Bioorganic & Medicinal Chemistry Letters 19 (2009) 5833–5836

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Design of new antifungal agents: synthesis and evaluation of 1-[(1*H*-indol-5-ylmethyl)amino]-2-phenyl-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ols

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ARTICLE INFO

Article history:
Received 9 July 2009
Revised 26 August 2009
Accepted 26 August 2009
Available online 31 August 2009

Keywords:
Azoles
Candida albicans
CYP51 inhibitors
Antifungal agents
SAR studies

ABSTRACT

We previously reported on the design and synthesis of 1-[((hetero)aryl- or piperidinylmethyl)amino]-2-phenyl-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ols showing various degrees of antifungal activity against *Candida albicans* and *Aspergillus fumigatus* strains. Now we have identified a series of 1-[(1*H*-indol-5-ylmethyl)amino] derivatives which exhibited potent MICs (<65 ng mL^{-1}) against *C. albicans* strain. The synthesis and SAR behind the indole scaffold will be discussed.

The growing population of immunocompromised hosts (patients suffering from AIDS or chemotherapy-induced neutropenia or transplant recipients receiving immunosuppressive therapy) has led to an increased incidence of invasive and systemic fungal infections due mainly to *Candida* and *Aspergillus* species which are the most common pathogens.[1] Among the current therapies used in clinics, azoles (the most widely studied class of antifungal agents) target the biosynthesis of ergosterol, a major component of fungal membranes (thereby preventing fungal growth), by inhibiting mainly the cytochrome P450-dependent lanosterol 14α-demethylase (CYP51), encoded by the ERG11 gene. Most azoles are orally active, show a broad-spectrum against most yeasts and filamentous fungi, and are relatively nontoxic. However, increased use of these compounds has likely led to the emergence of resistance showing the need to develop more effective new agents.

We recently reported on the design and synthesis of 1-[((hetero)aryl- or piperidinylmethyl)amino]-2-phenyl-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ols showing various degrees of antifungal activity against *Candida albicans* and *Aspergillus fumigatus* strains.[2] SAR studies demonstrated that the benzylamine series bearing H-bond acceptors entities such as NO_2 or CN in *para* position of the benzyl group and a *N*-methyl group in the linker gave the most active compounds with MIC_{80} values of 0.6 and 0.37 ng mL^{-1} on *C. albicans*, respectively. These results confirmed several molecular modeling studies highlighting the importance of hydrogen bonding, π–π stacking and hydrophobic interactions between azole inhibitors and the active site of CYP51-*C. albicans*.[3–6] Compared to their pyridinyl- and piperidinylmethylamine analogues, these compounds also exhibited an emergence of activity on *A. fumigatus* strain with MIC_{80} of 1.96 and 2.41 μg mL^{-1}, respectively.[2]

In this Letter, we describe the design, synthesis and evaluation of 1-[(1*H*-indol-5-ylmethyl)amino] derivatives (**I**, Fig. 1). From a synthetic point of view, these indole-based structures are easily prepared and should keep integrality of the above characteristics depending upon appropriate substituents.

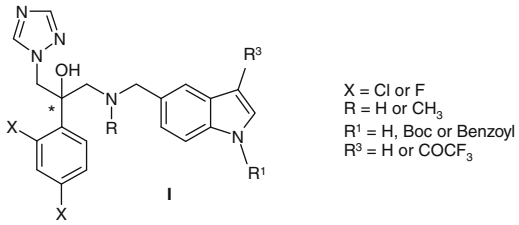

Figure 1. General structures of synthesized compounds.

