ORIGINAL ARTICLE

A C G publications

Org. Commun. 17:4 (2024) 205-217

organic communications

Synthesis of novel sulfamides derived from dopamine analogues with their *in silico* studies against hyperprolactinemia

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(Received October 05, 2024; Revised December 02, 2024; Accepted December 03,2024)

Abstract: Because of the important biological properties of sulfamides, in the present work six novel sulfamides were synthesized from dopamine derivatives and their *insilico* studies were carried out against hyperprolactinemia. Five sulfamides were synthesized via the reaction of known dopamine derivatives with *N,N*-dimethyl sulfamoyl chloride in the presence of NEt_3. For comparison of biological activity, a sulfamide without *N*-alkyl at the terminal nitrogen was also synthesized. For this synthesis, firstly benzyl alcohol was reacted with chlorosulfonyl isocyanate (CSI). Then, new sulfamoyl carbamate was obtained by the reaction of the formed carbamate derivative with a dopamine analogue in the presence of NEt_3. As a result of the hydrogenolysis of the formed sulfamoyl carbamate under Pd-C catalyst, a new sulfamide was obtained. Molecular docking simulations and ADME predictions were employed to assess the binding affinity and drug-like properties of sulfamide derivatives at the dopamine D_2 receptor, aiming to identify potential contributors to hyperprolactinemia. In the *in silico* docking studies, it was determined that the binding affinity of the R enantiomer of unsubstituted sulfamide **20** to the D_2 receptor was higher than that of Cabergoline and Quinagolide used as standards and there was no deviation from the Lipinski rule of five in the ADME evaluation.

Keywords: Dopamin derivatives; dopaminergic; sulfamides; hyperprolactinemia; molecular docking.

1. Introduction

Hyperprolactinemia, a condition characterized by elevated prolactin levels, is primarily regulated by the dopamine D_2 receptor (D_2R) system. Dopamine, a neurotransmitter, exerts inhibitory control over prolactin secretion by binding to D_2Rs on lactotroph cells in the anterior pituitary gland.[1]

The primary pharmacological treatment for hyperprolactinemia involves the use of dopamine agonists, which mimic the inhibitory effect of dopamine on prolactin secretion. These medications selectively stimulate dopamine D_2 receptors on lactotroph cells in the pituitary gland, leading to a reduction in prolactin release.[2]

Commonly used dopamine agonists for the treatment of hyperprolactinemia include Bromocriptine (**1**), Cabergoline (**2**) and Quinagolide (**3**). Bromocriptine (**1**), an ergot alkaloid derivative, has been used for many years and is effective in lowering prolactin levels. Cabergoline (**2**), a non-ergot dopamine agonist, is generally better tolerated and has a longer duration of action compared to Bromocriptine (**1**). It is often considered the first-line treatment for hyperprolactinemia due to its

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The article was published by ACG Publications
http://www.acgpubs.org/journal/organic-communications © October-December 2024 EISSN:1307-6175
DOI: http://doi.org/10.25135/acg.oc.176.2411.3361
Available online: December 30, 2024

efficacy and tolerability profile. Quinagolide (**3**) is a sulfamide derivative and selective dopamine D_2 receptor agonist used primarily in the treatment of hyperprolactinemia, especially for patients unresponsive to other dopamine agonists like Bromocriptine (**1**) (Figure 1).[3] However, both Bromocriptine (**1**) and Cabergoline (**2**) can cause side effects such as nausea, dizziness, headaches and vomiting.[4]

Sulfamides are bioisosteres of urea and sulfonamide derivatives that exhibit significant biological activities. Therefore, they are the focus of attention in drug research and development studies. Their synthesis, biological activity, structure and activity relationships (SAR) have been extensively studied.[5] These studies reveal that sulfamides exhibit a broad spectrum of biological activities. C(2)-symmetric HIV-1 protease inhibition,[6] selective histamine H_3 receptor antagonist,[7] anticanser,[8] potent and selective β_3-adrenergic receptor agonist,[9] carbonic anhydrase inhibition,[10] NLRP3 inflammasome inhibition,[11] norovirus inhibition,[12] antimicrobial,[13] anticonvulsant[14] properties can be given as examples. Because of the diverse activities of sulfamides, some drugs containing the sulfamide functional group are sold in the market. Doripenem (Doribax, Finibax, **4**) is a member of carbapenem class of antibiotics. It is used against gram-positive and gram-negative bacteria.[15] An endothelin receptor antagonist Macitentan (Opsumit, **5**) is used for the treatment of hypertension.[16] Famotidine (**6**) commercially known as Pepcid, is a histamine H_2 receptor antagonist used in the treatment of gastroesophageal reflux and peptic ulcer[17] (Figure 1).

