J. Chem. Sci. (2019) 131:45
https://doi.org/10.1007/s12039-019-1621-x

REGULAR ARTICLE

Design, synthesis, and molecular docking of new 5-HT reuptake inhibitors based on modified 1,2-dihydrocyclopenta[b] indol-3(4H)-one scaffold

MILENA SZEWCZYK, PAWEŁ PUNDA, KAROLINA JANIKOWSKA and SŁAWOMIR MAKOWIEC*

Department of Organic Chemistry, Faculty of Chemistry, Gdańsk University of Technology, Narutowicza 11/12, 80-233 Gdańsk, Poland
E-mail: mak@pg.edu.pl

MS received 17 September 2018; revised 22 November 2018; accepted 18 March 2019; published online 14 May 2019

Abstract. A new group of serotonin reuptake inhibitors containing 1,2-dihydrocyclopenta[b]indol-3(4H)-one scaffold was synthesized, starting from indole 5-((1H-indol-3-yl)(1,3-dioxane-4,6-diones as a key intermediates. Following three transformations including intramolecular cyclization and formation of imines, a series of new ligand for human serotonin transporter was obtained. The ability of these ligands to inhibit human TS3 serotonin transporter as well as selectivity toward human D3 dopamine receptor and dopamine transporter were tested in silico using docking software.

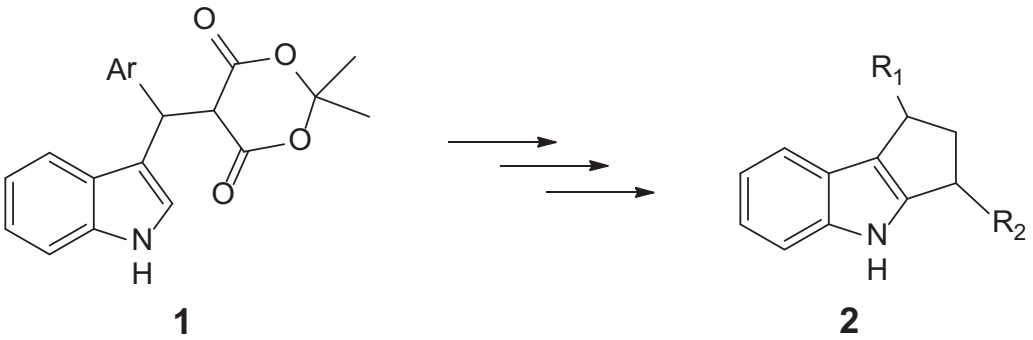
Keywords. Meldrum's acid; cyclization; 5-HT; SSRI.

1. Introduction

Molecules containing indole motif are often biologically active species such as: anti-inflammatory agents,[1–5] phytohormones,[6,7] anticancer medication,[8–10] or treatment for human papillomavirus disease.[11] One of the most important neurotransmitters - serotonin is an indole derivative.[12,13] Probably the most well-known uses of compounds containing the indole structure is the modulation of serotonergic receptors or serotonin transporters.[14–16] Pharmacological treatment of mental illnesses such as mood or anxiety disorders is associated mainly with manipulating the serotonin level in the central nervous system. Thus, design and synthesis of molecules targeted at serotonin receptors and/or serotonin transporters are still in the focus of medicinal chemistry. The invention[17] and introduction of fluoxetine[18] have revolutionized the treatment of depressive disorders. This is one of the most popular antidepressants; together with other selective serotonin reuptake inhibitors (SSRIs) such as sertraline, paroxetine, citalopram it is invaluable in the treatment of mental disorders for the vast majority of patients.[19] However, there still exists a large group of patients with drug-resistant depression.[20] Moreover, most of the currently used antidepressants are not completely devoid of side effects. Examples of less dangerous side effects are sleep disorders, dermatological problems, and sexual function. The most disturbing is the impact on the suicidal tendency during the initial stage of therapy, especially in the under-25 age group.[21,22] Therefore, the search for new substances that modulate serotonin levels in the central nervous system (CNS), particularly targeted as (SSRIs) is still an ongoing topic of interest in research. Among the various groups of chemical compounds exhibiting affinity for serotonin receptors or transporters, our attention was drawn to carbazole derivatives. This rigid molecule contains an indole moiety and is conductive to derivatization. SmithKline Beecham has obtained a series of patents for the synthesis and application of tetrahydrocarbazoles[23,24] as 5-HT agonists. They focused the investigation on an indole moiety fused with a six-membered saturated ring-functionalized with an amine group in position 3. In contrast, in our work, we have focused on derivatives with smaller rings. We planned

*For correspondence

Electronic supplementary material: The online version of this article (https://doi.org/10.1007/s12039-019-1621-x) contains supplementary material, which is available to authorized users.



Scheme 1. Approach to preparation of target 1,2,3,4-tetrahydrocyclopenta[b]indole.

to use 2,2-dimethyl-5-(aryl(1H-indol-3-yl)methyl)-1,3-dioxane-4,6-diones (**1**) as a starting material; however, due to a reactive and thermally labile dioxanedione ring, it may be a source of ketenes. This multipurpose reagent is conducive to preparing our target molecule with 1,2,3,4-tetrahydrocyclopenta[b]indole (**2**) substituted in 1 and 3 positions (Scheme 1).

2. Experimental

2.1 *Materials and reagents*

Commercially available reagents were purchased from Sigma-Aldrich. Sodium triacetoxyborohydride was of 97%, polyphosphoric acid was of reagent grade, indole was of 99%, all other chemicals were of 98% and solvents were of analytical grade. Analytical TLC was performed on aluminum sheets of silica gel UV-254 Merck and visualized with UV lamp at 254 nm. Flash chromatography was performed using 40–63 microns of Zeochem silica gel. The ^{1}H, ^{13}C were recorded on Bruker Avance III HD 400 MHz, Varian Gemini 200 and Varian Unity Plus 500, chemical shifts (δ) in ppm rel. to internal Me_4Si; coupling constants J in Hz. High-resolution (HRMS) was recorded on Agilent 6540 Q-TOF.

2.2 *General procedure for preparation of 5-((1H-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**6a**–**d**)*

According to original procedure.[25] To a stirred mixture of Meldrum's acid 1.44 g (10 mmol), appropriate aryl aldehyde (10 mmol) and indole 1.17 g (10 mmol) in acetonitrile 50 mL was added. L-proline 57 mg (0.5 mmol) was also added. The mixture was stirred for 18 h at 30 °C. After completion of the reaction, the solvent was removed under reduced pressure and the residue was purified with flash chromatography, (EtOAc/Hex, 1:2).

2.2a *5-((1H-Indol-3-yl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**6a**)*[25]: Yellow oil, yield 48%, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (s, NH), 7.44–7.35 (*m*, 5 H, Ar-H); 7.30–7.17 (*m*, 4 H, Ar-H); 7.08–7.05 (*m*, 1 H, Ar-H); 5.65 (*d*, 1 H, J = 2.0, H-6); 4.31 (*d*, 1 H, J = 2.4, H-11); 1.71 (s, CH_3); 1.42 (*s*, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.8 (C-1); 164.9 (C-5); 140.0 (C-12); 136.0 (C-20); 129.3 (C-14, C-18); 128.6 (C-16); 127.4 (C-15, C-17); 127.2 (C-19); 124.4 (C-25); 122.5 (C-22); 119.9 (C-24); 119.3 (C-23); 115.2 (C-13); 111.4 (C-26); 105.4 (C-3); 52.1 (C-6); 41.9 (C-11); 28.3 (C-9); 28.2 (C-10).

2.2b *5-((1-Methyl-1H-indol-3-yl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**6b**)*[26]: Yellow oil, yield 50%, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49–7.43 (*m*, 3 H, Ar-H); 7.34–7.22 (*m*, 6 H, Ar-H); 7.10–7.07 (*m*, 1 H, Ar-H); 5.67 (*d*, 1 H, J = 2.4, H-6); 4.31 (*d*, 1 H, J = 2.4, H-11); 3.81 (*s*, NCH_3); 1.74 (*s*, CH_3); 1.45 (*s*, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.5 (C-1); 164.7 (C-5); 140.09 (C-20); 136.6 (C-12); 128.9 (C-14, C-18); 128.9 (C-22); 128.4 (C-15, C-17); 127.5 (C-19); 127.1 (C-16); 121.8 (C-25); 119.2 (C-24); 119.0 (C-23); 113.3 (C-13); 109.2 (C-26); 105.1 (C-3); 52.1 (C-6); 41.5 (C-11); 32,9 (C-27) 28.1 (C-9); 27.9 (C-10).

2.2c *5-((1H-Indol-3-yl)(4-(trifluoromethyl)phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**6c**)*: Yellow oil, yield 56%, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22 (*s*, NH); 7.55 (*s*, 4 H, Ar-H); 7.44–7.39 (*m*, 3 H, Ar-H); 7.25–7.121 (*m*, 1 H, Ar-H); 7.12–7.08 (*m*, 1 H, Ar-H); 5.73 (*d*, 1 H, J = 2.2, H-6); 4.33 (*d*, 1 H, J = 2.2, H-11); 1.78 (*s*, CH3); 1.57 (*s*, CH3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.1 (C-1); 164.3 (C-5); 144.0 (C-12); 135.8 (C-20); 129.4 (C-14, C-18); 129.2 (*q*, J^{C-F} = 32.1, C-16); 126.8 (C-19); 125.1 (*q*, J^{C-F} = 3.7, C-15,C-17); 124.1 (C-25); 124.1 (*q*, J^{C-F} = 270.3, C-27); 122.6 (C-22); 119.9 (C-24); 118.8 (C-23); 114.1 (C-13); 111.2 (C-26); 105.2 (C-3); 51.9 (C-6); 40.5 (C-11); 28.1 (C-9); 27.6 (C-10). HRMS (ESI-): m/z [M - H]$^-$ calcd for $C_{22}H_{17}F_3NO_4$: 416.1109; found: 416.1094

2.2d *5-((3-Chlorophenyl)(1H-indol-3-yl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**6d**)*[27]: Yellow oil, yield 60%, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23 (*s*, NH); 7.47–7.44

(*m*, 2 H, Ar-H); 7.40–7.37 (*m*, 2 H, Ar-H); 7.33–7.29 (*m*, 1 H, Ar-H); 7.24–7.19 (*m*, 3 H, Ar-H); 7.12–7.08 (*m*, 1 H, Ar-H); 5.66 (*d*, 1 H, J = 2.3, H-6); 4.31 (*d*, 1 H, J = 2.3, H-11); 1.76 (*s*, CH3); 1.54 (*s*, CH3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.2 (C-1); 164.4 (C-5); 142.1 (C-12); 135.7 (C-20); 134.2 (C-17); 129.5 (C-18); 129.2 (C-14); 127.4 (C-15); 127.3 (C-16); 126.8 (C-19); 124.2 (C-25); 122.5 (C-22); 119.9 (C-24); 118.8 (C-23); 114.2 (C-13); 111.2 (C-26); 105.2 (C-3); 51.9 (C-6); 40.6 (C-11); 28.2 (C-9); 27.7 (C-10).

