Synthesis, QSAR and docking studies of 5HT$_{2A}$ receptor antagonising thiazolo[3,2-a]pyrimidines as antipsychotic agents

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ABSTRACT

A series of twenty two compounds containing thiazolo[3,2-a] pyrimidine carboxamide nucleus was synthesized by using microwave. Substituted acetoacetanilide was condensed with thiourea and substituted benzaldehydes in the presence of *p*-toluenesulfonic acid as catalyst in ethanol to get 2-thioxo-1,2,3,4-tetrahydropyrimidine carboxamide. In the second step, 1,2,3,4-tetrahydropyrimidine carboxamides were treated with chloroacetic acid, anhydrous sodium acetate and glacial acetic acid to yield the title compounds. The reaction progress and purity of the synthesized compounds were monitored by TLC using silica gel G and by determining their melting points. Structures of title compounds were confirmed by elemental analysis, IR, ^{1}H NMR and mass spectral data. The antipsychotic activity for title compounds was performed using *albino* mice by rotarod and tail suspension method. Compounds have shown antipsychotic activity comparable with the standard risperidone. The 2D, 3D QSAR and molecular docking studies were performed using VLife MDS 3.5 software. The molecular modelling studies reveals that more potent antipsychotics from this series can be generated by substituting electronegative group at *para* and *meta* position of *N*-phenyl ring and less bulky group at 5-phenyl ring of thiazolo[3,2-a]pyrimidine-6-carboxamide nucleus.

Keywords: Molecular docking, QSAR, Schizophrenia, Thiazolo[3,2-a]pyrimidine, 5HT$_{2A}$ receptor antagonist.

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INTRODUCTION

Schizophrenia is a psychotic disorder characterized by positive symptoms such as hallucinations and disorganized thought, and negative symptoms such as apathy and social withdrawal. This socially and economically debilitating disease is fairly common and is striking approximately 1% of the population (1). Classical or typical antipsychotic drugs antagonizing central dopaminergic receptors have been used for several decades in the treatment of psychiatric disorders like schizophrenia (2). Although these drugs can reduce the positive symptoms of schizophrenia, they unfortunately often induce extrapyramidal motoric side effects and are furthermore often not able to ameliorate the negative symptoms of schizophrenia. The antipsychotic action has been suggested to be due to blockade of the mesocorticolimbic dopaminergic system, while the motoric side effects are believed to be due to antagonism of dopaminergic receptors in the nonlimbic nigro-striatal dopamine system of the brain (3). While a diversified group of the so called atypical antipsychotic drugs such as 5HT$_{2A}$ receptor antagonist express increased effectiveness in

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negative, affective and cognitive symptoms, including efficacy in patients resistant to standard therapy. Atypical antipsychotic drugs also have a low incidence of extrapyramidal side effects and prolactinaemia but may produce other undesirable side effects like agranulocytosis that limit their clinical use (4).

Thiazolo[3,2-a]pyrimidine and its derivatives are known to possess diverse biological activities such as antimicrobial (5), anti-inflammatory (6), antiviral (7), calcium antagonists (8) and antitumor (9). Recently it has been reported that thiazolo[3,2-a]pyrimidine possess selective $5HT_{2A}$ receptor antagonistic activity (10) and it possess high affinity for $5HT_{2A}$ receptor. In this direction our efforts were devoted to synthesize thiazolo[3,2-a]pyrimidine nucleus with different derivatives to obtain compounds having affinities for $5HT_{2A}$ receptor as well as also for dopamine receptors.

MATERIALS AND METHOD

Chemistry

Melting points of the synthesized compounds were determined using Veego electronic (VMP-D) apparatus in an open capillary tube and hence are uncorrected. The structures of the title compounds were established on the basis of spectral data. The IR spectra (KBr; ν, cm^{-1}) were recorded on a PerkineElmer spectrophotometer. ^{1}H NMR spectra (δ, ppm; J, Hz) were recorded on a Varian-NMR-mercury YH-300 spectrometer using DMSO as solvent with tetramethyl silane (TMS) as an internal standard. Mass spectra were recorded to know the M+1 peak on an LC-MS Thermo Finnigan spectrometer with electrospray ionization (ESI) technique. Purity of the synthesized compounds was checked by silica gel G plate using ethyl acetate : toluene as mobile phase. Compounds (**1a-1v**) were prepared following their procedures reported in the literature (11-12).

General procedure for synthesis of substituted 2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides (1a-1v)

The mixture of substituted acetoacetanilide (0.005 mol), thiourea (0.0075 mol) and substituted aldehyde (0.005 mol) with catalytic amount of *para* toluene sulphonic acid (0.025 g) was transferred to a round bottom flask containing ethanol (15 ml) to serve as a solvent, reflux were driven by irradiation with microwaves at 245 W power for about 30–40 mins. Intermittent cooling was given for 5 mins after every fifth minute of microwave irradiation. The completion of reaction was monitored by thin layer chromatography. The reaction mixture was cooled to room temperature and solid obtained was filtered.

General procedure for synthesis of substituted 3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxamides (2a-2v)

A mixture of tetrahydropyrimidine carboxamide derivative (0.005 mol), monochloroacetic acid (0.0075 mol), anhydrous sodium acetate and glacial acetic acid was refluxed. The reaction was carried out in microwaves at 350 W power for about 15–20 mins. Intermittent cooling was given for 5 mins after every fifth minute of microwave irradiation. The completion of reaction was monitored by thin layer chromatography. The reaction mixture was cooled to room temperature and solid obtained was filtered. Compound obtained was recrystallized from methanol.

7-Methyl-N-(4-nitrophenyl)-3-oxo-5-phenyl-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a] pyrimidine-6-carboxamide (2a)

Yield, 89.11 %; mp, 210-214ºC; IR (KBr), ν, cm^{-1}: 3274 (N-H), 1634 (C=O), 687 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ: 9.47 (s, 1H, CONH), 9.08 (s, 1H, NH), 7.35-7.94 (m, 9H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.76 (s, 1H, CH), 3.25 (s, 2H, CH$_2$), 2.46 (s, 3H, CH$_3$). MS, *m/z* (M+1): 411. Anal. Calcd. for $C_{20}H_{18}N_4O_4S$: C, 58.52; H, 4.42; N, 13.65. Found: C, 58.43; H, 4.48; N, 13.61.