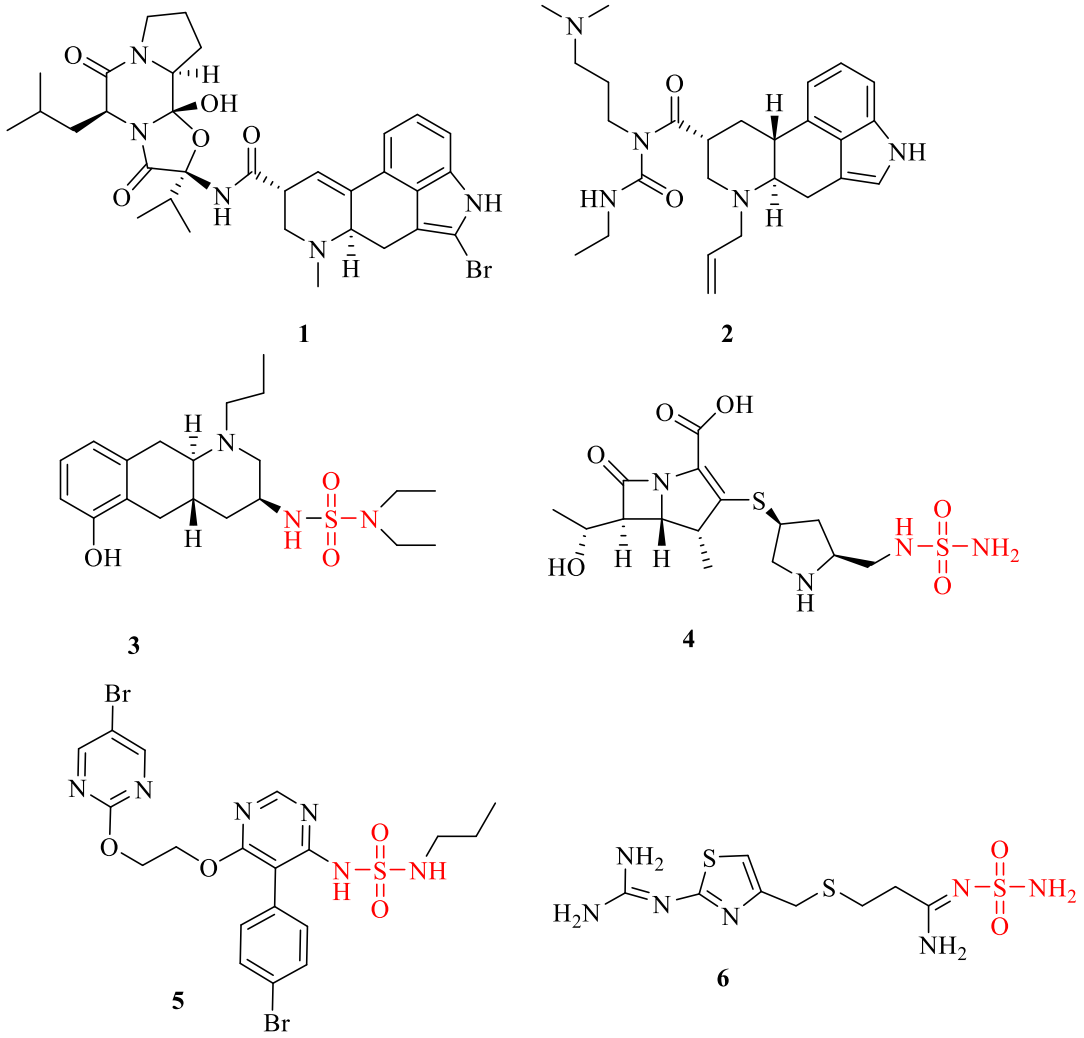


Figure 1. Commonly used antihyperprolactinemic drugs **1**-**3** and sulfamide drugs **4**-**6**.

Due to the noteworthiness of biological activities with pharmacological application, our research group has also focused on the synthesis and biological screening of sulfamides. In these studies, we have already reported hCA, AChE, and BChE inhibition of sulfamides derived from dopamine analogues.[18-20] . As explained above, sulfamides are indispensable organic compounds in synthetic organic chemistry and pharmaceutical chemistry. It is also known that there are very few drugs used in hyperprolactinemia. Therefore, the discovery of compounds that show high activity in hyperprolactinemia in drug research and development will be beneficial. For this purpose, in this study, we aimed to synthesize a series of novel sulfamide derivatives by starting from dopamine analogues and to examine their *in silico* antihyperprolactinemic and drug-likeness properties.

2. Experimental

2.1. Chemical Material and Apparatus

All chemicals and solvents are commercially available and were used without purification or after distillation and treatment with drying agents. Melting points are uncorrected and they were determined on a capillary melting apparatus (BUCHI 530). IR spectra were obtained from solutions in 0.1 mm cells with a Perkin-Elmer spectrophotometer. The ^{1}H and ^{13}C-NMR spectra were recorded on a 400 (100)-MHz Varian and 400 (100)-MHz Bruker spectrometer; δ in ppm, Me_4Si as the internal standard. Elemental analyses were performed on a Leco CHNS-932 apparatus. All column chromatography was performed on silica gel (60-mesh, Merck). PLC is preparative thick-layer chromatography: 1 mm of silica gel 60 PF (Merck) on glass plates.

2.2. Chemistry

2.2.1. Synthesis of Dopamine Derivative Amines

A series of amine salt derivatives **7-11** and **18** were synthesized following established procedures reported in the literature.[21] The spectroscopic data obtained for each derivative were consistent with previously reported values, confirming the expected structures.[21]

*2.2.2 General Procedure of N,N-dimethyl substituted sulfamide derivatives (N-[1-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)propan-2-yl]-N',N'-dimethylsulfamide (**13**)*

1-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)propan-2-amine hydrogen chloride salt (7) (0.400 g, 1.18 mmol) was dissolved in CH_2Cl_2 (50 mL) and NEt_3 (0.299 g, 2.95 mmol) was added to the solution and stirred at room temperature for 3 h. Then, the reaction mixture was cooled to 0°C and *N*,*N*-dimethylsulfamoyl chloride (**12**) (0.340 g, 2.37 mmol) was added dropwise and stirred at 0°C for 30 min. Then, the temperature of the reaction mixture was warmed to 25°C and stirred for 24 h. H_2O (100 mL) was added to the reaction mixture and the pH was adjusted to 7 with 0.1 M HCl. As a result of the extraction process, the organic phase was separated. The water phase was re-extracted with CH_2Cl_2 (2x50 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed by evaporation under reduced pressure. As a result of chromatographic purification with 20% EtOAc-hexane on a silica gel column (20 g), *N*-[1-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)propan-2-yl]-*N'*,*N'*-dimethylsulfamide (**13**) (0.373 g, 0.91 mmol) was synthesized as a yellow viscous with 77% yield. ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 7.10 (d, 2H, Ar-H, *J* = 8.5 Hz), 6.84 (d, 2H, Ar-H, *J* = 8.5 Hz), 6.84 (d, 2H, Ar-Hz, *J* = 8.5 Hz), 6.80 (d, 1H, Ar-H, *J* = 8.7 Hz), 6.74-6.73 (m, 2H, Ar-H), 4.10 (d, 1H, NH, *J* = 8.8 Hz), 3.86 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.69-3.64 (m, 1H, CH), 2.87-2.79 (m, 2H, CH_2), 2.74-2.68 (m, 2H, CH_2), 2.39 (s, 6H, $2CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$), δ (ppm): 158.6 (C), 149.1 (C), 148.0 (C), 130.9 (2CH), 130.2 (C), 129.9 (C), 122.0 (CH), 114.1 (2CH), 113.2 (CH), 111.4 (CH), 57.7 (CH), 56.1 ($2OCH_3$), 55.5 (OCH_3), 40.7 (CH_2), 40.2 (CH_2), 37.8 ($2CH_3$). IR (CH_2Cl_2, cm^{-1}): 3298, 3000, 2932, 2837, 2058, 1731, 1611, 1590, 1514, 1464, 1420, 1327, 1302, 1262, 1248, 1179, 1145, 1110,1074, 1030. Calcd for ($C_{20}H_{28}N_2O_5S$): C, 58.80; H, 6.91; N, 6.86; S, 7.85 Found: C, 58.83; H, 6.92; N, 6.87; S, 7.87.

