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Der Pharma Chemica, 2010, 2(4): 169-177
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X

3-(5*H*-[1,2,4]Triazino[5,6-*b*]indol-3-ylthio)-*N*-(substituted phenyl)propionamides: Synthesis and antidepressant activity evaluation

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Abstract

Present research work was undertaken to assess the effect of increased chain length of acyl group on the antidepressant activity of previously reported 2-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-(substituted phenyl)acetamides. Accordingly, various derivatives of 3-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-(substituted phenyl)propionamides C1–C18 were synthesized by reacting 1,2,4-triazino[5,6-b]indole-3-thione with 3-chloro-N-(substituted phenyl)propionamides and were characterized by IR, 1H NMR, 13C NMR, 13C DEPT, MS and elemental analysis. Synthesized compounds were evaluated for potential antidepressant activity by tail suspension test (TST). All the compounds exhibited moderate to weak antidepressant activity in comparison with standard drugs. Results of this study indicate that antidepressant activity of 2-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-(substituted phenyl)acetamides is severely mitigated on increasing chain length of its acyl group by one carbon.

Key words: 5H-[1,2,4]triazino[5,6-b]indole, 3-chloro-N-(substituted phenyl)propionamides, antidepressant , tail suspension test.

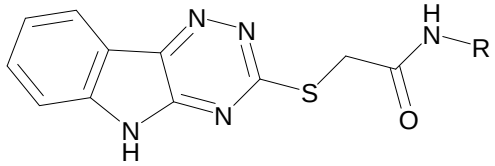
INTRODUCTION

Depression is a common but serious illness characterized by persistent feelings of sadness, hopelessness, pessimism, guilt, loss of interest in activities and decreased energy. Combination of these along with many other symptoms severely affects person's professional, social and family life [1]. Lifetime prevalence of depression is close to 17 % and it is one of the most significant cause of disability worldwide after cardiovascular diseases [2]. Conventionally, decreased levels of brain monoamines like norepinephrine, serotonin and dopamine are

considered responsible for depression. However, complex array of events occurring in central nervous system, which are yet not fully understood, are likely to be involved in depression [3-5]. Vast majority of antidepressants exert their effect by elevating the level of brain monoamines. Today, number of antidepressant drugs with varying mechanism of action, are at the physician's disposal. These include monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors and specific serotonin-norepinephrine reuptake inhibitors [6]. However, with clinically used antidepressants, significant number of patients fail to achieve lifetime remission, despite intensive management [7, 8] and only 60% of patients respond to them [9]. Also, currently available antidepressants exhibit delayed onset of action, requiring continuous treatment for at least 2-4 weeks before significant effects are seen [10]. In addition unpredictable clinical response to antidepressant drugs and high susceptibility to adverse effects are major clinical problems [11]. All these limitations of existing drugs along with sharp upsurge of depressive cases in today's world make the research in the field of antidepressants as a major thrust area.

Previously, we had revealed antidepressant potential of 3-(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylthio)-*N*-(substituted phenyl)acetamide derivatives (Figure 1) [12], wherein many of the synthesized compounds exhibited impressive activity in tail suspension test, comparable to standard drugs. These results prompted us to investigate the effect of increased chain length of acyl group on the antidepressant activity of acetamide derivatives. With that intention, the present series of 3-(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylthio)-*N*-(substituted phenyl)propionamides was designed by introducing an extra carbon linker in the acyl group of acetamide derivatives. This article deals with synthesis and antidepressant evaluation of the title compounds **C_1-C_{18}**.

Figure 1: Previously reported 2-(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylthio)-*N*-(substituted phenyl)acetamides as potential antidepressants [12]

