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Original Article

SYNTHESIS AND DOCKING STUDY OF 3-(*N*-ALKYL/ARYL PIPERIDYL) INDOLES WITH SEROTONIN-5HT, H1 AND CCR2 ANTAGONIST RECEPTORS

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ABSTRACT

Objective: Synthesis and *in silico* studies of 3-(*N*-alkyl/aryl piperidyl) indole derivatives **4a-m.**

Methods: The 3-(*N*-alkyl/aryl piperidyl)indole derivatives **4a-m** were synthesized *via* reductive amination of **3a-m** by reacting with various aldehydes and ketones in the presence of sodium cyanoborohydride in acetic acid medium in good to excellent yields.

Results: Excellent yields of 3-(*N*-alkyl/aryl piperidyl) indole derivatives **4a-m** were obtained in convenient and economical method. NMR and LCMS were recorded for all synthesized compounds. The binding site analysis of the synthesized compounds **4a-m** with serotonin-5HT, H1 and CCR2 antagonist receptors that are known to responsible for neurological disorders and inflammatory responses were checked through molecular docking study. The results reveal that the compounds **4a, 4b, 4i, 4k** and **4l** have shown significant interaction with serotonin-5HT and H1 receptors. These interactions attributes to the presence of aliphatic chain at the piperidyl nitrogen in their structures.

Conclusion: Library of 3-(*N*-alkyl/aryl piperidyl) indoles **4a-m** were constructed with appropriate substitution at different positions by simple and convenient method. This method tolerates different substitution on the indole ring nitrogen. The facile synthesis and easy isolation of products makes the method an attractive option for the large scale synthesis of various 3-(*N*-alkyl/aryl piperidyl) indoles. The docking study was performed with modelled receptor 5HT, H1 and CCR2 reveals that the compounds **4a-m** shows better interaction with serotonin-5HT, H1 receptor than with the CCR2 receptors.

Keywords: Piperidylindole; Serotonin; 5-hydroxytryptamine; CCR2; Histamine-1 receptor.

INTRODUCTION

The 3-substituted indoles have been found to be more versatile intermediates in organic synthesis due to the electrophilic feasibility of indole at 3-position [1]. Many 3-(piperidyl)indoles were found as common building blocks [1] in many pharmaceutical ingredients like CCR2 antagonist [2], antihistamine [3], H_1 antagonist [4], antiallergic [5], $5HT_1$ agonist [6], serotonergic and schizophrenia related pharmocophores [7]. Besides the importance of 3-(piperidyl)indoles, the protein serotonin (5-hydroxytryptamine, 5-HT) receptor was found to be highly effect in membrane-bound proteins, which found in different tissues in central nervous system (CNS) as well as nonneuronal tissue in the gut cardiovascular systems and blood [8]. The physiology of serotonin-5HT receptor in disease state shows it can involve in schizophrenia, anxiety, mood etc. The 5HT receptor inhibits presynaptic of 5-HT and elevate its concentration in the synaptic cleft [9]. *N,N*-dipropyl-8-hydroxy-2-aminotetralin binds with serotonergic-5HT receptor with great selectivity of GPCR and regulates cAMP formation to transport signal [10, 11]. The SAR study of agonist 5-chloro-2-methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole [12] and 2-methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indoles [13] also inhibits 5HT receptor.

The other biologically functional proteins CCR2 and histamine-1 (H^1) receptors also binds with 3-hydroxymethylbenzofuran and 2-(methoxymethyl)-2-(2′-methoxymethyl-4′-methylphenyl)-butanone derivatives shows antagonist property with selected proteins [14]. The structural activity relationship studies reveals that the substituents like -F,-CH_3,-CF_3 in the aryl ring of the 3-(piperidyl) indoles increases the receptor activity in antidepressants [3]. In synthetic point of view, the *N*-substitution at piperidyl ring, trifluoromethyl substitution at aromatic ring and substitution at indole nitrogen has become challenge for synthetic chemist. Based on the forgone evidence, in which various indole ligands that can effectively binds to 5HT, H1 and CCR2 receptors in specific, and in continuation of our study on bioactive molecules [15-20] in this paper we report the synthesis and docking study of 3-(*N*-alkyl/aryl piperidyl)indoles **4a-m** with 5HT, H1 and CCR2 receptor proteins. Hence, considering the difficulties in the preparation of 3-(piperidyl) indole derivatives [2-5, 21-32], difficulties such as use of expensive reagents, drastic reaction conditions and poor yield, in the present investigation we report simple, inexpensive and convenient general route for the synthesis of diversified 3-(piperidyl) indole derivatives **4a-m**.The molecular docking results and characterization data of various 3-(piperidyl) indoles are presented in experimental section.

MATERIALS AND METHODS

Chemistry

The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a 400 MHz and 100 MHz Bruker spectrometer using $CDCl_3$ or DMSO-d_6 solvents and TMS as internal standard. Mass spectra were recorded on LCMS Agilent1200 series single quadrapole mass analyzer. Melting points were recorded (uncorrected) in Buchi Melting Point B-545 instrument. The purity of the compounds was checked by TLC and was further purified by column chromatography. Synthesis of all the new compounds (**4a-m**) was carried out by using all commercially available indoles. The $NaBH_4$, $NaCNBH_3$, various aldehydes and amines are of analytical grade.

Synthesis of 5-(benzyloxy)-1-(cyclopropylmethyl)-3-[1-(3-methyl-butyl) piperidin-4-yl]-1*H*-indole (4a)

Step1: The 5-(benzyloxy)-1-(cyclopropylmethyl)-1*H*-indole **1a** (3.6 mmol, 1 g), 4-piperidone monohydrate hydrochloride (4.3 mmol, 0.66 g) were dissolved in glacial acetic acid (10 mL) and to this 1M phosphoric acid solution (4.2 mL) was added. The resulting suspension was magnetically stirred under heating at 95 ^{o}C for

about 16 h (complete solution was obtained at approximately 1h at the elevated temperature). The reaction mass was then cooled to room temperature, the solvent was removed under reduced pressure. The residue obtained was triturated in diethyl ether and ethyl acetate mixture (1:1 v/v) to get the product **2a**, which was then taken directly for step 2.