*2.2.3. N-[1-(3,4-dimethoxyphenyl)-3-phenylpropan-2-yl]-N',N'-dimethylsulfamide (**14**)*

The general procedure described at 2.2.2 was applied to amine hydrogen chloride salt **8** (0.400 g, 1.30 mmol) to give **14** (0.37 g, 75%), Yellow viscous. Purification by silica gel (25 g) column chromatography (EtOAc:hexane, 1:4). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ=7.33-7.19 (m, 5H, Ar-H), 6.83 (dd, 1H, Ar-H, *J* = 1.9 and *J* = 6.8 Hz), 6.77-6.75 (m, 2H, Ar-H), 3.96 (d, 1H, NH, *J* = 9.1 Hz), 3.88 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.86-3.71 (m, 1H, CH), 2.89 (dd, 1H, CH-Ha, *J* = 5.9 Hz and *J* = 13.8 Hz), 2.82-2.68 (m, 3H, CH_2 ve CH-Hb), 2.38 (s, 6H, $2CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ=149.1 (C), 148.1 (C), 138.0 (C), 130.0 (C), 129.9 (2C), 128.7 (2CH), 126.9 (CH), 122.0 (CH), 113.2 (CH), 111.4 (CH), 57.5 (CH), 56.1 ($2OCH_3$), 41.1 (CH_2), 40.9 (CH_2), 37.7 ($2CH_3$). IR (CH_2CI_2, cm^{-1}): 3293, 3002, 2931, 2845, 1590, 1516, 1454, 1327, 1262, 1238, 1143, 1028. Anal. Calcd for ($C_{19}H_{26}N_2O_4S$): C, 60.30; H, 6.92; N, 7.40; S, 8.47 Found: C, 60.30; H, 6.91; N, 7.41; S, 8.50.

*2.2.4. N-[1-(2,3-dimethoxy-6-methylphenyl)-3-(3,4-dimethoxyphenyl)propan-2-yl]-N',N'-dimethylsulfamide (**15**)*

The general procedure described at 2.2.2 was applied to amine hydrogen chloride salt **9** (0.400 g, 1.05 mmol) to give **15** (0.35 g, 79%), Yellow viscous. Purification by silica gel (25 g) column chromatography (EtOAc:hexane, 1:4). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ=6.98 (t, 1H, Ar-H, J = 7.9 Hz), 6.81 (dd, 1H, Ar-H, *J* =1.3 Hz and *J* = 8.2 Hz), 6.69-6.67 (m, 3H, Ar-Hz), 4.64 (d, 1H, NH, *J* = 7.7 Hz), 3.853 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.73-3.67 (m, 1H, CH), 3.01 (A part of AB, dd, 1H, CH-Ha, *J* = 6.2 Hz and *J* = 13.9 Hz), 2.82-2.76 (m, 2H, CH_2), 2.68 (B part of AB, dd, 1H, CH-Hb, *J* = 7.8 Hz and *J* = 13.9 Hz), 2.32 (s, 6H, $2CH_3$), 2.25 (s, 3H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ=153.0 (C), 147.5 (C), 147.0 (C), 132.3 (C), 128.9 (C), 128.6 (C), 124.4 (CH), 123.2 (CH), 114.3 (CH), 113.9 (CH), 111.3 (CH), 60.6 (CH), 57.2 (OCH_3), 56.3 (OCH_3), 56.1 (OCH_3), 55.9 (OCH_3), 39.8 (CH_2), 37.6 (CH_2), 35.5 ($2CH_3$), 19.3 (CH_3). IR (CH_2CI_2, cm^{-1}): 3295, 2932, 2845, 1585, 1518, 1473, 1271, 1227, 1146, 1104, 1082, 1005. Anal. Calcd for ($C_{22}H_{32}N_2O_6S$): C, 58.39; H, 7.13; N, 6.19; S, 7.09 Found: C, 58.38; H, 7.14; N, 6.20; S, 7.31.

*2.2.5. N-[1-(2,3-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propan-2-yl]-N',N'-dimethylsulfamide (**16**)*

The general procedure described at 2.2.2 was applied to amine hydrogen chloride salt **10** (0.400 g, 1.09 mmol) to give **16** (0.36 g, 74%), Yellow viscous. Purification by silica gel (25 g) column chromatography (EtOAc:hexane, 1:4). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ=6.96 (t, 1H, Ar-H, *J* = 7.9 Hz), 6.82-6.75 (m, 4H, Ar-H), 6.69 (dd, 1H, Ar-Hz, *J* = 1.3 Hz and *J* = 7.7 Hz), 4.60 (d, 1H, NH, *J*=8.0 Hz), 3.87 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.81-3.71 (m, 4H, OMe and CH), 2.89 (dd, 1H, CH-Ha, *J* = 5.4 Hz and *J* = 13.81), 2.81-2.72 (m, 3H, CH_2 and CH-Hb), 2.34 (s, 6H, $2CH_3$).^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ=153.0 (C), 149.0 (C), 147.9 (C), 147.5 (C), 132.3 (C), 130.6 (C), 124.3 (CH), 123.3 (CH), 122.0 (CH), 113.2 (CH), 111.4 (CH), 111.3 (CH), 60.6 (CH), 57.5 (OCH_3), 56.1 ($2OCH_3$), 55.9 (OCH_3), 41.7 (CH_2), 37.6 (CH_2), 35.3 ($2CH_3$). IR (CH_2CI_2, cm^{-1}): 3299, 2935, 2836, 1720, 1586, 1516, 1474, 1326, 1264, 1238, 1144, 1081, 1028, 1008. Anal. Calcd for ($C_{21}H_{30}N_2O_6S$): C, 57.51; H, 6.90; N, 6.39; S, 7.31 Found: C, 57.42; H, 6.80; N, 6.48; S, 7.41.

