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# Synthesis and molecular docking of indole and carbazole derivatives with potential pharmacological activity

**Abstract:** Indole and carbazole derivatives were designed as non-competitive antagonists of the GluK2 receptor. The synthesized compounds were found to interact with the transduction domain of the receptor. The binding pocket is situated within one receptor subunit.

**Keywords:** carbazole derivatives; GluK2 receptor; indole derivatives; kainate receptors.

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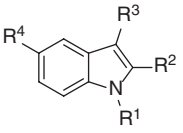
## Introduction

The indole system is an important component of many natural biologically active compounds including tryptophan, serotonin and melatonin, and synthetic drugs, such as fluvastatin, indomethacin, indapamide, indoramin, pindolol, sumatriptan, and tropisetron. Many known indole derivatives exhibit anticancer [1], antipsychotic, analgesic, and antiviral activity [2, 3]. Some indole derivatives act on ionotropic glutamate receptors [4–6]. Carbazole derivatives are also known for their pharmacological activities, including anti-HIV, anticancer, antibacterial, and antifungal properties [7].

Ionotropic glutamate receptors are interesting drug targets for pharmacological intervention. Ligands of kainate receptors are especially interesting because antagonists of these receptors are potential antiseizure and neuroprotective agents. They are usually well tolerated, similar to non-competitive antagonists of AMPA receptors [8]. The study of non-competitive antagonists of kainate receptors is difficult due to the fact that only three series of such compounds have been reported to date [9–11]. We have synthesized and studied 2,3,5-trisubstituted and 1,2,3,5-tetrasubstituted indole derivatives **1**–**7**, which belong to most active non-competitive antagonists of the GluK1 receptor and are the first known such ligands of the GluK2 receptor (Figure 1) [11–13]. We have also suggested a binding site for these in the receptor transduction domain [12, 13] owing to the construction of whole receptor models [12–14]. Here, we present further modifications of structures **8–14** of the lead compound E099-25011




**1**: $R^1$ = Et, $R^2$ = 4-OMePh, $R^3$ = Me, $R^4$ = OMe
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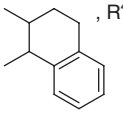
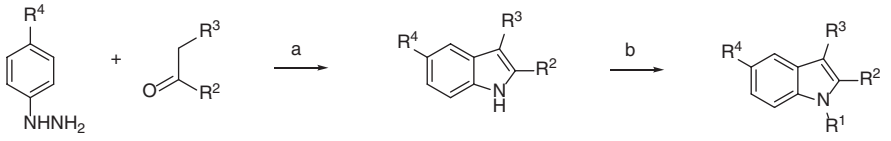
**3**: $R^1$ = 4-ClBn, $R^2$ = 4-OMePh, $R^3$ = Me, $R^4$ = OMe
**4**: $R^1$ = Et, $R^2$ = Ph, $R^3$ = H, $R^4$ = OMe
**5**: $R^1$ = Et, $R^2$ = 4-OMePh, $R^3$ = Me, $R^4$ = H
**6**: $R^1$ = Et, $R^2$ = Ph, $R^3$ = Me, $R^4$ = OMe
**7**: $R^1$ = Et, $R^2$, $R^3$ =  , $R^4$ = OMe

**Figure 1** The previously obtained indole-derived non-competitive antagonists of the GluK2 receptor.

(**1**). Its full systematic name is 1-ethyl-5-methoxy-2-(4-methoxyphenyl)-3-methylindole. The lead compound **1** was selected based on a search of internal databases of compounds in Elbion Institute, Radebul, Germany. This compound is an analog of zindoxifene, an antiestrogen, tumor-inhibiting agent [15]. We have previously optimized compound **1** varying substituents in the indole system [10]. The rationale towards compound **8** and **12** is bioisosteric replacement of phenyl ring with a 2-thienyl substituent. The rationale towards compound **9** and **13** is an attempt to design a derivative with the optimized interactions with the binding pocket, in particular, a bigger one and more rigid than in the previous series. We have also designed the simplified compounds **10** and **14** and the derivative **11** with a longer alkyl chain at the *N*1 atom. Furthermore, we show how these compounds may interact with the transduction domain of the previously constructed homology model of the GluK2 receptor [12].