Step2: To the suspension of $NaBH_4$ (5.4 mmol, 0.2 g) and the step **1** product **2a** (2.1 mmol, 1 g) in THF (15 mL) was slowly added glacial acetic acid (3 mL) while keeping the temperature below 30 ^oC and stirring was continued for 0.5 h at room temperature. Then 35% HCl solution (1.5 mL) was slowly added to the reaction mixture and stirred. The reaction mixture was allowed to stand for 0.5 h at room temperature and later water (5 mL) was added. Subsequently, the THF was removed from the reaction mixture under reduced pressure.

Further the reaction mass was neutralized with saturated Na_2CO_3 solution. The crude product was extracted with methylene dichloride (15 × 3 mL), the organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to residue. The residue, thus obtained was purified by column chromatography (using silica gel (230-400) as stationery phase, gradient of dichloromethane and methanol as mobile phase (9:1 v/v)) to get 94% yield of **3a** having melting point 79-80 ^oC. The product **3a** thus obtained was taken for step 3.

Step3: Step-2 product **3a** (2.7 mmol, 1 g) and 3-methylbutanal (3.0 mmol, 0.32 mL) were dissolved in methanol (10 mL), 2 drops of acetic acid was added and the mixture was stirred for 30 min. Further sodium cyanoborohydride (4.5 mmol, 0.25 g) was added and the mixture was again stirred at 40 ^oC for 2-3 h. After 3 h the reaction mixture was diluted with water (20 mL) and was extracted with ethyl acetate (20 × 3 mL). The organic layer thus obtained was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated to residue. The residue obtained was purified by column chromatography (using silica gel (230-400) as stationery phase, gradient of dichloromethane and methanol as mobile phase (9:1 v/v)) to obtain the desired product **4a**. Similarly, the compounds 4b-m were synthesized without isolating the intermediates (3b-m).

Spectral data

5-(benzyloxy)-1-(cyclopropylmethyl)-3-(piperidin-4-yl)-1*H*-indole (3a).

^{1}H-NMR (400 MHz, $CDCl_3$) δ= 0.34 (q, J = 5.2Hz, 2H), 0.61(q, J = 4.8 Hz, 2H), 1.21-1.25 (m, 1H), 1.66-1.82 (m, 2H), 2.03 (d, J = 12.4Hz, 2H), 2.79-2.90 (m, 3H) 3.21(d, J = 11.6 Hz, 2H), 3.89 (d, J = 6.8 Hz, 2H), 5.12 (s, 2H), 6.93 (d, J = 2.4 Hz, 1H), 6.96 (s, 1H), 7.17 (d, J = 2.4 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 7.32 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 7.2 Hz, 2H), 7.49 (d, J = 7.2 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ= 4.05, 11.27, 33.98, 34.15, 47.19, 50.68 71.27, 103.23, 110.09, 112.11, 119.94, 123.90, 127.14, 127.62, 127.71, 128.46, 132.17, 137.82, 152.61ppm; MS: m/z = 361.2 (M+1). Anal.Calcd. for $C_{24}H_{28}N_2O$= C, 79.96; H, 7.83; N, 7.77% Found: C, 79.85; H, 7.80; N, 7.72%.

5-(benzyloxy)-1-(cyclopropylmethyl)-3-[1-(3-methyl-butyl) piperidin-4-yl]-1*H*-indole (4a).

^{1}H-NMR (400 MHz, $CDCl_3$). δ=0.34 (q, J=4.8Hz,, J=4.8Hz,2H), 0.61(q, J=6Hz, J=4.8Hz,2H), 0.94 (d, J=6.44Hz,6H), 1.22-1.30(m, 1H), 1.53-1.64 (m, 3H), 2.08-2.38(m, 1H), 2.35(t, J=11.6Hz,2H), 2.61(t, J=8Hz,2H), 2.79-2.92(m, 1H), 3.28(d, J=11.6Hz,2H),3.89(d, J=6.8Hz,2H), 5.12 (s, 2H), 6.95 (dd, J_1=2.4Hz, J_2=6.4Hz,1H), 6.99(s. 1H), 7.168(d, J=2.4Hz,1H), 7.24(d, J=8.8Hz,1H), 7.31-7.34(m, 1H), 7.39(t, J=7.52Hz,2H), 7.51(d, J=1.6Hz,2H).^{13}C-NMR (100 MHz, DMSO-d_6) δ =4.07, 11.27, 22.63, 23.18, 26.79, 29.69, 31.80, 33.05, 34.57, 50.71, 53.70, 53.70, 56.70, 71.23, 76.69, 77.01, 77.33, 103.02, 110.18, 112.15, 124.11, 127.13, 127.65, 127.74, 128.47, 132.11, 137.77, 152.68ppm; MS: m/z = 431.4 (M+1). Anal.Calcd. for $C_{29}H_{38}N_2O$= C, 80.88; H, 8.89; N, 6.51% Found: C, 80.97; H, 8.92; N, 6.56%.

3-(1-isopentylpiperidin-4-yl)-1-methyl-2-phenyl-1*H*-indole (4b).

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 0.86 (d, J =6.8 Hz, 6H), 1.31 (q, J = 7.2 Hz, 2H), 1.53-1.62 (m, 3H), 1.87 (br, 1H), 2.11 (q, J = 9.6 Hz, 2H), 2.29-2.33 (m, 2H), 2.49-2.56 (m, 1H), 2.93 (d, J = 11.2 Hz, 2H), 3.48 (s, 3H), 7.03 (t, J = 7.2 Hz, 1H), 7.15 (t, J = 7.56Hz, 1H), 7.39-7.45 (m, 3H), 7.46-7.55 (m, 3H), 7.70 (d, J = 8 Hz, 1H);^{13}C-NMR (100 MHz, DMSO-d_6) δ = 23.08, 26.39, 30.97, 33.10, 54.56 57.00, 110.51, 116.56, 119.14, 120.19, 121.20, 128.71, 128.94, 131.05, 132.18, 137.19, 137.41ppm; MS: m/z = 361.2 (M+1). Anal.Calcd. for $C_{25}H_{32}N_2$ = C, 83.28; H, 8.25; N, 7.77% Found: C, 83.18; H, 8.97; N, 7.67%.