*2.2.6. N-[1-(2,4-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propan-2-yl]-N',N'-dimethylsulfamide (**17**)*

The general procedure described at 2.2.2 was applied to amine hydrogen chloride salt **11** (0.400 g, 1.09 mmol) to give **17** (0.36 g, 74%), Yellow viscous. Purification by silica gel (25 g) column chromatography (EtOAc:hexane, 1:4). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ= 6.95 (d, 1H, Ar-H, *J* = 8.1 Hz), 6.82-6.75 (m, 3H, Ar-H), 6.43 (d, 1H, Ar-H, *J* = 2.3 Hz), 6.41 (dd, 1H, Ar-H, *J* = 2.3 Hz and *J* = 8.1 Hz), 4.41 (d, 1H, NH, *J* = 8.1 Hz), 3.87 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.74-3.68 (m, 1H, CH), 2.86-2.80 (m, 2H, CH_2), 2.73 (A part of AB, 1H, CH-Ha, *J* = 4.7 Hz and *J* = 13.8 Hz), 2.60 (B part of AB, 1H, CH-Hb, *J* = 9.0 Hz and *J* = 13.8 Hz), 2.37 (s, 6H, $2CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ=160.1 (C), 158.7 (C), 149.0 (C), 147.8 (C), 131.9 (CH), 130.5 (C), 122.1 (CH), 119.1 (C), 113.3 (CH), 111.3 (CH), 104.5 (CH), 98.8 (CH), 57.1 (CH), 56.1 ($2OCH_3$),

55.6 (OCH_3), 55.5 (OCH_3), 41.5 (CH_2), 37.7 (CH_2), 34.5 ($2CH_3$). IR (CH_2CI_2, cm^{-1}): 3302, 3002, 2919, 2845, 1721, 1611, 1588, 1509, 1464, 1419, 1289, 1262, 1238, 1208, 1143, 1030. Anal. Calcd for ($C_{21}H_{30}N_2O_6S$): C, 57.51; H, 6.90; N, 6.39; S, 7.31 Found: C, 57.53; H, 6.88; N, 6.40; S, 7.32.

*2.2.7. Benzyl {N-[1-(2,4-dimethoxyphenyl)-3-(4-methoxyphenyl)propan-2-yl]sulfamoyl}carbamate (**19**)*

To a stirred solution of CSI (0.55 g, 3.91 mmol, 0.34 mL) in anhydrous CH_2Cl_2 (20 mL) at 0°C under a nitrogen atmosphere, BnOH (0.54 g, 4.97 mmol, 0.51 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 1 h. Subsequently, a solution of the amine salt **18** (1.20 g, 3.55 mmol) and NEt_3 (0.40 g, 3.94 mmol, 0.54 mL) in anhydrous CH_2Cl_2 (20 mL) was added dropwise to the reaction mixture, and the resulting mixture was stirred at room temperature for 4 h. The reaction mixture was then acidified with 0.1 N HCl (50 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel (30 g) column chromatography (EtOAc:hexane, 3:7) to give sulfamoylcarbamate **19** (1.46 g, 2.84 mmol, 80% yield) as a white solid. Mp: 110-112°C. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ= 7.33-7.26 (m, 5H, Ar-H), 7.13 (d, 2H, Ar-H, *J* = 8.6 Hz), 6.92 (d, 1H, Ar-H, *J* = 8.2 Hz), 6.84 (d, 2H, Ar-H, *J* = 8.6 Hz), 6.44 (d, 1H, Ar-H, *J* = 2.4 Hz), 6.39 (dd, 1H, Ar-H, *J* = 2.4 Hz), 6.39 (dd, 1H, Ar-H, *J* = 2.4 Hz and *J* = 8.2 Hz), 5.65 (d, 1H, NH, *J* = 6.1 Hz), 4.96 (A part of AB, 1H, CH-Ha, *J* = 12.1 Hz), 4.89 (B part of AB, 1H, CH-Hb, *J* = 12.1 Hz), 2.90 (A part of AB, 1H, CH-Ha', *J* = 5.4 Hz and *J* = 13.9 Hz), 2.77 (B part of AB, 1H, CH-Hb', *J* = 7.4 Hz and *J* = 13.9 Hz), 2.68-2.66 (m, 2H, CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ=160.1 (C), 158.6 (C), 158.5 (C), 150.7 (C), 131.8 (CH), 130.8 (2CH), 129.8 (C), 128.85 (2CH), 128.82 (CH), 128.4 (2CH), 118.2 (C), 114.1 (2CH), 104.5 (CH), 98.9 (CH), 68.3 (CH_2), 58.1 (OCH_3), 55.54 (OCH_3), 55.51 (OCH_3), 40.9 (CH_2), 33.9 (CH_2). IR (CH_2CI_2, cm^{-1}): 3280, 3065, 3033, 3002, 2936, 2836, 2219, 2059,1732, 1613, 1587, 1511, 1455, 1355, 1289, 1247, 1209, 1180, 1128. Anal. Calcd for ($C_{26}H_{30}N_2O_7S$): C, 60.69; H, 5.88; N, 5.44; S, 6.23 Found: C, 60.70; H, 5.86; N, 5.45; S, 6.24.

*2.2.8. N-[1-(2,4-dimethoxyphenyl)-3-(4-methoxyphenyl)propan-2-yl]sulfamide (**20**)*