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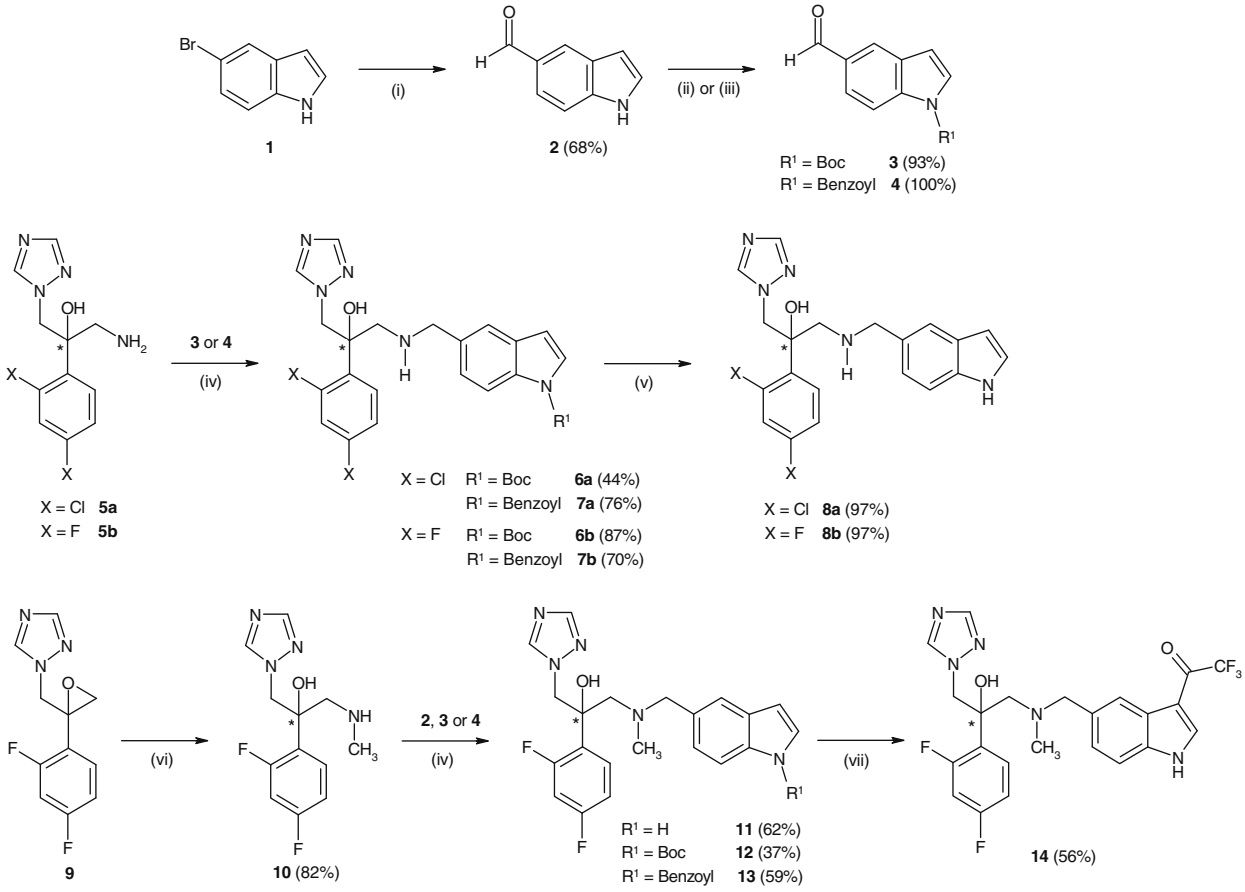
doi:10.1016/j.bmcl.2009.08.089



Scheme 1. Preparation of targeted compounds **6a**,**b**, **7a**,**b**, **8a**,**b** and **11–14**. Reagents and conditions: (i) KH, *t*-BuLi, DMF, THF, −78 °C to rt, 16 h; (ii) NaH, Boc_2O, DMF, rt, 1 h 30 min; (iii) benzoyl chloride, DMAP, Et_3N, CH_2Cl_2, rt, 2 h; (iv) **2**, **3** or **4**, $NaBH_3CN$, AcOH/MeOH 2% v/v, rt; (v) from compounds **7a**,**b**: NaOH 2 M, MeOH, 60 °C, 4 h; (vi) methylamine (33% in EtOH), EtOH, reflux, 2 h; (vii) from compound **11**: trifluoroacetic anhydride, 1,2-dichloroethane, rt, 3 h.

