Full Paper

Synthesis and Biological Screening of Novel Indolalkyl Arenes Targeting the Serotonine Transporter

Claudia Ojeda-Gómez[1], Hernán Pessoa-Mahana[1], Patricio Iturriaga-Vásquez[2], Carlos David Pessoa-Mahana[3], Gonzalo Recabarren-Gajardo[3], and Claudio Méndez-Rojas[1]

[1] Faculty of Chemical and Pharmaceutical Sciences, Department of Organic and Physical Chemistry, University of Chile, Santiago, Chile
[2] Millennium Institute for Cell Dynamics and Biotechnology, Santiago, Chile
[3] Faculty of Chemistry, Pharmacy Department, Pontificia Universidad Católica de Chile, Santiago, Chile

A series of functionalized indolylalkylarenes **3**–**16**(**a** and **b**) were synthesized and their affinities for the serotonin transporter were investigated *in vitro*. Compounds **3**–**12**(**a** and **b**) were obtained by nucleophilic substitution of 3-(1*H*-indol-3-yl)propyl-4-methylbenzenesulfonates **2**(**a** and **b**) with a series of azaheterocycles. Compounds **14**–**16**(**a** and **b**) were prepared in a two-step sequence by reaction of 3-(1*H*-indol-3-yl)-2-methylpropanal with substituted 1,2-phenylenediamines. Compounds **3b**, **4b**, and **5b** showed good binding affinities ($K_i = 33.0$, 48.0, and 17 nM, respectively). The other synthesized compounds showed moderate or no affinity in the binding studies.

Keywords: Benzimidazole / Indole / Serotonine transporter

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Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter that plays an important role in a variety of physiological functions, either in the central nervous system or in the peripheral tissues. It is synthesized mainly at the central level in the *raphe nucleus* and *substantia nigra*. At the peripheral level, it is found in the enterochromaffin cells of the gastrointestinal tract [1–5]. The serotonin transporter (SERT) is a specific monoaminergic carrier protein, which regulates the serotonin level at the intersynaptic cleft. Alterations of SERT densities in the brain are related to several neurodegenerative and psychiatric disorders such as Parkinson's disease and depression [6, 7]. For these reasons, the SERT protein has become recognized as an interesting molecular target in antidepressant therapy. Selective serotonin reuptake inhibitors (SSRIs) are considered the second generation of antidepressants and represent the most widely prescribed drugs in the world. However, antidepressants in general, including SSRIs, suffer from a variety of drawbacks, and the fact that up to a third of patients do not respond to treatment, including a delayed onset of action of about 4–6 weeks, supports new research in this field [8–10].

The indole framework has been extensively studied and recognized as an SSRI [6, 11–17]; examples of promising structures together with their binding affinities are given in Fig. 1.

Recently, the FDA approved the use of vilazodone (VIII, Fig. 2), an indole derivative, as a new antidepressant drug acting as dual ligand, SERT inhibitor ($IC_{50} = 0.5$ nM; $K_i = 0.1$ nM), and partial agonist at the $5HT_{1A}$ receptor ($IC_{50} = 0.2$ nM) [18–21].

Given our interest in the search of novel indole derivatives with antidepressant properties [22], we decided to synthesize a new series of indolalkylarenes in order to obtain better affinities in SERT binding. The strategy followed was to connect the indole framework with different heterocyclic moieties using two to three carbon linkers as spacer.

The series were built based mainly on the idea of combining the well-known SERT affinity of the 3-indolyl(alkyl) moiety, with different azaheterocyclic skeletons bearing electron-acceptor functional groups or directly connected to π-deficient rings, a decision which allowed us to assess their impact on binding of the serotonine transporter.

Compounds **3**–**5**(**a** and **b**) were chosen based on their structural analogy to the well-known long chain arylpiperazine

Correspondence: Dr. Claudia Ojeda-Gómez and Dr. Hernán Pessoa-Mahana, Faculty of Chemical and Pharmaceutical Sciences, Department of Organic and Physical Chemistry, University of Chile, Casilla 233, Santiago, Chile.
E-mail: claudia.ojeda.g@gmail.com, hpessoa@ciq.uchile.cl

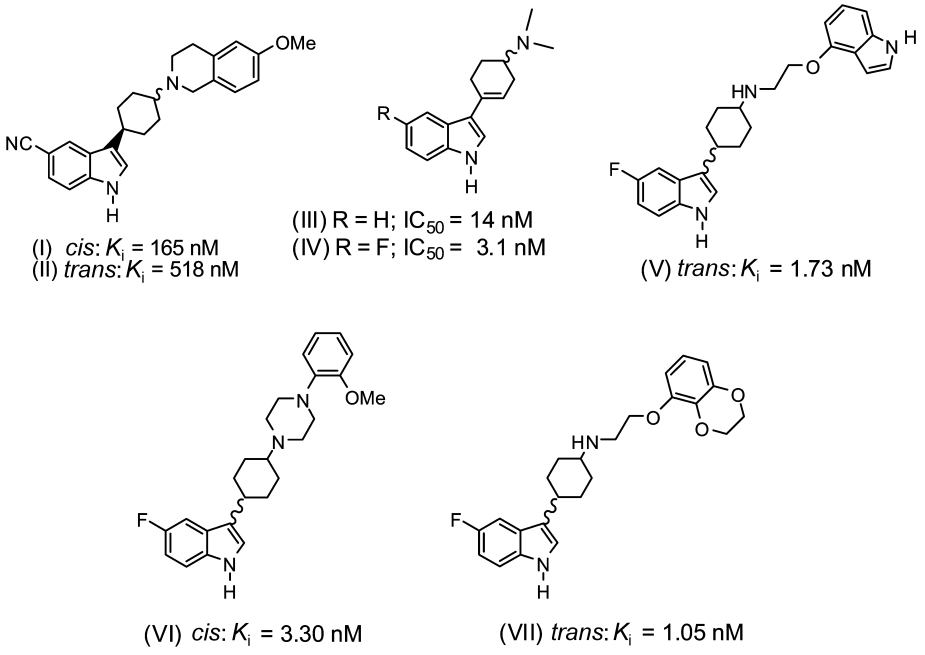


Figure 1. Bioactive indole analogs.

family, with different methylenic spacers connecting the piperazine ring and the phenyl-haloarene ring. As has been described, arylpiperazine compounds have been shown to possess high affinities in both SERT and 5-HT_{1A} receptor binding studies [23, 24]. On the other hand, derivatives **6**–**7**(**a** and **b**) were mainly considered due to their 5-HT_{1A} and SERT/DAT activity, described for these kinds of compounds [25–27]. As far as we know, there are no reports for compounds **8**(**a** and **b**) in relation to antidepressant effects. However, the benzoxazinone ring, which is structurally related to compound **8**, has been described as a multitarget agent in the central nervous system [28]. The phenylpyrazole scaffold **9**–**11**(**a** and **b**) has been reported to exhibit pharmacological activity as promiscuous ligand in D_2, 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} receptors [29, 30].

Finally, a short series of indole ethylbenzimidazole derivatives, **14**–**16**(**a** and **b**), were synthesized and their SERT affinities evaluated. These compounds, to the best of our knowledge, have not been described in SERT studies, only compounds structurally related, such as the benzothiazole

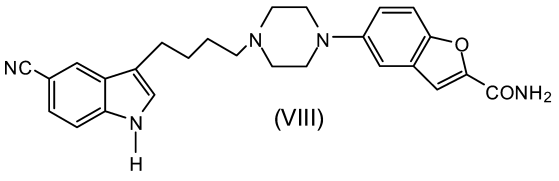


Figure 2. Vilazodone structure.

ring [31]. Furthermore, the benzimidazole ring has been successfully incorporated in a variety of structures displaying high bioactivity on serotonine 5-HT_{1A}/5-HT_3 receptors [32, 33].