Pd-C (50 mg) and sulfamoylcarbamate **19** (0.50 g, 0.97 mmol) were added to a 100 mL flask containing 50 mL of MeOH. The flask was equipped with a balloon filled with 3 L of H_2 gas. The reaction mixture was deoxygenated by purging with H_2 gas and then hydrogenated at room temperature for 4 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel (25 g) column chromatography (EtOAc:hexane, 1:4) to obtaine desired sulfamide **20** (0.27 g, 73% yield) as a yellow viscous. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ= 7.16 (d, 2H, Ar-H, *J* = 8.8), 6.99 (d, 1H, Ar-H, *J* = 8.1 Hz), 6.84 (d, 2H, Ar-H, *J* = 8.8 Hz), 6.45 (d, 1H, Ar-H, *J* = 2.3 Hz), 6.41 (dd, 1H, Ar-H, *J* = 2.3 Hz and *J* = 8.1 Hz), 4.87 (d, 1H, NH, *J* = 7.7 Hz), 3.91 (bs, 2H, NH_2), 3.82-3.74 (m, 10H, 3OMe and CH), 2.80 (d, 2H, CH_2, *J* = 6.4 Hz), 2.77 (A part of AB, 1H, CH-Ha, *J* = 5.0 Hz and *J* = 13.9 Hz), 2.65 (B part of AB, 1H, CH-Hb, *J* = 8.7 Hz and *J* = 13.9 Hz), 2.65 (A part of AB 1H, CH-Ha', *J* = 8.7 Hz and *J* =13.9 Hz), 2.66 (B part of AB, 1H, CH-Hb', *J* = 8.7 Hz and *J* = 13.9 Hz).^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ= 160.1 (C), 158.6 (C), 158.5 (C), 131.9 (CH), 130.9 (2CH), 130.3 (C), 119.0 (C), 114.0 (2CH), 104.6 (CH), 98.9 (CH), 57.2 (CH), 55.7 (OCH_3), 55.5 (OCH_3), 55.4 (OCH_3), 41.3 (CH_2), 34.8 (CH_2). IR (CH_2CI_2, cm^{-1}): 3281, 3001, 2953, 2836, 1612, 1586, 1511, 1464, 1440, 1327, 1290, 1247, 1208, 1157, 1127, 1035. Anal. Calcd for ($C_{18}H_{24}N_2O_5S$): C, 56.83; H, 6.36; N, 7.36; S, 8.43 Found: C, 56.75; H, 6.22; N, 7.33; S, 8.40.

2.3. Protein Preparation

Receptors for induced fit docking were obtained from the RCSB Protein Data Bank (http://www.rcsb.org/). The human dopamine D_2 receptor (7DFP) was prepared using Maestro 13.4.134[22] Protein Preparation tool[23]. All receptors underwent preprocessing at pH 7.4, addressing missing residues and adjusting hydrogen atom conformations and charges. Receptor energy levels and geometries were optimized using the OPLS2004 force field, which accurately models molecular interactions in biomolecular systems. This approach ensures precise docking simulations and realistic results.

2.4. Ligand Preparation

Prior to conducting induced fit docking, we generated two-dimensional ligand structures using ChemDraw 15 in cdx format. These structures were subsequently imported into Maestro 13.4.134 for conversion to three-dimensional representations. Ligand ionization was performed utilizing LigPrep[24] within Maestro 13.4.134, maintaining pH conditions of 7.0 ± 2. We employed the OPLS2004 force field to achieve low-energy molecular geometries. This process involved the refinement of conformations and hydrogen atom positions, resulting in the production of structures with appropriate protonation states.

2.5. Induced Fit Docking

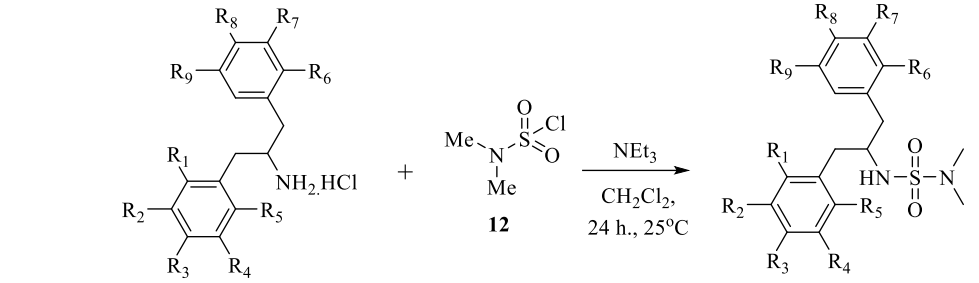
The Maestro 13.4.134 Induced Fit Docking[25] software was employed to analyze the interactions between ligands and receptors, following the IFD protocol. This process involved determining the coordinates of co-crystallized molecules within the catalytic active sites of receptors and generating grids in these areas. For the Human dopamine D_2 receptor (7DFP-SIP-A:1201), the coordinates were x: -93.17, y: -21.77, z: 213.25. The IFD procedure was executed by configuring the residues within a 5.0 Å radius of the ligand and utilizing a region comparable to the ligand's dimensions.

2.6. ADME Study

An analysis of drug likeness and adherence to Lipinski's Rule of Five was conducted for the compounds. The molecular structures, initially designed using ChemDraw 15, were subsequently imported into Maestro 13.4.134 for three-dimensional modeling. Employing the QikProb tool[26] in Maestro 13.4.134, we calculated various physicochemical properties including molecular weight, hydrogen bond donors and acceptors, solvent accessible surface area (SASA), predicted blood-brain barrier permeability (QPlogBB), predicted aqueous solubility (QPlogS), estimated human oral absorption, and potential violations of Lipinski's Rule of Five.

3. Results and Discussion

In one of our lately published studies, we have reported the synthesis of some dopamine derivatives including **7-11** and we described their anticholinergic properties.[21] The synthesis of starting compounds **7-11** were accomplished according to the literature procedure.[21]There are widespread studies on the development of new synthetic methods for the synthesis of sulfamides. The synthesis of these compounds from Ni(II),[27] Pd(II)[28] and Cu(II)[29] catalyzed intramolecular diamination, CSI,[30] SO_2Cl_2,[31,32] Burgess reagent,[33] *N,N'*-sulfuryldiimidazole,[34] catechol sulfate[35] and *N,N*-dimethylsulfamoyl chloride[36] has been addressed in the literature. In this study, we chosen to use the last method given above.[36] According to this method amine hydrochloride salts are reacted with **12** in the presence of excess amount of NEt_3 at rt. Therefore, the reactions of dopamine analogues **7-11** with *N,N*-dimethylsulfamoyl chloride (**12**) in the presence of NEt_3 gave sulfamide derivatives **13-17** incorporating dimethyl at terminal nitrogen with good yields (Scheme 1).