Scheme 1 outlines the synthesis of compounds **6a,b**, **7a,b**, **8a,b** and **11–14**. Treatment of the commercially available 5-bromo-1*H*-indole **1** with KH, *t*BuLi and DMF in THF afforded 1*H*-indole-5-carbaldehyde **2** in a 68% yield.[7] Carbamate **3** was prepared from compound **2** using a standard procedure with sodium hydride and di-*tert*-butyl dicarbonate.[8] On the other hand, treatment of **2** with benzoyl chloride in methylene chloride and in the presence of triethylamine and 4-dimethylaminopyridine (DMAP) gave the *N*-benzoylated indole **4**.[9,10] Derivatives **6a,b** and **7a,b** were synthesized from previously described key intermediates **5a** and **5b**[2] by reductive amination with **3** or **4**.[11,12] Removal of the Boc protective group under acidic condition (HCl 3 M/AcOEt)[13] or with tetra-*n*-butylammonium fluoride in THF[14] failed. Thus, targeted compounds **8a,b** were obtained by basic hydrolysis of *N*-benzoylated derivatives **7a,b**.[15]

N-methylated analogues **11–13** could be obtained from the previously described epoxide **9**[16] which can be opened by methylamine in ethanol to afford 2-(2,4-difluorophenyl)-1-methylamino-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol **10** in a 82% yield,[17] following a reductive amination with compounds **2–4**.[18] Finally, acylation of indole **11** using trifluoroacetic anhydride in 1,2-dichloroethane gave product **14**.[19]

All these compounds were screened for their antifungal activity against *C. albicans* CA98001 and *A. fumigatus* AF98003 strains. Inhibition growth was measured as previously described.[20] Fluconazole and itraconazole were used as positive controls. The minimum inhibitory concentration (MIC_{80}) values (in ng mL^{-1}) are presented in Table 1.

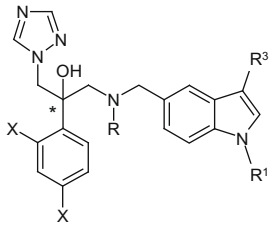
On *C. albicans* strain, our compounds displayed a high level of activity with MIC values 3- to 60-fold lower than that of fluconazole. Interestingly, the best result is obtained with fluorinated compound **6b** bearing a *N*-Boc protective group on the indole moiety and a N–H linker (MIC_{80} = 3.0 ng mL^{-1}). In contrast, neither the *N*-benzoyl **7b** nor the unsubstituted **8b** derivatives improved the inhibitory potency (MIC_{80} of 27.0 and 34.0 ng mL^{-1}, respectively), suggesting that an appropriate substitution at position 1 of the indole ring should be important for potent antifungal activity.

Moreover, introduction of a *N*-methyl group in the linker (**11–13**) would not play a major role on the two tested strains (*C. albicans* and *A. fumigatus*), even causing a significant decline in activity for compound **12** (MIC_{80} = 60.0 ng mL^{-1}) compared to compound **6b** (MIC_{80} = 3.0 ng mL^{-1}).

The supposed binding mode of the docked molecule **6b** (GOLD version 4.0; CCDC, Cambridge, UK) in our homology model of CYP51-*C. albicans*[2b] suggests a key hydrogen bonding interaction between the carbonyl group and the protonated imidazole side chain of His377 (Fig. 2). The (*S*)-configuration was retained since in a precedented series, these isomers were much more active than (*R*)-enantiomers.[21] In addition, the pyrrolo portion of indole may be involved in π–π interactions with the phenyl ring of residue Phe380, but not with the phenol group of Tyr118, a highly conserved residue in CYP51 family.

Even if the key elements of this new scaffold were conserved (a H-bond acceptor positioned on an aromatic moiety), the lack of activity on *A. fumigatus* strain could be explained either by a steric hindrance within the active site induced by the bulky indole ring

Table 1
In vitro antifungal activities of indol-5-ylmethylamino derivatives



Compd	R	R^1	R^3	X	MIC_{80} values[a] (ng mL^{-1})	
					Candida albicans CA98001	*Aspergillus fumigatus* AF98003
6a	H	Boc	H	Cl	39.0 (±8.00)	na
6b	H	Boc	H	F	3.0 (±0.50)	na
7a	H	Benzoyl	H	Cl	31.0 (±15.0)	na
7b	H	Benzoyl	H	F	27.0 (±2.00)	na
8a	H	H	H	Cl	31.0 (±0.80)	na
8b	H	H	H	F	34.0 (±4.00)	na
11	CH_3	H	H	F	35.0 (±0.40)	na
12	CH_3	Boc	H	F	60.0 (±10.0)	na
13	CH_3	Benzoyl	H	F	32.0 (±0.50)	na
14	CH_3	H	$COCF_3$	F	64.0 (±15.0)	na
Fluconazole					190.0 (±6.0)	—
Itraconazole					—	420.0 (±40.0)

[a] Values are means of triplicate, standard deviation is given in parentheses (na = not active, MIC_{80} >30,000.0 ng mL^{-1}).