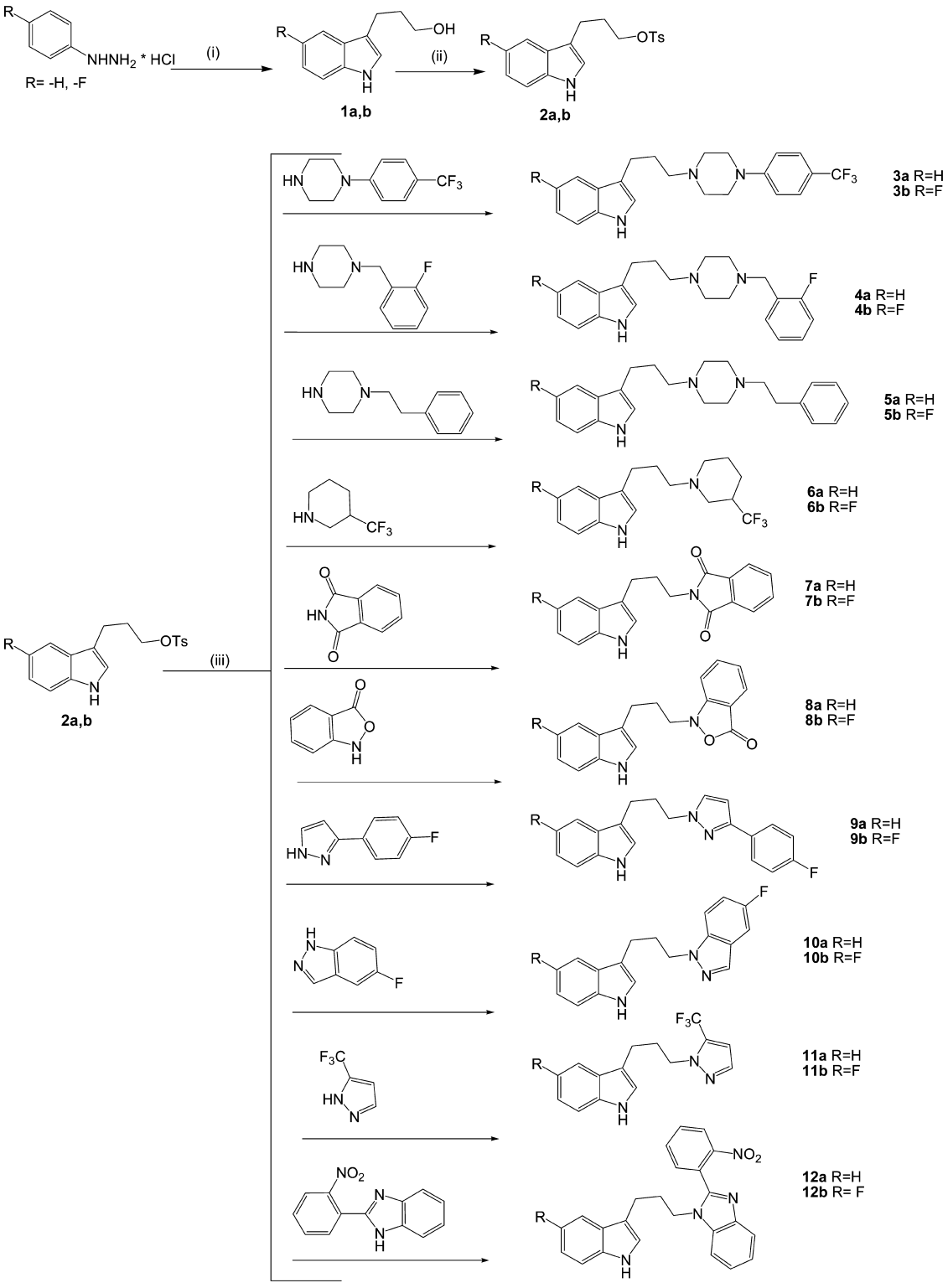
In summary, the aim of this work was to assess the impact of incorporating new bioactive π-deficient heterocyclic moieties on the well-known SERT effect of 5-fluoroindole derivatives.

Results and discussion

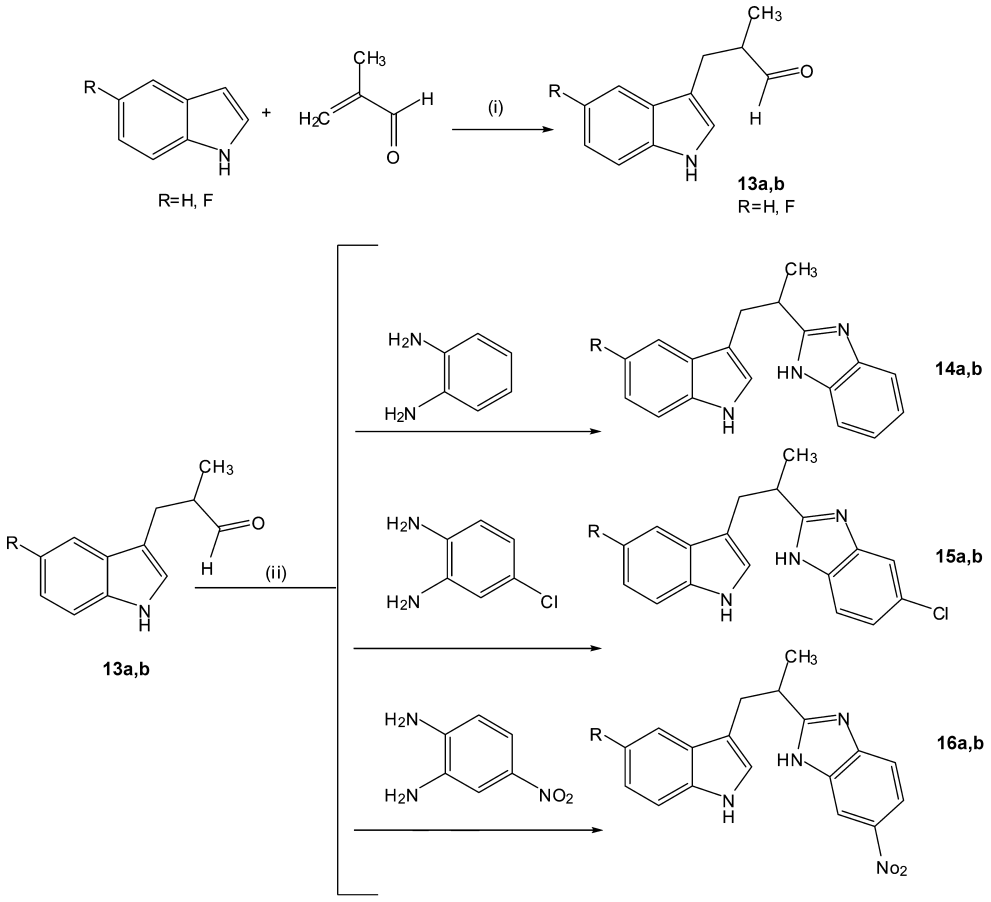
Chemistry

The novel compounds were synthesized according to Scheme 1. Compounds **1**(**a** and **b**) were prepared as previously reported [22]. These compounds **1**(**a** and **b**) were reacted with *p*-toluenesulfonyl chloride in CH_2Cl_2 to give tosyl derivatives **2** (**a** and **b**) in 65–82% yield. Subsequent reaction of **2**(**a** and **b**) in basic medium with substituted commercial heterocyclic amines (piperazine, piperidine, pyrazole, phthalimide, benzoxazolinone, and benzimidazole) led to the expected substitution products **3**–**12**(**a** and **b**) as shown in Scheme 1.

As an extension of this work, six indole ethylbenzimidazole derivatives, compounds **14**–**16**(**a** and **b**), connected at C-1, were also prepared as biligands. As mentioned above, numerous compounds containing the benzimidazole ring have been described as having central activity at the level of 5-HT_{2A} and D_2 receptors. The planned synthetic strategy to get 3-indolylpropanal considered first the preparation of



Scheme 1. Synthesis of compounds **1**(**a** and **b**) to (**12a** and **b**). Reagents and conditions: (i) *N,N*-DMA, H_2SO_4 4%, 3,4-dihydro-2-pyran, reflux; (ii) TsCl, CH_2Cl_2, DMAP, $N(Et)_3$, room temperature; and (iii) K_2CO_3, DMF, reflux conditions.



Scheme 2. Synthesis of compounds **13(a** and **b**) to **16**(**a** and **b**). Reagents and conditions: (i) iodine, CH_2Cl_2, room temperature; and (ii) EtOH, reflux.

3-indolylpropanol **1**(**a** and **b**) followed by oxidation. However, the oxidative step was not successful under a variety of experimental conditions, causing both degradation and generation of multiple products. We therefore decided to carry out the proposed synthesis using Michael addition [34] by reaction between commercially available 1*H*-indoles and methacrolein in the presence of iodine as a catalyst [35]. The reaction produced 3-(1*H*-indol-3-yl)-2-methylpropanal **13a** and 3-(5-fluoro-1*H*-indol-3-yl)-2-methylpropanal **13b** (Scheme 2). These adducts were purified and further reacted with commercial substituted *o*-phenylendiamines, to give the corresponding 3-indolyethylbenzimidazoles **14**–**16**(**a** and **b**) [36, 37].

Pharmacology

The affinities of compounds **3**(**a** and **b**) to **16**(**a** and **b**) for the human SERT (K_i) expressed in HEK-293 cells (PerkinElmer) were assessed by displacement of [^{3}H]paroxetine binding. Inhibition constants (K_i) were calculated from the Cheng–Prushoff equation [38].

The SERT binding affinities of 3-indolylpropylpiperazine series **3**(**a** and **b**)–**5**(**a** and **b**) are shown in Table 1. The affinities for SERT were strongly dependent on the aromatic frameworks linked to the piperazine ring, along with the substitution pattern on the indole moiety. The binding affinities for compounds **3a**–**5a** (R = H) showed that by increasing the methylenic chain ($n = 0$–2) between the aromatic and the piperazine ring, higher binding affinities are obtained ($K_i = 28{,}570$, 8710, and 65 nM for **3a**, **4a**, and **5a**, respectively). Compounds **3b**–**5b** (R = F) showed higher affinities ($K_i = 33.0$, 48.0, and 17.7 nM, respectively), compared to the unfluorinated derivatives **3a**–**5a** (R = H), supporting the observation that SERT affinity at the indole family is favored by electron-withdrawing groups attached to the C-5 position, as has been described. We think that the influence of the spacer between the piperazine ring and the aryl group may be a second contributing factor to the final effect. The results are summarized in Table 1.

Table 1. Binding affinity of indole derivatives toward SERT.