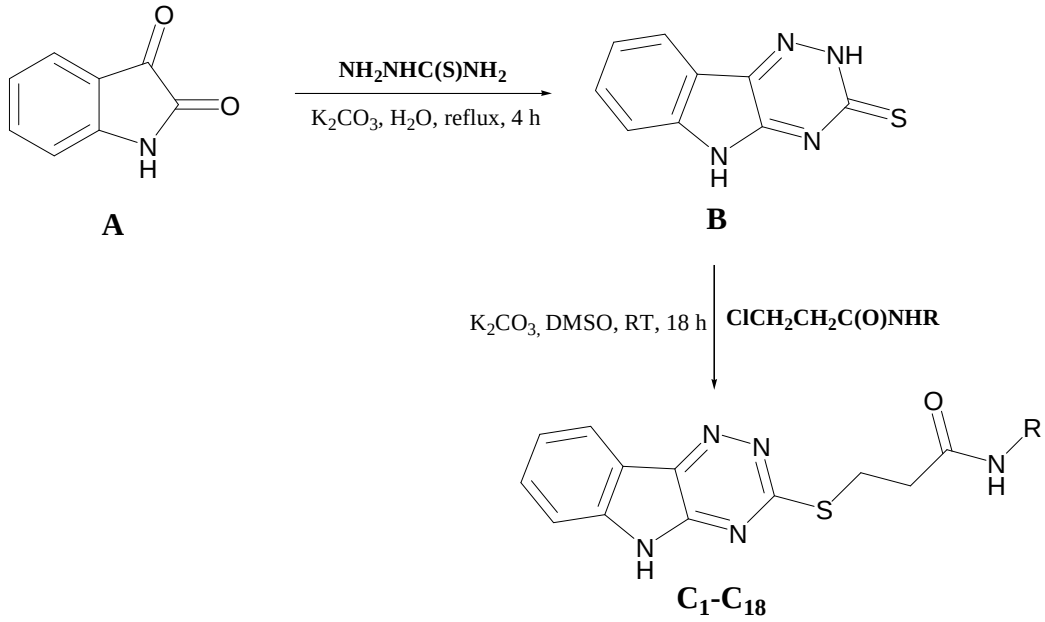


MATERIALS AND METHODS

All the chemicals and solvents used were of synthetic grade. Melting points were determined by Veego VMP-D digital melting point apparatus and are uncorrected. Jasco FT/IR-4100 was used for recording IR spectra in KBr. ^{1}H NMR, ^{13}C NMR and ^{13}C DEPT spectra were obtained on Varian-Mercury 300 MHz instrument using DMSO-d_6 as solvent with chemical shifts reported in δ ppm relative to tetramethylsilane. Splitting patterns are abbreviated as: s, singlet; d, doublet; t, triplet; m, multiplet; br s, broad singlet; br d, broad doublet. Mass spectra were recorded on 410 Prostar Binary LC with 500 MS IT PDA Detectors, Varian Inc using direct infusion mass with APCI. Elemental analysis (C, H, N, S) was performed on FLASH EA 1112, Thermo-Finnigan. Results of elemental analysis are within ± 0.4 % range of theoretical values for all the compounds.

General procedure for synthesis of 3-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-(substituted phenyl)propionamides **(C_1 –C_{18}):**

To a solution of 5*H*-[1,2,4]triazino[5,6-*b*]indole-3-thione **A** (5 mmol) in dry dimethylsulfoxide (DMSO) (25 mL) containing anhydrous milled potassium carbonate (10 mmol), was added appropriate 3-chloro *N*-(susbtitued phenyl)propionamide. Reaction mixture was kept stirring at room temperature for 18 h. Reaction mixture was then slowly poured into water with stirring to precipitate the formed product. Once the addition was over, the suspension containing precipitated product was allowed to stir for further 5 min. The product precipitated was then filtered, washed with water and dilute methanol, dried and recrystallised from *N*,*N*-dimethylformamide-water to yield **C_1-C_{18}** (Scheme 1).



Scheme 1: Synthetic route for 3-(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylthio)-*N*-(substituted phenyl)propionamides

Following products were synthesized using above method:

3-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-phenylpropionamide **C_1** : Yield 68 %; mp 250-254 ºC; IR (KBr, ν cm^{-1}): 3293, 3206, 3064, 2970, 1658, 1603, 1536, 1423. ^{1}H NMR (DMSO-d_6, δ): 2.90 (t, 2H, -CH_2-CO-), 3.53 (t, 2H, -S-CH_2-), 7.03 (t, 1H, Ar-H), 7.29 (t, 2H, Ar-H), 7.43 (t, 1H, Ar-H), 7.58 (m, 3H, Ar-H), 7.69 (t, 1H, Ar-H), 8.31 (d, 1H, Ar-H), 9.99 (s, 1H, -NH-), 12.72 (br s, 1H, -NH-).^{13}C NMR (DMSO-d_6, δ): 26.02, 36.09, 112.89, 117.85, 119.26 (2C), 121.66, 122.70, 123.38, 128.94 (2C), 131.08, 139.29, 140.48, 141.22, 146.91, 167.08, 169.61. ^{13}C DEPT (DMSO-d_6, δ): Positive peaks: 112.89, 119.26 (2C), 121.67, 122.70, 123.39, 128.95 (2C), 131.08. Inverse peaks: 26.02, 36.66. MS (APCI) *m/z*: 350.1 (M^+; 100%). Elemental analysis $C_{18}H_{15}N_5OS$ Calcd. (Found): C, 61.87 (62.06); H, 4.33 (4.59); N, 20.04 (19.68); S, 9.18 (9.24).

3-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-(2-methylphenyl)propionamide **C_2:** Yield 69 %; mp 252-256 ºC; IR (KBr, ν cm^{-1}): 3268, 3211, 3060, 2968, 1647, 1609, 1544, 1420. ^{1}H NMR (DMSO-d_6, δ): 2.26 (s, 3H, -CH_3), 2.89 (t, 2H, -CH_2-CO-), 3.52 (t, 2H, -S-CH_2-), 7.09 (t, 1H, Ar-

H), 7.13 (t, 1H, Ar-H), 7.19 (d, 1H, Ar-H), 7.47 (m, 2H, Ar-H), 7.62 (d, 1H, Ar-H), 7.70 (t, 1H, Ar-H), 8.27 (d, 1H, Ar-H), 10.02 (br s, 1H, -NH). Elemental analysis $C_{19}H_{17}N_5OS$ Calcd. (Found): C, 62.79 (62.52); H, 4.71 (4.98); N, 19.27 (19.02); S, 8.82 (9.10).

3-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-(2-methoxyphenyl)propionamide **C_3:** Yield 63 %; mp 249-255 ºC; IR (KBr, ν cm^{-1}): 3309, 3210, 3118, 3067, 2963, 1653, 1605, 1536, 1419. ^{1}H NMR (DMSO-d_6, δ): 2.86 (t, 2H, -CH_2-CO-), 3.54 (t, 2H, -S-CH_2-), 3.75 (s, 3H, -OCH_3), 7.28 (t, 1H, Ar-H), 7.43 (t, 1H, Ar-H), 7.50 (d, 1H, Ar-H), 7.63 (m, 2H, Ar-H), 7.75 (d, 1H, Ar-H), 7.92 (d, 1H, Ar-H), 8.37 (d, 1H, Ar-H), 10.53 (br s, 1H, -NH-).

3-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-(2-chlorophenyl)propionamide **C_4:** Yield 65 %; mp 238-242 ºC; IR (KBr, ν cm^{-1}): 3278, 3192, 3107, 3063, 2970, 1661, 1584, 1531, 1422. ^{1}H NMR (DMSO-d_6, δ): 2.91 (t, 2H, -CH_2-CO-), 3.53 (t, 2H, -S-CH_2-), 7.21 (t, 1H, Ar-H), 7.34 (t, 1H, Ar-H), 7.44 (m, 2H, Ar-H), 7.55 (d, 1H, Ar-H), 7.72 (t, 1H, Ar-H), 7.78 (d, 1H, Ar-H), 8.33 (d, 1H, Ar-H), 10.12 (br s, 1H, -NH-H).

3-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-(2-bromophenyl)propionamide **C_5:** Yield 68 %; mp 235-241 ºC; IR (KBr, ν cm^{-1}): 3273, 3165, 3059, 2985, 1655, 1589, 1538, 1421. ^{1}H NMR (DMSO-d_6, δ): 2.90 (t, 2H, -CH_2-CO-), 3.53 (t, 2H, -S-CH_2-), 7.24 (t, 1H, Ar-H), 7.40 (t, 1H, Ar-H), 7.44 (m, 2H, Ar-H), 7.61 (d, 1H, Ar-H), 7.68 (t, 1H, Ar-H), 7. 76 (d, 1H, Ar-H), 8.30 (d, 1H, Ar-H), 9.97 (br s, 1H, -NH-).