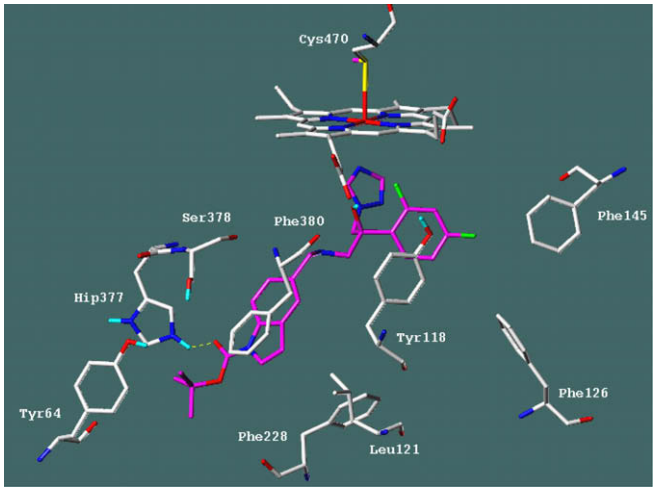


Figure 2. Docking solution of compound (*S*)-**6b** in the supposed active site pocket (channel 2) of CYP51-*Candida albicans*. Hip377 is the protonated form of histidine residue.

and/or an inappropriate position of the electron-withdrawing substituents compared to our previous more flexible and linear benzylamine series.[2a] Of course, azoles are known to inhibit mainly CYP51 enzymes but we can not exclude other factors such as lipophilicity parameters, differences in the membrane structures between the two fungi or in molecular mechanisms and only results on the isolated CYP51 could confirm our hypotheses.

To determine the potential of the indole moiety on various *Candida* species, our best compound **6b** was evaluated against fluconazole-resistant (CA424, CA284, CK506, CG468, CP-Houdeau and CP-Rolland) and fluconazole low-sensitive (CK8) species (Table 2).[20] The MIC_{80} values (in μg mL^{-1}) in comparison with fluconazole are given.

Compound **6b** exhibited moderate antifungal activities against all fungi tested with MIC values ranging from 3.8 to 33.0 μg mL^{-1}, lower than those of fluconazole.

Table 2
In vitro antifungal activities on *Candida* species of compound **6b**

Compd	MIC_{80} values[a] (μg mL^{-1})						
	CA424	CA284	CK506	CK8	CG468	CP-Houdeau	CP-Rolland
6b	33.0	32.0	27.0	3.8	12.0	24.0	19.0
Fluconazole	>64.0	>64.0	>64.0	19.0	>64.0	>64.0	>64.0

[a] CA = *Candida albicans*, CK = *Candida krusei*, CG = *Candida glabrata*, CP = *Candida parapsilosis*.

Therefore, although these indol-5-ylmethylamino compounds are more active than fluconazole on the *Candida* species, further investigations are needed to design broad-spectrum antifungal agents and to pinpoint the exact molecular mechanism of this inhibition. From a purely chemical point of view, the role of H-bond acceptors at position 2 of the indole or modification of the aromatic heterocycle could be explored, since preliminary work at position 3 (compound **14**) gave the same results. In addition, due to the limited range of variations at the indole moiety, the synthesis of indol-3-ylmethylamino derivatives could also be explored to check the utility of this scaffold for further optimization.

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8. *Synthesis of 1-(tert-butoxycarbonyl)-1H-indole-5-carbaldehyde* (**3**). To a solution of **2** (415 mg, 2.86 mmol) in 8 mL of *N*,*N*-dimethylformamide at room

temperature under argon was added sodium hydride (60% in mineral oil) (165 mg, 4.29 mmol). The solution was stirred at room temperature for 1 h. Then di-*tert*-butyl dicarbonate (936 mg, 4.29 mmol) was added and the mixture was stirred for 30 min. Mixture was diluted with water and product was extracted with diethyl ether. Organic layers were washed with water, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified on silica gel column chromatography (dichloromethane) and compound **3** was obtained in a 93% yield as a yellow oil. ^{1}H NMR (DMSO-d_6): δ 1.68 (s, 9H), 6.94 (d, 1H, ^3J = 3.6 Hz), 7.85 (d, 1H, ^3J = 3.6 Hz), 7.90 (dd, 1H, ^3J = 8.8 Hz, ^4J = 1.5 Hz), 8.25–8.28 (m, 2H), 10.09 (s, 1H). IR (NaCl cm^{-1}): 1215 (ν C–N), 1461, 1533 (ν C=C), 1687 (ν C=O), 1740 (ν C=O), 2957 (ν C–$H_{aliph.}$).