Binding data, HEK-293			
Compound	**K_i (nM)**	**Compound**	**K_i (nM)**
[^{3}H]Paroxetine	1.1[a)]		
3a R = H	28570	**10a** R = H	NE
3b R = F	33.0	**10b** R = F	14540
4a R = H	8710	**11a** R = H	NE
4b R = F	48.0	**11b** R = F	NE
5a R = H	65.0	**12a** R = H	NE
5b R = F	17.7	**12b** R = F	10057
6a R = H	14690	**14a** R = H	NE
6b R = F	557	**14b** R = F	1829
7a R = H	NE	**15a** R = H	NE
7b R = F	1969	**15b** R = F	NE
8a R = H	NE	**16a** R = H	NE
8b R = F	NE	**16b** R = F	NE
9a R = H	90285		
9b R = F	1723		

[a)] According to Thomas et al. [39].

In general, compounds **6**–**16**(**a** and **b**) showed lower affinities for serotonine binding transporter experiments, varying from inactive to poorly active, and they were shown as NE (no effect). The piperidinyl derivatives **6**(**a** and **b**), together with **7**(**a** and **b**) phthalimide derivatives, showed lower affinities than **3** and **5**(**a** and **b**), except for derivative **7a**, which did not display any effect. The same can be seen for the benzoxazolinones **8**(**a** and **b**), pyrazoles **9**–**11**(**a** and **b**), and the benzimidazoles **14**–**16**(**a** and **b**) derivatives, which were not able to displace the tritiated paroxetine, except compounds **9b** and **14b** in the SERT binding site.

The low affinities found for these compounds may be attributed to the characteristic π-deficient effect exhibited by both the pyrazole and imidazole rings, along with the electron-withdrawing effect of the substituents such as chlorine, fluorine, trifluoromethane, and nitro groups at these systems; on the contrary, electron-donor groups may probably have a more favorable effect on SERT binding in these molecules.

However, compounds **9**(**a** and **b**), bearing a 4-fluorophenyl group on the pyrazole ring, showed moderate affinities for SERT, which may be ascribed in this case to the electronic resonance effect on the aromatic ring. Compound **9b** showed a $K_i = 1723$ nM, compared with **9a**, $K_i = 90{,}285$ nM. Furthermore, compounds **6** (piperidine derivatives) and **7** (phthalimide derivatives) showed the same tendency to increase the affinities for SERT when a fluorine atom is attached to the C-5 indolyl group.

Conclusion

In summary, the indole framework connected either to π-deficient ring arenes or arenes bearing electron-withdrawing substituents resulted detrimental for SERT affinity. The importance of the C-5 fluorinated indolyl portion on SERT affinity was confirmed. Considering the obtained results, strong π-donor molecular frameworks linked to the indolylpropyl moiety may probably increase the K_i affinities for SERT.

Experimental

Melting points were determined on a hot-stage apparatus and are uncorrected. The IR spectra were recorded in KBr discs on an FT-IR Bruker IFS 55 spectrophotometer, and wave numbers are reported in cm^{-1}. The ^{1}H and ^{13}C NMR spectra were run on a Bruker DRX-300 spectrometer (300 and 75 MHz, respectively) in $CDCl_3$ or DMSO-d_6. Chemical shifts were recorded in ppm (δ) relative to TMS as an internal standard; J values are given in Hz. Microanalyses were made on a Fisons EA 1108 analyzer. High-resolution mass spectra were recorded on a Thermo Finnigan MAT 95XP mass spectrometer. Silica gel Merck 60 (70–230 mesh), and aluminum sheets coated with silica gel 60 F254 were used for column and TLC chromatography, respectively.

Typical procedure for 3-[3-(4-{4-(trifluoromethyl)-phenyl}-1-piperazinyl)propyl]-5-substituted-1*H*-indol derivatives

*3-[3-(4-{4-(Trifluoromethyl)phenyl}-1-piperazinyl)propyl]-1H-indol derivative (**3a**) as a model*

A mixture of 3-(3-indolyl)propyl-4-methylbenzenesulfonate (**2a**) (0.2000 g, 0.61 mmol) in dry acetonitrile (30 mL), anhydrous potassium carbonate (0.0840 g, 0.61 mmol), and 1-[4-(trifluoromethyl)phenyl]piperazine (0.1400 g, 0.61 mmol) was stirred for 6 h under reflux. After this time, water was added (30 mL) and extracted with AcOEt (3 × 30 mL). The combined organic layers were washed and dried over anhydrous Na_2SO_4. The organic portion was filtered and the solvent evaporated to yield a crude, that was purified by column chromatography (AcOEt), to afford pure (**3a**) (0.1740 g, 74%); m.p.: 149–150°C. IR cm^{-1}: 3413 (N–H), 3062 (C–H arom.), 2939–2789 (C–H aliph.), 1614 (C=C arom.). ^{1}H NMR ($CDCl_3$): 1.84 (q, 2H, H-2′, $J = 7.2$), 2.37 (t, 2H, H-3′, $J = 7.5$ Hz), 2.49 (m, 4H, H-4′ and H-6′), 2.71 (t, 2H, H-1′, $J = 7.5$ Hz), 3.24 (m, 4H, H-5′ and H-7′), 6.9–7.1 (m, 5H, H-2, H-5, H-7, H-2″ and H-6″), 7.33 (d, 1H, H-4, $J = 8.1$), 7.49 (m, 3H, H-6, H-3″ and H-5″), 10.75 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 22.8 (CH_2, C-1′), 27.5 (CH_2, C-2′), 47.4 (CH_2, C-5′ and C-7′), 52.9 (CH_2, C-4′ and C-6′), 57.9 (CH_2, C-3′), 111.7, 114.4, 114.7, 117.9, 118.3, 118.4, 118.6, 121.1, 122.5, 123.6, 126.4, 126.5, 127.2, 127.6, 136.7 (C–N, C-3), 153.6 (C–N, C-1″). Anal. calcd. for $C_{22}H_{24}F_3N_3$: C, 68.20; H, 6.24; N, 10.85; Found: C, 68.36; H, 6.40; N, 10.78.

*3-[3-(4-{4-(Trifluoromethyl)phenyl}-1-piperazinyl)propyl]-5-fluoro-1H-indole (**3b**)*

Prepared from 3-(5-fluoro-3-indolyl)propyl-4-methylbenzenesulfonate (**2b**) (0.200 g, 0.58 mmol), anhydrous potassium carbonate (0.080 g, 0.58 mmol), and 1-[4-(trifluoromethyl)phenyl]piperazine (0.132 g, 0.58 mmol). The crude was purified by column chromatography (AcOEt), 73% yield, m.p.: 122–123°C. IR cm^{-1}: 3431 (N–H), 3058 (C–H arom.), 2938–2792 (C–H aliph.), 1614 (C=C). ^{1}H NMR ($CDCl_3$): 1.92 (q, 2H, H-2′, $J = 7.5$ Hz), 2.47 (t, 2H, H-3′, $J = 7.5$ Hz), 2.60 (m, 4H, H-4′ and H-6′), 2.76 (t, 2H, H-1′, $J = 7.5$ Hz), 3.97 (m, 4H, H-5′ and H-7′), 6.8–6.9 (m, 3H, H-2, H-2″

and H-6″), 7.02 (s, 1H, H-7), 7.2 (m, 2H, H-4, H-5), 7.47 (d, 2H, H-3″ and H-5″, $J = 8.7$), 8.01 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 21.9 (CH_2, C-1′), 26.3 (CH_2, C-2′), 47.0 (CH_2, C-5′ and C-7′), 52.1 (CH_2, C-4′ and C-6′), 57.2 (CH_2, C-3′), 102.8, 103.1, 109.2, 109.6, 110.7, 110.8, 113.5, 115.5, 115.6, 119.3, 119.7, 122.1, 125.4, 125.5, 125.7, 127.0, 127.1, 131.9 (C–N, C-3), 152.4 (C–N, C-1″), 155.2 and 158.3 (C–F, C-6). Anal. calcd. for $C_{22}H_{23}F_4N_3$: C, 65.17; H, 5.32; N, 10.36; Found: C, 64.98; H, 5.40; N, 10.38.

*3-[3-(4-{2-Fluorobenzyl}-1-piperazinyl)propyl]-1H-indole (**4a**)*

Prepared from 3-(3-indolyl)propyl-4-methylbenzenesulfonate (**2a**) (0.200 g, 0.61 mmol), anhydrous potassium carbonate (0.084 g, 0.61 mmol), and 1-(2-fluorobenzyl)piperazine (0.106 g, 0.61 mmol). The crude was purified by column chromatography (AcOEt–hexane–MeOH 2.0:0.5:0.3), 56% yield, oil. IR cm^{-1}: 3409 (N–H), 3055 (C–H arom.), 2945–2779 (C–H aliph.), 1618 (C=C). ^{1}H NMR ($CDCl_3$): 1.90 (q, 2H, H-2′, $J = 7.6$ Hz), 2.44–2.54 (m, 10H, H-3′, H-4′, H-5′, H-6′ and H-7′), 2.73 (t, 2H, H-1′, $J = 7.5$ Hz), 3.58 (s, 2H, H-8′), 6.89 (s, 1H, H-2), 6.9–7.3 (m, 7H, H-5, H-6, H-7 and H-fluorobenzyl), 7.56 (d, 1H, H-4, $J = 7.8$), 8.49 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 22.9 (CH_2, C-1′), 26.8 (CH_2, C-2′), 52.2 (CH_2, C-4′ and C-6′), 52.8 (CH_2, C-5′ and C-7′), 55.1 (CH_2, C-8′), 58.1 (CH_2, C-3′), 111.0, 115.1, 115.4, 115.8, 118.8, 118.9, 121.2, 121.7, 123.7, 123.8, 124.1, 124.3, 127.5, 128.8, 128.9, 131.6, 131.7 (C–N, C-3), 159.7 and 163.0 (C–F, C-6″). Anal. calcd. for $C_{22}H_{26}FN_3$: C, 75.18; H, 7.46; N, 11.96; Found: C, 75.02; H, 7.54; N, 12.03.