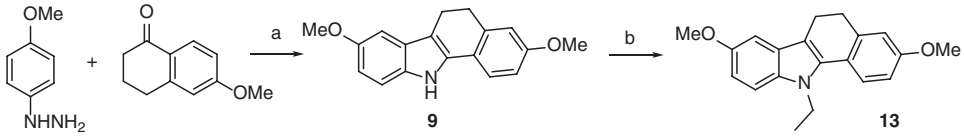



**2, 8, 10** **11, 12, 14**

a: EtOH/HCl, reflux
b: $R^1Br$ or $(R^1)_2SO_4$, NaH, DMF

**2**: $R^1$ = Et, $R^2$ = 4-OMePh, $R^3$ = Me, $R^4$ = OMe
**8**: $R^1$ = H, $R^2$ = 2-thienyl, $R^3$ = Me, $R^4$ = OMe
**10**: $R^1$ = H, $R^2$ = Et, $R^3$ = Me, $R^4$ = OMe
**11**: $R^1$ = Pr, $R^2$ = 4-OMePh, $R^3$ = Me, $R^4$ = OMe
**12**: $R^1$ = Et, $R^2$ = 2-thienyl, $R^3$ = Me, $R^4$ = OMe
**14**: $R^1$ = Et, $R^2$ = Et, $R^3$ = Me, $R^4$ = OMe

**Scheme 1**




**9** **13**

a: EtOH/HCl, reflux
b: EtBr, NaH, DMF

**Scheme 2**

**Table 1** Structural parameters of indole derivatives.

| Compound | Surface (Å²) | Ovality | Volume (Å³) | Dipole moment, D | | | |
|---|---|---|---|---|---|---|---|
| | | | | Total | Components | | |
| | | | | | μx | μy | μz |
| **1** | 343.73 | 1.6637 | 324.86 | 3.97 | -1.99 | 3.01 | -1.65 |
| **11** | 360.60 | 1.7081 | 342.99 | 3.96 | -1.87 | 2.55 | -2.37 |
| **12** | 304.98 | 1.5973 | 285.59 | 2.80 | -1.31 | 2.46 | -0.30 |
| **13** | 339.50 | 1.6325 | 329.66 | 4.11 | -1.30 | 3.88 | -0.48 |
| **14** | 271.50 | 1.5625 | 251.16 | 3.13 | 1.91 | 2.46 | 0.29 |

**Table 2** Electronic parameters of indole derivatives.

| Compound | $E_{LUMO}$ (kJ/mol) | $E_{HOMO}$ (kJ/mol) | Charges | | | | |
|---|---|---|---|---|---|---|---|
| | | | N | O/C2 | O/C5 | S | Cl |
| **1** | 335.30 | -695.28 | -0.271 | -0.455 | -0.447 | – | – |
| **11** | 332.97 | -695.48 | -0.036 | -0.458 | -0.450 | – | – |
| **12** | 300.76 | -705.94 | -0.272 | – | -0.459 | -0.011 | – |
| **13** | 278.66 | -664.30 | -0.196 | -0.457 | -0.454 | – | – |
| **14** | 358.05 | -694.67 | -0.162 | – | -0.462 | – | – |

# Results and discussion

## Chemistry

Synthesis of compounds **8**–**14** is presented in Schemes 1 and 2. Compounds **2** and **8–10** were obtained by Fischer indolization reaction. Alkylation was performed with dipropyl sulfate to obtain compound **11** or ethyl bromide to obtain compounds **12**–**14**. The lead compound **1** and derivatives **2, 8–10**, and **13** were previously characterized as antiestrogens [16–19]. Compounds **12** and **14** are new. We have previously determined that compounds **1** and **2** are non-competitive antagonists of the GluK2 receptor. The $IC_{50}$ value of both compounds is in a micromolar range of 0.7 μM and 2.5 μM for **1** and **2**, respectively [11]. Thus, we also hypothesize that compounds **11**–**14** have similar pharmacological activity.