2.3 *General procedure for preparation of 3-(1H-indol-3-yl)-3-arylpropanoic acids (**7a–d**)*

5-((1H-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**6a–d**) (1 mmol) was dissolved in mixture of DMF (10 mL) and water (1mL). Resulted solution was stirred and heated in oil bath at 100°C for 4 h. After completion of the reaction, solvent was removed under reduced pressure and the residue was dissolved in ethyl ether and extracted with $NaHCO_3$ (2x10 mL, sat. aq). Water layer was acidified with conc. aq. HCl. Resulted suspension was extracted with DCM (4x10 mL). Organic extract was dried with $MgSO_4$, filtered and solvents was removed under reduced pressure to give acid **7a–d**.

2.3a *3-(1H-Indol-3-yl)-3-phenylpropanoic acid (**7a**)*[28]: Yield 45%, ^{1}H NMR (acetone-d_6, 400 MHz): δ 10.1 (*s*, 1 H, OH); 7.98 (*s*, NH); 7.44–7.33 (*m*, 5 H, Ar-H); 7.28–7.24 (*m*,2 H, Ar-H); 7.17–7.13 (*m*, 1 H, Ar-H); 7.08–7.04 (*m*, 1 H, Ar-H); 6.94–6.90 (*m*, 1 H, Ar-H); 4.80 (*t*, 1 H, J = 7.6, H-5); 3.20 (*dd*, 1 H, J^2 = 15.5, J^3 = 7.6, H-3); 3.06 (*dd*, 1 H, J^2 = 15.5, J^3 = 7.6, H-3). ^{13}C NMR (acetone-d_6, 100 MHz): δ 172.7 (C-14); 145.1 (C-10); 137.3 (C-4); 128.4 (C-16, C-20); 128.0 (C-17, C-19); 126.3 (C-18); 121.8 (C-5); 121.7 (C-3); 121.6 (C-8); 119.2 (C-2); 118.8 (C-1); 111.5 (C-9); 111.4 (C-6); 40.9 (C-11); 39.4 (C-12). HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_{17}H_{16}NO_2$: 266.1180; found: 266.1139.

2.3b *3-(1-Methyl-1H-indol-3-yl)-3-phenylpropanoic acid (**7b**)*: Yield 60%, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.2 (*s*, 1 H, OH); 7.47–7.44 (*m*, 1 H, Ar-H); 7.38–7.34 (*m*, 2 H, Ar-H); 7.33–7.28 (*m*, 3 H, Ar-H); 7.25–7.19 (*m*, 2 H, Ar-H); 7.08–7.03 (*m*, 1 H, Ar-H); 6.93–6.91 (*m*, 1 H, Ar-H); 4.83 (*t*, 1 H, J = 7.8, H-5); 3.77(*s*, CH3); 3.22 (*dd*, 1 H, J^2 = 15.7, J^3 = 7.8, H-3); 3.09 (*dd*, 1 H, J^2 = 15.7, J^3 = 7.8, H-3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.1(C-1); 143.6 (C-6); 137.3 (C-14); 128.5 (C-8, C-12); 127.7 (C-9-C-11); 126.9 (C-13); 126.5 (C-14); 125.9 (C-10); 121.8 (C-19); 119.5 (C-18); 118.9 (C-17); 116.9 (C-7); 109.2 (C-20); 41.2 (C-3); 38.9 (C-5); 32.8 (C-21). HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_{18}H_{18}NO_2$: 280.1337; found: 280.1295.

2.3c *3-(1H-Indol-3-yl)-3-(4-(trifluoromethyl)phenyl) propanoic acid (**7c**)*: Yield 60%, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (*s*, NH); 7.56–7.53 (*m*, 2 H, Ar-H); 7.47–7.44 (*m*, 2 H, Ar-H); 7.39–7.36 (*m*, 2 H, Ar-H); 7.22–7.19 (*m*, 1 H, Ar-H); 7.10–7.04 (*m*, 2 H, Ar-H); 4.87 (*t*, 3H, J = 7.6, H-5); 3.23 (*dd*, 1 H, J^2 = 15.8, J^3 = 7.7, H-3); 3.08 (*dd*, 1 H, J^2 = 15.8, J^3 = 7.7, H-3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.9 (C-1); 147.5 (C-6); 136.5 (C-14); 128.8 (*q*, J^{C-F} = 32.1, C-10); 128.1 (C-8, C-12); 126.2 (C-13); 125.5 (*q*, J^{C-F} = 3.7, C-9, C-11); 124.2 (*q*, J^{C-F} = 270.0, C-21); 122.5 (C-16); 121.2 (C-19); 119.7 (C-18); 119.1 (C-17); 117.6 (C-7); 111.3 (C-20); 40.6 (C-3); 38.7 (C-5). HRM*S* (ESI+): m/z [M + H]$^+$ calcd for $C_{18}H_{15}F_3NO_2$: 334.1055; found: 334.1003.

2.3d *3-(3-Chlorophenyl)-3-(1H-indol-3-yl)propanoic acid (**7d**)*: Yield 58%, ^{1}H NMR (acetone-d_6, 400 MHz): δ 10.21 (*s*, 1 H, OH); 8.01 (*s*, NH); 7.51–7.39 (*m*, 5 H, Ar-H); 7.35–7.31 (*m*, 1 H, Ar-H); 7.31–7.27 (*m*, 1 H, Ar-H); 7.20–7.18 (*m*, 1 H, Ar-H); 7.10–7.06 (*m*, 1 H, Ar-H); 6.97-6.93 (*m*, 1 H, Ar-H); 4.81 (*t*, 1 H, J = 7.8, H-5); 3.21 (*dd*, 1 H, J^2 = 15.6, J^3 = 7.3, H-3); 3.10 (*dd*, 1 H, J^2 = 15.6, J^3 = 7.3, H-3). ^{13}C NMR (acetone-d_6, 100 MHz): δ 172.1 (C-1); 147.5 (C-6); 136.9 (C-14); 133.5 (C-11); 129.8 (C-12); 127.8 (C-8); 126.6 (C-13); 126.4 (C-9); 126.2 (C-10); 121.6 (C-16); 121.5 (C-19); 118.8 (C-18); 118.7 (C-17); 117.3 (C-7); 111.3 (C-20); 40.3 (C-3); 38.8 (C-5). HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_{17}H_{15}ClNO_2$: 300.0790; found: 300.0746.

2.4 *General procedure for preparation of 1-aryl-1,2-dihydrocyclopenta[b]indol-3(4H)-ones (**5a–d**)*

Solution of 3-(1H-indol-3-yl)-3-arylpropanoic acid (**7a–d**) (5 mmol) in toluene (125 mL) and polyphosphoric acid (7.5 g) was stirred and mixed at 60 °C for the time selected in the Table 2. After completion of the reaction, solvent was removed under reduced pressure and the residue was dissolved in water (150 mL) and extracted with DCM 3x50 mL Organic layer was dried with $MgSO_4$, filtered and solvents was removed under reduced pressure. Residue was purified with flash chromatography, (EtOAc/Hex, 1:3).

2.4a *1-Phenyl-1,2-dihydrocyclopenta[b]indol-3(4H)-one (**5a**)*[29]: Yield 38%, ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.83 (*s*, 1 H, Ar-H); 7.48–7.46 (*m*, 1 H, Ar-H); 7.34–7.20 (*m*, 7 H, Ar-H); 7.03–6.99 (*m*, 1 H, Ar-H); 4.72 (*dd*, 1 H, J^3 = 2.1, J^3 = 6.6, H-12); 3.58 (*dd*, 1 H, J^2 = 18.3, J^3 = 6.6, H-11); 2.95 (*dd*, 1 H, J^2 = 18.3, J^3 = 2.1, H-11). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 193.1 (C-10); 147.3 (C-8); 144.3 (C-14); 143.6 (C-4); 139.2 (C-9); 129.1 (C-15, C-18); 127.5 (C-16, C-18); 127.1 (C-17); 127.0 (C-5); 122.8 (C-2); 121.7 (C-1); 120.6 (C-6); 114.3 (C-3); 51.4 (C-12); 39.0 (C-11). HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_{17}H_{14}NO$: 248.1074; found: 248.1065.

2.4b *4-methyl-1-phenyl-1,2-dihydrocyclopenta[b] indol-3(4H)-one (**5b**)*[29]: Yield 33%, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44–7.42 (*m*, 2 H, Ar-H); 7.41–7.38 (*m*, 1 H, Ar-H); 7.36–7.31 (*m*, 2 H, Ar-H); 7.29–7.24 (*m*, 3 H, Ar-H);

7.13–7.08 (*m*, 1 H, Ar-H); 4.67 (*dd*, 1 H, J^3 = 6.8, J^3 = 2.4, H-12); 4.01 (*s*, 3 H, H-20); 3.54 (*dd*, 1 H, J^2 = 18.4, J^3 = 6.8, H-11); 2.92 (*dd*, 1 H, J^2 = 18.4, J^3 = 2.4, H-11). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.8 (C-10); 146.4 (C-14); 145.1 (C-4); 142.9 (C-8); 138.9 (C-9);128.8 (C-15, C-19); 127.2 (C-16, C-18); 126.8 (C-5, C-17); 122.7 (C-2); 122.2 (C-6); 120.5 (C-1); 111.0 (C-3); 52.1(C-12); 39.0 (C-11); 30.2 (C-20). HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{18}H_{16}NO$: 262.1232; found: 262.1248.