3-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-(2-nitrophenyl)propionamide **C_6:** Yield 58 %; mp 275-280 ºC; IR (KBr, ν cm^{-1}): 3254, 3186, 3053, 2989, 1655, 1606, 1536, 1452. ^{1}H NMR (DMSO-d_6, δ): 3.32 (t, 2H, -CH_2CO-), 4.94 (t, 2H, -S-CH_2-), 7.33-7.46 (m, 3H, Ar-H), 7.58-7.68 (m, 3H, Ar-H), 7.91-7.97 (m, 2H, Ar-H), 10.48 (br s, 1H, -NH-).

3-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-(3-methylphenyl)propionamide **C_7:** Yield 69 %; mp 252 257 ºC; IR (KBr, ν cm^{-1}): 3281, 3145, 3061, 2978, 1652, 1608, 1540, 1419. ^{1}H NMR (DMSO-d_6, δ): 2.24 (s, 3H, -CH_3), 2.87 (t, 2H, -CH_2-CO-), 3.51 (t, 2H, -S-CH_2-), 6.63 (d, 1H, Ar-H), 7.13 (t, 1H Ar-H), 7.34 (d, 1H, Ar-H), 7.41 (t, 2H, Ar-H), 7.56 (d, 1H, Ar-H), 7.68 (t, 1H, Ar-H), 8.28 (d, 1H, Ar-H), 9.94 (br s, 1H, -NH-).

3-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-(3-methoxyphenyl)propionamide **C_8:** Yield 62 %; mp 248-252 ºC; ; IR (KBr, ν cm^{-1}): 3308, 3285, 3069, 2931, 1639, 1601, 1545, 1419. ^{1}H NMR (DMSO-d_6, δ): 2.85 (t, 2H, -CH_2-CO-), 3.52 (t, 2H, -S-CH_2-), 3.70 (s, 3H, -OCH_3), 7.45 (t, 1H, Ar-H), 7.49 (d, 2H, Ar-H), 7.58 (t, 3H, Ar-H), 7.73 (t, 1H, Ar-H), 8.30 (d, 1H, Ar-H), 10.23 (br s, 1H, -NH-).

3-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-(3-chlorophenyl)propionamide **C_9:** Yield 59 %; mp 244-247 ºC; IR(KBr, ν cm^{-1}): 3275, 3189, 3106, 3066, 2975, 1663, 1587, 1534, 1420. ^{1}H NMR (DMSO-d_6, δ): 2.91 (t, 2H, -CH_2-CO-), 3.53 (t, 2H, -S-CH_2-), 7.10 (d, 1H, Ar-H), 7.30 (t, 1H, Ar-H), 7.41 (t, 2H, Ar-H), 7.56 (d, 1H, Ar-H), 7.69 (t, 1H, Ar-H), 7.81 (s, 1H, Ar-H), 8.30 (d, 1H, Ar-H), 10.19 (br s, 1H, -NH-). Elemental analysis $C_{18}H_{14}ClN_5OS$ Calcd. (Found): C, 56.32 (56.55); H, 3.68 (3.83); N, 18.24 (18.07); S, 8.35 (8.19).

3-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-(3-bromophenyl)propionamide **C_{10}:** Yield 60 %; mp 243-246 ºC; IR(KBr, ν cm^{-1}): 3271, 3126, 3052, 2983, 1657, 1582, 1538, 1422. ^{1}H NMR (DMSO-d_6, δ): 2.90 (t, 2H, -CH_2-CO-), 3.51 (t, 2H, -S-CH_2-), 7.11 (d, 1H, Ar-H), 7.24 (t, 1H, Ar-H), 7.44 (t, 1H, Ar-H), 7.59 (m, 2H, Ar-H), 7.68 (t, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 8.32 (d, 1H, Ar-H), 10.23 (br s, 1H, -NH-).

3-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-(3-nitrophenyl)propionamide **C_{11}:** Yield 57 %; mp > 290 ºC; IR(KBr, ν cm^{-1}): 3363, 3194, 3083, 2979, 1677, 1613, 1542, 1430. ^{1}H NMR (DMSO-d_6, δ): 3.12 (t, 2H, -CH_2CO-), 3.93 (t, 2H, -S-CH_2-), 7.40 (t, 1H, Ar-H), 7.58 (d, 1H, Ar-H), 7.60 (t, 1H, Ar-H), 7.73 (t, 1H, Ar-H), 7.93 (t, 2H, Ar-H), 8.29 (d, 1H, Ar-H), 8.69 (s, 1H, Ar-H), 10.74 (br s, 1H, -NH-).