5-(4-Chlorophenyl)-7-methyl-N-(4-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxamide (2b)

Yield, 73.87 %; mp, 239-242ºC; IR (KBr), ν, cm^{-1}: 3386 (N-H), 1643 (C=O), 705 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ: 9.38 (s, 1H, CONH), 9.06 (s, 1H, NH), 7.29-7.84 (m, 8H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.65 (s, 1H, CH), 3.28 (s, 2H, CH$_2$), 2.33 (s, 3H, CH$_3$). MS, *m/z* (M+1): 446. Anal. Calcd. for $C_{20}H_{17}ClN_4O_4S$: C, 53.97; H, 3.85; N, 12.59. Found: C, 53.81; H, 3.92; N, 12.51.

5-(4-Hydroxyphenyl)-7-methyl-N-(4-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxamide (2c)

Yield, 68.44 %; mp, 180-183ºC; IR (KBr), ν, cm^{-1}: 3485 (O-H), 3358 (N-H), 1647 (C=O), 695 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ: 9.54 (s, 1H, CONH), 9.14 (s, 1H, NH), 7.51-7.95 (m, 8H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.72 (s, 1H, OH), 5.36 (s, 1H, CH), 2.40 (s, 2H, CH$_2$), 1.98 (s, 3H, CH$_3$). MS, *m/z* (M+1): 427. Anal. Calcd. for $C_{20}H_{18}N_4O_5S$: C, 56.33; H, 4.25; N, 13.14. Found: C, 56.23; H, 4.32; N, 13.18.

5-[4-(Dimethylamino)phenyl]-7-methyl-N-(4-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxamide (2d)

Yield, 75.55 %; mp, 214-215ºC; IR (KBr), v, cm^{-1}: 3279 (N-H), 1637 (C=O), 698 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ: 9.26 (s, 1H, CONH), 9.07 (s, 1H, NH), 7.42-7.96 (m, 8H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.78 (s, 1H, CH), 3.57 (s, 6H, N(CH$_3$)$_2$), 3.24 (s, 2H, CH$_2$), 2.64 (s, 3H, CH$_3$). MS, *m/z* (M+1): 454. Anal. Calcd. for C$_{22}$H$_{23}$N$_5$O$_4$S: C, 58.26; H, 5.11; N, 15.44. Found: C, 58.32; H, 5.08; N, 15.36.

7-Methyl-5-(3-nitrophenyl)-N-(4-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxamide (2e)

Yield, 80.68 %; mp, 213-217ºC; IR (KBr), v, cm^{-1}: 3327 (N-H), 1686 (C=O), 708 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ: 9.45 (s, 1H, CONH), 9.35 (s, 1H, NH), 7.57-7.44 (m, 8H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.82 (s, 1H, CH), 3.26 (s, 2H, CH$_2$), 2.34 (s, 3H, CH$_3$). MS, *m/z* (M+1): 456. Anal. Calcd. for C$_{20}$H$_{17}$N$_5$O$_6$S: C, 52.74; H, 3.76; N, 15.38. Found: C, 52.71; H, 3.81; N, 15.31.

5-(3,4,5-Trimethoxyphenyl)-7-methyl-N-(4-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxamide (2f)

Yield, 86.30 %; mp, 208-212ºC; IR (KBr), v, cm^{-1}: 3339 (N-H), 1657 (C=O), 782 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ: 8.36 (s, 1H, CONH), 8.12 (s, 1H, NH), 7.23-7.85 (m, 6H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.73 (s, 1H, CH), 3.84 (s, 9H, OCH$_3$), 3.37 (s, 2H, CH$_2$), 2.25 (s, 3H, CH$_3$). MS, *m/z* (M+1): 501. Anal. Calcd. for C$_{23}$H$_{24}$N$_4$O$_7$S: C, 55.19; H, 4.83; N, 11.19. Found: C, 55.13; H, 4.87; N, 11.22.

7-Methyl-N-(4-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a] pyrimidine-6-carboxamide (2g)

Yield, 88.83 %; mp, 182-186ºC; IR (KBr), v, cm^{-1}: 3252 (N-H), 1688 (C=O), 689 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ: 9.38 (s, 1H, CONH), 9.15 (s, 1H, NH), 8.36-8.89 (m, 4H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.67 (s, 1H, CH), 3.23 (s, 2H, CH$_2$), 2.42 (s, 3H, CH$_3$). MS, *m/z* (M+1): 335. Anal. Calcd. for C$_{14}$H$_{14}$N$_4$O$_4$S: C, 50.29; H, 4.22; N, 16.76. Found: C, 50.23; H, 4.09; N, 16.81.

5-(4-Methoxyphenyl)-7-methyl-N-(4-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxamide (2h)

Yield, 63.90 %; mp, 235-236ºC; IR (KBr), v, cm^{-1}: 3248

(N-H), 1693 (C=O), 796 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ: 8.48 (s, 1H, CONH), 8.16 (s, 1H, NH), 7.24-7.94 (m, 8H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.68 (s, 1H, CH), 3.65 (s, 3H, OCH$_3$), 3.43 (s, 2H, CH$_2$), 2.45 (s, 3H). MS, *m/z* (M+1): 441. Anal. Calcd. for C$_{21}$H$_{20}$N$_4$O$_5$S: C, 57.26; H, 4.58; N, 12.72. Found: C, 57.13; H, 4.64; N, 12.81.

5-(3-Hydroxyphenyl)-7-methyl-N-(4-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxamide (2i)

Yield, 78.63 %; mp, 196-198ºC; IR (KBr), v, cm^{-1}: 3482 (O-H), 3278 (N-H), 1641 (C=O), 703 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ: 9.47 (s, 1H, CONH), 9.31 (s, 1H, NH), 7.49-7.97 (m, 8H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.72 (s, 1H, OH), 5.34 (s, 1H, CH), 3.48 (s, 2H, CH$_2$), 2.49 (s, 3H, CH$_3$). MS, *m/z* (M+1): 427. Anal. Calcd. for C$_{20}$H$_{18}$N$_4$O$_5$S: C, 56.33; H, 4.25; N, 13.14. Found: C, 56.23; H, 4.31; N, 13.21.

5,7-Dimethyl-N-(4-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxamide (2j)

Yield, 80.78 %; mp, 230-240ºC; IR (KBr), v, cm^{-1}: 3482 (N-H), 1630 (C=O), 697 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ: 9.46 (s, 1H, CONH), 9.06 (s, 1H, NH), 7.34-7.92 (m, 4H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.79 (s, 1H, CH), 3.28 (s, 2H, CH$_2$), 2.44 (s, 6H, CH$_3$). MS, *m/z* (M+1): 349. Anal. Calcd. for C$_{15}$H$_{16}$N$_4$O$_4$S: C, 51.71; H, 4.63; N, 16.08. Found: C, 51.82; H, 4.54; N, 15.98.