2.4c *1-(4-(trifluoromethyl)phenyl)-1,2-dihydrocyclopenta[b]indol-3(4H)-one (**5c**)*: Yield 25%, ^{1}H NMR (acetone-d_6, 400 MHz): δ 10.93 (*s*, NH); 7.71–7.68 (*m*, 2 H, Ar-H); 7.63–7.59 (*m*, 1 H, Ar-H); 7.55–7.53 (*m*, 2 H, Ar-H); 7.42–7.31 (*m*, 2 H, Ar-H); 7.13–7.05 (*m*, 1 H, Ar-H); 4.91 (*dd*, 1 H, J^3 = 7.2, J^3 = 2.4, H-12); 3.55 (*dd*, 1 H, J^2 = 18.4, J^3 = 7.2, H-11); 2.79 (*dd*, 1 H, J^2 = 18.4, J^3 = 2.4, H-11). ^{13}C NMR (acetone-d_6, 100 MHz): δ 191.4 (C-10); 148.3 (C-8); 145.9 (C-14); 144.1(C-4); 139.3 (C-5); 128.3 (*q*, J^{C-F} = 31.8, C-17); 127.9 (C-15, C-19); 126.7 (C-2); 125.6 (*q*, J^{C-F} = 3.8, C-16, C-18); 124.5 (*q*, J^{C-F} = 269.4, C-20); 122.9 (C-9); 121.2 (C-1); 120.5 (C-6); 113.7 (C-3); 50.8 (C-12); 38.8 (C-11). HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{18}H_{13}F_3NO$: 316.0948; found: 316.0951.

2.4d *1-(3-chlorophenyl)-1,2-dihydrocyclopenta[b]indol-3(4H)-one (**5d**)*: Yield 15%, ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.87 (*s*, NH); 7.52–7.46 (*m*, 1 H, Ar-H); 7.37–7.25 (*m*, 5 H, Ar-H); 7.22–7.18 (*m*, 1 H, Ar-H); 7.07–7.02 (*m*, 1 H, Ar-H); 4.76 (*dd*, 1 H, J^3 = 6.8, J^3 = 2.4, H-12); 3.48 (*dd*, 1 H, J^2 = 18.3, J^3 = 6.8, H-11); 2.74 (*dd*, 1 H, J^2 = 18.3, J^3 = 2.4, H-11). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 192.7 (C-10); 146.4 (C-14); 146.3 (C-8); 144.3 (C-4); 139.4 (C-18); 133.7 (C-16); 131.0 (C-19); 127.4 (C-15); 127.1 (C-17); 127.0 (C-9) 126.3 (C-2); 122.7 (C-5); 121.6 (C-1); 120.8 (C-6); 114.4 (C-3); 51.1 (C-12); 38.6 (C-11). HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{17}H_{13}ClNO$: 282.0686; found: 282.0679.

2.5 *General procedure for preparation N-(1-aryl-1,2-dihydrocyclopenta[b]indol-3(4H)-ylidene)amines (**4aaa–acb**)*

To a cooled solution of 1-aryl-1,2-dihydrocyclopenta[b]indol-3(4H)-ones (**5a–d**) (0.5 mmol) in DCM (2 mL) 2-phenylethylamine or cyclohexylamine (2.5 mmol) was added. Followed by dropwise addition of $TiCl_4$ solution in DCM (0.33 mmol, 1M) through 30'. Resulted mixture was allowed to warm to ambient temperature and stirred for 12 h. Reaction was quenched with aqueous NaOH solution (10 mL, 0.5 M) and extracted with DCM (2x20 mL). Organic layer was dried with $MgSO_4$, filtered and solvents was removed under reduced pressure. Residue was purified with flash chromatography, (DCM/MeOH, 60:1).

2.5a *2-phenyl-N-(1-phenyl-1,2-dihydrocyclopenta[b]indol-3(4H)-ylidene)ethanamine (**4aaa**)*: Yield 29%, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.78 (brs, NH); 7.45–7.43 (*m*, 1 H, Ar-H); 7.37–7.22 (*m*, 1 H); 7.32–7.22 (*m*, 9 H, Ar-H); 7.06–7.02 (*m*, 1 H, Ar-H); 4.58 (*dd*, 1 H, J^3 = 7.1, J^3 = 2.4, H-12); 3.75 (*td*, 2 H, J^3 = 7.4, J^3 = 2.4, H-20); 3.50 (*dd*, 1 H, J^2 = 17.5, J^3 = 7.1, H-11); 3.07 (*t*, 2 H, *J*= 7.4, H-21) 2.74 (*dd*, 1 H, J^2 = 17.5, J^3 = 2.4, H-11). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.6 (C-10); 143.6 (C-14); 142.9 (C-22); 140.5 (C-4); 139.9 (C-8); 138.0 (C-5); 128.9 (C-24, C-26); 128.7 (C-23, C-27); 128.4 (C-15, C-19); 127.2 (C-16, C-18); 126.7 (C-17); 126.2 (C-25); 125.1 (C-2); 123.5 (C-9); 120.7 (C-1); 120.2 (C-6); 112.9 (C-3); 54.6 (C-20); 44.3 (C-12); 41.2 (C-11); 37.2 (C-21). HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{25}H_{23}N_2$: 351.1860; found: 351.1873.

2.5b *N-(1-phenyl-1,2-dihydrocyclopenta[b]indol-3(4H)-ylidene)cyclohexanamine (**4aab**)*: Yield 65%, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.07 (brs, NH); 7.58–7.53 (m, 1 H, Ar-H); 7.37–7.27 (*m*, 5 H, Ar-H); 7.19–7.16 (*m*, 2 H, Ar-H); 7.09–7.05 (*m*, 1 H, Ar-H); 4.83 (*dd*, 1 H, J^3 = 6.0, J^3 = 1.4, H-12); 4.02 (*dd*, 1 H, J^2 = 18.8, J^3 = 6.0, H-11); 3.57–3.48 (*m*, 1 H, C-20); 3.24 (*dd*, 1 H, J^2 = 18.8, J^3 = 1.4, H-11); 2.10–2.00 (*m*, 2 H, H-25); 1.98–1.82 (*m*, 4 H, H-24); 1.71–1.65 (*m*, 1 H, H-23); 1.38–1.23 (*m*, 3 H, H-23, H-25); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.8 (C-10); 149.3 (C-8); 146.5 (C-14); 140.2 (C-4); 133.4 (C-5); 129.7 (C-17); 129.2 (C-15, C-19); 127.8 (C-2); 127.0 (C-16, C-18); 122.2 (C-9); 122.1 (C-1); 121.5 (C-6); 114.6 (C-3); 58.8 (C-20); 45.2 (C-12); 41.7 (C-11); 32.0 (C-21); 31.9 (C-25); 24.5 (C-22); 24.5 (C-24); 24.4 (C-23). HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{23}H_{25}N_2$: 329.2018; found: 329.2191.

2.5c *N-(4-methyl-1-phenyl-1,2-dihydrocyclopenta[b]indol-3(4H)-ylidene)-2-phenylethanamine (**4baa**)*: Yield 85%, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43–7.39 (m, 1 H, Ar-H); 7.36–7.28 (*m*, 8 H, Ar-H); 7.27–7.17 (*m*, 4 H, Ar-H); 7.09–7.03 (*m*, 1 H, Ar-H); 4.54 (*dd*, 1 H, J^3 = 7.3, J^3 = 2.8, H-12); 4.13 (*s*, CH3); 3.76–3.67 (*t*, 2 H,J^3 = 7.1, H-20); 3.49 (*dd*, 1 H, J^2 = 17.3, J^3 = 7.3, H-11); 3.09 (*t*, 2 H, J^3 = 7.1, H-21); 2.75 (*dd*, 1 H, J^2 = 17.3, J^3 = 2.8, H-11). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.3 (C-10); 144.3 (C-8); 144.2 (C-14); 140.7 (C-4); 129.0 (C-24, C-26); 128.8 (C-22); 128.6 (C-23, C-27); 128.3 (C-15, C-19); 127.2 (C-16, C-18); 126.8 (C-5); 126.5 (C-17); 126.0 (C-25); 124.1 (C-9); 123.2 (C-2); 120.7 (C-6); 119.7 (C-1); 110.3 (3); 55.4 (C-20); 44.5 (C-12); 40.7 (C-11); 37.7 (C-21); 30.5 (C-28). HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{26}H_{25}N_2$: 365.2018; found: 365.2021.

2.5d *N-(4-methyl-1-phenyl-1,2-dihydrocyclopenta[b]indol-3(4H)-ylidene)cyclohexanamine (**4bab**)*: Yield 90%, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42–7.36 (*m*, 1 H, Ar-H); 7.35–7.21 (*m*, 7 H, Ar-H); 7.09–7.01 (*m*, 1 H, Ar-H); 4.67–4.57 (*m*, 1 H, H-12); 4.11 (*s*, 3 H, H-20); 3.66 (*dd*, 1 H, J^2 = 16.4, J^3 = 6.4, H-11); 3.36–3.22 (*m*, 1 H, H-21); 2.91–2.85 (*m*, 1 H, H-11); 1.94–1.64 (*m*, 5 H, H-22, H-23, H-25, H-26); 1.62–1.48 (*m*, 2 H, H-23, H-25); 1.45–1.28 (*m*, 3 H, H-24, H-25). ^{13}C NMR ($CDCl_3$, 100 MHz): δ

161.7 (C-10); 144.8 (C-8); 143.9 (C-14); 142.0 (C-4) 133.6, (C-5); 128.6 (C-15, C-19); 127.2 (C-16, C-18); 126.4 (C-17); 123.6 (C-9); 123.2 (C-2); 120.5 (C-6); 119.5 (C-1); 110.2 (C-3); 61.8 (C-21); 43.8 (C-12); 40.7 (C-11); 34.0 (C-20); 33.9 (C-22, C-26); 30.3 (C-23); 25.9 (C-25); 24.8 (C-24). HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{24}H_{27}N_2$: 343.2173; found: 343.2247.