*3-[3-(4-{2-Fluorobenzyl}-1-piperazinyl)propyl]-5-fluoro-1H-indole (**4b**)*

Prepared from 3-(5-fluoro-3-indolyl)propyl-4-methylbenzenesulfonate (**2b**) (0.200 g, 0.58 mmol), anhydrous potassium carbonate (0.800 g, 0.58 mmol), and 1-(2-fluorobenzyl)piperazine (0.112 g, 0.58 mmol). The crude was purified by column chromatography (AcOEt–hexane–MeOH 2.0:0.5:0.3), 78% yield, m.p.: 112–113 °C. IR cm^{-1}: 3411 (N–H), 3054 (C–H arom.), 2945–2778 (C–H aliph.), 1625 (C=C). ^{1}H NMR ($CDCl_3$): 1.91 (q, 2H, H-2′, $J = 7.5$ Hz), 2.44–2.74 (m, 12H, H-1′, H-3′, H-4′, H-5′, H-6′ and H-7′), 3.64 (s, 2H, H-8′), 6.8–7.2 (m, 7H, H-2, H-5, H-7 and H-fluorobenzyl), 7.69 (td, 1H, H-4, $J = 7.3$, $J = 1.8$), 8.67 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 22.0 (CH_2, C-1′), 26.1 (CH_2, C-2′), 51.6 (CH_2, C-4′ and C-6′), 52.2 (CH_2, C-5′ and C-7′), 54.3 (CH_2, C-8′), 57.3 (CH_2, C-3′), 102.7, 103.0, 109.0, 109.3, 110.7, 110.8, 114.3, 114.6, 115.2, 115.3, 122.3, 122.9, 123.0, 123.3, 123.5, 126.9, 127.0, 128.0, 128.1, 130.8, 130.9, 131.9 (C–N, C-3), 155.1 and 158.2 (C–F, C-6), 158.9 and 162.2 (C–F, C-6″). Anal. calcd. for $C_{22}H_{25}F_2N_3$: C, 71.52; H, 6.82; N, 11.37; Found: C, 71.49; H, 6.83; N, 11.37.

*3-[3-(4-Phenylethyl-1-piperazinyl)propyl]-1H-indole (**5a**)*

Prepared from 3-(3-indolyl)propyl-4-methylbenzenesulfonate (**2a**) (0.200 g, 0.61 mmol), anhydrous potassium carbonate (0.084 g, 0.61 mmol), and 1-phenylethylpiperazine (0.116 g, 0.61 mmol). The crude was purified by column chromatography (AcOEt–hexane–MeOH 2.0:0.5:0.3), 80% yield, m.p.: 126.5–17.5 °C. IR cm^{-1}: 3423 (N–H), 3055 (C–H arom.), 2946–2772 (C–H aliph.), 1617 (C=C). ^{1}H NMR ($CDCl_3$): 1.91 (q, 2H, H-2′, $J = 7.5$ Hz), 2.43–2.61 (m, 12H, H-3′, H-4′, H-5′, H-6′, H-7′ and H-2″), 2.77 (m, 4H, H-1′ and 1″), 6.86 (s, 1H, H-2), 7.0–7.18 (m, 5H, H-5, H-6, H-7, H-4″ and H-8″), 7.25 (m, 3H, H-5″, H-6″ and H-7″), 7.58 (d, 1H, H-4, $J = 7.5$), 8.60 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 22.8 (CH_2, C-1′), 27.1 (CH_2, C-2′), 33.3 (CH_2, C-2″), 52.9 (CH_2, C-4′ and C-6′), 53.0 (CH_2, C-5′ and C-7′), 58.2 (CH_2, C-1″), 60.3 (CH_2, C-3′), 110.9, 115.8, 118.7, 121.1, 121.5, 125.9, 127.3 (CH, C-6″), 128.2 (CH, C-4″ and C-8″), 128.5 (CH, C-5″ and C-7″), 136.1 (C–N, C-3) and 140.0 (C–C, C-3″). Anal. calcd. for $C_{23}H_{29}N_3$: C, 79.50; H, 8.41; N, 12.09; Found: C, 79.22; H, 8.39; N, 12.20.

*5-Fluoro-3-[3-(4-phenylethyl-1-piperazinyl)propyl]-1H-indole (**5b**)*

Prepared from 3-(5-fluoro-3-indolyl)propyl-4-methylbenzenesulfonate (**2b**) (0.200 g, 0.58 mmol), anhydrous potassium carbonate (0.080 g, 0.58 mmol), and 1-phenylethylpiperazine (0.110 g, 0.58 mmol). The crude was purified by column chromatography (AcOEt–hexane–MeOH 2.0:0.5:0.3), 76% yield, m.p.: 121–122 °C. IR cm^{-1}: 3423 (N–H), 3057 (C–H arom.), 2998–2780 (C–H aliph.), 1626 (C=C). ^{1}H NMR ($CDCl_3$): 1.93 (q, 2H, H-2′, $J = 7.5$ Hz), 2.46–2.7 (m, 16H, H-1′, H-3′, H-4′, H-5′, H-6′, H-7′ and H-1″, H-2″), 6.9–7.0 (m, 2H, H-4 and H-7), 7.22–7.34 (m, 7H, H-2, H-5, and H-phenylpip.), 8.74 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 22.0 (CH_2, C-1′), 26.3 (CH_2, C-2′), 32.6 (CH_2, C-2″), 52.2 (CH_2, C-4′ and C-6′), 52.3 (CH_2, C-5′ and C-7′), 57.4 (CH_2, C-1″), 59.6 (CH_2, C-3′), 102.7, 103.0, 109.0, 109.3, 110.7, 110.8, 115.3, 122.3, 125.2, 126.9, and 127.1 (CH, C-6″), 127.5 (CH, C-4″ and C-8″), 127.8 (CH, C-5″ and C-7″), 132.0 (C–N, C-3) and 139.3 (C–C, C-3″). Anal. calcd. for $C_{23}H_{28}FN_3$: C, 75.58; H, 7.72; N, 11.50; Found: C, 75.61; H, 7.73; N, 11.53.

*3-[3-(3-(Trifluoromethyl)-1-piperidinyl)propyl]-1H-indole (**6a**)*

Prepared from 3-(3-indolyl)propyl-4-methylbenzenesulfonate (**2a**) (0.200 g, 0.61 mmol), anhydrous potassium carbonate (0.084 g, 0.61 mmol), and 3-(trifluoromethyl)piperidine (0.093 g, 0.61 mmol). The crude was purified by column chromatography (hexane–AcOEt 1.0:2.0), 80% yield, as a pale-yellow oil. IR cm^{-1}: 3416 (N–H), 3056 (C–H arom.), 2946–2860 (C–H aliph.), 1619 (C=C). ^{1}H NMR ($CDCl_3$): 1.18–193 (m, 9H, H-2′, H-2″, H-3″, H-4″ and H-5″), 2.31–2.34 (m, 1H, H-5″), 2.41–2.46 (m, 2H, H-3′), 2.76 (t, 2H, H-1′), 2.88–3.08 (m, 2H, H-1″), 6.92 (s, 1H, H-7), 7.15 (m, 2H, H-5 and H-6), 7.31 (d, 1H, H-2, $J = 8.1$), 7.59 (d, 1H, H-4), 8.03 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 22.9 (CH_2, C-1′), 23.4 (CH_2, C-4″), 24.2 (CH_2, C-2′), 27.3 (CH_2, C-3″), 40.5, 40.9, 41.2, 41.6 (CH, C-2″), 52.3, 52.4 (CH_2, C-1″), 53.4 (CH_2, C-5″), 58.6 (CH_2, C-3′), 111.1 (CH, C-4), 116.3 (C–C, C-1), 118.9 (CH, C-7), 119.1 (CH, C-6), 121.2 (CH–C-5), 121.9 (CH, C-2), 127.5 (C–C, C-8), 125.2, 128.9, 132.6 (CF, CF_3) and 136.3 (C–C, C-3). Anal. calcd. for $C_{17}H_{21}F_3N_2$: C, 65.79; H, 6.82; N, 9.03; Found: C, 65.91; H, 6.72; N, 8.99.

