) *m/z* (%): 82.8 (78), 217.6 (100), 261.1 (50), 521.2 (12) $[M+H]^+$; UPLC purity 96%.

2-(2,4-Difluorophenyl)-1-({4-[6-(diphenylmethylideneamino)-pyridin-3-yl]benzyl}methylamino)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (18): The synthetic procedure for compound **16** was used, beginning from **15** (100 mg, 0.19 mmol) and benzophenone imine (39 μL, 0.23 mmol), to yield compound **18** as a yellow powder (83 mg, 70%): R_f=0.10 (CH_2Cl_2/EtOH, 98:2); mp: 71–72 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.10 (s, 3H), 2.79 (d, 1H, J=13.5 Hz), 3.07 (d, 1H, J=13.5 Hz), 3.45 (d, 1H, J=13.2 Hz), 3.62 (d, 1H, J= 13.2 Hz), 4.54 (d, 1H, J=14.4 Hz), 4.60 (d, 1H, J=14.4 Hz), 5.79 (s, 1H), 6.79 (d, 1H, J=8.4 Hz), 7.00 (ddd, 1H, $J_{H-F}=J_{H-H}$=8.4 Hz, J_{H-H}=2.4 Hz), 7.19 (m, 5H), 7.36 (m, 2H), 7.44 (ddd, 1H, J_{H-H}= 8.4 Hz, $J_{H-F}=J'_{H-F}$=6.8 Hz), 7.59 (m, 6H), 7.74 (m, 2H), 7.78 (s, 1H), 7.79 (dd, 1H, J=8.4 Hz, J=1.6 Hz), 8.33 (s, 1H), 8.59 ppm (d, 1H, J=1.6 Hz); IR (KBr): $\tilde{\nu}$=3448, 1630, 1497, 1272 cm^{-1}.

1-{[4-(6-Aminopyridin-3-yl)benzyl]methylamino}-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (19): Sodium acetate (255 mg, 3.11 mmol) was added under argon to a stirred solution of **18** (210 mg, 0.34 mmol) in MeOH (21 mL), followed by the addition of hydroxylamine hydrochloride (163 mg, 2.34 mmol). The solution was stirred at RT for 2 h. The solvent was removed in vacuo and the residue was diluted with CH_2Cl_2. Organic layers were washed with 0.1 M aq NaOH, dried over anhyd Na_2SO_4, and concentrated in vacuo. The residue was triturated in Et_2O to yield compound **19** after filtration as a white powder (127 mg, 82%): R_f= 0.45 (CH_2Cl_2/EtOH, 98:2); mp: 151–152 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.11 (s, 3H), 2.80 (d, 1H, J=13.6 Hz), 3.06 (d, 1H, J=13.6 Hz), 3.45 (d, 1H, J=13.6 Hz), 3.59 (d, 1H, J=13.6 Hz), 4.56 (d, 1H, J=14.4 Hz), 4.58 (d, 1H, J=14.4 Hz), 5.78 (s, 1H), 6.06 (s, 2H), 6.54 (d, 1H, J=8.8 Hz), 7.01 (dd, 1H, $J_{H-F}=J_{H-H}$=8.8 Hz), 7.13 (d, 2H, J=8.0 Hz), 7.19 (dd, 1H, $J_{H-F}=J'_{H-F}$=9.2 Hz), 7.46 (d, 2H, J=8.0 Hz), 7.47 (m, 1H), 7.70 (dd, 1H, J=8.8 Hz, J=2.0 Hz), 7.78 (s, 1H), 8.24 (d, 1H, J=2.0 Hz), 8.33 ppm (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=43.7, 56.1, 62.5, 63.2, 75.2, 103.9, 108.1, 110.8, 123.9, 125.2 (2C), 126.4, 129.4 (2C), 130.1, 135.4, 136.9, 137.1, 145.1,

145.8, 150.6, 159.3 ppm (CF not visible); IR (KBr): $\tilde{\nu}$ = 3451, 1638, 1492, 1272, 1133 cm^{-1}; MS (ESI) *m/z* (%): 182.6 (100), 203.1 (43), 226.1 (7), 451.1 (9) $[M+H]^+$; UPLC purity 100%.