2.5e *2-phenyl-N-(1-(4-(trifluoromethyl)phenyl)-1,2-dihydrocyclopenta[b]indol-3(4H)-ylidene)ethanamine (**4aba**)*: Yield 73%, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.41 (1H, brs, NH); 7.58–7.53 (*m*, 2 H, Ar-H); 7.48–7.44 (*m*, 1 H, Ar-H); 7.36–7.30 (*m*, 8 H, Ar-H); 7.26–7.22 (*m*, 7 H, Ar-H); 7.20–7.14 (*m*, 1 H, Ar-H); 7.09–7.05 (*m*, 1 H, Ar-H); 4.63 (*dd*, 1 H, $J^3 = 7.1$, $J^3 = 2.4$, H-12); 3.88–3.73 (*m*, 2 H, H-20); 3.51 (*dd*, 1 H, $J^2 = 17.7$, $J^3 = 7.0$, H-11); 3.09 (*t*, 2 H, $J = 7.2$, H-21) 2.62 (*dd*, 1 H, $J^2 = 17.7$, $J^3 = 2.4$, H-11). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.7 (C-10); 147.3 (C-14); 143.5 (C-22); 139.7 (C-4); 139.5 (C-5); 138.4 (C-8); 129.2 (*q*, $J^{C-F} = 32.2$, C-17); 129.0 (C-15, C-19); 128.5 (C-24, C-26); 127.5 (C-23, C-27); 126.4 (C-25); 125.9 (C-9); 125.7 (*q*, $J^{C-F} = 3.7$, C-16, C-18); 124.1 (*q*, $J^{C-F} = 270.2$, C-28); 123.1 (C-2); 120.7 (C-1); 120.6 (C-6); 113.3 (C-3); 54.2 (C-20); 44.1 (C-12); 40.9 (C-11); 36.8 (C-21). HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{26}H_{22}F_3N_2$: 419.1734; found: 419.1878.

2.5f *N-(1-(4-(trifluoromethyl)phenyl)-1,2-dihydrocyclopenta[b]indol-3(4H)-ylidene) cyclohexanamine (**4abb**)*: Yield 77%, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.42 (1H, brs, NH); 7.60–7.55 (*m*, 2 H, Ar-H); 7.44–7.40 (*m*, 1 H, Ar-H); 7.39–7.34 (*m*, 2 H, Ar-H); 7.31–7.25 (*m*, 2 H, Ar-H); 7.09–7.03 (*m*, 1 H, Ar-H); 4.72 (*dd*, 1 H, $J^3 = 7.3$, $J^3 = 2.6$, H-12); 3.73 (*dd*, $J^2 = 17.4$, $J^3 = 7.3$, H-11); 3.34–3.22 (*m*, 1 H, H-20); 2.90 (*dd*, 1 H, $J^2 = 17.4$, $J^3 = 2.6$, H-11); 1.85–1.62 (*m*, 4H, H-21, H-25); 1.59–1.47 (*m*, 2 H, H-22, H-24); 1.43–1.2 (*m*, 4H, H-22, H-23, H-24). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.7 (C-10); 148.1 (C-14); 142.6 (C-4); 141.1 (C-8); 135.8, (C-5) 129.1 (*q*, $J^{C-F} = 32.2$, C-17); 127.5 (C-9, C-15, C-19); 125.7 (*q*, $J^{C-F} = 3.7$, C-16, C-18); 125.0 (C-2); 124.2 (*q*, $J^{C-F} = 270.2$, C-26); 123.3 (C-1); 120.4 (C-6); 113.0 (C-3); 61.6 (C-20); 43.5 (C-12); 41.0 (C-11); 33.8 (C-25); 33.7 (C-21); 25.5 (C-23); 24.9 (C-24); 24.8 (C-22). HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{24}H_{24}F_3N_2$: 397.1891; found: 397.2385.

2.5g *N-(1-(3-chlorophenyl)-1,2-dihydrocyclopenta[b]indol-3(4H)-ylidene)-2-phenylethanamine (**4aca**)*: Yield 55%, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.39 (1H, brs, Ar-H); 7.49–7.44 (*m*, 1 H, Ar-H); 7.37–7.31 (*m*, 1 H, Ar-H); 7.30–7.29 (*m*, 1 H, Ar-H); 7.27–7.22 (*m*, 6 H, Ar-H); 7.20–7.13 (*m*, 2 H, Ar-H); 7.10–7.04 (*m*, 2 H, Ar-H); 4.54 (*dd*, 1 H, $J^3 = 7.8$, $J^3 = 2.4$, H-12); 3.87–3.71 (*m*, 2 H, H-21); 3.47 (*dd*, 1 H, $J^2 = 17.6$, $J^3 = 7.8$, H-11); 3.09 (*t*, 2 H,$J^3 = 7.2$, H-22); 2.62 (*dd*, 1 H, $J^2 = 17.6$, $J^3 = 2.4$, H-11). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.9 (C-10); 145.3 (C-14); 143.5 (C-23); 139.7 (C-4); 139.5 (C-8); 138.6 (C-18); 134.6 (C-5); 130.0 (C-16); 129.0 (C-25, C-27); 128.5 (C-24, C-28); 127.3 (C-19); 127.1 (C-15); 126.4 (C-26); 125.8 (C-9); 125.4 (C-17); 123.2 (C-2); 120.7 (C-1); 120.5 (C-6); 113.3 (C-3); 54.2 (21); 44.3 (C-12); 40.9 (C-11); 36.9 (C-22). HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{25}H_{22}ClN_2$: 385.1470; found: 385.1551.

2.5h *N-(1-(3-chlorophenyl)-1,2-dihydrocyclopenta[b]indol-3(4H)-ylidene)cyclohexanamine (**4acb**)*: Yield 58%, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45–7.40 (*m*, 1 H, Ar-H); 7.31–7.26 (*m*, 2 H, Ar-H); 7.25–7.22 (*m*, 3 H, Ar-H); 7.14–7.10 (*m*, 1 H, Ar-H); 7.09–7.04 (*m*, 1 H, Ar-H); 4.64 (*dd*, 1 H, $J^3 = 7.2$, $J^3 = 2.6$, H-12); 3.71 (*dd*, 1 H, $J^2 = 17.5$, $J^3 = 7.2$, H-11); 3.33–3.25 (*m*, 1 H, H-21); 2.92 (*dd*, 1 H, $J^2 = 17.5$, $J^3 = 2.6$, H-11); 1.90–1.76 (*m*, 4 H, H-22, H-26); 1.72–1.65 (*m*, 1 H, H-24); 1.60–1.50 (*m*, 2 H, H-23, H-25); 1.40–1.22 (*m*, 3 H, H-23, H-24, H-25); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.1 (C-10); 145.9 (C-14); 142.7 (C-4); 140.6 (C-8); 136.6 (C-18); 134.6 (C-16); 130.1 (C-19); 127.4 (C-15); 127.0 (C-17); 125.3 (C-2); 125.2 (C-5); 123.2 (C-9); 120.5 (C-1); 120.4 (C-6); 113.0 (C-3); 61.5 (C-21); 43.7 (C-12); 40.9 (C-11); 33.7 (C-22); 33.6 (C-26); 25.5 (C-24); 24.9 (C-25); 24.8 (C-23). HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{23}H_{24}ClN_2$: 363.1627; found: 363.1660.

2.6 *N-benzyl-1-(3-chlorophenyl)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-amine (**3cc**)*

To a solution of 1-(3-chlorophenyl)-1,2-dihydrocyclopenta[b] indol-3(4H)-one (**5d**) 147 mg (0.52 mmol) in DCM (5 mL); $NaBH(OAc)_3$ 170 mg (0.80 mmol) was added followed by acetic acid 46 μL (0.80 mmol) and benzylamine 0.087 μL (0.80 mmol). Mixture was stirred at room temperature trough 24 h. Saturated aqueous $NaHCO_3$ (5 mL) and EtOAc (5 mL) was added and stirred for 30 min. Layers were separated, water phase was washed with EtOAc (2 x 5 mL). Organic solution was dried with anh. $MgSO_4$, filtered and solvents were removed under reduced pressure. The residue was purified with flash column chromatography on silica gel, using (EtOAc/Hex, 1:2, NEt_3 0.5%) to obtain amine **3** as a yellow oil, 128 mg, yield 64%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22 (1H, brs, NH); 7.40–7.29 (*m*, 7 H, Ar-H); 7.26–7.14 (*m*, 5 H, Ar-H); 7.05–7.01 (*m*, 1 H, Ar-H); 4.48 (1H, dt, $J = 1.1$, $J = 6.2$, H-12); 4.35 (*t*, 1 H, $J = 6.8$, H-10); 3.99 (*d*, 1 H, $J = 13.0$, H-21); 3.86 (*d*, 1 H, $J = 13.0$, H-21); 3.42 (*ddd*, 1 H, $J = 6.8$, $J = 6.2$, $J = 13$, H-11); 2.18 (1H, brs, NH); 2.13–2.07 (*m*, 1 H, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.5 (C-8); 144.3 (C-14); 141.1 (C-22); 139.3 (C-4); 134.4 (C-18); 129.8 (C-16); 128.7 (C-24, C-26); 128.5 (C-23, C-27); 127.6 (C-19); 127.5 (C-15); 126.5 (C-25); 125.6 (C-17); 123.7 (C-5); 121.7 (C-2); 121.2 (C-1); 119.8 (C-6); 119.2 (C-9); 111.9 (C-3); 57.0 (C-10); 51.3 (C-21); 48.4 (C-12); 42.5 (C-11). HRMS (ESI-): m/z $[M - H]^-$ calcd for $C_{24}H_{20}ClN_2$: 371.1315; found: 371.1256.

2.7 *Molecular docking*

Molecular docking for designed molecules was performed with AutoDock Tools software package.[30] Structures of receptors were obtained from the PDB database. We used crystallographic structures of human serotonin TS3 transporter,[31] human dopamine D3 receptor,[32] and Drosophila dopamine transporter.[33] In case of crystallographic structures, including complexed ligand, atoms of ligand were selectively removed from the crystallographic structures of the proteins if necessary. The energy of ligand molecules was minimized using an MM2 force field. During docking, the ligands had torsion allowed for all rotating dihedral angles.