*5-Fluoro-3-[3-(3-(trifluoromethyl)-1-piperidinyl)propyl]-1H-indole (**6b**)*

Prepared from 3-(5-fluoro-3-indolyl)propyl-4-methylbenzenesulfonate (**2b**) (0.210 g, 0.60 mmol), anhydrous potassium carbonate (0.084 g, 0.60 mmol), and 3-(trifluoromethyl)piperidine (0.093 g, 0.60 mmol). The crude was purified by column chromatography (hexane–AcOEt 1.0:2.0), 75% yield, as a pale-yellow oil. IR cm^{-1}: 3425 (N–H), 3057 (C–H arom.), 2947–2861 (C–H aliph.), 1628 (C=C). ^{1}H NMR ($CDCl_3$): 1.19–1.94 (m, 9H, H-2′, H-2″, H-3″, H-4″ and H-5″), 2.24–2.32 (m, 1H, H-5″), 2.43 (t, 2H, H-3′, $J = 7.5$), 2.71 (t, 2H, H-1′, $J = 7.5$), 2.88–3.07 (m, 2H, H-1″), 6.92 (td, 1H, H-5, $J = 9$, $J = 2.4$), 6.99 (s, 1H, H-7), 7.21–7.25 (m, 2H, H-2 and H-4), 8.03 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 22.7 (CH_2, C-1′), 23.3 (CH_2, C-4″), 24.1 (CH_2, C-2′), 27.2 (CH_2, C-3″), 40.8, 41.2 (CH, C-2″), 52.4 (CH_2, C-1″), 53.4

(CH_2, C-5″), 58.4 (CH_2, C-3′), 103.6, 103.9 (CH, C-5), 110.0, 110.4 (CH, C-3), 111.5, 111.6 (CH, C-4), 116.4, 116.5 (C–C, C-1), 123.0 (CH–C-2), 125.1, 127.8, 128.8 (C–F, CF_3), 128.0 (C–C, C-8), 132.8 (C–C, C-3), 156.1 and 159.2 (C–F, C-6). Anal. calcd. for $C_{17}H_{20}F_4N_2$: C, 62.18; H, 6.14; N, 8.53; Found: C, 61.97; H, 6.16; N, 8.60.

General method for the preparation of compounds 7a,b and 8a,b

*2-[3-(3-Indolyl)propyl]isoindoline-1,3-dione (**7a**)*

A mixture of phthalimide (0.090 g, 0.61 mmol) in dry DMF (5 mL) and anhydrous potassium carbonate (0.085 g, 0.61 mmol) was stirred under reflux for 1 h. Then the derivative **2a** (0.200 g, 0.61 mmol) was added. The reaction mixture was stirred under reflux overnight. The solvent was evaporated *in vacuo* to obtain a crude, which was purified by column chromatography (hexane/AcOEt 2:1) to yield pure **7a** (0.110 g, 59%). m.p.: 121–122°C. IR cm^{-1}: 3390 (N–H), 3047 (C–H arom.), 2977–2836 (C–H aliph.), 1697 (C=O), 1617 (C=C arom.). ^1H NMR ($CDCl_3$): 2.12 (q, 2H, H-2′, $J = 7.2$), 2.82 (t, 2H, H-1′, $J = 7.5$ Hz), 3.79 (t, 2H, H-3′, $J = 7.2$ Hz), 7.06–7.17 (m, 3H, H-2, H-5, H-6), 7.30 (d, 1H, H-7, $J = 7.8$), 7.58 (d, 1H, H-4), 7.67 (m, 2H, H-2″ and H-5″), 7.81 (m, 2H, H-3″ and H-4″), 8.02 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 22.4 (CH_2, C-1′), 28.5 (CH_2, C-2′), 37.8 (CH_2, C-3′), 111.5 (CH, C-4′), 115.1 (C–C, C-1), 118.7 (CH, C-7), 119.1 (CH, C-6), 121.4 (CH, C-5), 121.8 (CH, C-2), 123.0 (CH, C-2″ and C-5″), 127.2 (C–C, C-8), 132.0 (C–C, C-1″ and C-6″), 133.8 (CH, C-3″ and C-4″), 136.2 (C–N, C-3), 168.5 (C=O). Anal. calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 10.51; Found: C, 75.02; H, 5.27; N, 10.41.

*2-[3-(5-Fluoro-3-indolyl)propyl]isoindoline-1,3-dione (**7b**)*

Prepared from phthalimide (0.085 g, 0.58 mmol), anhydrous potassium carbonate (0.080 g, 0.58 mmol), and 3-(5-fluoro-3-indolyl)propyl-4-methylbenzenesulfonate **2b** (0.200 g, 0.58 mmol). The crude was purified by column chromatography (hexane/AcOEt 2:1); 56% yield, m.p.: 133–135°C. IR cm^{-1}: 3409 (N–H), 3047 (C–H arom.), 2979–2859 (C–H aliph.), 1697 (C=O), 1627 and 1612 (C=C). ^1H NMR ($CDCl_3$): 2.10 (m, 2H, H-2′), 2.77 (t, 2H, H-1′, $J = 7.5$ Hz), 3.78 (t, 2H, H-3′, $J = 7.2$ Hz), 6.90 (td, 1H, H-5, $J = 9.0$, $J = 2.4$), 7.12 (s, 1H, H-7), 7.22 (m, 2H, H-4 and H-2), 7.70 (m, 2H, H-2″ and H-5″), 7.83 (m, 2H, H-3″ and H-4″), 8.03 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 22.8 (CH_2, C-1′), 28.8 (CH_2, C-2′), 38.1 (CH_2, C-3′), 100.9 and 104.2 (CH, C-5), 110.5 and 110.8 (CH, C-7), 111.9 and 112.1 (CH, C-4), 123.5 (CH, C-2″ and C-5″), 123.7 (CH, C-2), 128.1 (C–C, C-8), 132.5 (C–C, C-1″ and C-6″), 133.2 (C–N, C-3), 134.3 (CH, C-3″ and C-4″), 168.9 (C=O). Anal. calcd. for $C_{19}H_{15}FN_2O_2$: C, 70.80; H, 4.69; N, 8.69; Found: C, 70.78; H, 4.71; N, 8.69.

*1-[3-(3-Indolyl)propyl]benzo[c]-3-isoxazolone (**8a**)*

Prepared from 2-benzoxazolinone (0.083 g, 0.61 mmol), anhydrous potassium carbonate (0.085 g, 0.61 mmol), and 3-(3-indolyl)-propyl-4-methylbenzenesulfonate derivative **2a** (0.200 g, 0.61 mmol). The crude was purified by column chromatography (hexane/AcOEt 2:1), 80% yield, m.p.: 91–93°C. IR cm^{-1}: 3300 (N–H), 3057 (C–H arom.), 2927–2843 (C–H aliph.), 1750 (C=O), 1615 (C=C). ^1H NMR ($CDCl_3$): 2.16 (q, 2H, H-2′, $J = 7.2$), 2.82 (t, 2H, H-1′, $J = 7.2$ Hz), 3.84 (t, 2H, H-3′, $J = 7.2$ Hz), 6.82 (d, 1H, H-7, $J = 7.6$), 7.00–7.21 (m, 6H, H-2, H-4, H-5, H-6, H-2″ and H-4″), 7.33 (d, 1H, H-3″, $J = 8.1$), 7.52 (d, 1H, H-5″, $J = 7.8$), 8.30 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 22.3 (CH_2, C-1′), 27.8 (CH_2, C-2′), 41.8 (CH_2, C-3′), 108.3 (CH, C-2″), 110.0 (CH, C-4), 111.2 (CH, C-7), 114.5 (C–C, C-1), 118.6 (CH, C-6), 119.3 (CH, C-4″), 121.7 (CH, C-5), 122.0 (C–H, C-2), 122.3 (CH, C-5″), 123.7 (CH, C-3″), 127.2 (C–C, C-6″), 131.1 (C–C, C-8), 136.4 (C–C, C-3), 142.2 (C–C, C-1″), 168.9 (C=O). Anal. calcd. for $C_{18}H_{16}N_2O_2$: C, 73.98; H, 5.52; N, 10.95; Found: C, 74.04; H, 5.50; N, 10.88.

*1-[3-(5-Fluoro-3-indolyl)propyl]benzo[c]-3-isoxazolone (**8b**)*

Prepared from 2-benzoxazolinone (0.078 g, 0.58 mmol), anhydrous potassium carbonate (0.080 g, 0.58 mmol), and 3-(5-fluoro-3-indolyl)propyl-4-methylbenzenesulfonate derivative **2b** (0.200 g, 0.58 mmol). The crude was purified by column chromatography (hexane/AcOEt 2:1), 78% yield, m.p.: 112–113°C. IR cm^{-1}: 3305 (N–H), 3056 (C–H arom.), 2929–2848 (C–H aliph.), 1750 (C=O), 1607 (C=C). ^1H NMR ($CDCl_3$): 2.11 (q, 2H, H-2′, $J = 7.2$), 2.73 (t, 2H, H-1′, $J = 7.2$ Hz), 3.81 (t, 2H, H-3′, $J = 7.2$ Hz), 6.79–6.89 (m, 2H, H-4 and H-7), 6.99–7.22 (m, 6H, H-2, H-5, H-2″, H-3″, H-4″ and H-5″), 8.04 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 22.1 (CH_2, C-1′), 27.6 (CH_2, C-2′), 41.7 (CH_2, C-3′), 103.4 and 103.7 (CH, C-2″), 108.3 (CH, C-7), 110.2 and 110.6 (CH, C-4), 111.7 and 111.9 (CH, C-4″), 114.7 (C–C, C-1), 122.4 (CH, C-2), 123.6 (CH, C-5″), 123.8 (CH, C-3), 127.6 (C–C, 2.7 (CH, C-6″), 131.1 (C–C, C-8), 132.8 (C–C, C-3), 142.7 (C–C, C-1″), 154.6 (C–F, C-6), 169.2 (C=O). Anal. calcd. for $C_{18}H_{15}FN_2O_2$: C, 69.67; H, 4.87; N, 9.03; Found: C, 69.76; H, 4.95; N, 9.08.