***N*-{5-[4-({[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl]methylamino}methyl)phenyl]pyridin-2-yl}methanesulfonamide (20)**: MsCl (42 μL, 0.53 mmol) was added under argon to a stirred solution of **19** (100 mg, 0.22 mmol) in pyridine (3.4 mL), and the solution was heated at 55 °C for 2 h. Solvent was removed in vacuo, and the residue was diluted with H_2O. The product was extracted with CH_2Cl_2, and the organic layers were dried over anhyd Na_2SO_4 and concentrated in vacuo. The residue was purified using silica gel column chromatography (CH_2Cl_2 and CH_2Cl_2/EtOH, 99:1) to yield compound **20** as a white powder (86 mg, 73%): R_f = 0.40 (CH_2Cl_2/EtOH, 95:5); mp: 120–121 °C; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 2.12 (s, 3H), 2.81 (d, 1H, J = 13.7 Hz), 3.09 (d, 1H, J = 13.7 Hz), 3.35 (s, 3H), 3.49 (d, 1H, J = 13.3 Hz), 3.64 (d, 1H, J = 13.3 Hz), 4.55 (d, 1H, J = 14.4 Hz), 4.60 (d, 1H, J = 14.4 Hz), 5.79 (s, 1H), 7.01 (ddd, 1H, J_{H-F} = J_{H-H} = 8.4 Hz, J_{H-H} = 2.4 Hz), 7.09 (d, 1H, J = 8.8 Hz), 7.18 (m, 1H), 7.20 (d, 2H, J = 8.0 Hz), 7.48 (ddd, 1H, J_{H-H} = 8.8 Hz, J_{H-F} = J'_{H-F} = 6.8 Hz), 7.58 (d, 2H, J = 8.0 Hz), 7.78 (s, 1H), 8.07 (dd, 1H, J = 8.8 Hz, J = 2.4 Hz), 8.33 (s, 1H), 8.58 (d, 1H, J = 2.4 Hz), 10.70 ppm (s, 1H); ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 41.9, 43.8, 56.1, 62.4, 63.2, 75.2, 103.9, 110.9, 112.5, 126.2 (2C), 126.5, 127.0, 129.5 (2C), 130.1, 135.4, 137.1, 138.7, 145.1, 147.8, 150.6, 151.7 ppm (CF not visible); IR (KBr): $\tilde{\nu}$ = 3457, 1646, 1497, 1374, 1272, 1124 cm^{-1}; MS (ESI) *m/z* (%) 529.2 (100) $[M+H]^+$; UPLC purity 98%.

***N*-{5-[4-({[2-(2,4-Difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl]methylamino}methyl)phenyl]pyridin-2-yl}benzenesulfonamide (21)**: The synthetic procedure for compound **20** was used, beginning from **19** (115 mg, 0.26 mmol) and benzenesulfonyl chloride (78 μL, 0.61 mmol), to yield compound **21** as a yellow powder (115 mg, 76%): R_f = 0.40 (CH_2Cl_2/EtOH, 95:5); mp: 105–106 °C; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 2.05 (s, 3H), 2.74 (d, 1H, J = 14.0 Hz), 3.02 (d, 1H, J = 14.0 Hz), 3.40 (d, 1H, J = 13.6 Hz), 3.57 (d, 1H, J = 13.6 Hz), 4.49 (d, 1H, J = 14.0 Hz), 4.54 (d, 1H, J = 14.0 Hz), 5.74 (s, 1H), 6.96 (m, 1H), 7.11–7.30 (m, 4H), 7.44 (m, 1H), 7.48 (d, 2H, J = 7.6 Hz), 7.54–7.62 (m, 3H), 7.73 (s, 1H), 7.91 (d, 2H, J = 7.6 Hz), 8.01 (d, 1H, d, J = 8.8 Hz), 8.27 (s, 1H), 8.35 (s, 1H), 11.75 ppm (s, 1H); ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 43.7, 56.0, 62.4 63.1, 75.2, 103.9, 110.8, 113.3, 125.7, 126.0 (2C), 126.3, 126.8 (2C), 129.2 (2C), 129.4 (2C), 130.0, 132.7, 134.7, 138.0, 138.8, 141.7, 145.1, 147.8, 151.8, 159.3, 159.4, 161.8 ppm; IR (KBr): $\tilde{\nu}$ = 3443, 1640, 1605, 1500, 1370, 1274, 1142, 1089 cm^{-1}; MS (ESI) *m/z* (%): 591.3 (100) $[M+H]^+$; UPLC purity 100%.