Structural and electronic parameters for compounds **1** and **11**–**14** are presented in Tables 1 and 2, respectively. The data compared to our earlier studies [11] confirm favorable properties of the investigated compounds. All compounds are relatively polar and have comparable size to a slightly smaller compound **14** (Table 1). The distribution of electrostatic potential in the studied derivatives reveals the high electron density on oxygen atoms, with nearly identical values in all ligands. The values of atomic charges on the nitrogen atoms vary more: from -0.271 for the lead compound **1** to -0.036 for compound **11** (Table 2). The significant difference between HOMO and LUMO values (Table 2) indicates that the compounds are nucleophilic and may participate as acceptors (through oxygen atoms) in hydrogen bonds with the binding pocket residues, which is in agreement with our earlier studies [11–13].

## Ligand-receptor interactions

The binding site for non-competitive GluK2 receptor antagonists was identified in the receptor transduction domain, that is, in the site which connects the ligand-binding domain and the transmembrane domain (Figure 2) [20]. The interactions of compounds **11**, **12**, and **13** with the GluK2 receptor are presented in Figure 3A–F, respectively. The methoxy group at C5 of compound **11** forms a hydrogen bond with the main chain of Gly756. In the case of compound **13**, one methoxy group is involved in the hydrogen bond with the main chain of Leu755. Other residues present in the binding pocket are also shown in Figure 3. The ligand-receptor complexes were found to be stable in the short molecular dynamics run.

# Conclusions

Indole and carbazole derivatives, which are potential non-competitive antagonists of the GluK2 receptor, were synthesized and characterized. Molecular docking and molecular dynamics of the ligand-receptor complexes are consistent with the location of the binding site in the receptor transduction domain within one receptor subunit. The synthesized compounds are potential prototypic new drugs for the treatment of diseases with unbalanced glutamatergic transmission, such as neurodegenerative diseases (Parkinson's disease, Alzheimer's disease, Huntington's disease) and epilepsy. It should be noted that the assumed non-competitive method of receptor blocking is favorable for the drug profile and may reduce side effects.