5-Benzylidene-7-methyl-N-(4-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3] thiazolo[3,2-a]pyrimidine-6-carboxamide (2k)

Yield, 72.28 %; mp, 212-215ºC; IR (KBr), v, cm^{-1}: 3373 (N-H), 1651 (C=O), 691 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ: 8.47 (s, 1H, CONH), 8.31 (s, 1H, NH), 7.42-8.86 (m, 11H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.54 (s, 1H, CH), 3.37 (s, 2H, CH$_2$), 2.54 (s, 3H, CH$_3$). MS, *m/z* (M+1): 337. Anal. Calcd. for C$_{22}$H$_{20}$N$_4$O$_4$S: C, 60.54; H, 4.62; N, 14.84. Found: C, 60.45; H, 4.68; N, 14.92.

7-Methyl-N,5-bis(4-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxamide (2l)

Yield, 83.44 %; mp, 225-230ºC; IR (KBr), v, cm^{-1}: 3371 (N-H), 1671 (C=O), 692 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ: 8.58 (s, 1H, CONH), 8.36 (s, 1H, NH), 7.24-7.94 (m, 8H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.73 (s, 1H,

CH), 3.47 (s, 2H, CH$_2$), 2.52 (s, 3H, CH$_3$). MS, *m/z* (M+1): 456. Anal. Calcd. for C$_{20}$H$_{17}$N$_5$O$_6$S: C, 52.74; H, 3.76; N, 15.38. Found: C, 52.63; H, 3.87; N, 15.46.

7-Methyl-N-(3-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a] pyrimidine-6-carboxamide (2m)

Yield, 76.45 %; mp, 233-236ºC; IR (KBr), *v*, cm^{-1}: 3257 (N-H), 1687 (C=O), 701 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ: 9.25 (s, 1H, CONH), 9.14 (s, 1H, NH), 8.24-8.94 (m, 4H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.64 (s, 1H, CH), 3.37 (s, 2H, CH$_2$), 2.38 (s, 3H, CH$_3$). MS, *m/z* (M+1): 335. Anal. Calcd. for C$_{14}$H$_{14}$N$_4$O$_4$S: C, 50.29; H, 4.22; N, 16.76. Found: C, 50.13; H, 4.33; N, 16.81.

5-[4-(Dimethylamino)phenyl]-7-methyl-N-(3-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3] thiazolo[3,2-a]pyrimidine-6-carboxamide (2n)

Yield, 85.32 %; mp, 240-243ºC; IR (KBr), *v*, cm^{-1}: 3259 (N-H), 1642 (C=O), 682 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ: 9.53 (s, 1H, CONH), 9.24 (s, 1H, NH), 8.44-8.97 (m, 8H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.78 (s, 1H, CH), 3.69 (s, 6H, N(CH$_3$)), 3.42 (s, 2H, CH$_2$), 3.25 (s, 3H, CH$_3$). MS, *m/z* (M+1): 454. Anal. Calcd. for C$_{22}$H$_{23}$N$_5$O$_4$S: C, 58.26; H, 5.11; N, 11.44. Found: C, 58.13; H, 5.19; N, 11.48.

7-Methyl-N-(3-nitrophenyl)-3-oxo-5-phenyl-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxamide (2o)

Yield, 77.33 %; mp, 210-213ºC; IR (KBr), *v*, cm^{-1}: 3246 (N-H), 1641 (C=O), 680 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ: 9.42 (s, 1H, CONH), 9.08 (s, 1H, NH), 7.52-7.87 (m, 9H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.68 (s, 1H, CH), 3.52 (s, 2H, CH$_2$), 2.51 (s, 3H, CH$_3$). MS, *m/z* (M+1): 411. Anal. Calcd. for C$_{20}$H$_{18}$N$_4$O$_4$S: C, 58.52; H, 4.42; N, 13.65. Found: C, 58.63; H, 4.38; N, 13.58.

7-Methyl-N,5-bis(3-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxamide (2p)

Yield, 84.49 %; mp, 224-227ºC; IR (KBr), *v*, cm^{-1}: 3367 (N-H), 1696 (C=O), 707 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ: 9.37 (s, 1H, CONH), 9.14 (s, 1H, NH), 7.38-7.97 (m, 8H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.59 (s, 1H, CH), 3.42 (s, 2H, CH$_2$), 2.46 (s, 3H, CH$_3$). MS, *m/z* (M+1): 456. Anal. Calcd. for C$_{20}$H$_{17}$N$_5$O$_6$S: C, 52.74; H, 3.76; N, 15.38. Found: C, 52.79; H, 3.85; N, 15.29.

7-Methyl-N-(3-nitrophenyl)-5-(4-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxamide (2q)

Yield, 76.22 %; mp, 206-208ºC; IR (KBr), *v*, cm^{-1}: 3249 (N-H), 1658 (C=O), 687 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ: 8.53 (s, 1H, CONH), 8.17 (s, 1H, NH), 7.39-7.93 (m, 8H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.45 (s, 1H, CH), 3.51 (s, 2H, CH$_2$), 2.57 (s, 3H, CH$_3$). MS, *m/z* (M+1): 456. Anal. Calcd. for C$_{20}$H$_{17}$N$_5$O$_6$S: C, 52.74; H, 3.76; N, 15.38. Found: C, 52.61; H, 3.81; N, 15.29.

5-(4-Methoxyphenyl)-7-methyl-N-(3-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxamide (2r)

Yield, 87.37 %; mp, 218-221ºC; IR (KBr), *v*, cm^{-1}: 3238 (N-H), 1672 (C=O), 704 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ:); 9.76 (s, 1H, CONH), 9.38 (s, 1H, NH), 8.46-8.98 (m, 8H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.42 (s, 1H, CH), 3.87 (s, 3H, OCH$_3$), 3.61 (s, 2H, CH$_2$), 2.51 (s, 3H, CH$_3$). MS, *m/z* (M+1): 441. Anal. Calcd. for C$_{21}$H$_{20}$N$_4$O$_5$S: C, 57.26; H, 4.58; N, 12.72. Found: C, 57.13; H, 4.49; N, 12.81.

5-(3-Hydroxyphenyl)-7-methyl-N-(3-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxamide (2s)

Yield, 80.65 %; mp, 211-214ºC; IR (KBr), *v*, cm^{-1}: 3475 (O-H), 3264 (N-H), 1668 (C=O), 697 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ: 8.52 (s, 1H, CONH), 8.23 (s, 1H, NH), 7.32-7.87 (m, 8H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.67 (s, 1H, OH), 5.45 (s, 1H, CH), 3.63 (s, 2H, CH$_2$), 2.64 (s, 3H, CH$_3$). MS, *m/z* (M+1): 427. Anal. Calcd. for C$_{20}$H$_{18}$N$_4$O$_5$S: C, 56.33; H, 4.25; N, 13.14. Found: C, 56.23; H, 4.32; N, 13.22.