3-(1-(2,3-difluorobenzyl)piperidin-4yl)-6-trifluoromethyl)-1*H*-indole (4c).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.90 (q, J = 12.4 Hz, 2H), 2.04 (d, J = 11.2 Hz, 2H), 2.34 (t, J = 12 Hz, 2H), 2.85-2.86 (m, 1H), 3.14 (d, J = 11.6 Hz, 2H), 3.75 (s, 2H), 4.28 (br, 2H), 6.80-6.91 (m, 2H), 7.10 (s, 1H), 7.32 (d, J = 8 Hz, 1H), 7.45 (q, J = 8.4 Hz, 1H), 7.62 (s, 1H), 7.69 (d, J = 8 Hz, 1H), 8.45 (s, br); ^{13}C-NMR (100 MHz, DMSO-d_6) δ = 33.16, 53.83, 54.92, 104.03, 104.29, 109.20, 111.55, 111.75, 114.76, 119.87, 120.58, 121.55, 124.73, 129.20, 133.17, 133.23, 135.54ppm; MS: m/z = 395.2 (M+1). Anal.Calcd. for $C_{21}H_{19}F_5N_2$= C, 63.95; H, 4.86; N, 7.10% Found: C, 64.06; H, 4.89; N, 7.21%.

3-(1-(2,3-diflurobenzyl)piperidin-4-yl)-5-chloro-1-(cyclopropylmethyl)-1*H*-indole (4d).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.34 (q, J = 5.2 Hz, 2H), 0.62 (q, J = 5.0 Hz, 2H), 1.20-1.24 (m, 1H), 1.72 (q, J = 3.16 Hz, 2H), 2.15 (d, J = 12.8 Hz, 2H), 2.25 (t, J = 11.36 Hz, 2H), 3.04 (d, J = 11.6 Hz, 2H), 3.34-3.42 (m, 1H), 3.63 (s, 2H), 3.91 (d, J=6.8 Hz, 2H), 6.79-6.89 (m, 2H), 7.03-7.09 (m, 3H), 7.20-7.23 (m, 1H), 7.32 (q, J = 6.84 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ = 3.66, 11.39, 32.31, 33.6, 49.78, 52.31, 53.97, 59.19, 109.14, 119.28, 120.31, 121.51, 123.07, 124.62, 125.74, 137.52, 142.11ppm; MS : m/z = 415.2 (M+1). Anal.Calcd. for $C_{24}H_{25}ClF_2N_2$= C, 69.47; H, 6.07; N, 6.75% Found: C, 69.55; H, 6.09; N, 6.79%.

***N,N*-dimethyl-4-((4-(2-phenyl-1*H*-indol-3-yl)piperidin-1-yl)methyl)benzenamine (4e).**

^{1}H-NMR (400 MHz, DMSO-d_6) δ= 1.66 (d, J = 11.4 Hz, 2H), 1.91 (t, J = 11.48 Hz, 2H), 2.22 (q, J = 9.84 Hz, 2H), 2.85 (s, 6H), 2.89-2.92 (m, 3H), 3.37 (s, 2H), 6.68 (d, J = 8.44 Hz, 2H), 6.97 (t, J = 7.84 Hz, 1H), 7.06 (t, J = 7.16 Hz, 1H), 7.12 (d, J = 8.44 Hz, 2H), 7.33(d, J = 8.04 Hz, 1H), 7.37 (s, 1H), 7.38-7.52 (m, 4H), 7.69 (d, J=8 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 29.69, 32.25, 34.67, 40.72, 54.25, 62.93, 110.92, 112.36, 117.29, 119.21, 121.18, 121.88, 127.53, 127.71, 128.74, 130.29, 133.61, 134.11, 136.22, 149.80ppm; MS: m/z = 410.2 (M+1). Anal.Calcd. for $C_{28}H_{31}N_3$ = C, 82.11; H, 7.63; N, 10.26% Found: C, 82.00; H, 7.64; N, 10.15%.

3-(1-(2-fluoro-5-methylbenzyl)piperidin-4-yl)-2-phenyl-1*H*-indole (4f).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.78 (d, J = 12.8 Hz, 2H), 2.12 (t, J = 11.6 Hz, 2H), 2.34 (s, 3H), 2.38-2.46 (m, 2H), 2.89-2.93 (m, 1H), 3.04 (d, J = 11.2 Hz, 2H), 3.62 (s, 2H), 6.92 (t, J = 9.6 Hz, 1H), 7.02-7.05 (br, 1H), 7.10 (t, J = 7.6 Hz, 1H) 7.18 (t, J =7.2 Hz 1H) 7.23 (d, J = 6.8 Hz, 1H) 7.35-7.41 (m, 2H) 7.47-7.50 (m, 3H) 7.94 (d, J = 8 Hz, 1H)8.0 (br, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 20.72, 32.30, 34.54, 54.22, 55.63, 110.95, 114.64, 114.87, 117.19, 119.22, 121.12, 121.90, 127.51, 128.72, 132.07, 133.16, 134.16, 136.21ppm; MS: m/z = 399.2 (M+1). Anal.Calcd. for $C_{27}H_{27}FN_2$= C, 81.37; H, 6.83; N, 7.03% Found: C, 81.50; H, 6.86; N, 7.10%.

3-(1-(2,3-difluorobenzyl)piperidin-4-yl)-2-phenyl-1*H*-indole (4g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.79 (d, J = 13.04 Hz, 2H), 2.10 (t, J = 11.2 Hz, 2H), 2.43 (q, J = 13.04 Hz, 2H), 2.91-2.94 (m, 1H), 3.01(d, J = 10.4, 2H), 3.62 (s, 2H), 6.79 (t, J = 7.2 Hz, 1H), 6.89 (t, J = 8 Hz, 1H), 7.12 (t, J = 7.2 Hz, 1H), 7.19 (t, J = 7.2 Hz, 1H), 7.32 (d, J= 7.6 Hz, 1H), 7.37-7.44 (m, 2H), 7.47–7.49 (m, 5H), 7.93 (d, J = 7.6 Hz, 1H), 8.00 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ = 32.43, 34.51, 54.22, 54.90, 103.76, 104.02, 104.28, 111.61, 111.81, 115.80, 118.84, 120.53, 121.45, 121.67, 127.25, 127.95, 129.13, 133.09, 133.67, 134.54,

136.83ppm; MS: m/z = 403.2 (M+1). Anal.Calcd. for $C_{26}H_{24}F_2N_2$= C, 77.59; H, 6.01; N, 6.96% Found: C, 77.71; H, 6.07; N, 7.05%.