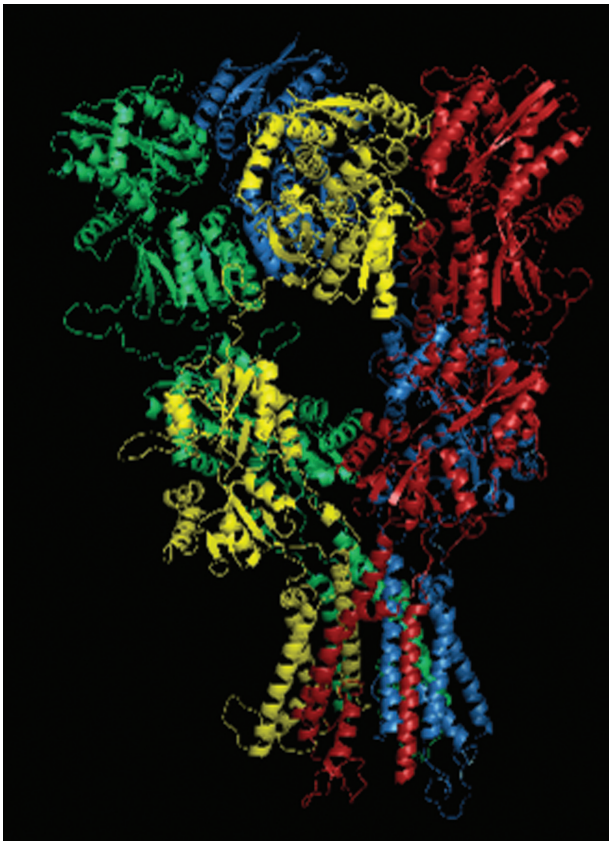


**Figure 2** Model of the GluK2 receptor [12].

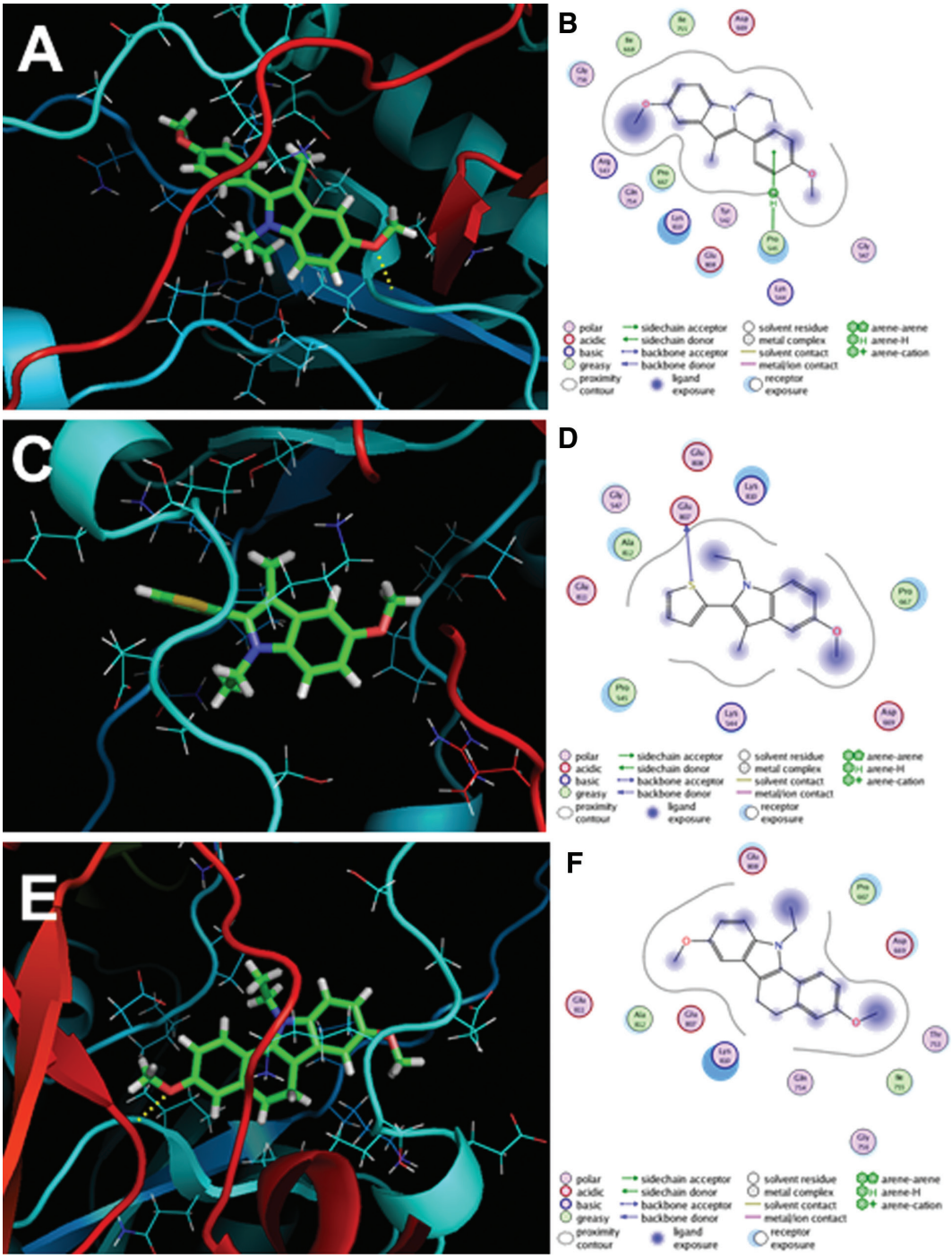



**Figure 3** Interactions of compounds **11** (A, B), **12** (C, D), and **13** (E, F) with the binding pocket of the GluK2 receptor.

# Experimental

## Chemistry

NMR spectra were recorded on a Bruker Avance 500 (500 MHz for $^{1}$H NMR and 125 MHz for $^{13}$C NMR) fitted with a BBO Z gradient probe. $CDCl_3$ was used as a solvent at 25°C with non-spinning sample and TMS as the internal standard. During acquisition, single-pulse excitation and a 30° flip angle were employed. Recorded spectra were processed utilizing Bruker XWin NMR software applying 1 Hz exponential weighing for $^{13}$C proton-decoupled spectra. The originally installed Bruker cosygpmfqf pulse program was used for gradient selected DQF-COSY spectra, as was noesygpph for gradient selected NOESY spectra, hsqcetgpsisp.2 for $^{1}$H-$^{13}$C HSQC spectra and hmbcgplpndqf for $^{1}$H-$^{13}$C HMBC. The electron ionization (EI) mass spectra were acquired on a VG ZABSpec mass spectrometer (VG Analytical, Division of Fisons, Manchester, UK) with the Opus

V3.3X program package (Fisons Instruments, Manchester, UK) installed.