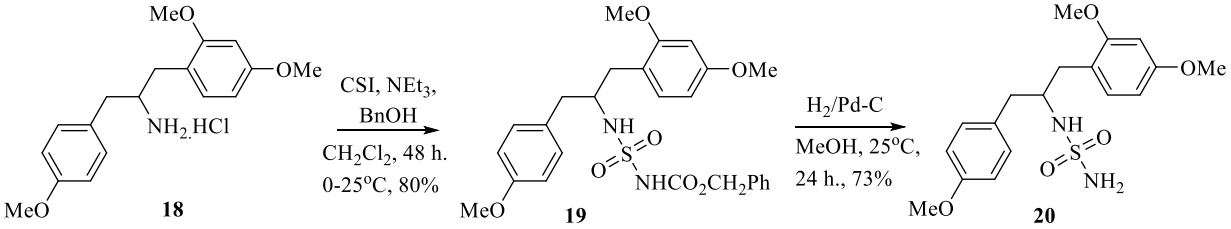


7 R_3=R_7=R_8=OMe, R_1=R_2=R_4=R_5=R_6=R_9=H
8 R_7=R_8=OMe, R_1=R_2=R_3=R_4=R_5=R_6=R_9=H
9 R_1=R_2=R_8=R_9=OMe, R_6=CH_3, R_3=R_4=R_5=R_7=H
10 R_1=R_2=R_7=R_8=OMe, R_3=R_4=R_5=R_6=R_9=H
11 R_2=R_3=R_6=R_8=OMe, R_1=R_4=R_5=R_7=R_9=H

13 R_3=R_7=R_8=OMe, R_1=R_2=R_4=R_5=R_6=R_9=H, 77%
14 R_7=R_8=OMe, R_1=R_2=R_3=R_4=R_5=R_6=R_9=H, 75%
15 R_1=R_2=R_8=R_9=OMe, R_6=CH_3, R_3=R_4=R_5=R_7=H, 79%
16 R_1=R_2=R_7=R_8=OMe, R_3=R_4=R_5=R_6=R_9=H, 74%
17 R_2=R_3=R_6=R_8=OMe, R_1=R_4=R_5=R_7=R_9=H, 76%

Scheme 1. Synthesis of sulfamide derivatives **13-17**

We thought that it would be more appropriate to synthesize a sulfamide that does not contain *N,N*-dialkyl substituted amine of sulfamide group and compare its activity with the compounds containing the *N,N*-dialkyl substituent at sulfamide functional group described above. The CSI method is widely used in the synthesis of sulfamides that do not contain an alkyl group in the terminal nitrogen.[30] In the synthesis of sulfamides with CSI method, firstly CSI is reacted with t-BuOH or BnOH. Then, the formed reactant is reacted with amines in the presence of NEt_3 to obtain the relevant sulfamoyl carbamates. If t-BuOH is used in the reaction, the Boc group of sulfamoyl carbamate is removed with trifluoroacetic acid.[20] If BnOH is used, then the relevant sulfamide is synthesized by using Pd-C catalyzed hydrogenolysis reaction.[37] In the present work BnOH was chosen for the synthesis of the title compound. In this context, BnOH was reacted with CSI at 0-25°C for 1 h then the occurred reactant benzyl (chlorosulfonyl)carbamate was treated with dopamine derivative amine hydrochloride salt **18** in the presence of NEt_3 to give benzyloxycarbamate **19** with very good yield. Pd-C catalyzed hydrogenolysis of carbamate **19** in MeOH at 25°C afforded the desired sulfamide **20** with the yield of 73% (Scheme 2).



Scheme 2. Synthesis of sulfamoylcarbamate **19** and sulfamide **20**

The dimethyl groups attached to the sulfamide functional group appear as singlets in the range of 2.39-2.32 ppm in the ^{1}H NMR spectrum. In addition, it was observed that the characteristic peaks of diasteretopic benzylic protons resonated as either an AB system or multiplets in the ranges of 2.87-2.79 ppm and 3.01-2.60 ppm. In the ^{1}H NMR spectrum, a characteristic peak corresponding to the CH protons on the carbon attached to the sulfamide functional groups were observed, resonating as a multiplet around 3.86–3.64 ppm. It was determined that methoxy substituents attached to aryl rings resonated as singlets in the range of 3.88-3.77 ppm. The NH protons of the *N,N*-dialkyl-substituted sulfamides **13–17** resonated as doublets between 4.60 and 4.10 ppm, while the NH proton of the unsubstituted sulfamide **20** appeared as a doublet at 4.87 ppm. The NH_2 protons of sulfamide **20** showed a singlet peak at 3.91 ppm in the ^{1}H NMR spectrum.

^{13}C NMR of the resulting products were examined and characteristic peaks supporting the structures were determined and explained below. Accordingly, it was determined that the peaks belonging to the CH_3s of *N,N*-dimethyl substituted sulfamides **13-17** were resonated in the range of

37.8-34.5 ppm. The carbons of two distinct CH_2 groups in the benzylic position were observed to resonate in the ranges of 41.5–39.8 ppm and 40.9–34.8 ppm, respectively. In addition to the determination of the resonance of the methoxy groups attached to the aryl ring in the range of 57.5-55.4 ppm, it was determined that the CH carbons to which the sulfamide functional groups are attached have a resonance in the range of 60.6-57.2 ppm. These NMR results confirm that the chemical structures of the synthesized final products are consistent with the expected spectroscopic data, supporting the successful synthesis and structural integrity of the compounds.

3.1 Molecular Docking Studies

3.1.1 Molecular Docking Validation

Prior to the induced fit docking procedure, a comprehensive validation process was implemented. This validation involved re-docking utilizing receptors (7DFP for Human dopamine D_2 receptor) and co-crystals (Human dopamine D_2 receptor for SIP-A:1201) of the receptors. Both proteins and co-crystals underwent preparation for the re-docking procedure. Grids comparable in dimensions to co-crystals were established within predetermined primary binding regions of the proteins. The re-docking process with human dopamine D_2 receptor and co-crystals yielded docking scores of -7.091, with a Glide emodel value of -68.388. The superposition tool was employed to calculate Root Mean Square Deviation (RMSD) values for these poses. For SIP-A:1201, the RMSD value was determined to be 0.3136 Å (Figure 2). The reliability of the validation is substantiated by the fact that the obtained RMSD values are below the threshold of 2.[38] The validation conducted from this viewpoint was deemed accurate.