5-(4-Chlorophenyl)-7-methyl-N-(3-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxamide (2t)

Yield, 75.29 %; mp, 223-226ºC; IR (KBr), *v*, cm^{-1}: 3369 (N-H), 1669 (C=O), 685 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ: 8.47 (s, 1H, CONH), 8.39 (s, 1H, NH), 7.49-8.96 (m, 8H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.74 (s, 1H, CH), 3.53 (s, 2H, CH$_2$), 2.37 (s, 3H, CH$_3$). MS, *m/z* (M+1): 446. Anal. Calcd. for C$_{20}$H$_{17}$Cl N$_4$O$_4$S: C, 53.97; H, 3.85; N, 13.59. Found: C, 53.93; H, 3.79; N, 13.51.

5-(3,4,5-Trimethoxyphenyl)-7-methyl-N-(3-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a] pyrimidine-6-carboxamide (2u)

Yield, 81.60 %; mp, 235-238ºC; IR (KBr), v, cm^{-1}: 3275 (N-H), 1695 (C=O), 709 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ: 8.42 (s, 1H, CONH), 8.12 (s, 1H, NH), 7.38-7.82 (m, 6H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.57 (s, 1H, CH), 3.86 (s, 9H, OCH$_3$), 3.48 (s, 2H, CH$_2$), 2.46 (s, 3H, CH$_3$). MS, *m/z* (M+1): 501. Anal. Calcd. for C$_{23}$H$_{24}$N$_4$O$_7$S: C, 55.19; H, 4.83; N, 11.19. Found: C, 55.13; H, 4.79; N, 11.21.

5-(4-Hydroxyphenyl)-7-methyl-N-(3-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxamide (2v)

Yield, 72.66 %; mp, 241-243ºC; IR (KBr), v, cm^{-1}: 3476 (O-H), 3249 (N-H), 1677 (C=O), 699 (C-S). ^{1}H NMR (300 MHz, DMSO, TMS), δ: 9.52 (s, 1H, CONH), 9.36 (s, 1H, NH), 8.38-8.95 (m, 8H, Ar-H), 5.95 (s, 1H, CH pyrimidine), 5.74 (s, 1H, OH), 5.43 (s, 1H, CH), 3.49 (s, 2H, CH$_2$), 2.47 (s, 3H, CH$_3$). MS, *m/z* (M+1): 427. Anal. Calcd. for C$_{20}$H$_{18}$N$_4$O$_5$S: C, 56.33; H, 4.25; N, 13.14. Found: C, 56.43; H, 4.19; N, 13.21.

Antipsychotic activity

Antipsychotic activity of the thiazolo[3,2-a]pyrimidine derivatives (**2a-2v**) and the reference drug risperidone were performed by locomotor activity, rota rod and tail suspension test method. The ethical clearance was obtained from the Institutional Animal Ethical Committee (Approval no. 1670/po/a/12/CPCSEA). The experiments were carried out on albino mice (25–30 g). Each group comprised six animals (n=6), weighed and marked. Group 1 served as control group which received carboxy methyl cellulose solution (0.5%) in sterile water for injection in which sample was being prepared and given by oral route. Group 2 received risperidone (0.2 mg/kg, p.o.) as a suspension thirty minutes before ketamine (10 mg/kg, i.p.) administration. Group 3 to 24 received the test compounds (25 mg/kg, p.o.) as a suspension thirty minutes before ketamine (10 mg/kg, i.p.) administration. After 15 minutes of administration of ketamine, (a) animals were placed in actophotometer for measurement of locomotor activity, (b) animals were placed with the paws on a 2.5 cm diameter bar, 25 cm above the floor, which rotates 12 times per minute for rota rod method and the time of permanence on the bar for one minute were registered, (c) mice were suspended by tail on the edge of a shelf 58 cm above a table top by adhesive tape placed approximately 1cm from the tip of the tail for tail suspension test and duration of immobility was recorded during a period of five minutes (13-15).

Molecular modelling methods

2D QSAR

All twenty two compounds were built on workspace of molecular modelling software VLife MDS 3.5 (16). The structures were then converted to three-dimensional space for further analysis. All molecules were batch optimized for the minimization of energies using merck molecular force field (MMFF) (17) followed by considering distance-dependent dielectric constant of 1.0, convergence criterion or root mean-square (RMS) gradient at 0.01 kcal/mol/Å and the iteration limit to 10,000.

A data set of twenty two compounds of thiazolo[3,2-a] pyrimidine derivatives was used for the present 2D QSAR study. There is high structural diversity and a sufficient range of the biological activity in the selected series of these derivatives. The biological activity (locomotar activity) values were converted to logarithmic scale (log BA) and subsequently used as the dependent variable for the QSAR analysis. The energy-minimized geometry of the compounds was used for the calculation of the various 2D descriptors (Individual, Chi, ChiV, Path count, ChiChain, ChiVChain, Chainpathcount, Cluster, Pathcluster, Kapa, Element Count, Estate number, Estate contribution, Semi empirical, Polar surface area and Hydophillic-hydophobic) using compute descriptors module of VLife MDS 3.5 software. The various Alignment Independent (AI) descriptors were also calculated. For calculation of alignment, the independent descriptor was assigned the utmost three attributes. The first attribute was T to characterize the topology of the molecule. The second attribute was the atom type, and the third attribute was assigned to atoms taking part in the double or triple bond. The pre-processing of the independent variables (2D descriptors) was done by removing invariable (constant column).

3D QSAR

A data set of biological activity values (locomotor activity) of twenty two compounds was used for 3D QSAR investigations. The molecules were optimized for energy minimization using MMFF (Merck Molecular Force Field) in the MOPAC module of VLife MDS 3.5 software. The threshold value for root mean square (rms) gradient was kept at 0.001 kcal/mol/Å. All molecules were subsequently aligned by a template based alignment technique using a common structure as a template. The most active compound **2e** was selected as a template for alignment of the molecules. The alignment is useful for studying shape variation with respect to the base structure selected for

alignment. After suitable alignment of a given set of molecules, a common rectangular grid (lattice) was generated around the molecules. The steric, electrostatic and hydrophobic interaction energies were computed at the lattice points of the grid using a methyl probe of charge +1. These interaction energy values were considered for relationship generation and utilized as descriptors.