*3-[3-(3-{4-Fluorophenyl}-1H-1-pyrazolyl)propyl]-1H-indole (**9a**)*

Prepared from 3-(4-fluorophenyl)-1*H*-pyrazole (0.099 g, 0.61 mmol), anhydrous potassium carbonate (0.083 g, 0.61 mmol), and 3-(3-indolyl)propyl-4-methylbenzenesulfonate derivative **2a** (0.200 g, 0.61 mmol). The crude was purified by column chromatography (hexane/AcOEt 2:1), 31% yield, oil. IR cm^{-1}: 3448 (N–H), 3050 (C–H arom.), 2959–2919 (C–H aliph.), 1606 (C=N), 1507 and 1524 (C=C). ^1H NMR ($CDCl_3$): 2.30 (q, 2H, H-2′, $J = 7.2$), 2.78 (t, 2H, H-1′, $J = 7.2$ Hz), 4.17 (t, 2H, H-3′, $J = 7.2$ Hz), 6.47 (s, 1H, H-5′), 6.95 (s, 1H, H-7), 7.03–7.22 (m, 4H, H-2, H-4, H-5 and H-6), 7.33 (m, 2H, H-2″ and 6″), 7.56 (d, 1H, H-4′, $J = 7.8$), 7.77 (m, 2H, H-3″ and H-5″), 8.10 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 21.3 (CH_2, C-1′), 29.6 (CH_2, C-2′), 50.8 (CH_2, C-3′), 101.4 (CH, C-5′), 110.2 (CH, C-4), 114.0 (C–C, C-1), 114.4 (CH, C-7), 114.4 and 117.8 (CH, C-3″ and C-5″), 118.3 (CH, C-6), 120.6 (C–H, C-5), 121.1 (CH, C-2), 126.2 and 126.3 (CH, C-2″ and C-6″), 126.4 (C–C, C-1″), 129.0 (C–C, C-8), 129.7 (CH–N, C-4′), 135.4 (C–N, C-3), 149.5 (C–N, C-6′), 159.8 and 163.1 (C–F, C-4″). Anal. calcd. for $C_{20}H_{18}FN_3$: C, 75.21; H, 5.68; N, 13.16; Found: C, 75.25; H, 5.60; N, 13.21.

*5-Fluoro-3-[3-(3-(4-fluorophenyl)-1-pyrazolyl)propyl]-1H-indole (**9b**)*

Prepared from 3-(4-fluorophenyl)-1*H*-pyrazole (0.080 g, 0.58 mmol), anhydrous potassium carbonate (0.080 g, 0.58 mmol), and 3-(5-fluoro-3-indolyl)propyl-4-methylbenzenesulfonate derivative **2b** (0.200 g, 0.58 mmol). The crude was purified by column chromatography (hexane/AcOEt 2:1), 35% yield, m.p.: 80–81°C. IR cm^{-1}: 3446 (N–H), 3058 (C–H arom.), 2952–2892 (C–H aliph.), 1603 (C=N), 1505 and 1488 (C=C). ^1H NMR ($CDCl_3$): 2.22 (q, 2H, H-2′, $J = 7.2$), 2.67 (t, 2H, H-1′, $J = 7.2$ Hz), 4.12 (t, 2H, H-3′, $J = 7.2$ Hz), 6.42 (s, 1H, H-5′), 6.86 (td, 1H, H-5′, $J = 9.0$ and $J = 2.4$), 6.97–7.03 (m, 3H, H-2, H-4 and H-7), 7.11–7.20 (m, 2H, H-2″ and 6″), 7.31 (d, 1H, H-4′), 7.68–7.72 (m, 2H, H-3″ and H-5″), 7.99 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 22.4 (CH_2, C-1′), 30.8 (CH_2, C-2′), 52.0 (CH_2, C-3′), 101.4 (CH, C-5′), 103.9 and 104.3 (CH, C-5), 110.6 and 111.0 (CH, C-7), 112.1 and 112.2 (CH,

C-4), 115.5 and 115.6 (C–C, C-1″), 115.7 and 116.0 (CH, C-3″ and C-5″), 123.8 (CH, C-2), 127.5 and 127.6 (CH, C-2″ and C-6″), 128.4 and 128.1 (C–C, C-1″), 130.3 (C–C, C-8), 131.0 (CH–N, C-4′), 133.2 (C–N, C-3), 150.9 (C–N, C-6′), 156.5 and 159.6 (C–F, C-6), 161.2 and 164.4 (C–F, C-4″). Anal. calcd. for $C_{20}H_{17}F_2N_3$: C, 71.20; H, 5.08; N, 12.46; Found: C, 71.12; H, 5.13; N, 12.54.

*1-[3-(3-Indolyl)propyl]-5-fluoro-1H-indazole (**10a**)*

Prepared from 5-fluoro-1*H*-indazole (0.083 g, 0.61 mmol), anhydrous potassium carbonate (0.083 g, 0.61 mmol), and 3-(3-indolyl)-propyl-4-methylbenzenesulfonate derivative **2a** (0.200 g, 0.61 mmol). The crude was purified by column chromatography (hexane/AcOEt 2:1), 36% yield, m.p.: 106–107°C. IR cm^{-1}: 3411 (N–H), 3058 (C–H arom.), 2931–2873 (C–H aliph.), 1616 (C=N), 1504 (C=C). ^1H NMR ($CDCl_3$): 2.33 (q, 2H, H-2′, $J = 7.2$), 2.74 (t, 2H, H-1′, $J = 7.2$ Hz), 4.38 (t, 2H, H-3′, $J = 6.9$ Hz), 6.91 (s, 1H, H-7), 7.05–7.22 (m, 4H, H-2, H-5, H-6 and H-8′), 7.32 (m, 2H, H-4 and 10′), 7.51 (d, 1H, H-7′, $J = 7.8$), 7.96 (s, 1H, H-4′), 8.10 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 21.8 (CH_2, C-1′), 27.6 (CH_2, C-2′), 50.7 (CH_2, C-3′), 108.4, 108.6, 110.2, 110.3, 111.5, 111.6, 111.9, 118.8, 119.5, 120.4, 123.1, 125.2, 126.3, 130.3, 136.4, 138.2, 147.5, 154.8. Anal. calcd. for $C_{18}H_{16}FN_3$: C, 73.70; H, 5.50; N, 14.32; Found: C, 73.68; H, 5.51; N, 14.28.

*1-(3-(5-Fluoro-1H-indol-3-yl)propyl)- 5-fluoro-1H-indazole (**10b**)*

Prepared from 5-fluoro-1*H*-indazole (0.80 g, 0.58 mmol), anhydrous potassium carbonate (0.080 g, 0.58 mmol), and 3-(5-fluoro-3-indolyl)propyl-4-methylbenzenesulfonate derivative **2b** (0.200 g, 0.58 mmol). The crude was purified by column chromatography (hexane/AcOEt 2:1), 36% yield, m.p.: 106–107°C. IR cm^{-1}: 3411 (N–H), 3056 (C–H arom.), 2933–2875 (C–H aliph.), 1613 (C=N), 1505 (C=C). ^1H NMR ($CDCl_3$): 2.33 (q, 2H, H-2′, $J = 7.2$), 2.74 (t, 2H, H-1′, $J = 7.2$ Hz), 4.38 (t, 2H, H-3′, $J = 6.9$ Hz), 6.91 (s, 1H, H-7), 7.05–7.22 (m, 4H, H-2, H-5, H-6 and H-8′), 7.32 (m, 2H, H-4 and 10′), 7.51 (d, 1H, H-7′, $J = 7.8$), 7.96 (s, 1H, H-4′), 8.10 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 21.8 (CH_2, C-1′), 28.8 (CH_2, C-2′), 51.4 (CH_2, C-3′), 106.4, 109.6, 109.9, 110.0, 112.5, 112.6, 120.4, 123.1, 125.7, 130.3, 133.3, 132.5, 136.4, 136.5, 144.8, 146.8, 154.3, 154.8. Anal. calcd. for $C_{18}H_{15}F_2N_3$: C, 69.44; H, 4.86; N, 13.50; Found: C, 69.33; H, 4.90; N, 13.62.

*3-[3-(5-{Trifluoromethyl}-1H-pyrazolyl)propyl]-1H-indole (**11a**)*

Prepared from 5-(trifluoromethyl)-1*H*-pyrazole 0.083 g, 0.61 mmol), anhydrous potassium carbonate (0.083 g, 0.61 mmol), and 3-(3-indolyl)propyl-4-methylbenzenesulfonate derivative **2a** (0.200 g, 0.61 mmol). The crude was purified by column chromatography (hexane/AcOEt 2:1), 55% yield, oil. IR cm^{-1}: 3415 (N–H), 3057 (C–H arom.), 2939–2852 (C–H aliph.), 1619 (C=N), 1493 (C=C), 1239 (CF_3). ^1H NMR ($CDCl_3$): 2.17 (q, 2H, H-2′, $J = 7.0$), 2.60 (t, 2H, H-1′, $J =$ ^1H NMR ($CDCl_3$): 2.30 (q, 2H, H-2′, $J = 7.2$), 2.76 (t, 2H, H-1′, $J = 7.2$ Hz), 4.19 (t, 2H, H-3′, $J = 7.2$ Hz), 6.50 (s, 1H, H-7), 6.97 (s, 1H, H-5), 7.09–7.24 (m, 2H, H-2 and H-6), 7.35 (d, 2H, H-4 and 6′, $J = 8.1$), 7.54 (d, 1H, H-5′, $J = 7.8$), 8.01 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 21.8 (CH_2, C-1′), 30.3 (CH_2, C-2′), 52.2 (CH_2, C-3′), 104.1 (CH, C-5′), 111.1 (CH, C-4), 114.4 (C–C, C-1), 118.6 (CH, C-7), 119.3 (CH, C-6), 121.6 (C–H, C-5), 122.1 (CH, C-2), 127.1 (C–C, C-8), 130.4 (CH, C-6′), 136.3 (C–N, C-3), 141.9 and 142.4 (C–F, C-4′). Anal. calcd. for $C_{15}H_{14}F_3N_3$: C, 61.43; H, 4.81; N, 14.33; Found: C, 61.50; H, 4.79; N, 14.30.