2-phenyl-3-(1-((thiazol-4-yl)methyl)piperidin-4-yl)-1*H*-indole (4h).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.80 (d, *J* = 12.8 Hz, 2H), 2.27 (t, *J*=11.6 Hz, 2H), 2.46 (q, *J* = 12.8 Hz, 2H), 2.94-2.99 (m, 1H), 3.10 (d, *J* = 10.8 Hz, 2H), 3.92 (s, 2H), 7.12-7.16 (m, 1H), 7.20 (t, *J* = 6.8 Hz, 1H), 7.32 (s,1H), 7.37-7.42 (m, 2H), 7.48-7.50 (m, 4H),7.72 (s, 1H), 7.94-7.98 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) *δ* = 32.45, 34.2, 54.61, 59.65, 112.01, 115.70, 118.90, 120.42, 120.84, 121.49, 127.24, 128.00, 129.15, 133.65, 134.59, 136.86, 142.63ppm; MS: m/z = 374.2 (M+1). Anal.Calcd. for $C_{23}H_{23}N_3S$ = C, 73.96; H, 6.21; N, 11.25; S, 8.58% Found: C, 73.89; H, 6.19; N, 11.23; S, 8.55%.

3-(1-(cyclopropylmethyl)piperidin-4yl)-1-methyl-2-phenyl-1*H*-indole (4i).

^{1}H-NMR (400 MHz, DMSO-d_6) *δ* = 0.11 (d, *J* = 4.48 Hz, 2H), 0.48 (d, *J* = 5.6 Hz, 2H), 0.82-0.92 (m,1H), 1.67 (d, *J* = 12 Hz, 2H), 2.10-2.20 (m, 4H), 2.2 (br,2H), 2.58-2.67 (m, 1H), 3.14 (d, *J* = 9.6 Hz, 2H), 3.48 (s, 3H), 7.05 (t, *J* = 7.16 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.40-7.43 (m, 3H) 7.50 (d, *J* = 8 Hz, 1H), 7.5-7.56 (m, 2H), 7.75 (d, *J* = 8 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) *δ* 4.33, 21.56, 30.99, 54.07, 110.56, 119.16, 120.20, 121.61, 126.12, 128.74, 128.98, 131.06, 132.10, 137.24, 137.39ppm; MS: m/z = 345.2 (M+1). Anal.Calcd. for $C_{24}H_{28}N_2$ = C, 83.68; H, 8.19; N, 8.13% Found: C, 83.63; H, 8.17; N, 8.07%.

5-chloro-1-methyl-3-(1-(thiazol-4-yl)methyl)piperidin-4-yl)-1*H*-indole (4j).

^{1}H-NMR (400 MHz, $CDCl_3$)*δ* = 1.76 (q, *J*= 12, 10.8 Hz, 2H), 2.15 (d, *J* = 12.8 Hz, 2H), 2.40 (t, *J* = 11.6 Hz, 2H), 3.11 (d, *J* = 11.2 Hz, 2H), 3.37-3.43 (m, 1H), 3.74 (s, 3H), 3.96 (s, 2H), 6.9 (s, 1H), 7.04-7.17 (m, 2H), 7.18 (d, *J* = 8 Hz, 1H), 7.31 (d, *J* = 3.2 Hz, 1H), 7.74 (d, *J* = 3.2 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) *δ*= 32.60, 32.76, 34.05, 53.94, 59.14, 108.96, 119.12, 119.42, 120.33, 121.59, 126.95, 142.13ppm; MS: m/z = 346.0 (M+1). Anal.Calcd. for $C_{18}H_{20}ClN_3S$ = C, 62.50; H, 5.83; N, 12.15; S, 9.27% Found: C, 62.56; H, 5.86; N, 12.25; S, 9.12%.

5-chloro-3-(1-isopentylpiperidin-4-yl)-1*H*-indole (4k).

^{1}H-NMR (400MHz, $CDCl_3$) *δ* = 0.95 (d, *J* = 6Hz, 6H), 1.55-1.68 (m, 3H), 1.94-2.03 (m, 2H), 2.1-2.22 (m, 4H), 2.54 (t, *J* = 11.2 Hz, 2H), 2.8-2.84 (m, 2H), 3.44-3.5 (m, 3H), 7.03-7.07 (m, 3H), 7.30 (d, *J* = 4Hz, 1H), 9.77 (br, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) *δ*= 22.47, 26.64, 31.99, 32.46, 33.27, 53.09, 56.03, 110.28,120.0, 120.3, 121.38, 122.2, 123.32, 125.73, 138.01ppm; MS: m/z = 305.2 (M+1). Anal.Calcd. for $C_{18}H_{25}ClN_2$ = C, 70.92; H, 8.27; N, 9.19% Found: C, 70.99; H, 8.25; N, 9.12%.

5-chloro-1-(cyclopropylmethyl)-3-[1-(1,3-thiazol-2-ylmethyl)piperidin-4-yl]-1*H*-indole (4l).