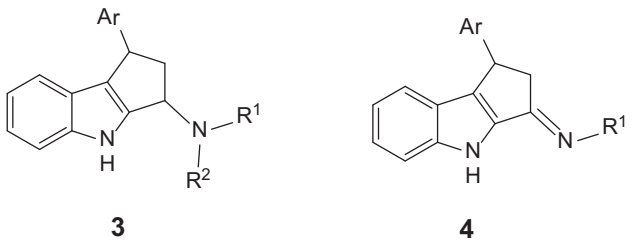


Figure 1. Ligands for the human serotonin transporter.

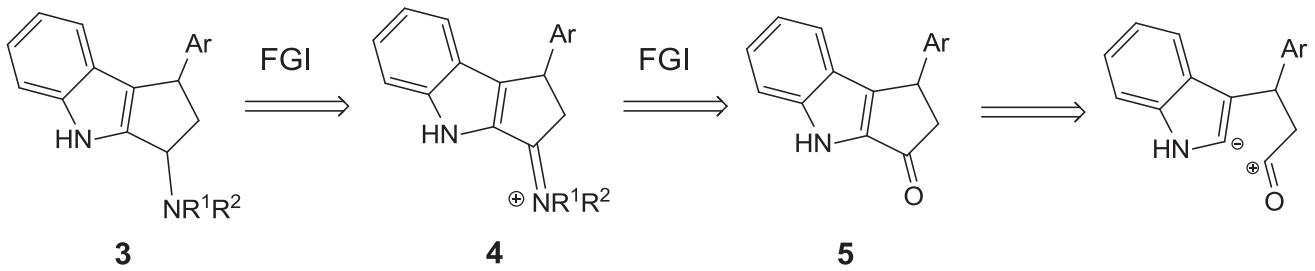
3. Results and Discussion

3.1 *Synthesis*

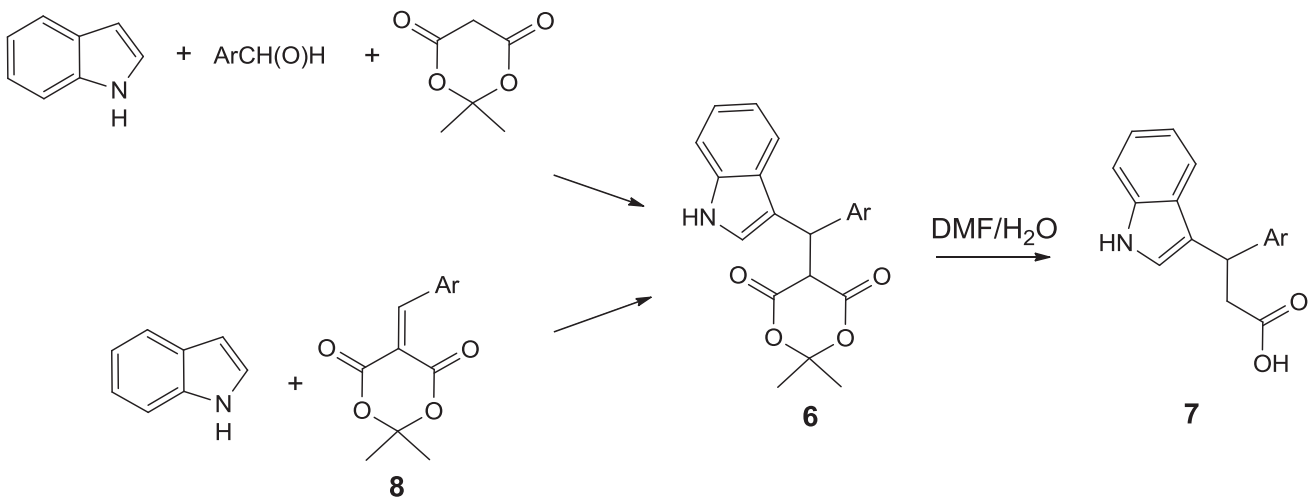
In the present study, we have focused our research efforts on formation ligands for human serotonin transporter based on rigid tricyclic scaffold containing an amine **3** or imine **4** side chain together with an aryl moiety placed on the first asymmetry centre, as presented in Figure 1.

The first step in designing a new bioactive molecule is the synthetic pathway, which allows easy and efficient preparation of the compound. The scaffold containing the indole moiety fused with an alicyclic ring might be formed in a few different ways, including Fisher indolization,[34] oxidative cyclizations of arylenaminones,[35] Heck-type cyclizations,[36] reductive cyclizations,[37] or Friedel-Crafts acylation.[38] Retrosynthetic analysis (Scheme 2) led us to assume that the desired key intermediate 1-aryl-1,2-dihydrocyclopenta [b]indol-3(4H)-one (**5**) might be easily formed through intramolecular Friedel-Crafts acylation.

However, for such a route of synthesis, a source of 3-(1H-indol-3-yl)-3-arylpropanoic acids is required.

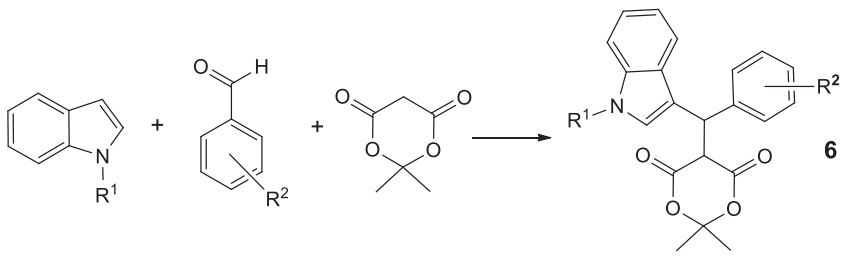


Scheme 2. Retrosynthetic analysis for the preparation of serotonin transporter ligands.



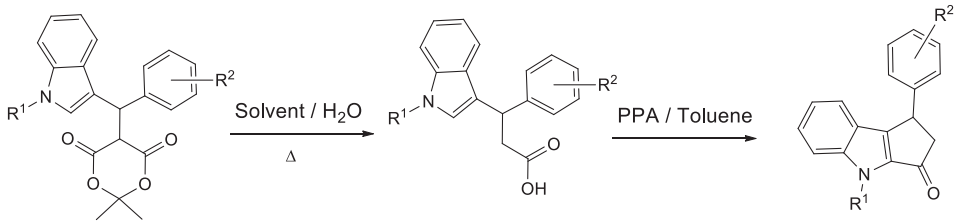
Scheme 3. Possible routes for the preparation of 3-(1H-indol-3-yl)-3-arylpropanoic acids (**7**).

Table 1. Synthesis of 5-((1H-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-diones **6a–d**.



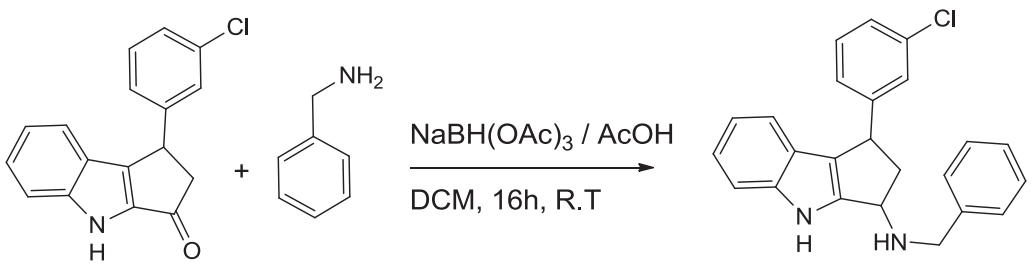
Entry	R^1	R^2	6	Yield [%]
1	H	H	**a**	48
2	CH_3	H	**b**	50
3	H	4-CF_3	**c**	56
4	H	3-Cl	**d**	60

Table 2. Hydrolysis of 5-((1H-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-diones 6a–d and cyclization to 1-aryl-1,2-dihydrocyclopenta[b]indol-3(4H)-ones (**5**).



6 7 5

Entry	R^1	R^2	5, 6, 7	Hydrolysis Conditions			Yield of 7 [%]	Cyclization time [h]	Yield of 5 [%]
				Solvent	Time [h]	Temp. [°C]			
1	H	H	**a**	DMF	4	100	45	5	38
				Acetone	24	56	31		
2	CH_3	H	**b**	DMF	4	100	60	120	33
3	H	4-CF_3	**c**	DMF	4	100	60	213	25
4	H	3-Cl	**d**	DMF	4	100	58	25	15
				THF	23	66	58		
				Acetone	24	56	23		

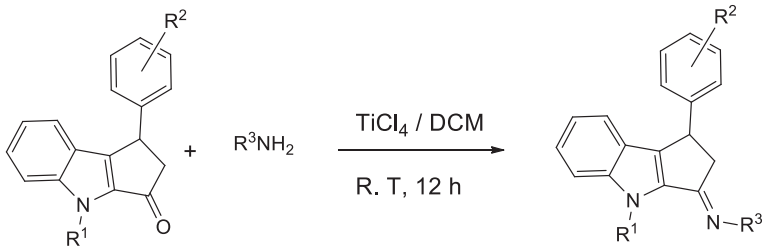


5d 3cc

Scheme 4. Reductive amination of 1-(3-chlorophenyl)-1,2-dihydrocyclopenta[b]indol-3(4H)-one.

Simultaneously solving two synthetic problems, means the formation of 3-aryl propionic acid with an additional indole moiety on 3 positions, would be achieved *via the* application of 5-((1H-indol-3-yl)(aryl) methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**6**). Based on analogous processes described in the literature,[39]

Table 3. Synthesis of N-(1-aryl-1,2-dihydrocyclopenta[b]indol-3(4H)-ylidene)alkylamines **4aaa–acb**.