Statistical analysis

The descriptors were taken as independent variables and biological activity as dependent variables. The multiple linear regression (MLR) method of analysis was used to derive the 2D and 3D QSAR equations. Statistical parameters employed were the number of compounds in regression n, the regression coefficient r^2, the F-test (Fischer's value) for statistical significance F, the cross-validated correlation coefficient q^2 and predictive r^2. The regression coefficient r^2 represents the part of variation in the observed data that is explained by the regression. Correlation coefficient values closer to 1.0 represent the better fit of the regression. The F-test is the ratio of the variance explained by the model and the variance due to error in the regression. High values of the F-test indicate that the model is statistically significant. The predictive ability (internal) of the generated models was evaluated by a cross validation method using a leaveone-out (LOO) scheme. Validation parameters considered were cross validated q^2. The predictive ability (external) of the selected model was also confirmed by external validation of test set compounds which is denoted with pred_r^2.

Docking

Docking studies of the title compounds (**2a-2v**) was done on VLife MDS 3.5 using crystal structure of 5HT$_{2A}$ receptor. The 2D structure of the compounds were built and converted into the 3D. The 3D structures were energetically minimized up to the rms gradient of 0.01 using MMFF. The cavities in the receptor were mapped to assign an appropriate active site, the basic feature used to map the cavities are the surface mapping of the receptor and identifying the geometric voids as well as scaling the void for its hydrophobic characteristics. Hence all the cavities that are present in receptor are identified and ranked based on their size and hydrophobic surface area. Cavity no.1 is selected for docking. The active site for docking was defined as all atoms within 5A° radius. Then keep all compounds for batch docking, after completion of batch docking it will give dock score. Finally check the interaction between ligand and receptor from docked ligand-receptor complex.

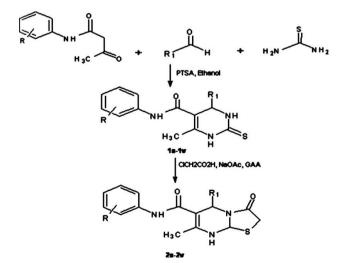## RESULTS AND DISCUSSION

Chemistry

Scheme 1 outlines the synthetic pathway used to obtain title compounds (**2a-2v**) by using microwave. Substituted acetoacetanilide was condensed with thiourea and substituted benzaldehydes in the presence of p-toluenesulfonic acid as catalyst in ethanol to get 2-thioxo-1,2,3,4-tetrahydropyrimidine carboxamide. In the second step, 1,2,3,4-tetrahydropyrimidine carboxamides were treated with chloroacetic acid, anhydrous sodium acetate and glacial acetic acid to yield the title compounds (Table 1). The reaction progress and purity of the synthesized compounds was monitored by TLC using silica gel G and by determining its melting point. Structures of title compounds were confirmed by elemental analysis, IR, ^{1}H NMR and mass spectral data.

Antipsychotic activity

Compounds (**2a-2v**) in addition to the reference risperidone were tested for their *in vivo* antipsychotic activity, this study presents the actions of series of thiazolo[3,2-a] pyrimidine on the behavioral effects elicited by ketamine on locomotor activity, rota rod and tail suspension tests in mice. Ketamine increased the locomotor activity compared to control, while risperidone shows reverse effect. Compounds **2e**, **2i**, **2l**, **2q** and **2t** showed comparable activity to risperidone (Table 2).

QSAR

Selection of molecules in the training set and test is a key and important feature of any QSAR model. Therefore the

SCHEME 1. Scheme for synthesis of 3-oxo-2,3,8,8a-tetrahydro-5H-[1,3] thiazolo[3,2-a]pyrimidine-6-carboxamide (**2a-2v**).

TABLE 1. Structural modifications in thiazolo[3,2-a]pyrimidines.

Compound	R	R₁	Compound	R	R₁
2a	p-NO$_2$	phenyl	2l	p-NO$_2$	phenyl-NO$_2$
2b	p-NO$_2$	phenyl-Cl	2m	m-NO$_2$	H
2c	p-NO$_2$	phenyl-OH	2n	m-NO$_2$	phenyl-N(CH$_3$)$_2$
2d	p-NO$_2$	phenyl-N(CH$_3$)$_2$	2o	m-NO$_2$	phenyl
2e	p-NO$_2$	phenyl-NO$_2$	2p	m-NO$_2$	phenyl-NO$_2$
2f	p-NO$_2$	phenyl-(OCH$_3$)$_3$	2q	m-NO$_2$	phenyl-NO$_2$
2g	p-NO$_2$	H	2r	m-NO$_2$	phenyl-OCH$_3$
2h	p-NO$_2$	phenyl-OCH$_3$	2s	m-NO$_2$	phenyl-OH
2i	p-NO$_2$	phenyl-OH	2t	m-NO$_2$	phenyl-Cl
2j	p-NO$_2$	CH$_3$	2u	m-NO$_2$	phenyl-(OCH$_3$)$_3$
2k	p-NO$_2$	=CH-phenyl	2v	m-NO$_2$	phenyl-OH

TABLE 2. *In vivo* antipsychotic activity of ketamine, risperidone and test compounds (**2a-2v**).

Compound	Locomotor activity (Sec) ± SEM	Rota rod Time of performance (Sec) ± SEM	Tail suspension Time of immobility (Sec) ± SEM
Ketamine	159.35 ± 1.73	12.33 ± 1.44	17.30 ± 5.60
Risperidone	112.33 ± 1.34	56.59 ± 1.32	80.20 ± 10.20
2a	137.84 ± 1.78	18.43 ± 1.33	34.66 ± 2.88
2b	125.50 ± 1.10	39.68 ± 1.39	57.33 ± **2.60**
2c	127.33 ± 0.69	38.26 ± 0.96	51.56 ± **2.51**
2d	143.83 ± 1.06	18.04 ± 1.37	22.14 ± **2.17**
2e	118.24 ± 0.84	48.49 ± 1.25	71.33 ± **1.85**
2f	131.04 ± 1.35	27.16 ± 1.46	32.33 ± **1.52**
2g	140.44 ± 1.07	32.14 ± 1.08	47.33 ± **2.18**
2h	132.58 ± 1.51	29.15 ± 1.54	39.22 ± **3.90**
2i	122.26 ± 1.04	44.33 ± 1.85	67.53 ± **2.17**
2j	139.08 ± 1.43	26.72 ± 1.52	45.33 ± **2.33**
2k	144.16 ± 0.77	20.53 ± 1.55	27.45 ± **2.90**
2l	120.37 ± 0.72	46.62 ± 1.73	69.45 ± **1.15**
2m	132.12 ± 1.55	28.47 ± 1.04	52.41 ± **1.73**
2n	144.24 ± 0.63	19.35 ± 1.28	23.33 ± **7.76**
2o	136.24 ± 1.40	30.66 ± 1.45	49.45 ± **1.73**
2p	128.36 ± 1.54	34.33 ± 1.85	51.66 ± **2.60**
2q	121.21 ± 1.53	45.53 ± 1.55	72.66 ± **2.90**
2r	137.50 ± 1.67	25.23 ± 1.52	45.33 ± **1.76**
2s	142.19 ± 1.44	23.48 ± 1.55	48.67 ± **1.52**
2t	122.21 ± 1.50	43.74 ± 1.73	70.66 ± **2.02**
2u	138.56 ± 1.27	31.33 ± 1.76	56.33 ± **1.45**
2v	126.15 ± 1.44	38.33 ± 1.45	60.45 ± **1.52**

TABLE 3. Comparative data of validation parameters employed for QSAR equations.