^{1}H-NMR (400 MHz, DMSO-d_6) *δ* = 0.39 (q, *J* = 8.8, 2H), 0.49 (q, *J* = 7.6, 2H), 1.19-1.12 (m, 1H), 1.65 (q, *J* = 12.0, 2H), 2.02 (d, *J* = 12, 2H), 2.28(t, *J* = 10.8, 2H), 3.01 (d, *J* = 11.2, 2H), 3.25 (t, *J* = 12, 2H), 3.87 (s, 2H), 4.0 (d, *J* = 6.9, 2H), 7.0 (d, *J* = 7.36, 1H), 7.07 (t, *J* = 7.68, 1H), 7.38 (s, 1H), 7.46 (d, *J* = 8, 2H), 7.65 (d, *J* = 3.24, 1H), 7.73 (d, *J* = 3.2, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) *δ* = 3.74, 11.48, 32.87, 34.14, 49.85, 54.05, 59.27, 109.23, 119.35, 119.45, 120.4, 121.59, 123.14, 124.69, 125.83, 137.59, 142.18ppm; MS: m/z = 386.0 (M+1). Anal.Calcd. for $C_{21}H_{24}ClN_3S$ = C, 65.35; H, 6.27; N, 10.89; S, 8.31% Found: C, 65.31; H, 6.25; N, 10.85; S, 8.26%.

3-(1-isopentylpiperidin-4-yl)-6-isopropyl-1*H*-indole (4m).

^{1}H-NMR (400 MHz, DMSO-d_6) *δ* = 0.87 (d, *J* = 6.6, 6H), 1.22 (d, *J* = 6.88, 6H), 1.34 (q, *J* = 7.92, 2H), 1.55-1.70 (m, 3H), 1.91 (br, 2H), 2.03 (t, *J* = 11.4, 2H), 2.32(t, *J* = 7.48, 2H), 2.66-2.69 (m, 1H), 2.91-2.96 (m, 3H), 6.85 (d, *J* = 8.24, 1H), 6.98 (s, 1H), 7.13 (s, 1H), 7.42 (d, *J* = 8.16, 1H), 10.59(br, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) *δ* = 21.31, 22.69, 25.94, 32.81, 33.35, 33.67, 35.59, 54.04, 56.50, 108.41, 117.35, 118.42, 119.47, 119.95, 124.66, 136.75, 141.32ppm; MS: m/z = 313.2 (M+1). Anal.Calcd. for $C_{21}H_{32}N_2$ = C, 80.71; H, 10.32; N, 8.96% Found: C, 80.69; H, 10.34; N, 8.87%.

***In silico* molecular docking studies**

Selection of target protein

H1 antihistamines, CCR2 antagonists and 5HT-antagonists protein structures were retrieved from PDB database. Serotonin 5HT receptors complex with cytochrome-b with 3D structure (PDBID: 4IAR) shows antipsychotics propertiy. Histamine H(1) receptor antagonists protein (PDB ID: 3RZE) structure is effective on allergic reactions, Chemokine receptor type 2 (CCR2) proteins play an important role in inflammatory reactions and cognitive function in immune system (PDB ID: 1KAD) and these proteins were potentially targeted for binding with 3-(*N*-alkyl/aryl piperidyl)indole derivatives **4a-m**.

Active site prediction

Identifying the position of active site and ligand binding sites were predicted using Q-SiteFinder. The structural analysis of ligand coordinates should be separated from LigandSeek and remaining HETATM was converted into ATOM. Q-SiteFinder succeeds in this case because it uses the probe energy as ranking schema rather than the size of the pocket.

RESULTS AND DISCUSSION

Our aim was to prepare structurally distinct library of 3-(piperidyl) indole (**4a-m**) under less hazardous and more economical condition. Thus we started the initial synthesis by treating indole **1a** with 4-piperidone monohydrate hydrochloride in acetic acid/H_3PO_4 reflux condition.

The obtained phosphate salt **2a¹** was basified to get **2a** and it was taken to next step for reduction. However, we found from the literature that the phosphate salt can be used as such for reduction step [10]. To our delight reduction of the phosphate salt **2a¹** was smooth and furnished good yield of **3a**. (Scheme 1).In order to avoid tedious removal of phosphoric acid, indole and 4-piperidone monohydrate hydrochloride was taken in stiochiomitric amount of phosphoric acid. After the reaction completion the solvent acetic acid was removed under reduced pressure and taken as such for next step.

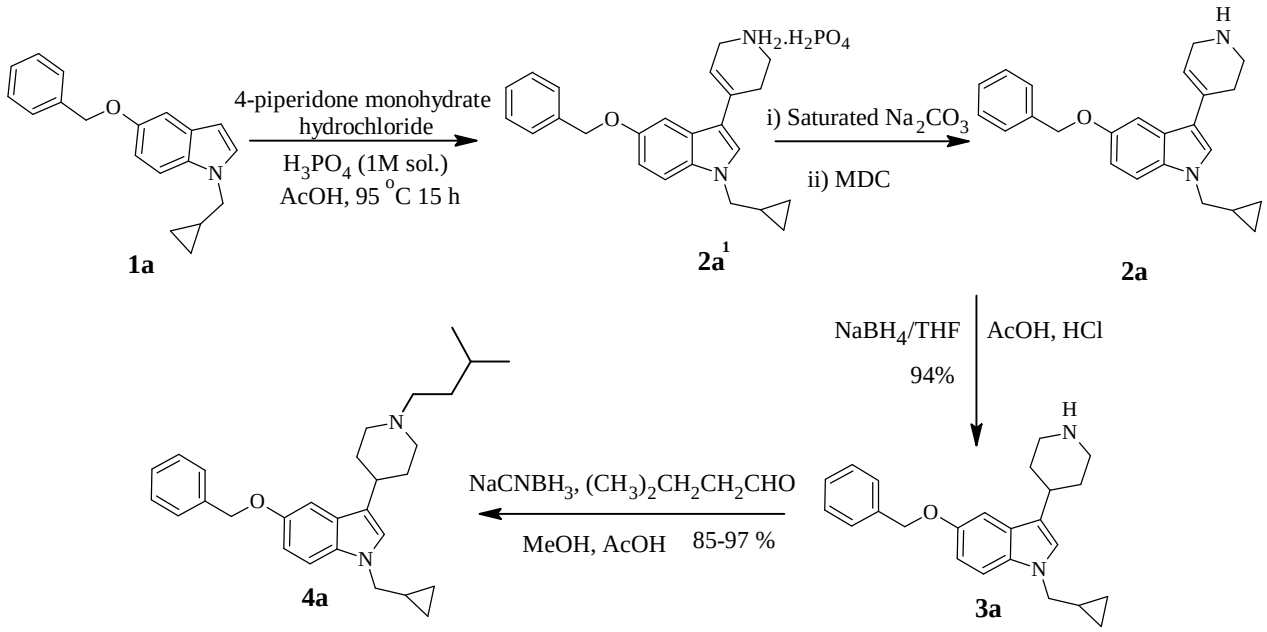
Here the reduction of endocyclic double bond normally done under palladium hydrogenation condition. In order to make the process convenient, we have chosen sodium borohydride as a non pyrophoric and easy to handle catalyst to carry out this transformation.