5 4aaa-acb

Entry	R^1	R^2	R^3	4	Yield [%]
1	H	H	$PhCH_2CH_2$	**aaa**	29
2	H	H	c-Hex	**aab**	65
3	CH_3	H	$PhCH_2CH_2$	**baa**	85
4	CH_3	H	c-Hex	**bab**	90
5	H	4-CF_3	$PhCH_2CH_2$	**aba**	73
6	H	4-CF_3	c-Hex	**abb**	77
7	H	3-Cl	$PhCH_2CH_2$	**aca**	55
8	H	3-Cl	c-Hex	**acb**	58

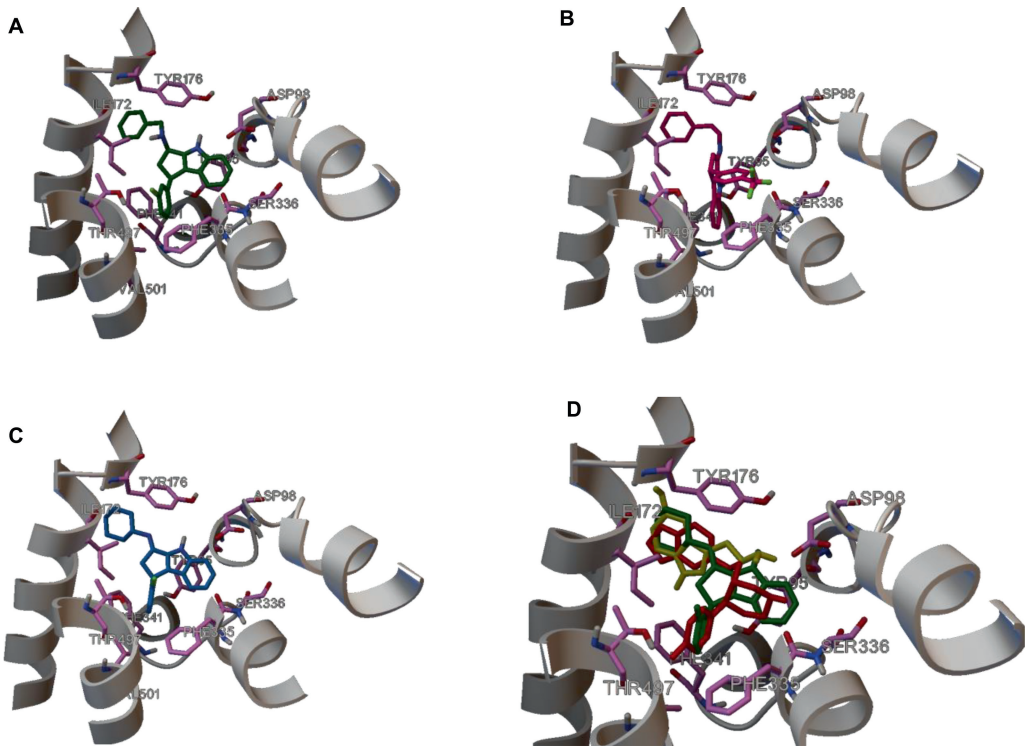
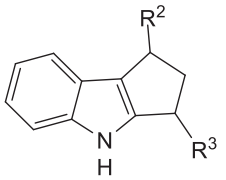


Figure 2. Binding modes on TS3 transporter active site a) amine **3cc** (1*R*, 3*R*), b) imine **4aba** (*R*), c) imine **4acb** (*R*) d) binding comparison of **4acb** (*R*) (green), paroxetine (red) and serotonin (yellow).

(**6**) the compound can be easily transformed to 3-(1 H-indol-3-yl)-3-arylpropanoic acid (7) through hydrolysis in DMF/water solution. On the other hand, (**6**) can be prepared in two ways, either through a three-component reaction composed of indole, aromatic aldehyde, and Meldrum's acid in the process originally proposed by Oikawa,[25] or through Friedel-Crafts alkylation of indole with arylidene Meldrum's acid

Table 4. Binding energy of amines **3aa–ed** to human serotonin transporter TS3.



Entry	R^2	R^3	3	Binding energy [kcal/mol]			
				(1*R*, 3*R*)	(1*R*, 3*S*)	(1*S*, 3*R*)	(1*S*, 3*S*)
1	Ph	$PhCH_2CH_2NH$	**aa**	−10.4	−10.1	−11.2	−10.8
2	Ph	c-HexNH	**ab**	−11.6	−11.8	−10.5	−11.0
3	Ph	$PhCH_2NH$	**ac**	−11.9	−11.9	−11.1	−10.5
4	Ph	$(Et)_2NH$	**ad**	−9.2	−9.3	−9.8	−9.3
5	4-$CF_3(C_6H_4)$	$PhCH_2CH_2NH$	**ba**	−12.1	−11.3	−11.3	−10.4
6	4-$CF_3(C_6H_4)$	c-HexNH	**bb**	−11.3	−11.5	−11.7	−11.4
7	4-$CF_3(C_6H_4)$	$PhCH_2NH$	**bc**	−11.9	−11.9	−11.9	−10.9
8	4-$CF_3(C_6H_4)$	$(Et)_2NH$	**bd**	−10.4	−9.9	−10.7	−10.2
9	3-$Cl(C_6H_4)$	$PhCH_2CH_2NH$	**ca**	−10.5	−10.6	−11.5	−11.0
10	3-$Cl(C_6H_4)$	c-HexNH	**cb**	−11.9	−12.2	−11.0	−11.1
11	3-$Cl(C_6H_4)$	$PhCH_2NH$	**cc**	−12.3	−12.2	−11.7	−10.2
12	3-$Cl(C_6H_4)$	$(Et)_2NH$	**cd**	−9.6	−9.5	−9.9	−9.2
13	4-$F(C_6H_4)$	$PhCH_2CH_2NH$	**da**	−10.2	−10.4	−11.5	−10.9
14	4-$F(C_6H_4)$	c-HexNH	**db**	−11.6	−11.5	−10.8	−10.8
15	4-$F(C_6H_4)$	$PhCH_2NH$	**dc**	−11.4	−12.0	−11.4	−10.7
16	4-$F(C_6H_4)$	$(Et)_2NH$	**dd**	−9.5	−9.4	−10.1	−9.5
17	t-Bu	$PhCH_2CH_2NH$	**ea**	−10.6	−10.3	−10.6	−10.0
18	t-Bu	c-HexNH	**eb**	−9.9	−10.6	−10.5	−9.1
19	t-Bu	$PhCH_2NH$	**ec**	−10.2	−10.1	−10.5	−9.9
20	t-Bu	$(Et)_2NH$	**ed**	−8.4	−8.4	−8.5	−8.3

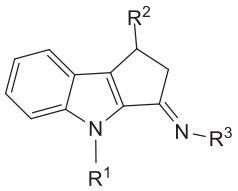
(**8**)[40] (Scheme 3). Due to the use of simple indole models, it was possible to apply a three-component reaction for the preparation of **6**. Thus, we prepared a series of 5-((1H-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-diones (**6a–d**) in the reaction of indole or N-methyl indole, Meldrum's acid, and an appropriate derivative of benzaldehyde in acetonitrile in the presence of L-proline.

Yields and constitution of prepared **6a–d** are presented in Table 1. At this point, compound **6** possesses a chiral center; however, as the application of L-proline does not affect enantiomeric excess, the prepared 5-((1H-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-diones were racemic. Nevertheless, stereoselective synthesis of 5-((1H-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-diones is possible with the application of thiourea organocatalysts.[41]

In the next synthetic step compound, **6** should be converted into the desired 1-aryl-1,2-dihydrocyclopenta[b]indol-3(4H)-one (**5**). We should take into consideration the work of Fillion[42,43] describing intramolecular Friedel-Crafts acylation with Meldrum's acid derivatives catalysed by metal trifluoromethanesulphonates, where the aryl ring was activated with acyloxy groups. Thus, we anticipated that our model with highly π-excess indole system would be superior for such an approach and it will be possible to transform **6** to **5** in one step. We performed experiments where **6d** was refluxed in nitromethane in the presence of scandium (III) triflate or without Lewis acid; we also treated of **6d** with polyphosphoric acid in toluene at 50 °C. However, regardless of the applied method, we were unable to isolate any pure product, but we observed complicated reaction mixtures in all cases. Therefore, we had to abandon this one-step cyclization idea and tried the two-step approach. Compounds **6a–d** were hydrolysed to propionic acids **7a–d** and after purification, acids were treated with PPA in toluene to form 1-aryl-1,2-dihydrocyclopenta[b]indol-3(4H)-ones (**5a–d**).[44] The yields for each step are presented in Table 2.

The most optimal condition for hydrolysis required application of 10% solution of water in DMF. In this situation, hydrolysis is quick with moderate yield; however, isolation of propionic acid from DMF solution is tedious. We attempted to perform a second-step intramolecular cyclization in a few different ways. First, we tested the application of hydrochloric acid for the catalysis of Friedel-Crafts acylation of **7** to **5**.[45] We

Table 5. Binding energy of imines **4aaa–bcc** to human serotonin transporter TS3.



Entry	R^1	R^2	R^3	4	Binding energy [kcal/mol]	
					(***R***)	(***S***)
1	H	Ph	$PhCH_2CH_2$	**aaa**	−11.6	−11.8
2	H	Ph	c-Hex	**aab**	−11.7	−10.8
3	H	Ph	$PhCH_2$	**aac**	−11.7	−11.2
4	H	4-$CF_3(C_6H_4)$	$PhCH_2CH_2$	**aba**	−11.7	−11.4
5	H	4-$CF_3(C_6H_4)$	c-Hex	**abb**	−11.3	−11.2
6	H	4-$CF_3(C_6H_4)$	$PhCH_2$	**abc**	−11.8	−12.0
7	H	3-Cl(C_6H_4)	$PhCH_2CH_2$	**aca**	−11.3	−11.6
8	H	3-Cl(C_6H_4)	c-Hex	**acb**	−12.4	−10.8
9	H	3-Cl(C_6H_4)	$PhCH_2$	**acc**	−11.9	−11.5
10	CH_3	Ph	$PhCH_2CH_2$	**baa**	−11.2	−10.9
11	CH_3	Ph	c-Hex	**bab**	−11.3	−10.7
12	CH_3	Ph	$PhCH_2$	**bac**	−11.2	−11.1
13	CH_3	4-$CF_3(C_6H_4)$	$PhCH_2CH_2$	**bba**	−11.2	−11.8
14	CH_3	4-$CF_3(C_6H_4)$	c-Hex	**bbb**	−11.9	−11.6
15	CH_3	4-$CF_3(C_6H_4)$	$PhCH_2$	**bbc**	−11.4	−11.7
16	CH_3	3-Cl(C_6H_4)	$PhCH_2CH_2$	**bca**	−10.1	−11.0
17	CH_3	3-Cl(C_6H_4)	c-Hex	**bcb**	−11.6	−11.0
18	CH_3	3-Cl(C_6H_4)	$PhCH_2$	**bcc**	−11.4	−11.4

also tried the formation of acid chloride with subsequent ring closure with use of thionyl chloride.[46] Both these attempts were not successful; therefore we applied a third method with PPA as a cyclization agent.[47] Application of PPA, however successful, has some disadvantages, especially in the case of hydrophobic carboxylic acid undergoing cyclization. The problem is connected with phase transfer of reagents and efficient stirring of the reaction mixture. On the micro scale, the effect is negligible, but on the macro scale, we observed a significant drop in yield (the results presented in Table 2 correspond to the gram scale of reaction).