Model/Parameters	(2D QSAR) Model 1	(3D QSAR) Model 2
Equation	logBA = 1.3854 + 0.0167T_C_O_5 −0.0293T_2_T_3 + 0.0178SdOE-index	logBA = 2.1206 + 0.0026E_320 −0.0031S_570 − 0.0013S_851
Training set size (n)	17	17
Test set size	5 (2e, 2m, 2g, 2u, 2v)	5 (2m, 2o, 2p, 2s, 2v)
Degree of freedom	12	12
r^2	0.93	0.97
***F* test**	37.88	97.29
q^2	0.81	0.91
pred_r^2	0.5731	0.8781
R^2 **for fitness plot**	0.81	0.84

care was taken in such a way that biological activities of all compounds in test set lies within the maximum and minimum value range of biological activities of training set of compounds. A Uni-Column statistics for training set and test set were generated to check correctness of selection criteria for trainings and test set molecules. The maximum and minimum value in training and test set were compared in a way that the maximum value of log BA of test set should be less than or equal to maximum value of log BA of training set and the minimum value of log BA of test set should be higher than or equal to minimum value of log BA of training set. This observation showed that test set was interpolative and derived within the minimum to maximum range of training set. The mean and standard deviation of log BA values of sets of training and test provide insights to

relative difference of mean and point density distribution of two sets.

The 2D QSAR and 3D QSAR models (Table 3) were generated for training set of seventeen compounds using

TABLE 4. Comparative observed and predicted activities (LOO) of thiazolo[3,2-a]pyrimidine derivatives by 2D QSAR and 3D QSAR model.

Compound	2D QSAR			3D QSAR		
	Actual (logBA)	Predicted (logBA)	Residual	Actual (logBA)	Predicted (logBA)	Residual
2a	2.13	2.13	0.00	2.08	2.08	0.00
2b	2.10	2.10	0.00	2.12	2.12	0.00
2c	2.08	2.08	0.00	2.15	2.15	0.00
2d	2.14	2.14	0.00	2.07	2.07	0.00
2e	2.12	2.12	0.00	2.12	2.12	0.00
2f	2.13	2.13	0.00	2.15	2.15	0.00
2g	2.15	2.15	0.00	2.14	2.14	0.00
2h	2.15	2.15	0.00	2.15	2.15	0.00
2i	2.15	2.15	0.00	2.13	2.13	0.00
2j	2.14	2.14	0.00	2.10	2.10	0.00
2k	2.12	2.13	-0.01	2.14	2.14	0.00
2l	2.14	2.14	0.00	2.14	2.14	0.00
2m	2.08	2.08	0.00	2.12	2.09	0.03
2n	2.14	2.13	0.01	2.08	2.08	0.00
2o	2.14	2.14	0.00	2.13	2.11	0.02
2p	2.08	2.08	0.00	2.10	2.14	-0.04
2q	2.07	2.08	-0.01	2.14	2.14	0.00
2r	2.13	2.13	0.00	2.14	2.14	0.00
2s	2.16	2.16	0.00	2.15	2.12	0.03
2t	2.12	2.12	0.00	2.12	2.12	0.00
2u	2.10	2.10	0.00	2.08	2.08	0.00
2v	2.10	2.10	0.00	2.10	2.10	0.00

MLR method. The best QSAR model was selected on the basis of value of statistical parameters like r^2 (square of correlation coefficient for training set of compounds), q^2 (cross-validated r^2), and pred_r^2 (predictive r^2 for the test set of compounds). All QSAR models were validated and tested for its predictability using an external test set of five compounds. Statistical results generated by 2D QSAR and 3D QSAR analysis showed that QSAR models have good internal as well as external predictability. The results obtained for actual and predicted activity of 2D QSAR and 3D QSAR models are presented in Table 4 and the residuals were found to be minimal.

Validation of QSAR models

Model 1 and model 2 was obtained by a random method of training and test set data selection (18). As indicated, both QSAR models were found to be statistically

significant and predictive in terms of r^2, q^2, F and pred_r^2 values (19-23).

From the equations, it could be concluded that 92.66% ($r^2 = 0.9266$) and 97.01% ($r^2 = 0.9701$) of the variation in the biological activity was accounted for the parameters used in model 1 and 2, respectively. This signifies that in both models, a good correlation exists between their corresponding descriptors and biological activity. Further, in both cases the high values of F tests indicates that the statistical significance of 99.99% of the models meant that probability of failure of the models was 1 in 10,000.

Interpretation of QSAR models
2D QSAR

The model 1 suggests that the locomotor activity depends on descriptors T_C_O_5, T_2_T_3 and SdOE-index. 2D
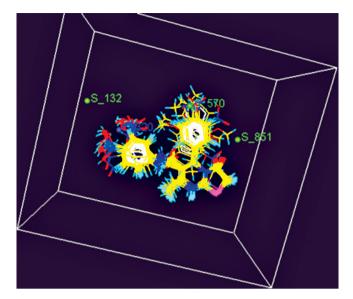
FIGURE 1. Grid point interaction for model 2.

TABLE 5. Docking score of title compounds (**2a-2v**) with 5HT$_{2A}$ receptor.

Compound	Docking score (Kcal/mol)	Compound	Docking score (Kcal/mol)
2a	-5.63	**2m**	-5.63
2b	-5.67	**2n**	-5.51
2c	-5.39	**2o**	-5.62
2d	-5.33	**2p**	-5.35
2e	-5.71	**2q**	-5.74
2f	-5.20	**2r**	-5.28
2g	-5.45	**2s**	5.45
2h	-5.38	**2t**	-5.69
2i	-5.70	**2u**	-4.62
2j	-5.62	**2v**	-5.62
2k	-5.58	**Risperidone**	-4.56
2l	-5.68		

QSAR model 1 reveals that descriptor T_C_O_5 is positive contributor to activity which indicate a number of carbon atoms (single double or triple bonded) separated from any oxygen atom (single or double bonded) by 5 bond distance in a molecule. The next influencing descriptor is T_2_T_3 which is negative contributor, suggest that the count of number of double bonded atoms (i.e. any double bonded atom, T_2) separated from any atom by 3 bonds, negative contribution shows that there should not be any atom separated from any atom by 3 bonds and the descriptor SdOE-index is positive contributor to activity which indicate electrotopological state indices for number of oxygen atom connected with one double bond, positive contribution shows that there should be more number of oxygen atom connected with one double bond will determine the activity.