Thus the conversion of crude **2a** to **3a** was achieved by treating with sodium borhydride in THF and AcOH solvent condition gave good to moderate yield of **3a**. Here the intermediate boron complex was cleaved by treating it with HCl solution for 0.5 h.

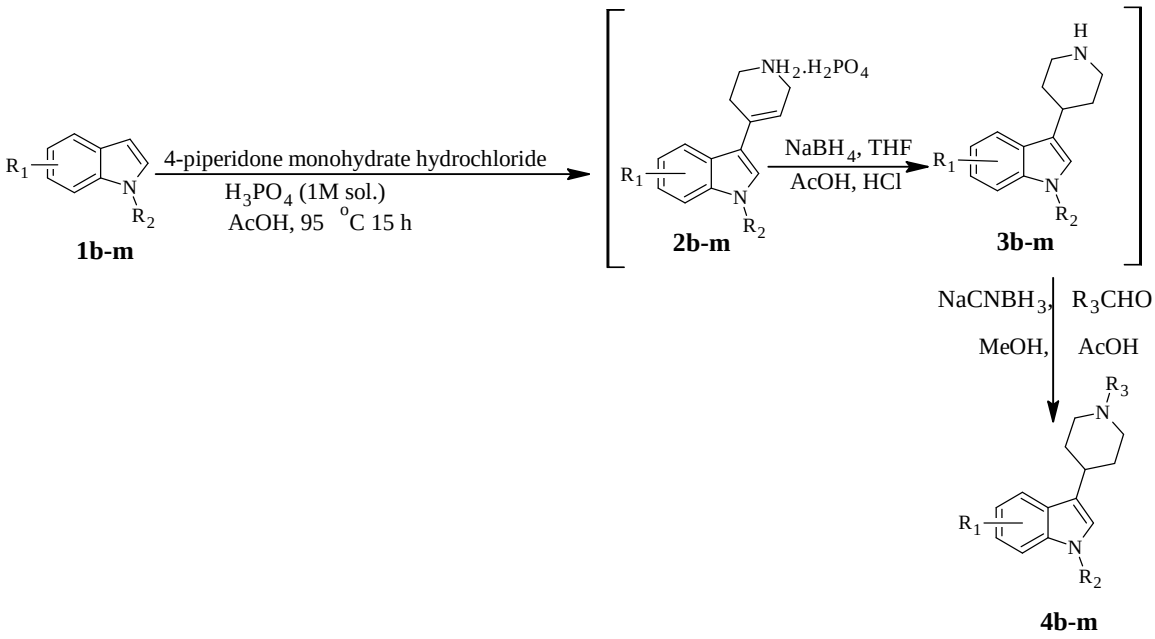
After the workup the crude amine **3a** thus obtained was taken for reductive amination with various aromatic amines to get novel 3-(piperidyl) indole derivative **4a** (Scheme 1). We also tried out *N*-alkylation of **3a** using bases like K_2CO_3 and found, along with the product indole ring *N*-alkylation was occurred [6] and also the reaction was incomplete in some cases. However the reductive amination of **3a** using sodium cyano borhydride (Scheme 2) in MeOH solvent smoothly gave **4a** with more than 90% yield without any side reaction. Whereas in later method there was a chance of indole ring *N*-alkylation, formation of quaternery amine salt and also found incomplete n-alkylation [2].

Thus we were able to synthesis 3-(piperidyl) indole derivatives **4a-m** easily, overcoming the difficulties faced in reported methods by reductive amination rather than simple alkylation.

Thus the optimized method was then applied to remaining indole 1b-m to obtain novel 3-(piperidyl) indole derivatives 4b-m (Scheme 2 and Table 1). Since this method is more economical and less hazardous, it can be applied even for large scale preparation. Further the structures of all synthesized compounds were subjected to *in silco* studies.



Scheme1: Synthesis of 5-(benzyloxy)-1-(cyclopropylmethyl)-3-[1-(3-methyl-butyl) piperidin-4-yl]-1*H*-indole (4a).



Scheme2: Synthesis of 3-(*N*-alkyl/aryl piperdyl) indoles (4b-m).

NMR was recorded for all the synthesized compounds **4a-m**. The proton signal of piperidine hydrogen of the all 3-(piperidyl) indole derivatives **4a-m** are in the range δ 1.5 to 3.5. This entire proton appeared as multiplet or doublet of doublet, this might be due to the piperdine ring which can exist in conformational structure and hence, the proton signals are not simple for all these series [33]. However in the C-13 spectra, three peaks corresponds to piperidine carbon atom appeared between δ 30 to 50.

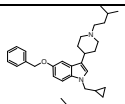
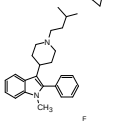
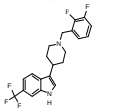
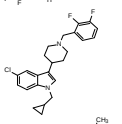
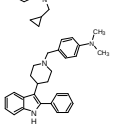
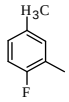
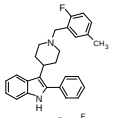
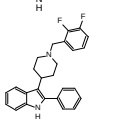
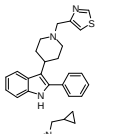
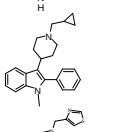
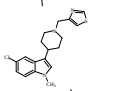
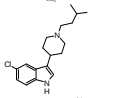
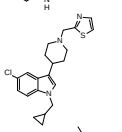
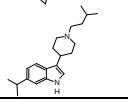
Molecular docking s*tudies*

The molecular docking was carried out with **4a-m** compounds using AutoGrid v. 1.5.4 and AutoDock 4.2. The grid maps of different grid points for keeping peptides to cover binding pockets. A set of Lamarckian genetic algorithm was substantially used for molecular docking simulation.