3-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-(4-methylphenyl)propionamide **C_{12}:** Yield 71 %; mp 266 - 270 ºC; IR(KBr, ν cm^{-1}):3297, 3117, 3060, 2979, 1658, 1603, 1534, 1408. ^{1}H NMR (DMSO-d_6, δ): 2.24 (s, 3H, -CH_3), 2.88 (t, 2H, -CH_2-CO-), 3.52 (t, 2H, -S-CH_2-), 7.10 (d, 2H, Ar-H), 7.45 (t, 1H, Ar-H), 7.49 (d, 2H, Ar-H), 7.55 (d, 1H, Ar-H), 7.69 (t, 1H, Ar-H), 8.30 (d, 1H, Ar-H), 10.11 (br s, 1H, -NH-).

3-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-(4-methoxyphenyl)propionamide **C_{13}:** Yield : 63 %; mp 254–258 ºC; IR(KBr, ν cm^{-1}): 3305, 3211, 3066, 2980, 1654, 1603, 1536, 1415. ^{1}H NMR (DMSO-d_6, δ): 2.85 (t, 2H, -CH_2-CO-), 3.52 (t, 2H, -S-CH_2-), 3.70 (s, 3H, -OCH_3), 6.85 (d, 2H, Ar-H), 7.43 (t, 1H, Ar-H), 7.48 (d, 2H, Ar-H), 7.58 (d, 1H, Ar-H), 7.69 (t, 1H, Ar-H), 8.29 (t, 1H, Ar-H), 9.85 (br s, 1H, -NH-).^{13}C NMR (DMSO-d_6, δ): 26.13, 35.94, 55.35, 112.91, 114.05 (2C), 117.86, 120.81 (2C), 121.68, 122.72, 131.0, 132.46, 140.51, 141.23, 146.94, 155.34, 167.11, 169.06. ^{13}C DEPT (DMSO-d_6, δ): Positive peaks: 55.36, 112.92, 114.06 (2C), 120.81(2C), 121.69, 122.73, 131.11; Inverse peaks: 26.13, 35.95. MS (ESI) *m/z*: 380.0 (M^+; 100%) Elemental analysis $C_{19}H_{17}N_5O_2S$ Calcd. (Found): C, 60.14 (59.90); H, 4.52 (4.84); N, 18.46 (18.33); S, 8.45 (8.11).

3-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-(4-chlorophenyl)propionamide **C_{14}:** Yield : 64 %; mp 248-253 ºC; IR(KBr, ν cm^{-1}): 3276, 3110, 3061, 2984, 1664, 1581, 1535, 1419. ^{1}H NMR (DMSO-d_6, δ): 2.90 (t, 2H, -CH_2-CO-), 3.54 (t, 2H, -S-CH_2-), 7.33 (t, 1H, Ar-H), 7.42 (d, 2H, Ar-H), 7.59 (m, 3H, Ar-H), 7.70 (t, 1H, Ar-H), 8.28 (d, 1H, Ar-H), 10.53 (br s, 1H, -NH-).

3-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-(4-bromophenyl)propionamide **C_{15}:** Yield: 66 %; mp 245-251 ºC; IR(KBr, ν cm^{-1}): 3271, 3115, 3057, 2976, 1658, 1585, 1537, 1420. ^{1}H NMR (DMSO-d_6, δ): 2.90 (t, 2H, -CH_2-CO-), 3.52 (t, 2H, -S-CH_2-), 7.45 (t, 1H, Ar-H), 7.52 (d, 2H, Ar-H), 7.57 (m, 3H, Ar-H), 7.69 (t, 1H, Ar-H), 8.28 (d, 1H, Ar-H), 9.93 (br s, 1H, -NH-).