3D QSAR

As per model 2 and Figure 1, negative steric field at grid point 570 and 851 indicates that steric field needs to be decreased at the 5-phenyl ring of thiazolo[3,2-a]pyrimidine-6-carboxamide to enhance the locomotor activity. The positive contribution of electrostatic field at grid point 320 indicates the electronegative groups are necessary at the third position of N-phenyl ring attached to thiazolo[3,2-*a*] pyrimidine-6-carboxamide to increase the locomotor activity. Thus these relative positions and ranges of the corresponding important electrostatic and steric fields in the above model could be helpful in design of new molecules with improved locomotor activity.
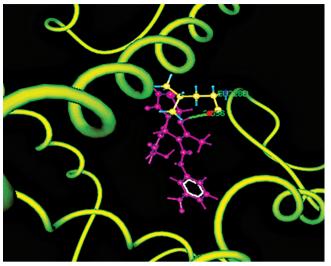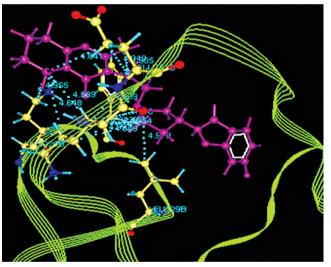
Docking studies

Docking studies of the title compounds (**2a-2v**) was done on VLife MDS 3.5 using Grid based docking method. The crystal structure of 5HT$_{2A}$ receptor was used as a target. By using VLife MDS, crystal structure of 5HT$_{2A}$ receptor was open in MDS sheet and saved as .mol2 format by removing water molecule and then this enzyme structure was used further for docking purpose. The protein-ligand complex was constructed and the active site of the enzyme was defined to include residues within a 10.0 Å radius to any of the inhibitor atoms. The scoring functions of the compounds were calculated from minimized ligand protein complexes. The 3D structures of 5HT$_{2A}$ receptor obtained from the X-ray crystal structure of β_2-adrenergic receptor (PDB code 2RH1) as a template and FASTA sequence of 5HT$_{2A}$ receptor from SWISS-MODEL workspace. β_2-adrenergic receptor X-ray structure of GPCRs provided a solid template for modelling the accurate 3D structures of 5HT$_{2A}$ receptor because sequences of aminergic receptors i.e. β-adrenergic and serotonin receptors, are highly conservative within the transmembrane (TM) domains, which indicates the common ligand binding sites of these receptors.
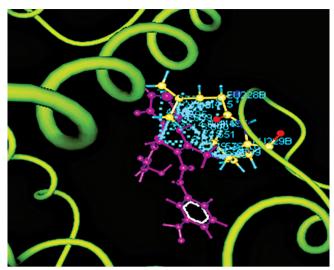
The docking of the title compounds with 5HT$_{2A}$ receptor yielded dock scores ranging from -5.20 to -5.74 (Table 5). From the dock score, compounds **2e, 2i, 2q** and **2t** were found to have highest negative dock score as -5.71, -5.70, -5.74 and -5.69 respectively compared to the risperidone. It means that these formed most stable drug-receptor complex. All the docked compounds were analyzed for various types
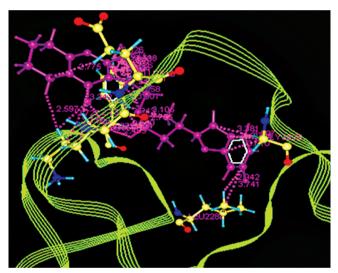
a. Compound **2q** shows a hydrogen bond interaction with LEU228 amino acid residue of 5HT$_{2A}$ receptor.

b. Compound **2q** shows eighteen hydrophobic interactions; thirteen with LEU228 and five with LEU229.

c. Resperidone shows twelve hydrophobic interactions; one with LYS220, one with PHE222, one with LEU229, seven with LYS350 and two with GLU351.

d. Van der Waals interations of resperidone with 5HT$_{2A}$ receptor.

FIGURE 2. Docking interactions.

of interactions like hydrogen bonding, hydrophobic bonding and van der Waals interactions.

From above study it is clear that compound **2e**, **2i** and **2q** bind with 5HT$_{2A}$ receptor by forming hydrogen bond interaction with amino acid residue LYS223, LYS350, LEU228, LEU361 and LEU362. Compound **2e, 2i, 2q** and **2t** have same hydrophobic interaction as like risperidone. Compound **2e, 2i, 2q** and **2t** are showing hydrophobic bond interaction with amino acid residue LYS350, LEU228, LEU229, and GLU351. Compound **2e, 2i, 2q** and **2t** also shows van der Waals interaction with 5HT$_{2A}$. The

bonding interactions of compound **2q** and risperidone are shown in **Figure 2**.

CONCLUSION

In the present series of nitro substituted 3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxamides have shown potent antipsychotic activity. The molecular modelling studies reveal that more potent antipsychotics from this series can be generated by substituting electronegative group at *para* and *meta* position of *N*-phenyl ring and less bulky group at 5-phenyl ring of thiazolo[3,2-a]pyrimidine-6-carboxamide.

Tiyazolo[3,2-a]pirimidin türevi 5HT₂ₐ reseptör antagonisti antipsikotiklerin sentezi, yapı-etki ilişkileri ve docking çalışmaları

ÖZET

Mikrodalga yöntemi kullanılarak tiyazolo[3,2-a]pirimidin karboksamit yapılı 22 yeni madde sentezlenmiştir. Sübstitüe asetoasetanilit'lerin, tiyoüre ve substitüe benzaldehitler'le etanol içerisinde ve p-toluensülfonik asit katalizörlüğünde tepkimesinden 2-tiyokso-1,2,3,4-tetrahidropirimidin-2-karboksamit'ler elde edilmiştir. Elde edilen ürün, buzlu asetik asit içerisinde ve susuuz sodyum asetat varlığında klororasetik asit'le muamele edilerek hedef bileşikler kazanılmıştır. Tepkime takibi ve bileşiklerin saflıklarının belirlenmesi için ince tabaka kromatografisi yöntemi (sabit faz; silikkajel G) uygulanmış ve bileşiklerin erime noktaları saptanmıştır.