*5-Fluoro-3-[3-(5-{trifluoromethyl}-1H-pyrazolyl)propyl]-1H-indole (**11b**)*

Prepared from 5-(trifluoromethyl)-1*H*-pyrazole (0.078 g, 0.58 mmol), anhydrous potassium carbonate (0.080 g, 0.58 mmol) and 3-(5-fluoro-3-indolyl)propyl-4-methylbenzenesulfonate derivative **2b** (0.200 g, 0.58 mmol). The crude was purified by column chromatography (hexane/AcOEt 2:1), 61% yield, oil. IR cm^{-1}: 3422 (N–H), 3058 (C–H arom.), 2937–2853 (C–H aliph.), 1628 (C=N), 1487 (C=C), 1239 (CF_3). ^1H NMR ($CDCl_3$): 2.17 (q, 2H, H-2′, $J = 7.0$), 2.60 (t, 2H, H-1′, $J = 7.0$ Hz), 4.09 (t, 2H, H-3′, $J = 6.9$ Hz), 6.42 (s, 1H, H-7), 6.83 (t, 1H, H-7, $J = 9.0$), 6.93 (s, 1H, H-2), 7.07 (d, 1H, H-4, $J = 9.6$), 7.17 (m, 1H, H-6′), 7.30 (s, 1H, H-5′), 8.57 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 22.2 (CH_2, C-1′), 30.6 (CH_2, C-2′), 52.5 (CH_2, C-3′), 103.6 and 103.9 (CH, C-5′), 104.6 and 104.7 (CH, C-5), 110.4 and 110.7 (CH, C-7), 112.3 and 112.4 (CH, C-4), 114.6 and 114.7 (C–C, C-1), 116.5, 120.0, 123.6 and 127.8 (C–F, CF_3), 124.1 (CH, C-2), 127.9 (C–C, C-8), 131.0 (CH–N, C-6′), 133.4 (C–N, C-3), 141.8, 142.3, 142.8 and 143.3 (C–CF, C-4′), 156.4 and 159.5 (C–F, C-6). Anal. calcd. for $C_{15}H_{13}F_4N_3$: C, 57.88; H, 4.21; N, 13.50; Found: C, 57.71; H, 4.17; N, 13.44.

*1-[3-(3-Indolyl)propyl]-2-(2-nitrophenyl-)1H-benzo[d]-imidazole (**12a**)*

Prepared from 2-(2-nitrophenyl)-1*H*-benzo[*d*]imidazole (0.200 g, 0.84 mmol), anhydrous potassium carbonate (0.116 g, 0.84 mmol), and 3-(3-indolyl)propyl-4-methylbenzenesulfonate derivative **2a** (0.275 g, 0.84 mmol). The crude was purified by column chromatography (hexane/AcOEt 2:1), 92% yield, m.p.: 161–162°C. IR cm^{-1}: 3451 (N–H), 3057 (C–H arom.), 2937–2852 (C–H aliph.), 1530 (NO_2 asim), 1364 (NO_2 sim), 1448 (C=C). ^1H NMR (DMSO-d_6): 2.07 (q, 2H, H-2′, $J = 7.5$), 2.64 (t, 2H, H-1′, $J = 7.2$ Hz), 4.21 (t, 2H, H-3′, $J = 7.5$ Hz), 6.92 (m, 2H, H-5 and H-7), 7.05 (t, 1H, H-6, $J = 7.2$), 7.29 (m, 4H, H-2, H-4, H-8′and 10′), 7.64–7.76 (m, 5H, H-7′, H-9′, 2″, 3″ and 4″ $J = 7.8$), 8.13 (d, 1H, H-5″, $J = 6.9$), 10.7 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 21.3 (CH_2, C-1′), 28.9 (CH_2, C-2′), 43.2 (CH_2, C-3′), 110.4 (CH, C-10′), 110.8 (CH, C-4), 112.4 (C–C, C-1), 117.6 (CH, C-7′), 117.7 (CH, C-7), 118.8 (CH, C-6), 120.4 (C–H, C-5), 121.8 (CH, C-8′), 121.7 (CH, C-9′), 122.2 (C–C, C-1″), 124.1 (CH, C-2″), 124.4 (CH, C-2), 126.3 (C–C, C-8), 130.8 (CH, C-5″), 131.4 (CH, C3″), 132.8 (CH, C-4″), 134.4 (C–C, C-3), 135.8 (C–C, C-5′), 142.1 (C–C–NO_2, C-6″), 148.2 (C–C, C-6′), 148.4 (N–C–N, C-4′). Anal. calcd. for $C_{24}H_{20}N_4O_2$: C, 72.81; H, 5.08; N, 14.23; Found: C, 71.97; H, 5.11; N, 14.27.

*1-[3-(5-Fluoro-3-indolyl)propyl]-2-(2-nitrophenyl)-1H-benzo[d]imidazole (**12b**)*

Prepared from 2-(2-nitrophenyl)-1*H*-benzo[*d*]imidazole (0.200 g, 0.84 mmol), anhydrous potassium carbonate (0.116 g, 0.84 mmol), and 3-(5-fluoro-3-indolyl)propyl-4-methylbenzenesulfonate derivative **2b** (0.150 g, 0.36 mmol). The crude was purified by column chromatography (hexane/AcOEt 2:1), 57% yield, m.p.: 161.5–162°C. IR cm^{-1}: 3453 (N–H), 3064 (C–H arom.), 2957–2860 (C–H aliph.), 1533 (NO_2 asym), 1366 (NO_2 sym), 1486 (C=C). ^1H NMR (DMSO-d_6): 2.03 (q, 2H, H-2′, $J = 7.5$), 2.60 (t, 2H, H-1′, $J = 7.5$ Hz), 4.19 (t, 2H, H-3′, $J = 7.5$ Hz), 6.87 (m, 2H, H-5 and H-7), 7.32 (m, 4H, H-2, H-4, H-8′ and 10′), 7.60–7.75 (m, 5H, H-7′, H-9′, 2″, 3″ and 4″), 8.14 (d, 1H, H-5″, $J = 6.9$), 10.9 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 21.8 (CH_2, C-1′), 29.1 (CH_2, C-2′), 44.2 (CH_2, C-3′), 110.6, 110.8, 112.4, 116.6, 118.7, 120.8, 121.9, 121.5, 122.3, 124.1, 125.0, 126.9, 130.8, 131.8, 132.8, 134.4, 135.8, 142.6, 148.2, 146.7, 149.4, 152.6. Anal.

calcd. for $C_{24}H_{19}FN_4O_2$: C, 69.55; H, 4.62; N, 13.52; Found: C, 69.37; H, 4.55; N, 13.51.

*3-(1H-Indol-3-yl)-2-methylpropanal (**13a**)*

A mixture of indole (0.500 g, 4.23 mmol) and methacrolein (0.440 g, 2.35 mmol) was dissolved in dry CH_2Cl_2 (30 mL) in the presence of molecular iodine as a catalyst. The reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated *in vacuo* to obtain a crude, which was purified by column chromatography (hexane/AcOEt 2:3), to produce pure **13a** as an oil (0.110 g, 55%). IR cm^{-1}: 3408 (N–H), 3051 (C–H arom.), 2959–2926 (C–H aldehyde), 1717 (C=O), 1372 (sym) and 1457 (asym) (CH_3). ^{1}H NMR (DMSO-d_6): 1.40 (d, 3H, CH_3, $J = 7.2$), 2.98 and 3.45 (m, 2H, H-1′), 3.16 (m, 1H, H-2′), 6.90 (m, 3H, H-2, H-5 and H-7), 7.00 (m, 2H, H-4 and H-6), 8.02 (s, 1H, NH). 9.50 (s, 1H, H–C=O). ^{13}C NMR (DMSO-d_6): 13.8, 31.7, 46.9, 111.2, 118.7, 119.5, 122.1, 122.4, 136.2, 205.5.

General procedure for the preparation of indolylbenzimidazoles 14a,b, 15a,b, and 16a,b

*2-{1-(1H-Indol-3-yl)propan-2-yl}-1H-benzo[d]imidazole (**14a**)*

A mixture of 3-(1*H*-indol-3-yl)-2-methylpropanal (**13a**) (0.220 g, 1.17 mmol) and *o*-phenylenediamine (0.127 g, 1.17 mmol) was stirred in ethanol (50 mL) for 24 h under reflux. The solvent was evaporated *in vacuo* to give an oily crude, which was purified by column chromatography (hexane/AcOEt 1:2) to produce pure **14a** in 42% yield as a pale brown oil. IR cm^{-1}: 3420 (N–H), 3055 (C–H arom.), 2930–2890 (C–H aliph.), 1495 (C=C). ^{1}H NMR (DMSO-d_6): 1.44 (d, 3H, CH_3, $J = 6.7$), 2.83–3.12 (m, 2H, H-1′), 3.33 (m, 1H, H-2′), 6.90–7.28 (m, 5H, H-2, H-4, H-5, H-6 and H-7), 7.30–7.44 (m, 4H, H-3″, H-4″, H-5″ and H-6″), 9.77 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 18.3 (CH_3), 30.2 (CH_2, C-2′), 35.5 (CH_2, C-1′), 110.2, 112.4, 113.9, 114.0, 118.9, 120.7, 120.8, 121.2, 122.7, 122.8, 127.5, 135.8, 136.1, 136.8, 160.5 (C=N). Anal. calcd. for $C_{18}H_{17}N_3$: C, 78.52; H, 6.22; N, 15.26; Found: C, 78.48; H, 6.34; N, 15.32.