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10. *Synthesis of 1-benzoyl-1H-indole-5-carbaldehyde (**4**).* To a solution of **2** (2.68 g, 18.48 mmol) in 30 mL of dichloromethane at room temperature under argon was added 4-dimethylaminopyridine (452 mg, 3.70 mmol) and triethylamine (5.15 mL, 69.96 mmol). Then benzoyl chloride was added and the solution was stirred for 2 h. Mixture was diluted with water and product was extracted with dichloromethane. Organic layers were washed with water, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified on silica gel column chromatography (dichloromethane) and compound **4** was obtained in quantitative yield as a white powder. Mp 124–125 °C; ^{1}H NMR (DMSO-d_6): δ 6.98 (d, 1H, ^3J = 3.7 Hz), 7.60 (d, 1H, ^3J = 3.7 Hz), 7.66–7.69 (m, 2H), 7.74–7.77 (m, 1H), 7.82–7.89 (m, 2H), 7.96 (dd, 1H, ^3J = 8.5 Hz, ^4J = 1.2 Hz), 8.33 (d, 1H, ^4J = 1.2 Hz), 8.46 (d, 1H, ^3J = 8.5 Hz), 10.13 (s, 1H). IR (KBr cm^{-1}): 1274 (ν C–N), 1461, 1535 (ν C=C), 1688 (ν C=O).

11. *Synthesis of 1-{[(1-tert-butoxycarbonylindol-5-yl)methyl]amino}-2-(2,4-difluorophenyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (**6b**). To a solution of **5b** (415 mg, 1.63 mmol) in 8 mL of methanol and 0.16 mL of acetic acid was added **3** (200 mg, 0.82 mmol) in 8 mL of dichloromethane at room temperature under argon. The solution was stirred at room temperature for 48 h. Then sodium cyanoborohydride (61 mg, 0.98 mmol) was added and the mixture was stirred for 16 h. Mixture was diluted with water and product was extracted with diethyl ether. Organic layers were washed with satd sodium bicarbonate, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified on silica gel column chromatography (dichloromethane and dichloromethane/ethanol, 98:2) and compound **6b** was obtained in a 87% yield as a green oil. ^{1}H NMR (DMSO-d_6): δ 1.66 (s, 9H), 2.93 (s, 2H), 3.77 (s, 2H), 4.56 (d, 1H, ^2J = 14.0 Hz), 4.63 (d, 1H, ^2J = 14.0 Hz), 5.82 (s, 1H, OH), 6.68 (d, 1H, ^3J = 3.6 Hz), 6.98 (ddd, 1H, $^3J_{H-F} = {}^3J_{H-H}$ = 8.8 Hz, $^4J_{H-H}$ = 2.4 Hz), 7.15 (ddd, 1H, $^3J_{H-F} = {}^3J'_{H-F}$ = 9.2 Hz, $^4J_{H-H}$ = 2.4 Hz), 7.23 (dd, 1H, ^3J = 8.2 Hz, ^4J = 3.7 Hz), 7.39 (ddd, 1H, $^3J_{H-H}$ = 8.4 Hz, $^4J_{H-F} = {}^4J'_{H-F}$ = 6.8 Hz), 7.48 (s, 1H), 7.67 (d, 1H, ^4J = 3.7 Hz), 7.74 (s, 1H), 7.97 (d, 1H, ^3J = 8.2 Hz), 8.30 (s, 1H). IR (NaCl cm^{-1}): 1136 (ν C–F), 1270 (ν C–N), 1482, 1501, 1585 (ν C=C), 1732 (ν C=O), 2956 (ν $CH_{aliph.}$), 3250–3600 (ν O–H and ν N–H). MS *m/z* 483.9 (M).