3-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-(4-nitrophenyl)propionamide **C_{16}:** Yield: 54 %; mp 260-265 ºC; IR(KBr, ν cm^{-1}): 3267, 3154, 3051, 2989, 1663, 1606, 1592, 1539. ^{1}H NMR (DMSO-d_6, δ): 2.94 (t, 2H, -CH_2-CO-), 3.57 (t, 2H, -S-CH_2-), 7.36 (t, 1H, Ar-H), 7.54 (d, 2H, Ar-H), 7.65 (m, 2H, Ar-H), 7.89 (d, 1H, Ar-H), 8.15 (d, 1H, Ar-H), 8.31 (d, 1H, Ar-H), 10.96 (br s, 1H, -NH-).

3-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-benzylpropionamide **C_{17}:** Yield: 69 %; mp 240-244 ºC; IR (KBr, ν cm^{-1}): 3292, 3109, 3059, 2976, 1641, 1603, 1543, 1417. ^{1}H NMR (DMSO-d_6, δ): 2.72 (t, 2H, -CH_2-CO-), 3.48 (t, 2H, -S-CH_2-), 4.31 (d, 2H, -CH_2-Ph), 7.21-7.33 (m, 5H, Ar-H), 7.43 (t, 1H, Ar-H), 7.58 (t, 1H, Ar-H), 7.69 (t, 1H, Ar-H), 8.31 (d, 1H, Ar-H), 8.44 (d, 1H, -NH-CH_2-), 12.57 (br s, 1H, -NH-).

3-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-cyclohexylpropionamide **C_{18}:** Yield: 72 %; mp 258-262 ºC; IR (KBr, ν cm^{-1}): 3302, 3069, 2931, 2853, 1639, 1601, 1545, 1419. ^{1}H NMR (DMSO-d_6, δ): 1.10-1.23 (m, 5H, cyclohexyl-H), 1.52-1.74 (m, 5H, cyclohexyl-H), 2.59 (t, 2H, -CH_2-CO-), 3.43 (t, 2H, -S-CH_2-), 3.53 (m. 1H, cyclohexyl-H), 7.43(t, 1H, Ar-H), 7.56 (d, 1H, Ar-H), 7.68 (d, 1H, Ar-H), 7.78 (br d, 1H, -NH-C_6H_{11}), 8.29 (d, 1H, Ar-H), 12.64 (br s, 1H, -NH-).

Pharmacology

Adult male Swiss Albino mice in the weight range of 22 ± 2 g were used for the purpose of pharmacological evaluation. Mice were stored in quiet, temperature and humidity controlled rooms with a 12 h light / dark cycle and had free access to food and water. One week acclimatization period was given before the commencement of experiments. Prior to initiation of these experiments, approval was obtained from Institutional Animal Ethics Committee regarding use of animals for experimentation. Animals were divided into three groups: control, test and standard, each comprising of six animals. Solutions of standard drugs as well as test compounds were prepared in DMSO and administered intraperetoneally (i.p) at a dose of 30 mg/kg. Animals in the control group were treated with DMSO administered at a fixed volume of 5 mL/kg, i.p.

Tail suspension test (TST)

For evaluating antidepressant potential of the synthesized compounds, tail suspension test, a well established behavioral model, was employed. Test as well as standard drugs were given sub-chronically, involving administration of three doses in 24 h duration at t = 0, 18 and 24 h. Test was performed 1 h after the last dose was administered. In TST, mice were suspended 80 cm above the floor by tail with the help of adhesive tape attached approximately 1 cm from the tip of the tail. After initial escape orientated movements, mice gradually became immobile. The duration of immobility was recorded for the duration of 6 min. Mice were considered as immobile when they hung completely motionless. In TST, compounds ability to decrease immobility duration is correlated with its antidepressant potential [13, 14]. Antidepressant activity was expressed in terms of % decrease in immobility duration (%DID), which was calculated as: % DID = [(X-Y)/X]*100; where, X is duration of immobility in control group (s) & Y is duration of immobility in test group (s).