## General procedure for synthesis of 2 and 8–10

Ethanol (10 mL) saturated with HCl was added to a mixture of 0.05 mol of ketone and 0.05 mol of arylhydrazine hydrochloride in 100 mL of anhydrous ethanol. The mixture was stirred under mild reflux for 4 h. After cooling, the mixture was left overnight and the resulting precipitate was filtered and crystallized from ethanol followed by repeated washing with *n*-hexane. The obtained product was kept in the dark in a fridge due to its tendency to photooxidation.

**5-Methoxy-2-(4-methoxyphenyl)-3-methylindole (2)** Compound **2** was obtained in 79% yield as colorless crystalline needles; mp 148–150°C; spectral characteristics are given in [11].

**5-Methoxy-3-methyl-2-(2-thienyl)indole (8)** Compound **8** was obtained in 69% yield as colorless crystalline needles; mp 100–102°C; $^1$H NMR: δ 10.82 (s, 1H), 7.47 (dd, 1H, *J* = 1.2 Hz and 5.3 Hz), 7.25 (d, 1H, *J* = 8.8 Hz), 7.19 (dd, 1H, *J* = 3.6 Hz and 5.3 Hz), 7.11 (dd, 1H, *J* = 1.2 Hz and 3.6 Hz), 7.04 (d, 1H, *J* = 2.4 Hz), 6.93 (dd, 1H, *J* = 2.4 Hz and 8.8 Hz), 3.78 (s, 3H), 2.29 (s, 3H); $^{13}$C NMR: δ 157.1, 140.3, 132.5, 117.4, 111.9, 83.0, 78.3, 78.2, 76.1, 67.8, 67.5, 54.0, 36.0, 9.4; HR-MS. Calcd for $C_{14}H_{13}NOS$: m/z 243.3282; found: m/z 243.3278. Anal. Calcd for $C_{14}H_{13}NOS$: C, 69.10; H, 5.38; N, 5.76; S, 13.18. Found: C, 69.16; H, 5.42; N, 5.74; S, 13.14. $R_F$ A, 0.400; B, 0.457.

**3,8-Dimethoxy-5,6-dihydronaphto[1,2-*b*]indole (9)** Compound **9** was obtained in 62% yield as colorless crystalline needles; mp 195–198°C; $^1$H NMR: δ 8.03 (br, s, 1H), 7.25 (d, 1H, *J* = 8.8 Hz), 7.25 (d, 1H, *J* = 8.5 Hz), 6.97 (d, 1H, *J* = 2.4 Hz), 6.80 (dd, 1H, $J_1$ = 2.3 Hz, $J_2$ = 8.5 Hz), 6.79 (dd, 1H, $J_1$ = 2.4 Hz, $J_2$ = 8.8 Hz), 3.87 (s, 3H), 3.85 (s, 3H), 3.04 (br, t, 2H, *J* = 7.5 Hz), 2.93 (br, t, 2H, *J* = 7.5 Hz); $^{13}$C NMR: δ 158.6, 154.3, 138.4, 134.1, 131.9, 128.0, 122.1, 120.9, 114.8, 111.6, 111.6, 111.4, 110.7, 100.4, 55.9, 55.3, 30.0, 19.7. HR-MS. Calcd for $C_{18}H_{17}NO_2$: m/z 279.1259; found: m/z 279.1258. Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 5.84; N, 5.01. Found: C, 77.49; H, 5.82; N, 5.04. $R_F$ A, 0.345; B, 0.228.