12. *Synthesis of 1-{[(1-benzoylindol-5-yl)methyl]amino}-2-(2,4-difluorophenyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (**7b**). Compound **7b** was prepared from **5b** and **4** according to the protocol described for **6b**. Yield: 70%, yellow powder. Mp 70–71 °C. ^{1}H NMR (DMSO-d_6): δ 3.06 (d, 1H, ^2J = 12.2 Hz), 3.28 (d, 1H, ^2J = 12.2 Hz), 3.78 (s, 2H), 4.68 (d, 1H, ^2J = 14.3 Hz), 4.92 (d, 1H, ^2J = 14.3 Hz), 5.96 (s, 1H, OH), 6.74 (d, 1H, ^3J = 3.6 Hz), 7.27–7.80 (m, 12H), 8.19 (d, 1H, ^3J = 8.2 Hz), 8.32 (s, 1H). IR (KBr cm^{-1}): 809 (ν C–Cl), 1273 (ν C–N), 1464, 1508, 1585 (ν C=C and ν C=N), 1685 (ν C=O), 2927 (ν $CH_{aliph.}$), 3122–3525 (ν O–H and ν N–H). MS *m/z* 520.2 (M).

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15. *Synthesis of 2-(2,4-difluorophenyl)-1-[(1H-indol-5-ylmethyl)amino]-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (**8b**). To a solution of **7b** (671 mg, 1.38 mmol) in 15 mL of methanol was added a solution of sodium hydroxide 2 M (12 mL, 23.00 mmol) under argon at room temperature. The solution was stirred at 60 °C for 4 h. Mixture was diluted with water and product was extracted with diethyl ether. Organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was triturated in isopropyl ether and compound **8b** was obtained in a 97% yield as a green powder. Mp 53–54 °C; ^{1}H NMR (DMSO-d_6): δ 2.96 (s 2H), 3.73 (s, 2H), 4.57 (d, 1H, ^2J = 14.3 Hz), 4.63 (d, 1H, ^2J = 14.3 Hz), 5.80 (s, 1H, OH), 6.38 (s, 1H), 6.93–7.03 (m, 2H), 7.16 (ddd, 1H, $^3J_{H-F} = {}^3J'_{H-F}$ = 9.2 Hz, $^4J_{H-H}$ = 2.4 Hz), 7.31–7.45 (m, 4H), 7.74 (s, 1H), 8.30 (s, 1H), 11.01 (s, 1H). IR (KBr cm^{-1}): 1128 (ν C–F), 1272 (ν C–N), 1420, 1503, 1616 (ν C=C and ν C=N), 2927 (ν $CH_{aliph.}$), 3100–3560 (ν O–H and ν N–H). MS *m/z* 384.3 (M+H).

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17. *Synthesis of 2-(2,4-difluorophenyl)-1-methylamino-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (**10**). To a solution of **9** (200 mg, 0.84 mmol) in 0.75 mL of ethanol was added methylamine (33% in ethanol) (3.65 mL, 29.51 mmol) and the solution was refluxed for 2 h. Solvent was removed under reduced pressure and residue was partitioned between dichloromethane and water. Product was extracted with dichloromethane and organic layers were dried over anhydrous Na_2SO_4 then concentrated in vacuo. The residue was purified on silica gel column chromatography (dichloromethane and dichloromethane /ethanol, 90:10) and compound **10** was obtained in a 82% yield as a brown oil. ^{1}H NMR (DMSO-d_6): δ 2.26 (s, 3H), 2.85 (d, 1H, ^2J = 12.5 Hz), 2.96 (d, 1H, ^2J = 12.5 Hz), 4.58 (s, 2H), 5.95 (s, 1H, OH), 6.98 (ddd, 1H, $^3J_{H-F} = {}^3J_{H-H}$ = 8.4 Hz, $^4J_{H-H}$ = 2.4 Hz), 7.18 (ddd, 1H, $^3J_{H-F} = {}^3J'_{H-F}$ = 9.2 Hz, $^4J_{H-H}$ = 2.4 Hz), 7.40 (ddd, 1H, $^3J_{H-H}$ = 8.4 Hz, $^4J_{H-F} = {}^4J'_{H-F}$ = 6.8 Hz), 7.77 (s, 1H), 8.31 (s, 1H). IR (NaCl cm^{-1}): 1131 (ν C–F), 1276 (ν C–N), 1420, 1499, 1612 (ν C=C and ν C=N), 3300 (ν O–H and ν N–H).