The final step of synthesis leading to amines seems to be a trivial procedure. We expected to run reductive amination in a typical one-pot procedure with *in situ* preparation of imine and subsequent reduction with borohydride. However, we were able to obtain amine with this procedure only in case of N-benzyl-1-(3-chlorophenyl)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-amine (**3cc**) (Scheme 4).

Application of the above procedure for other 1-aryl-1,2-dihydrocyclopenta[b]indol-3(4H)-ones (**5**) in combination with amines regardless of the used conditions led to unreacted substrates. We tried to apply cyanoborohydride in THF in the presence of acetic acid,[48] sodium acetate in methanol with amine hydrochloride and $NaBH_3CN$,[49] and we also tested the two-step approach with the preparation of imine in azeotropic condition, followed by reduction with $NaBH_3CN$.[50] Finally, we tried the formation of imine in the presence of $TiCl_4$,[51] two models were obtained: **4aca** (with 2-phenylethylamine) and **4acb** (with

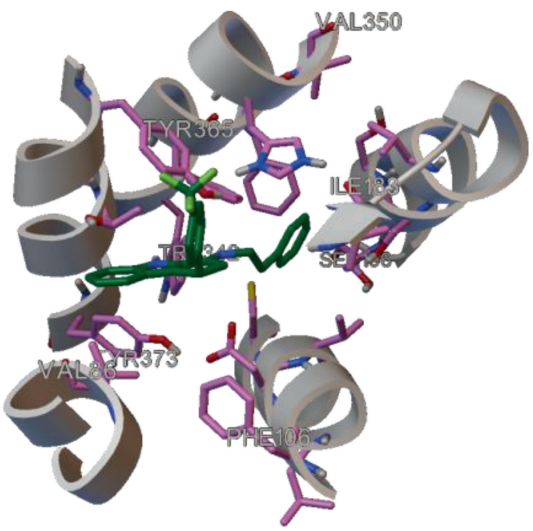


Figure 3. Unsuccessful fitting of **4aba** (*S*) in the active site of Dopamine D3 receptor.

cyclohexylamine). However, the attempts to reduce them with $LiBH_4$, $NaBH_4$, $NaBH(OAc)_3$ or even with $LiAlH_4$ yielded no results. Prepared imines revealed enormous stability and low electrophilicity, which can be explained with their electronic properties, imine group conjugated with a π-electronic system of indole. On the other hand, docking experiments revealed high affinity of imines to a used model of serotonin transporter, even higher than expected amines. These facts led us to change the intended objective; we decided to obtain a series of imines **4aaa**–**acb**. Having a proven method in hand, we have prepared imines in the reaction of **5a**–**d** and amines in the presence of $TiCl_4$; the results are collected in Table 3. Prepared imines were stable enough to allow purification with flash chromatography on silica gel.

3.2 *Docking study*

Preselection of molecules to synthesis as well as observation of binding to serotonin transporter was performed using the AutoDock Tools software package.[30] Since the structures of the human serotonin TS3 transporter,[31] we used contain paroxetine complexed in the central site, we verified if, in our docking procedure, paroxetine will dock in the same place as was observed in the crystallographic structure. The test was positive, docked paroxetine overlapped the molecule present in the crystallographic structure. Moreover, docking of serotonin was also similar, with indole ring near TYR 176 and ILE 172 and with amine residue oriented to the side chain COOH of ASP98. Thus, we could start a docking study with our designed ligands. In the first set, we docked a series of amines **3aa**–**ed** to a TS3 transporter; surprisingly, we observed a different way of docking in the central site of the transporter. In the case of our amine ligands **3cc** (1*R*, 3*R*), the region of TYR176 and ILE 172 was occupied with an alkylamino side chain of ligand, instead of indole or benzodioxole ring as in case of serotonin or paroxetine, respectively (Figure 2a).

In the case of **3aa**–**ed** ligands, the indole moiety was placed in the middle of the pocket. The value of free energy binding for four stereoisomers of amine types ligands are presented in Table 4.

Next, we tested the binding mode for the series of imines **4aaa**–**bcc**. Again we observed that alkyliminum side chain is placed near TYR176 and ILE 172 and the indole moiety is in the central place and interact with PHE 341 for **4aba** (*R*) (Figure 2b), or TYR 95 for **4acb** (*R*) (Figure 2c). In the case of imines, the affinity was even better than for amines in many cases (Table 5). This might be justified with the better fitting of planar imine side chain than alkylamino group located on chiral sp3 carbon. In the last figure, the binding mode of paroxetine, serotonin and **4acb** (*R*) were compared (Figure 2d). Summarizing, for proper binding mode of our designed ligand **3aa**–**ed** and **4aaa**–**bcc**, the crucial components are: primary or secondary alkyl amino side chain with aromatic or cycloaliphatic ring, introducing a secondary noncyclic amine moiety significantly decrees the affinity of molecule (Entry: 4, 8, 12, 16, 20; Table 4). The second side chain should be aromatic, but the type of substitution is not a critical factor as it interacts with PHE 335. Introducing the tert-butyl alkyl group disturbs the interaction of the ligand with transporter (Entry: 17–20; Table 4).

Additionally, we tried docking our imine ligands into human dopamine D3 receptor[46] and Drosophila dopamine transporter.[47] In the case of D3 dopamine receptor, we did not observe good binding modes of our ligands. Some docking results suggest steric hindrance caused by TYR365, which blocks entering of ligand inside of receptor pocket (Figure 3). Alkylamino side chain R3 tried to penetrate the binding site of the receptor, but the aryl side chain was hindered with a tyrosine ring.

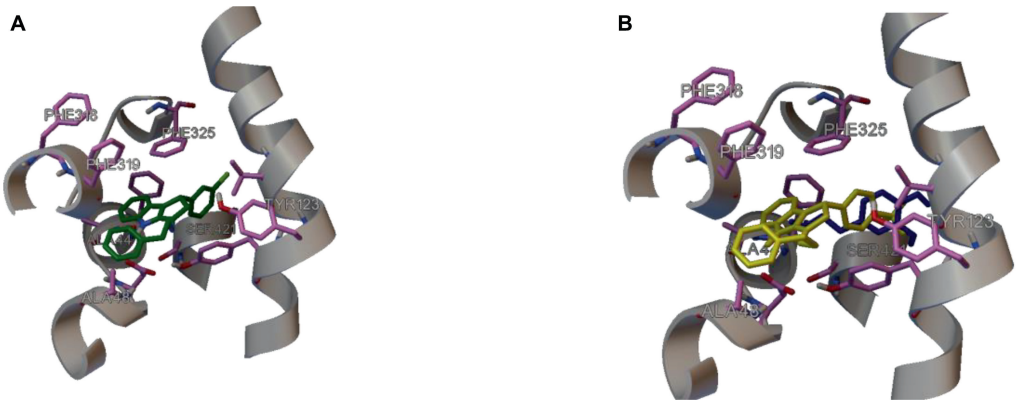


Figure 4. Binding modes on Dopamine Transporter active site (a) **4acb** (*S*) (b) binding comparison of **4aba** (*S*) (yellow) and dopamine (blue).

For dopamine transporter binding, the modes of our ligands were not perfect as they were for TS-3 transporter. However, the analysis of affinity energy exhibited a better interaction with enantiomeric forms. We observed moderately good interaction of **4acb** (*S*) (Figure 4a) and **4aba** (*S*) (Figure 4b). The side chain of the aromatic ring of our ligand fit at an angle to a place normally occupied by the aromatic ring of dopamine or RTI-55.

4. Conclusions

The series of 1,2-dihydrocyclopenta[b]indol-3(4H)-ones were synthesized based on a three-step procedure including the formation of Meldrum's acid adduct; a transformation to 3-substituted propionic acid followed with intramolecular cyclization. These tricyclic scaffolds were converted to a series of imines and amines as designed ligands for the human serotonin transporter. The binding energies of these ligands to human TS3 serotonin transporter as well as selectivity toward human D3 dopamine receptor and dopamine transporter were tested in silico using docking software. During docking, the prepared ligands exhibited high affinity to serotonin transporter together with very similar placement on active site compared to serotonin and paroxetine.

Supplementary Information (SI)

^{1}H NMR, ^{13}C NMR, and mass characterization data are submitted as Supplementary Information. Supplementary Information is available on www.ias.ac.in/chemsci.

Acknowledgements

The project was carried-out within the PARENT-BRIDGE programme of the Foundation for Polish Science (POMOST/2013-8/6), co-financed from the European Union under the European Regional Development Fund. We warmly thank undergraduate and graduate students Mateusz Leśniewski and Marek Cichon for their contribution to the project.