**2-Ethyl-5-methoxy-3-methylindole (10)** Compound **10** was obtained in 59% yield as colorless crystalline needles; mp 70–72°C. $^1$H NMR: δ 10.75 (s, 1H), 7.08 (d, 1H, *J* = 8.8 Hz), 6.84 (d, 1H, *J* = 2.4 Hz), 6.58 (dd, 1H, $J_1$ = 2.4 Hz, $J_2$ = 8.8 Hz), 3.76 (s, 1H), 2.64 (q, 1H, *J* = 7.2 Hz), 2.29 (s, 1H), 1.41 (t, 1H, *J* = 7.2 Hz); $^{13}$C NMR: δ 151.4, 135.8, 130.3, 102.5, 98.9, 97.4, 88.3, 81.8, 79.3, 66.7, 62.9, 35.9. HR-MS: Calcd for $C_{12}H_{15}NO$: m/z 189.2584; found: m/z 189.2580. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.21; H, 7.95; N, 7.44. $R_F$ A, 0.266; B, 0.239.

**5-Methoxy-2-(4-methoxyphenyl)-3-methyl-1-propylindole (11)** A chilled mixture of 0.4 g of sodium hydride as a 50% oil suspension in 10 mL of anhydrous DMF was treated dropwise with a solution of **2** (1 mmol) in 10 mL of anhydrous DMF. The mixture was stirred at 0°C for 45 min, followed by addition of 1 mmol of alkyl sulfate in 5 mL of anhydrous DMF. After 20 min, the ice bath was removed and stirring was continued for an additional 1.5 h at room temperature. After addition of water (2 mL) the mixture was filtered. The filtrate was cooled and combined with 20 mL of water. The resultant precipitate was filtered and crystallized from ethanol. Product **11** was washed several times with *n*-hexane.

Derivative **11** was obtained in 71% yield as colorless needles; mp 104–106°C; $^1$H NMR: δ 7.29 (d, 1H, *J* = 8 Hz), 7.23 (d, 1H, *J* = 8 Hz), 7.02 (d, 1H, *J* = 2 Hz), 7.01 (d, 1H, *J* = 8 Hz), 6.87 (dd, 2H, $J_1$ = 2 Hz, $J_2$ = 8 Hz), 3.93 (m, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 2.19 (s, 3H), 1.61 (m, 4H), 0.73 (t, 3H, *J* = 7 Hz); $^{13}$C NMR: δ 159.2, 153.8, 138.1, 131.7, 131.5, 128.7, 124.9, 113.8, 111.3, 110.4, 108.0, 100.7, 56.0, 55.3, 45.6, 23.4, 11.4, 9.3. HR-MS. Calcd for $C_{20}H_{23}NO_2$: m/z 309.1729; found: m/z 309.1728. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.68; H, 7.45; N, 4.56. $R_F$ A, 0.600; B, 0.429.

## General procedure for synthesis of 12–14

A solution of indole derivative **8**–**10** (0.01 mol) in anhydrous DMF (30 mL) and cooled to 0°C and treated with sodium hydride (0.8 g) as a 50% oil suspension. The mixture was stirred for 30 min at 0°C and then treated dropwise with a solution of alkyl halide (0.012 mol) in anhydrous DMF (20 mL) and stirred at room temperature for an additional 3 h. Then it was filtered and 10–15 mL of water was added to the filtrate. Resin-like substance separated and an additional 25–30 mL of water was added until a solution was formed. After storing for 2 h in a refrigerator, the resulting precipitate was filtered, crystallized from ethanol, and washed with *n*-hexane.

**1-Ethyl-5-methoxy-3-methyl-2-(2-thienyl)indole (12)** Compound **12** was obtained in 77% yield as colorless needles; mp 92–94°C; $^1$H NMR: δ 7.46 (dd, 1H, $J_1$ = 1.2 Hz, $J_2$ = 5.3 Hz), 7.23 (d, 1H, *J* = 8.8 Hz), 7.17 (dd, 1H, $J_1$ = 3.6 Hz, $J_2$ = 5.3 Hz), 7.09 (dd, 1H, $J_1$ = 1.2 Hz, $J_2$ = 3.6 Hz), 7.02 (d, 1H, *J* = 2.4 Hz), 6.91 (dd, 1H, $J_1$ = 2.4 Hz, $J_2$ = 8.8 Hz), 4.11 (q, 2H, *J* = 7.1 Hz), 3.88 (s, 3H), 2.28 (s, 3H), 1.27 (t, 3H, *J* = 7.1 Hz); $^{13}$C NMR: δ 153.9, 132.9, 131.5, 129.9, 128.7, 128.4, 127.2, 126.9, 112.5, 110.8, 110.3, 100.8, 56.0, 38.8, 15.7, 9.6. HR-MS. Calcd for $C_{16}H_{17}NOS$: m/z 271.1031; found: m/z 271.1033. Anal. Calcd for $C_{16}H_{17}NOS$: C, 70.81; H, 6.31; N, 5.16; S, 11.81. Found: C, 70.75; H, 6.28; N, 5.18; S, 11.85. $R_F$ A, 0.595; B, 0.675.