*2-(1-(5-Fluoro-1H-indol-3-yl)propan-2-yl)-1H-benzo[d]-imidazole (**14b**)*

Prepared from 3-(5-fluoro-1*H*-indol-3-yl)-2-methylpropanal (**13b**) (0.380 g, 0.203 mmol) and *o*-phenylenediamine (0.220 g, 0.200 mmol) in ethanol. The crude was purified by column chromatography (hexane/AcOEt 1:2), 30% yield, oil. IR cm^{-1}: 3418 (N–H), 3056 (C–H arom.), 2932–2891 (C–H aliph.), 1492 (C=C). ^{1}H NMR (DMSO-d_6): 1.45 (d, 3H, CH_3, $J = 6.8$), 2.84–3.04 (m, 2H, H-1′), 3.32 (m, 1H, H-2′), 6.92–7.30 (m, 4H, H-2, H-4, H-5 and H-7), 7.31–7.45 (m, 4H, H-3″, H-4″, H-5″ and H-6″), 9.80 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 18.5 (CH_3), 30.3 (CH_2, C-2′), 35.5 (CH_2, C-1′), 108.2, 108.3, 110.4, 110.8, 112.5, 112.7 113.8, 113.9, 114.0, 118.9, 120.7, 112.5, 122.9, 130.8, 130.9, 135.9, 136.8, 136.9, 147.7, 154.2, 160.5 (C=N). Anal. calcd. for $C_{18}H_{16}FN_3$: C, 73.70; H, 5.50; N, 14.32; Found: C, 73.88; H, 5.55; N, 14.40.

*2-(1-(1H-Indol-3-yl)propan-2-yl)-5-chloro-1H-benzo[d]-imidazole (**15a**)*

Prepared from 3-(1*H*-indol-3-yl)-2-methylpropanal **13a** (0.420 g, 2.25 mmol) and 4-chloro-*o*-phenylenediamine (0.320 g, 2.25 mmol) in ethanol. The crude was purified by column chromatography (hexane/AcOEt 1:1), 15% yield, oil. IR cm^{-1}: 3415 (N–H), 3050 (C–H arom.), 2973–2870 (C–H aliph.), 1488 (C=C). ^{1}H NMR (DMSO-d_6): 1.45 (d, 3H, CH_3, $J = 6.7$), 2.80–3.05 (m, 2H, H-1′), 3.35 (m, 1H, H-2′), 6.78–7.30 (m, 5H, H-2, H-4, H-5, H-6 and H-7), 7.36–7.45 (m, 3H, H-3″, H-4″ and H-5″), 9.80 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 18.9 (CH_3), 31.5 (CH_2, C-2′), 36.0 (CH_2, C-1′), 113.2, 116.6, 118.9, 120.9, 122.7, 126.5, 128.4, 128.5, 135.9, 136.1, 136.8, 161.8 (C=N). Anal. calcd. for $C_{18}H_{16}ClN_3$: C, 69.79; H, 5.21; N, 13.56; Found: C, 70.01; H, 5.24; N, 13.60.

*2-(1-(5-Fluoro-1H-indol-3-yl)propan-2-yl)-5-chloro-1H-benzo[d]imidazole (**15b**)*

Prepared from 3-(5-fluoro-1*H*-indol-3-yl)-2-methylpropanal **13b** (0.300 g, 1.46 mmol) and 4-chloro-*o*-phenylenediamine (0.210 g, 1.47 mmol) in ethanol. The crude was purified by column chromatography (hexane/AcOEt 2:1), 18% yield, oil. IR cm^{-1}: 3413 (N–H), 3052 (C–H arom.), 2979–2889 (C–H aliph.), 1495 (C=C). ^{1}H NMR (DMSO-d_6): 1.48 (d, 3H, CH_3, $J = 7.0$), 2.85–3.02 (m, 2H, H-1′), 3.34 (m, 1H, H-2′), 6.82–7.29 (m, 3H, H-2, H-4, H-5 and H-7), 7.31–7.45 (m, 3H, H-3″, H-4″ and H-6″), 9.98 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 19.1 (CH_3), 29.8 (CH_2, C-2′), 36.2 (CH_2, C-1′), 109.2, 109.3, 110.8, 111.0, 112.5, 112.7 113.5, 113.9, 114.0, 116.9, 120.7, 112.5, 122.9, 130.5, 130.9, 135.9, 136.8, 136.9, 148.5, 154.6, 161.5 (C=N). Anal. calcd. for $C_{18}H_{15}ClFN_3$: C, 65.96; H, 4.61; N, 12.82; Found: C, 66.06; H, 4.65; N, 12.80.

*2-(1-(1H-Indol-3-yl)propan-2-yl)-6-nitro-1H-benzo[d]-imidazole (**16a**)*

Prepared from 3-(1*H*-indol-3-yl)-2-methylpropanal (**13a**) (0.500 g, 2.75 mmol) and 4-nitro-*o*-phenylenediamine (0.420 g, 2.75 mmol) in ethanol. The crude was purified by column chromatography (hexane/AcOEt (2:1), 18% yield, oil. IR cm^{-1}: 3450 (N–H), 3058 (C–H arom.), 2937–2865 (C–H aliph.), 1532 (NO_2 asym), 1360 (NO_2 sym), 1452 (C=C). ^{1}H NMR (DMSO-d_6): 1.46 (d, 3H, CH_3, $J = 6.9$), 2.83–3.12 (m, 2H, H-1′), 3.38 (m, 1H, H-2′), 6.70–7.30 (m, 5H, H-2, H-4, H-5, H-6 and H-7), 7.50 (d, 1H, H-3″, $J = 7.5$), 7.71 (dd, 1H, H-4″, $J = 7.8$), 8.43 (s, 1H, H-6″), 9.85 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 19.2 (CH_3), 31.8 (CH_2, C-2′), 35.9 (CH_2, C-1′), 111.2, 112.5, 116.6, 118.8, 118.9, 120.9, 122.7, 126.5, 128.4, 128.5, 135.9, 136.1, 136.8, 144.5, 161.8 (C=N). Anal. calcd. for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49; Found: C, 67.54; H, 4.99; N, 17.54.

*2-(1-(5-Fluoro-1H-indol-3-yl)propan-2-yl)-6-nitro-1H-benzo[d]imidazole (**16b**)*

Prepared from 3-(5-fluoro-1*H*-indol-3-yl)-2-methylpropanal **13b** (0.250 g, 1.22 mmol) and 4-nitro-*o*-phenylenediamine (0.190 g, 1.23 mmol) in ethanol. The crude was purified by column chromatography (hexane/AcOEt 1:1), 14% yield, oil. 3448 (N–H), 3056 (C–H arom.), 2939–2896 (C–H aliph.), 1528 (NO_2 asym), 1358 (NO_2 sym), 1452 (C=C). ^{1}H NMR (DMSO-d_6): 1.49 (d, 3H, CH_3, $J = 6.9$), 2.84–3.12 (m, 2H, H-1′), 3.36 (m, 1H, H-2′), 6.86–7.32 (m, 3H, H-2, H-4, H-5 and H-7), 7.52 (d, 1H, H-3″, $J = 7.2$), 7.75 (dd, 1H, H-4″, $J = 7.4$), 8.48 (s, 1H, H-6″) 9.87 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 18.7 (CH_3), 30.3 (CH_2, C-2′), 35.9 (CH_2, C-1′), 108.2, 108.3, 111.8, 111.9, 112.5, 112.6, 113.5, 113.6, 120.7, 122.5, 122.9, 130.5, 130.9, 135.9, 136.8, 136.9, 144.8, 147.9, 154.6, 161.8 (C=N). Anal. calcd. for $C_{18}H_{15}FN_4O_2$: C, 63.90; H, 4.47; N, 16.56; Found: C, 64.02; H, 4.42; N, 16.56.

Pharmacological assays

Binding experiments for SERT was determined using [^{3}H]-paroxetine as radioligand and the clonal cell line HEK-293 that

overexpresses SERT (PerkinElmer). Briefly, assays were carried out in a total volume of 0.5 mL, containing 50 mM Tris–HCl buffer, pH 7.4, 120 mM NaCl, 5 mM KCl, membrane solution (100 μL; 9.0 μg/per tube assay) and (50 μL, 2 nM) of [^{3}H]paroxetine and the compound to be tested at different concentrations (10^{-9}–10^{-4} M). After 30 min at 27°C, incubations were terminated by rapid filtration, with two 5-mL washes of buffer, through Whatman GF/C filters that were presoaked with buffer containing 0.01% of polyethyleneimine, using a cell harvester (Brandel Instruments, Gaithersburg, MD). Radioactivity was counted in a Packard 1300 liquid scintillation counter with an efficiency of approximately 50%. Nonspecific binding for [^{3}H]paroxetine was defined in the presence of 0.1 mM of naphthyl-isopropylamine hydrochloride.

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