Biological assays

Antifungal activity: All of the compounds were screened for antifungal activity against *C. albicans* CA98001, *C. krusei* (CK506, CK8), *C. glabrata* (CG468), *C. parapsilosis* (CAPA1, CAPA2), and *A. fumigatus* (AF98003) strains. Two *C. albicans* strains (DSY735, CAAL74) known to have reduced susceptibility to fluconazole were also investigated.[31] DSY735 was a gift from Prof. D. Sanglard at the Institute of Microbiology (University of Lausanne, Switzerland). All other strains were issued from our collection, and growth inhibition was measured as previously described.[37] Fluconazole, voriconazole, and itraconazole were used as reference compounds. MIC values were defined as the concentrations that inhibit growth of *Candida* spp. or *A. fumigatus* by 50 or 80%, respectively, as recommended by the Clinical and Laboratory Standards Institute M27 A3 and M38 A2 guidelines.[38] MIC values are expressed in $\mu g\,mL^{-1}$.

Sterol extraction and analysis: To study sterol synthesis, *C. albicans* CA98001 cells were incubated in 50 mL Sabouraud broth medium (Sigma–Aldrich) for 18 h at 35 °C while stirring. Compound **6** was introduced into culture medium before incubation. Cells were collected by centrifugation at 1500 *g*. The pellet was suspended in 3 mL of saponification medium (25 g KOH, 36 mL of distilled water and brought to 100 mL with 100% ethanol). Then suspension was mixed by vortex for 1 min and incubated at 80 °C for 120 min. Sterols were then extracted by addition of 4 mL *n*-hexane (Merck, Darmstadt, Germany), and the hexane extract was evaporated. Samples were derivatized with 100 μL of silylating mixture (Fluka, Saint Quentin Fallavier, France) at RT for 30 min, evaporated, and diluted in 500 μL *n*-hexane. Aliquots of sample (2 μL) was injected into a gas chromatograph (model 6890N, Agilent Technologies, Palo Alto, CA, USA) coupled with a quadrupole mass spectrometer (5973i, Agilent Technologies, Palo Alto, CA, USA). Analyses were carried out in a splitless mode with helium as carrier gas (constant rate of 1.2 $mL\,min^{-1}$) at an injector temperature of 250 °C. The transfer line between gas chromatograph and mass spectrometer was operated at 290 °C, and the EI source was held at 280 °C. The GC capillary column was an HP-5MS (30 m × 0.25 mm ID, 0.25 μm film thickness, Agilent Technologies). The GC oven was programmed as follows: initial temperature 150 °C, hold for 0.5 min, increase to 280 °C at 40 $°C\,min^{-1}$, increase to 300 °C at 5 $°C\,min^{-1}$, then hold for 6 min. Sterols of interest were identified by mass spectrometry. In order to study the influence of treatment on sterol abundance, the area under the curve (AUC) of each peak was used to calculate a ratio: sterol AUC/sum of sterols AUC.

Molecular modeling

Molecular modeling studies were performed using Sybyl software version 8.0[39] running on a Dell Precision T3400 workstation. The structure of CYP51 from *Mycobacterium tuberculosis* complexed with fluconazole (PDB code: 1A1)[40] was used as the template for the homology model of CYP51–*C. albicans* using a previously described protocol.[30,36] Flexible docking of azoles into the enzyme active site was performed using GOLD software.[41] A distance constraint was applied from N4 of the triazole ring to the heme iron (2.0 < d < 2.4 Å). For each compound, the most stable docking model was selected according to the best scored conformation as predicted by the GoldScore scoring function.

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Keywords: antifungal agents · azoles · *Candida albicans* · CYP51 inhibitors · structure–activity relationships

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