References

1. Humber L G, Ferdinandi E, Demerson C A, Ahmed S, Shah U, Mobilio D, Sabatucci J, De Lange B and Labbadia F 1998 Etodolac, a novel antiinflammatory agent. The syntheses and biological evaluation of its metabolites *J. Med. Chem.* **31** 1712
2. Dejaco Ch, Duftner Ch and Schirmer M 2007 Lack of influence of body mass index on efficacy and tolerance of acemetacin in short-term treatment of musculoskeletal diseases *Rheumatol. Int.* **27** 351
3. Hughes P, DeVirgilio J, Humber L G, Weichman B and Neuman G 1989 Synthesis and biological evaluation of 4,6-diethyl-1,3,4,5-tetrahydropyrano[4,3-b]indole-4-acetic acid, an isomer of etodolac *J. Med. Chem.* **32** 2134
4. Lione A and Scialli A R 1995 The developmental toxicity of indomethacin and sulindac *Reprod. Toxicol.* **9** 7
5. Bellamy N 1997 Etodolac in the management of pain: a clinical review of a multipurpose analgesic *Inflammopharmacology* **5** 139
6. Affonso V Bizzo H Lage C and Sato A 2009 Influence of growth regulators in biomass production and volatile profile of in vitro plantlets of *Thymus vulgaris* L *J. Agric. Food Chem.* **57** 6392
7. Abel S 2007 Auxin Is Surfacing *ACS Chem. Biol.* **2** 380
8. Michnovicz J J 1991 Altered estrogen metabolism and excretion in humans following consumption of indole-3-carbinol *Nutr. Cancer* **16** 59
9. Michnovicz J J 1997 Changes in levels of urinary estrogen metabolites after oral indole-3-carbinol treatment in humans *Natl. Cancer Inst.* **89** 718
10. Holt D A, Yamashita D S, Konialian-Beck A L, Luengo J I, Abel A D, Bergsma D J, Brandt S M and Levy M A 1995 Benzophenone- and indolecarboxylic acids: potent Type-2 specific inhibitors of human steroid 5a-reductase *J. Med. Chem.* **38** 13
11. Boggs S D, Catalano J G, Gudmundsson K S, Richardson L D and Sebahar P R 2006 Novel cycloalkyl condensed Indoles U. S. Patent 0281804 A1
12. Baganz N L and Blakely R D A 2013 Dialogue between the immune system and brain, spoken in the language of serotonin *ACS Chem. Neurosci.* **4** 48
13. Angoa-Pérez M, Kane M J, Briggs D I, Herrera-Mundo N, Sykes C E, Francescutti D M and Kuhn D M 2014 Mice genetically depleted of brain serotonin do not display a depression-like behavioral phenotype *ACS Chem. Neurosci.* **5** 908
14. Kochanowska-Karamyan A J and Hamann M T 2010 Marine Indole alkaloids: potential new drug leads for the control of depression and anxiety *Chem. Rev.* **110** 4489
15. Ikarashi Y, Sekiguchi K and Mizoguchi K 2017 Serotonin receptor binding characteristics of Geissoschizine methyl ether, an indole alkaloid in Uncaria Hook *Cur. Med. Chem.* **24** 1
16. Vangveravong S, Kanthasamy A, Lucaites V L, Nelson D L and Nichols D E 1998 Synthesis and serotonin receptor affinities of a series of trans-2-(Indol-3-yl)cyclopropylamine derivatives *J. Med. Chem.* **41** 4995
17. Wong D T, Horng J S, Bymaster F P, Hauser K L and Molloy B B 1974 A selective inhibitor of serotonin uptake: Lilly 110140, 3-(p-Trifluoromethylphenoxy)-N-methyl-3-phenylpropylamine *Life Sci.* **15** 471
18. Wong D T, Bymaster F P and Engleman E A 1995 Prozac (fluoxetine, Lilly 110140), the first selective serotonin uptake inhibitor and an antidepressant drug: twenty years since its first publication *Life Sci.* **57** 411
19. Sanchez C, Reines E H and Montgomery S A 2014 A comparative review of escitalopram, paroxetine, and sertraline: Are they all alike? *Int. Clin. Psychopharmacol.* **29** 185
20. Al-Harbi K S 2012 Treatment-resistant depression: therapeutic trends, challenges, and future directions *Patient Prefer. Adherence.* **6** 369

21. Nischal A, Tripathi A, Nischal A and Trivedi J K 2012 Suicide and antidepressants: what current evidence indicates *Mens Sana Monogr.* **10** 33
22. Pompili M, Serafini G, Innamorati M, Ambrosi E, Giordano G, Girardi P, Tatarelli R and Lester D 2010 Antidepressants and suicide risk: a comprehensive overview *Pharmaceuticals* **3** 2861
23. Porter R A and Vimal M 1995 Teterahydricarbazole derivatives as 5-HT1-like agonists EP 0674622 B1
24. Bromidge S M 2000 Indole Derivatives as 5-HT Receptor Antagonist U. S. Patent 6028085
25. Oikawa Y, Hirasawa H and Yonemitsu O 1978 Meldrum's acid in organic synthesis. A convenient one-pot synthesis of ethyl indolepropionates. A convenient one-pot synthesis of ethyl indolepropionates *Tetrahedron Lett.* **20** 1759
26. Armstrong E L, Grover H K and Kerr M A 2013 Scandium triflate-catalyzed nucleophilic additions to indolylmethyl meldrum's acid derivatives *via* a gramine-type fragmentation: synthesis of substituted indolemethanes *J. Org. Chem.* **78** 10534
27. Lü Ch, Wang J, Liu Y, Shan W, Sun Q and Shi L 2017 A combination of green solvent and ultrasonic irradiation promotes the catalyst-free reaction of aldehydes, indoles and Meldrum's acid *Res. Chem. Intermed.* **43** 943
28. Adamo M F A and Konda V R 2007 Multicomponent synthesis of 3-indolepropionic acids *Org. Lett.* **9** 303
29. Vickerman K L and Stanley L M 2017 Catalytic, enantioselective synthesis of polycyclic nitrogen, oxygen, and sulfur heterocycles *via* Rh-catalyzed alkene hydroacylation *Org. Lett.* **19** 5054
30. Trott O and Olson A J 2010 AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *J. Comput. Chem.* **31** 455
31. Coleman J A, Green E M and Gouaux E 2016 X-ray structure of the ts3 human serotonin transporter complexed with paroxetine at the central site *Nature* **532** 334
32. Chien E Y, Liu W, Zhao Q, Katritch V, Han G W, Hanson M A, Shi L, Newman A H, Javitch J A, Cherezov V and Stevens R C 2010 Structure of the human dopamine d3 receptor in complex with a d2/d3 selective antagonist *Science* **330** 1091
33. Wang K H, Penmatsa A and Gouaux E 2015 Neurotransmitter and psychostimulant recognition by the dopamine transporter *Nature* **521** 322
34. Gore S, Baskaran S and König B 2012 Fischer indole synthesis in low melting mixtures *Org. Lett.* **14** 4568
35. Würtz S, Rakshit S, Neumann J J, Dröge T and Glorius F 2008 Palladium-catalyzed oxidative cyclization of N-aryl enamines: from anilines to indoles *Angew. Chem. Int. Ed.* **47** 7230
36. Iida H, Yuasa Y and Kibayashi 1980 Intramolecular cyclization of enaminones involving arylpalladium complexes synthesis of carbazoles *J. Org. Chem.* **45** 2938
37. Janreddy D, Kavala V, Bosco J W, Kuo Ch- and Yao Ch-F 2011 An easy access to carbazolones and 2,3-disubstituted indoles *Eur. J. Org. Chem.* **12** 2360
38. Bunce R A and Nammalwar B 2009 1,2,3,9-Tetrahydro-4H-carbazol-4-one and 8,9-dihydropyrido-[1,2-a]indol-6(7H)-one from 1H-indole-2-butanoic acid *J. Heterocycl. Chem.* **46** 172
39. Mishra S, Liu J and Aponick A 2017 Enantioselective Alkyne Conjugate Addition Enabled by Readily Tuned Atropisomeric P,N-Ligands *J. Am. Chem. Soc.* **139** 3352
40. Najda E, Zakaszewska A, Janikowska K and Makowiec S 2016 Practical method for the preparation of 2,2-dimethyl-5-[aryl(heteroaryl)methyl]-1,3-dioxane-4,6-diones - Synthesis and mechanistic study *Synthesis* **48** 3589
41. Najda-Mocarska E, Zakaszewska A, Janikowska K and Makowiec S 2018 New thiourea organocatalysts and their application for the synthesis of 5-(1H-indol-3-yl)methyl-2,2-dimethyl-1, 3-dioxane-4,6-diones a source of chiral 3-indoylmethyl ketenes *Synth. Commun.* **48** 14
42. Fillion E, Fishlock D, Wilsily A and Goll J M 2005 Meldrum's acids as acylating agents in the catalytic intramolecular Friedel-Crafts reaction *J. Org. Chem.* **70** 1316
43. Fillion E and Fishlock D 2003 Convenient access to polysubstituted 1-indanones by $Sc(OTf)_3$-catalyzed intramolecular Friedel-Crafts acylation of benzyl Meldrum's acid derivatives *Org. Lett.* **5** 4653
44. Prajakta N N, Nabil A H A and Radhika S K 2015 Beckmann rearrangement for the synthesis of derivatives of β- and γ-carbolinones, dihydropyrrolopyridinone and tetrahydroisoquinolinone *ARKIVOC* **7** 362
45. Banwell J M G and Smith J A 2002 Exploiting multiple nucleophilic sites on pyrrole for the assembly of polyheterocyclic frameworks: application to a formal total synthesis of (±)-aspidospermidine *Chem. Soc. Perkin Trans.* **10** 2613
46. Pamukcu R and Piazza G A 2002 Method of inhibiting neoplastic cells with indole derivatives U.S. Patent 6358992 B1
47. Maertens F, Toppet S, Hoornaert G J and Compernolle F 2005 Incorporation of an indole-containing diarylbutylamine pharmacophore into furo[2,3-a]carbazole ring systems *Tetrahedron* **61** 1715
48. Haddad M, Dorbais J and Larcheveque M 1997 Stereocontrolled reductive amination of 3-hydroxy ketones *Tetrahedron Lett.* **38** 5981
49. Cherukupally P, Vajrala V R, Adla V K, Rangineni S and Kanniah S 2011 Preparation of rasagiline salts therof U.S. Patent 20110218360 A1
50. Kang S, Cooper G, Dunne S F, Luan C, Surmeier D J and Silverman R B 2013 Structure–activity relationship of N,N'-disubstituted pyrimidinetriones as Ca 1.3 calcium channel-selective antagonists for Parkinson's disease *J. Med. Chem.* **56** 4786
51. Barluenga J, Jimenez-Aquino A, Aznar F and Valdes C 2009 Modular Synthesis of indoles from imines and o-Dihaloarenes or o-Chlorosulfonates by a Pd-catalyzed cascade process *J. Am. Chem. Soc.* **131** 4031