18. *Synthesis of 2-(2,4-difluorophenyl)-1-[(1H-indol-5-ylmethyl)methylamino]-3-(1H-1,2,4-triazol-1-yl)propan-2-ol* (**11**). To a solution of **10** (813 mg, 3.03 mmol) in 17 mL of methanol and 0.34 mL of acetic acid was added at room temperature under argon **2** (440 mg, 3.03 mmol). Then sodium cyanoborohydride (229 mg, 3.64 mmol) was added and the mixture was stirred for 24 h. Mixture was diluted with water and product was extracted with dichloromethane. Organic layers were washed with saturated sodium bicarbonate, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified on silica gel column chromatography (dichloromethane and dichloromethane/ethanol, 98:2) and compound **11** was obtained in a 62% yield as a white powder. Mp 130–131 °C; ^{1}H NMR (DMSO-d_6): δ 2.11 (s, 3H), 2.85 (d, 1H, ^2J = 13.6 Hz), 3.03 (d, 1H, ^2J = 13.6 Hz), 3.51 (d, 1H, ^2J = 12.8 Hz), 3.60 (d, 1H, ^2J = 12.8 Hz), 4.53 (d, 1H, ^2J = 14.0 Hz), 4.59 (d, 1H, ^2J = 14.0 Hz), 5.76 (s, 1H, OH), 6.34 (s, 1H), 6.87 (dd, 1H, ^3J = 8.0 Hz, ^4J = 1.2 Hz), 7.00 (ddd, 1H, $^3J_{H-F} = {}^3J_{H-H}$ = 8.4 Hz, $^4J_{H-H}$ = 2.4 Hz), 7.18 (ddd, 1H, $^3J_{H-F} = {}^3J'_{H-F}$ = 9.2 Hz, $^4J_{H-H}$ = 2.4 Hz), 7.27–7.33 (m, 3H), 7.46 (ddd, 1H, $^3J_{H-H}$ = 8.4 Hz, $^4J_{H-F} = {}^4J'_{H-F}$ = 6.8 Hz), 7.76 (s, 1H), 8.33 (s, 1H), 11.02 (s, 1H). IR (KBr cm^{-1}): 1133 (ν C–F), 1274 (ν C–N), 1421, 1499, 1614 (ν C=C and ν C=N), 3234 (ν O–H and ν N–H). MS *m/z* 398.0 (M+H).

19. *Synthesis of 1-(5-{[(2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)-propyl)methylamino]methyl}-1H-indol-3-yl)-2,2,2-trifluoroethanone* (**14**). To a solution of **11** (100 mg, 0.25 mmol) in 2 mL of 1,2-dichloroethane was added at 0 °C trifluoroacetic anhydride (70 μL, 0,50 mmol). The solution was stirred at room temperature for 3 h. Mixture was diluted with saturated sodium bicarbonate and product was extracted with dichloromethane. Organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was triturated in isopropyl ether/dichloromethane and compound **14** was obtained in a 56% yield as a white powder. Mp 178–179 °C; ^{1}H NMR (DMSO-d_6): δ 2.13 (s, 3H), 2.81 (d, 1H, ^2J = 13.6 Hz), 3.07 (d, 1H, ^2J = 13.6 Hz), 3.55 (d, 1H, ^2J = 13.0 Hz), 3.69 (d, 1H, ^2J = 13.0 Hz), 4.52 (d, 1H, ^2J = 14.2 Hz), 4.59 (d, 1H, ^2J = 14.2 Hz), 5.78 (s, 1H, OH), 6.98 (ddd, 1H, $^3J_{H-F} = {}^3J_{H-H}$ = 8.4 Hz, $^4J_{H-H}$ = 2.4 Hz), 7.09–7.13 (m, 2H), 7.42–7.49 (m, 2H), 7.76 (s, 1H), 7.97 (s, 1H), 8.33 (s, 1H), 8.47 (s, 1H), 12.67 (s, 1H). IR (KBr cm^{-1}): 1135 (ν C–F), 1276 (ν C–N), 1446, 1497, 1615 (ν C=C and ν C=N), 1667 (ν C=O), 3451 (ν O–H and ν N–H). MS *m/z* 494.0 (M+H).

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