Saflıkları elementel analiz ile doğrulanan bileşiklerin, yapıları, IR, ¹H NMR spektroskopisi ve kütle spektrometrisi yöntemleriyle aydınlatılmıştır. Bileşiklerin antipsikotik etkileri *albino* fareler kullanılarak rotarod ve kuyruk süspansiyon testleri ile saptanmıştır. Bileşiklerin risperidon'la kıyaslanabilir antipsikotik etki gösterdiği bildirilmiştir. 2D, 3D QSAR ve moleküler modelleme çalışmaları VLife MDS 3.5 yazılımı kullanılarak gerçekleştirilmiştir. Moleküler modelleme çalışmaları sonucunda en yüksek antipsikotik etkinin *N*-fenil halkasının *para* ve *meta* konumlarına elektronegatif grupların eklenmesi ile ve tiyazolo[3,2-a]pirimidin-6-karboksamit'in 5. konumuna fenil yerine daha küçük hacimli gruplar getirilmesi ile elde edilebileceği bildirilmiştir.

Anahtar Kelimeler; Moleküler Modelleme, QSAR, Tiyazolo[3,2-a]pirimidin, Şizofreni, 5HT₂ₐ reseptör antagonisti.

REFERENCES

1. Reynolds GP. Developments in the drug treatment of schizophrenia. Trends Pharmacol Sci 1992; 13:116-21.

2. Seeman P. Brain dopamine receptors. Pharmacol Rev 1980; 32:229-313.

3. Gudelsky GA, Nash JF, Berry SA, Meltzer HY. Basic biology of clozapine: electrophysiological and neuroendocrinological studies. Psychopharmacology (Berl) 1989; 99:S13–7.

4. Rang HP, Ritter JM, Dale MM, Moore PK. Pharmacology. Reed Elsevier India (p) Ltd., New Delhi. 2006.

5. Hawas UW, Al-Omar MA, Galil AE, Amr AGE, Hammam AEG. Synthesis of some thiopyrimidine and thiazolopyrimidines starting from 2,6-dibenzylidene-3-methylcyclohexanone and its antimicrobial activities. Arab J Chem 2012; 5:509-15.

6. Salem MA, Thabet HKH, Helal MH, Abdelaal AS, Ammar YA. Synthesis and pharmacological evaluation of some pyrazoles, thiazolopyrimidine, triazolopyrimidine, pyridone and 2-iminochromene containing naproxenoyl moiety as NSAIDs. Chem Sci 2011; 2:1-12.

7. Mohamed SF, Flefel EM, Galil AE, Amr AEE, El-Shafy DNA. Anti-HSV-1 activity and mechanism of action of some new synthesized substituted pyrimidine, thiopyrimidine and thiazolopyrimidine derivatives. Eur J Med Chem 2010; 45: 1494–501.

8. Balkan A, Uma S, Ertan M, Wiegrebe W. Thiazolo[3,2-a]pyrimidine derivatives as calcium antagonists. Pharmazie 1992; 47:687-88.

9. Abu-Hashem AA, Youssef MM, Husseina AR. Synthesis, antioxidant, antitumor activities of some new thiazolopyrimidines, pyrrolothiazolopyrimidines and triazolopyrrolothiazolopyrimidines derivatives. J Chin Chem Soc 2011; 58:41-8.

10. Awadallah FM. Synthesis, Pharmacophore modeling, and biological evaluation of novel 5H-thiazolo[3,2-a]pyrimidin-5-one derivatives as 5-HT2A receptor antagonists. Sci Pharm 2008; 76:415–38.

11. Prashantha Kumar BR, Sankar G, Nasir Baig RB, Chandrashekaran S. Novel Biginelli dihydropyrimidines with potential anticancer activity: A parallel synthesis and CoMSIA study. Eur J Med Chem 2009; 44:4192–8.

12. Ashok M, Holla BS, Kumari NS. Convenient one pot synthesis of some novel derivatives of thiazolo [2, 3-b] dihydropyrimidinone possessing 4-methylthiophenyl moiety and evaluation of their antibacterial and antifungal activities. Eur J Med Chem 2007; 42:380-5.

13. Arora P, Das S, Arora N, Gawai A, Baghel US. Synthesis and screening of some novel 7-Hydroxy 4-Methyl Coumarin derivatives for antipsychotic activity. Int J Pharm Life Sci 2010; 1:113-8.

14. Kaur H, Kumar S, Kumar A. Synthesis, antipsychotic and anticonvulsant activity of some new pyrazolinyl/isoxazolinylindol-2-ones. Int J ChemTech Res 2010; 2: 1010-9.

15. Arruda MOV, Soares PM, Honorio JER, Lima RC de S, Chaves EMC, Lobato R de FG, Martin AL de AR, Sales GTM, Carvalho K de M, Assreuy AMS, Brito EM, Vasconcelos SMM. Activities of the antipsychotic drugs haloperidol and risperidone on behavioural effects induced by ketamine in mice. Sci Pharm 2008; 76:673–87.

16. QSAR plus molecular design suit [MDS]. VLife Sciences Technology Pvt. Ltd. Pune.

17. Halgren TA. Merck molecular force field III, Molecular geometries and vibrational frequencies. J Comput Chem 1996; 17:553–86.

18. Chakraborti AK, Gopalakrishnan B, Sobhia ME, Malde A. 3D-QSAR studies of indole derivatives as phosphodiesterase IV inhibitors. Eur J Med Chem 2003; 38: 975-82.

19. Puratchikody A, Nagalakshmi G, Doble M. Experimental and QSAR studies on antimicrobial activity of benzimidazole derivatives. Chem Pharm Bull 2008; 56: 273-81.

20. Tropsha A, Gramatica P, Gombar VK. The importance of being Earnest: Validation is the absolute essential for successful application and interpretation of QSPR models. QSAR Comb Sci 2003; 22:69-77.

21. Golbraikh A, Tropsha A. Beware of q2!. J Mol Graph Model 2002; 20:269-76.

22. Afantitis A, Melagraki G, Sarimveis H, Igglessi–Markopoulou O, Kollias G. A novel QSAR model for predicting the inhibition of CXCR3 receptor by 4-N-aryl-[1,4] diazepane ureas. Eur J Med Chem 2009; 44:877-84.

23. Ravichandran V, Mourya VK, Agrawal RK. QSAR prediction of HIV–1 reverse transcriptase inhibitory activity of benzoxazinone derivatives. Internet Electron J Mol Des 2007; 6:363-74.