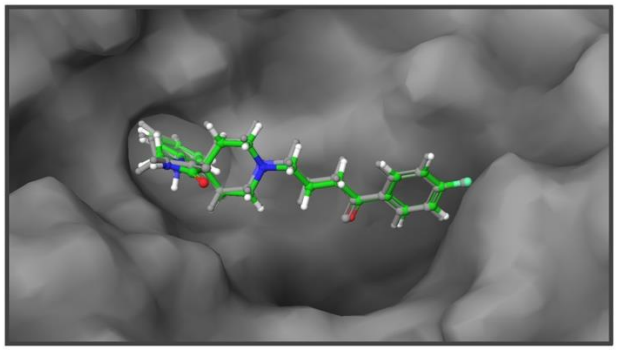


Figure 2. Docking methodology reliability test. The best-posed co-crystallized ligands are represented in green color ball and stick modelling and the best-posed docked ligands are represented in grey color ball and stick modelling for human dopamine D_2 receptor (SIP-A:1201).

3.1.2. Molecular Docking and ADME Studies

Molecular docking algorithms have been integral to the drug development process since their inception in the 1980s. The pioneering work in this field was conducted by Kuntz et al. in 1982,[39] who introduced an algorithm that treated both the ligand and receptor as rigid entities. This approach aligns with Emil Fischer's "key-lock" model of enzyme specificity, proposed in 1894.[40] However, this rigid model does not account for protein flexibility during ligand-receptor interactions. Koshland's induced fit theory, introduced in 1958, posits that protein-ligand interactions induce conformational changes in protein structures.[41] Consequently, our study employed the induced fit docking method, which incorporates the effects of ligand-receptor interactions on protein conformation in its calculations, providing a more comprehensive analysis.

For this purpose, proteins were obtained from the Protein Data Bank (https://www.rcsb.org/pdb) for the induced fit docking procedure. In particular, the human dopamine D_2 receptor structure (PDB

code: 7DFP) was selected. This structure, with a resolution of 3.10 Å, is suitable for the induced fit docking procedure.[42]

Human dopamine D_2 receptor (7DFP) is a protein with a mass of 88.31 kDa, consisting of 5925 atoms, 770 modeled residues, and a total of 795 residues. Active sites contain 8-[4-(4-fluorophenyl)-4-oxidanylidene-butyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one co-crystals of the receptor within an area of approximately 15 Å in diameter. 8-[4-(4-fluorophenyl)-4-oxidanylidene-butyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (SIP-A:1201) located in the catalytic active site is surrounded by ILE 184, ILE 183, CYS 182, TRP 100, PHE 110, VAL 111, VAL 87, ASP 114, VAL 115, CYS 118, THR 119, LYS 121, ILE 122, PHE 198 and SER 197 amino acids.

When examining the interactions between SIP and the active site, a salt bridge at a distance of 3.02 Å and H-bond interactions at a distance of 2.04 Å are observed between the amine in the piperidine ring and ASP 114. In addition, in the 3D diagram, aromatic H-bond interactions are observed between ASP 114 and the benzene ring at a distance of 2.54 Å, and also between the benzene ring and PHE 110. As a result of the study carried out according to the induced fit docking methodology, the IFD scores resulting from the interaction between the human dopamine D_2 receptor (7DFP) active site and compounds (**R**)-**13-17**, (**R**)-**20** and (**S**)-**13-17**, (**S**)-**20** were calculated (Table 1). It was determined that the best results belonged to the enantiomers of the unsubstituted sulfamide **20**. Based on these results, the IFD scores for (**R**)-**20** and (**S**)-**20** were calculated as -8.253 and -6.936, respectively. Additionally, the Glide emodel scores for these compounds were determined to be -55.892 and -65.235, respectively.

Table 1. IFD scores and glide emodel of compound (**R**)-**13-17,** (**R**)-**20,** (**S**)-**13-17,** (**S**)-**20,** Quinagolide and Cabergoline in the catalytic sites of human dopamine D_2 receptor (7DFP)

Compounds	**IFD Score**	**Glide emodel**
	Human dopamine D_2 receptor (7DFP)	
(R)-13	-6.491	-61.001
(R)-14	-6.915	-56.077
(R)-15	-6.641	-61.597
(R)-16	-6.143	-59.275
(R)-17	-6.103	-53.813
(R)-20	**-8.253**	**-53.892**
(S)-13	-6.230	-59.305
(S)-14	-6.871	-65.927
(S)-15	-6.658	-67.119
(S)-16	-6.424	-63.025
(S)-17	-5.572	-53.892
(S)-20	**-6.936**	**-65.235**
Quinagolide	-7.732	-53.813
Cabergoline	-7.729	-69.787

When the interactions observed between compound (**R**)-**20** and the active site of human dopamine D_2 receptor (7DFP) in the 2D diagram are examined, it is seen that ASP 114 amino acid forms an H-bond interaction with the amine (SNH) attached to the sulfamide at a distance of 1.67 Å and again between ASP 114 and the other amine (SNH_2) attached to the sulfamide at a distance of 2.00 Å. The aromatic H-bond interaction can be seen in the 3D diagram. This aromatic H-bond interaction is observed between VAL 87 and the anisole ring at a distance of 3.58 Å (Figure 3a).

When the interactions observed between compound (**S**)-**20** and the active site of the human dopamine D_2 receptor (7DFP) in the 2D diagram are examined, it is seen that the ASP 114 amino acid forms an H-bond interaction with the sulfamide amine (SNH_2) at a distance of 1.92 Å. In addition, an aromatic H-bond can be seen in the 3D diagram. This aromatic H-bond interaction is observed between the CYS 182 amino acid and the anisole ring at a distance of 2.55 Å (Figure 3b).