The synthesized 3-(piperidyl) indole derivatives **4a-m** were tested *in silico* for their inhibitory properties against Serotonin-5HT, H1 and CCR2 receptors which are responsible for physiology of inflammatory and cognitive immune system to develop antipsychotic properties.

The ligand binding poses within the 5HT, H1 and CCR2 receptors for all the synthesized compounds were studied using molecular docking and the results were interpreted in table 2 and table 3.

Table1: Characterization data of 3-(piperidyl)indole derivatives 4a-m

Entry	R_1	R_2	R_3	Products	Yield (%)	mp(°C)
4a	5-$OCH_2C_6H_5$				90	Gummy
4b	2-Ph	-CH_3			88	Gummy
4c	6-tri fluoro methyl	H			87	132-133
4d	5-Chloro				83	Gummy
4e	2-Ph	H			90	103-104
4f	2-Ph	H			95	162-163
4g	2-Ph	H			89	143-144
4h	2-Ph	H			85	165-166
4i[b]	2-Ph	-CH_3			89	122-123
4j	5-Chloro	-CH_3			86	113-11
4k	5-Chloro	H			93	138-139
4l	5-Chloro				95	82-83
4m	isopropyl	H			97	Gummy

As illustrated in table 2 the most potent ligand among the synthesized compounds are **4a** and 4l. The 5-(benzyloxy)-1-(cyclopropylmethyl)-1*H*-indole **4a** derivative interacts with 5HT1A receptor at the binding sites located within the active site amino acids. The interaction of **4a** with 5HT1A protein shows 3 hydrogen bonds at position C=O of Arg1062 amino acid and the steric interaction of Pro1045, Thr1044, Lys1047, Pro1046, Lys1051 and Asp1050, electrostatic interaction with Glu1049, Ala154 Ser158 and Pro1046 active site amino acids. The atomic interaction in **4a** shows the oxygen and nitrogen in C=O, and C-N bonds are deeply buried in the binding site. Further the indole ring is facing towards the extracellular side of the receptor. The other synthetic compound 4l ligand shows 2 hydrogen bonds with amino acids Arg308, Arg310, Lys314, Arg236, Ala235 and Pro1045 shows steric interactions with strong hydrogen bonds and internal energy of -52.6453 kcal/mol.

In the case of H1 protein (Table 3), the ligands **4b, 4i, 4k** and **4l** shows 3 hydrogen bonds with strong interaction energy of -1.82775, -10.371, -11.4181 and -6.78388 kcal/mol of energy. Moreover these ligands (**4b, 4i, 4k** and **4l**) established crucial interactions with important residues. In particular the indole *N* has large steric interactions and other amino acids in the pyrrolidine ring formed an electrostatic interaction with conserved Tyr431. The binding mode of the most active compound and its interaction with the active site residues potentially and hence can be used for the target for the antihistamine properties.

Although 3-(piperidyl) indole derivatives **4a-m** have good to moderate interaction with 5HT receptor and H1 proteins, they have no (affinity) interaction with CCR2 receptors. With this we can assess that **4a-m** were found to be a potent and selective H1 and 5HT antagonist inhibitors

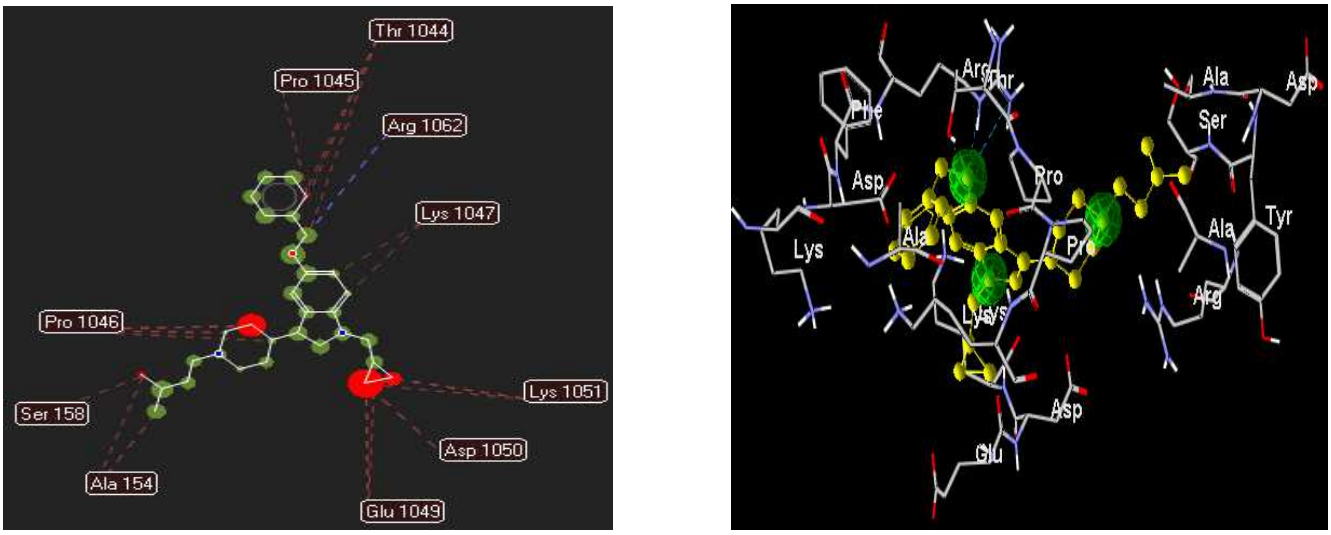


Fig.1: Docking images and interaction of 4a with 5HT1A protein shows 3 hydrogen bonds at position C=O of Arg1062 amino acid and the steric interaction of Pro1045, Thr1044, Lys1047, Pro1046, Lys1051 and Asp1050