**11-Ethyl-3,8-dimethoxy-5,6-dihydronaphto[1,2-*b*]indole (13)** Derivative **13** was obtained in 60% yield as a colorless crystalline (needles) solid, mp 185–187°C; $^1$H NMR: δ 7.45 (d, 1H, *J* = 8.5 Hz), 7.24 (d, 1H, *J* = 8.8 Hz), 6.99 (d, 1H, *J* = 7.4 Hz), 6.91 (d, 1H, *J* = 2.6 Hz), 6.85 (dd, 1H, $J_1$ = 2.4 Hz, $J_2$ = 8.8 Hz), 6.83 (dd, 1H, $J_1$ = 2.6 Hz, $J_2$ = 8.5 Hz), 4.38 (q, 2H, *J* = 7.2 Hz), 3.87 (s, 3H), 3.85 (s, 3H), 2.94 (m, 2H), 2.86 (m, 2H), 1.51 (t, 3H, *J* = 7.2 Hz); $^{13}$C NMR: δ 158.0, 154.1, 140.3, 134.8, 133.3, 126.5, 123.1, 122.7, 115.1, 111.8, 111.5, 111.3, 110.0, 100.3, 55.9, 55.3, 39.7, 31.3, 20.1, 15.7. HR-MS. Calcd for $C_{20}H_{21}NO_2$: m/z 307.1572; found: m/z 307.1582. Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56. Found: C, 78.10; H, 6.85; N, 4.61. $R_F$ A, 0.470; B, 0.443.

**1,2-Diethyl-5-methoxy-3-methylindole (14)** Compound **14** was obtained in 33% yield as colorless needles; mp 50–53°C; $^1$H NMR: δ 7.05 (d, 1H, *J* = 8.8 Hz), 6.81 (d, 1H, *J* = 2.4 Hz), 6.53 (dd, 1H, $J_1$ = 2.4 Hz, $J_2$ = 8.8 Hz), 4.01 (q, 2H, *J* = 7 Hz), 3.70 (s, 3H), 2.61 (q, 2H, *J* = 7 Hz), 2.24 (s, 3H), 1.42 (t, 3H, *J* = 7 Hz), 1.15 (t, 3H, *J* = 7 Hz); $^{13}$C NMR: δ 160.9, 156.9, 149.3, 149.3, 136.0, 107.5, 77.0, 73.7, 59.5, 49.6, 49.3, 43.7, 33.1, 22.7. HR-MS. Calcd for $C_{14}H_{19}NO$: m/z 217.3122; found: m/z 217.3123. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.44. Found: C, 77.32; H, 8.85; N, 6.49. $R_F$ A, 0.318; B, 0.287.

## Molecular modeling

A homology model of the GluK2 receptor was constructed, as described previously [12]. Input conformations of the studied compounds were obtained by applying the LigPrep protocol from the Schrödinger Suite. To sample different protonation states of ligands in physiological pH, the Epik module was used. Structural and electronic parameters of the ligands were calculated with VegaZZ v.2.4.0.25 [21], Gausian09 [22], and Discovery Studio 3.1. Molecular docking was performed with Glide from the Schrödinger Suite. Molecular dynamics of ligand-receptor complexes in POPC lipid bilayer was performed with Desmond v. 3.0.3.1 [23], as described previously [12]. The following software was also used for visualization of the results: Chimera v.1.5.3 [24], VegaZZ v.2.4.0.25, Yasara Structure v.11.9.18 [25], and PyMol v.0.99 [26].

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