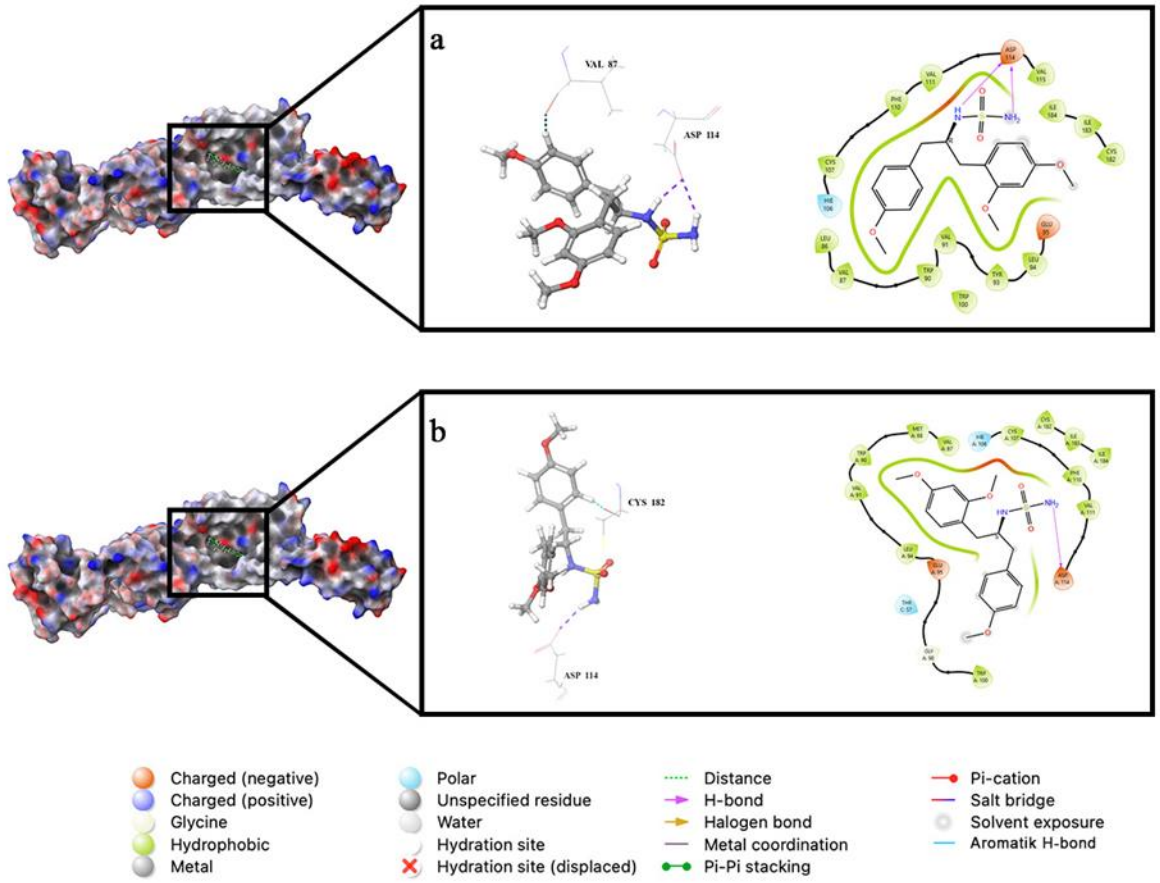


Figure 3. 2D and 3D ligand-receptor interaction profiles of best-posed ligand into the receptors. Compound **(R)-20 (a)** and **(S)-20 (b)** human dopamine D_2 receptor (7DFP)

Table 2. ADME properties and drug similarity results of compounds (**R**)-**13-17,** (**R**)-**20** and (**S**)-**13-17,** (**S**)-**20.**

Compounds	MW mol[a]	Donor HB[b]	Accpt HB[c]	SASA[d]	QPlog[e] Po/w	QPlog BB[f]	QPlogS[g]	% Human Oral Absorption[h]	Rule Of Five[i]
(R)-13	408.512	1.00	7.25	698.957	4.119	-0.615	-4.674	100.00	0
(R)-14	378.485	1.00	6.50	654.440	3.949	-0.517	-4.341	100.00	0
(R)-15	452.565	1.00	8.00	696.840	4.119	-0.700	-4.189	100.00	0
(R)-16	438.538	1.00	8.00	699.660	4.096	-0.639	-4.243	100.00	0
(R)-17	438.538	1.00	8.00	702.464	4.036	-0.678	-4.291	100.00	0
(R)-20	380.458	3.00	7.25	655.283	2.742	-1.322	-3.926	92.384	0
(S)-13	408.512	1.00	7.25	685.377	4.089	-0.600	-4.437	100.00	0
(S)-14	378.485	1.00	6.50	653.075	4.030	-0.482	-5.030	100.00	0
(S)-15	452.565	1.00	8.00	750.366	4.638	-0.782	-5.920	100.00	0
(S)-16	438.538	1.00	8.00	720.499	4.125	-0.707	-5.636	100.00	0
(S)-17	438.538	1.00	8.00	726.104	4.241	-0.655	-5.636	100.00	0
(S)-20	380.458	3.00	7.25	644.760	2.775	-1.183	-4.701	94.516	0

[a]Moleculer Weight (acceptable range:<500). [b]Donor HB: Hyrogen bond donor (acceptable range: 0-5). [c]Accpt HB: Hyrogen bond accetor (acceptable range: 0-5). [d]SASA:Total solvent accessible surface area using a probe with a 1.4 radius (acceptable range:300-1000). [e]QPlog Po/w Predicted octanol/water partition coefficient (–2.0 – 6.5). [f] QPlog BB Predicted Blood-brain partition coefficient (acceptable range: -2-1.2). [g]QPlogS: Predicted aqueous solubility (–6.5 – 0.5). [h]% Human Oral Absorption: Predicted human oral absorption on 0 to 100% scale (<24% is poor and >80% is high). [i]Lipinski Rule of Five

In-silico drug similarities were also calculated for (**R**)-**13**-**17**, (**R**)-**20** and (**S**)-**13**-**17**, (**S**)-**20**. From these results, it was understood that all ligands comply with Lipinski's rule of five[43] (Table 2).

4. Conclusion

In conclusion, starting from dopamine analogues six novel sulfamides were synthesized in good yield. As dopaminergic sulfamides show antihyperprolactinemic effects, the synthesized compounds were evaluated for their *in silico* antihyperprolactinemic actions. The R-enantiomer of unsubstituted sulfamide **20** demonstrated a higher binding affinity to the D_2 receptor compared to the standard dopaminergic agents Cabergoline and Quinagolide. Additionally, ADME assessment revealed that this compound adhered fully to Lipinski's Rule of Five, indicating favorable drug-likeness without deviations. Based on this study, it can be concluded that asymmetric syntheses of unsubstituted sulfamide derivatives can be performed, and these derivatives can be used as lead compounds for the treatment of hyperprolactinemia in advanced drug development studies.

Acknowledgements

We are greatly indebted to The Scientific and Technological Research Council of Turkey (TUBITAK, Grant no. TBAG-112T881) and Ataturk University for their financial supports of this work.

Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

Conflict of Interest

The authors declare no conflict of interest.

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