Table2: Docking results for 5HT protein

Ligands	H-Bonds	Binding Energy	Inhibitory Const.(uM)	Intermol Energy	Electrostatics Energy	Amino Acids
4a	3	-5.51751	164.292	-6.45	-2.34505	ARG161, ARG1062
4b	1	-5.11	178.14	-6.61	0.18	SER372
4c	1	-15.1711	112.385	-7.74	-1.89153	GLU374
4d	0	-5.98	41.44	-7.17	-0.33	LYS1104
4e	0	-6.95	8.1	-8.14	0.71	TYR228
4f	1	-5.1	183.57	-6.29	-0.62	PRO1045
4g	0	-6.45	18.73	-7.64	0.55	LYS1104
4h	0	-6.54	15.98	-7.74	-0.09	GLU309,
4i	0	-4.48	521.62	-5.67	-0.5	THR1044,
4j	1	-15.5408	108.211	-7.85	-0.680643	ASP129
4k	1	-5.74	61.57	-6.94	-0.25	ARG310
4l	2	-4.35	647.14	-5.54	0.56	ARG310
4m	1	-5.3	129.58	-6.5	0.16	THR370

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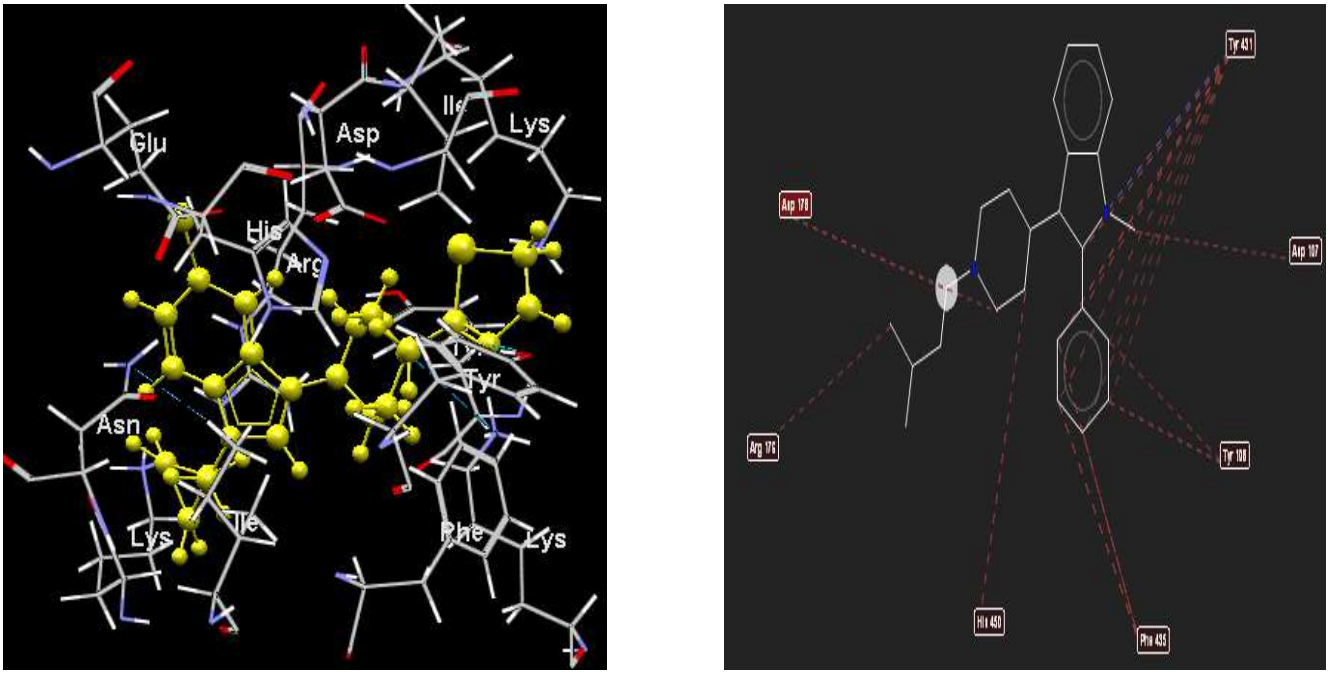

Fig. 2: Docking images of the compound 4b with H1 protein forming 3 hydrogen bonds having binding energy of -1.82775kcal/mol

Table 3: Docking results for H1 protein

Ligands	H-Bonds	H-Bond Energy	Inhibitory Constant	Electrostatic energy	Amino Acids
4a	2	-8.8676	156.553	1.55367	ASN443,LYS191
4b	3	-1.82775	70.278	-2.5	LYS191, TYR431,LYS179
4c	1	-23.2551	124.564	-2.47485	LYS179
4d	1	6.7957	204.554	-1.8067	LYS179
4e	2	7.50497	112.876	-2.5	TYR431, TYR108
4f	2	-14.3055	101.606	-1.92769	TYR185, ASN443
4g	1	-20.1799	150.034	-1.39148	ASN198
4h	2	-12.7646	117.783	-2.5	HIS450, LYS191
4i	3	-10.371	111.965	-2.5	ASN443, ARG176, LYS191
4j	2	-7.27377	116.465	-1.75694	TYR431, GLU447
4k	3	-11.4181	128.897	-2.5	TYR431, ASP107, TYR108
4l	3	-6.78388	115.99	-2.49382	LYS191, TYR431, ARG176
4m	2	-12.5468	105.605	-2.5	GLU447, ARG176

CONCLUSION

New synthetic route has been developed to generate library of 3-(*N*-alkyl/aryl piperidyl)indole **4a-m** compounds and *in silico* methodologies such as homology modeling and molecular docking was performed for all the new compounds. The modeled target proteins such as serotype-5HT, H1 and CCR2 were docked with indole derivatives (**4a-m**). It shows the structural analysis of 5HT, H1 and CCR2 protein possesses active sites of neurotransmission. Comparative study reveals that the synthesized compounds **4a** and **4l** shows strong interactions with 5HT protein, whereas, the compounds **4b, 4i, 4k** and **4l** were strongly interacting with H1 receptors. However, none of the compounds have shown interaction with CCR2 receptor. Thus, the proposed inhibitors have shown to be more effective against 5HT and H1 receptor since they exhibit strong interaction with them. Thus, the results in this study might be helpful to identify further promising new 3-(piperidyl)indole based potential inhibitor of 5HT and H1 receptor proteins in the future study.

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