RESULTS AND DISCUSSION

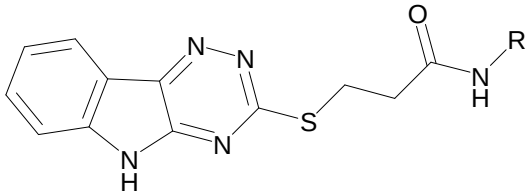
Chemistry

Synthesis of 5*H*-[1,2,4]triazino[5,6-*b*]indole-3-thione **B** was accomplished following a earlier reported procedure [15] involving reaction of isatin **A** with thiosemicarbazide in water containing excess of potassium carbonate, under reflux conditions. Acidification of reaction mixture with glacial acetic acid leads to formation of yellow precipitate of **B** in copious amounts. Various 3-chloro- *N*-substitutedpropionamides were synthesized as per usual method [16],

involving reaction of appropriate primary amines with 3-chloropropionyl chloride in glacial acetic acid. Synthesis of 3-(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylthio)-*N*-substitutedpropionamides **C_1-C_{18}** involved simple overnight stirring of **B** with 3-chloro- *N*-substitutedpropionamides in DMSO containing potassium carbonate.

The structures of **C_1-C_{18}** were in accordance with IR, ^{1}H NMR, ^{13}C NMR, ^{13}C DEPT, MS and elemental analysis data. For example, IR spectrum of **C_{13}** shows a broad absorption peak of N-H stretching in secondary amides at 3305 cm^{-1} and aromatic C-H stretching at 3066 $cm^{-1.}$ The presence of aliphatic linkage is confirmed by peak at 2980 $cm^{-1.}$ Strong absorption band at 1654, 1603 and 1536 cm^{-1} represent respectively amide carbonyl stretching, aromatic C=C stretching and N-H bending in secondary amides. C-N stretching band is seen at 1415 cm^{-1}. ^{1}H NMR spectrum of **C_{13}** showed the triplets at δ 2.80 and 3.52, indicating respectively the presence of two α and two β protons in propionamide. Further, presence of methoxy group in **C_{13}** is ascertained by the singlet at δ 3.70 corresponding to three protons. Multiplets in the range of δ 6.85-8.29 integrating for eight protons confirm the presence of necessary aromatic system, whereas broad singlet at δ 9.85 verify –NH- proton in the structure. ^{13}C NMR spectrum of **C_{13}** displayed peaks at δ 26.13 and 35.94 for α and β carbon atoms of propionamide respectively. Methoxy carbon and carbonyl carbon are correspondingly responsible for the peaks at δ 55.35 and 169.06. Peaks for fifteen carbon atoms ranging from δ 112.91-167.11 satisfy the requirement for desired aromatic makeup of **C_{13}**. Finally, a mass spectrum (APCI) shows a molecular ion peak at *m/z* 380 which is consistent with molecular weight of **C_{13}**.

Table 1: Evaluation of antidepressant activity of the synthesized compounds by TST



Compound [a]	R	Duration of Immobility (s) (Mean ± SEM)	% DID
C_1	**Phenyl**	191.2 ± 8.3^{ns}	14.79
C_2	**2-Methylphenyl**	201.0 ± 6.6^{ns}	10.00
C_3	**2-Methoxylphenyl**	216.2 ± 12.7^{ns}	2.95
C_4	**2-Chlorophenyl**	158.7 ± 11.9*	29.51
C_5	**2-Bromophenyl**	161.5 ± 8.2*	28.18
C_6	**2-Nitrophenyl**	218.7 ± 8.6^{ns}	2.51
C_7	**3-Methylphenyl**	183.7 ± 9.8*	18.20
C_8	**3-Methoxyphenyl**	190.8 ± 13.0^{ns}	15.14
C_9	**3-Chlorophenyl**	169.3 ± 10.6*	24.55
C_{10}	**3-Bromophenyl**	182.3 ± 9.3*	18.62
C_{11}	**3-Nitrophenyl**	153.3 ± 6.3*	31.62
C_{12}	**4-Methylphenyl**	194.0 ± 5.2^{ns}	13.49
C_{13}	**4-Methoxyphenyl**	217.5 ± 11.5^{ns}	3.11
C_{14}	**4-Chlorophenyl**	155.5 ± 7.7*	30.90
C_{15}	**4-Bromophenyl**	153.0 ± 6.3*	31.62
C_{16}	**4-Nitrophenyl**	183.7 ± 11.1*	17.78
C_{17}	**Benzyl**	161.7 ± 7.9*	28.18
C_{18}	**Cyclohexyl**	146.8 ± 10.3*	34.67

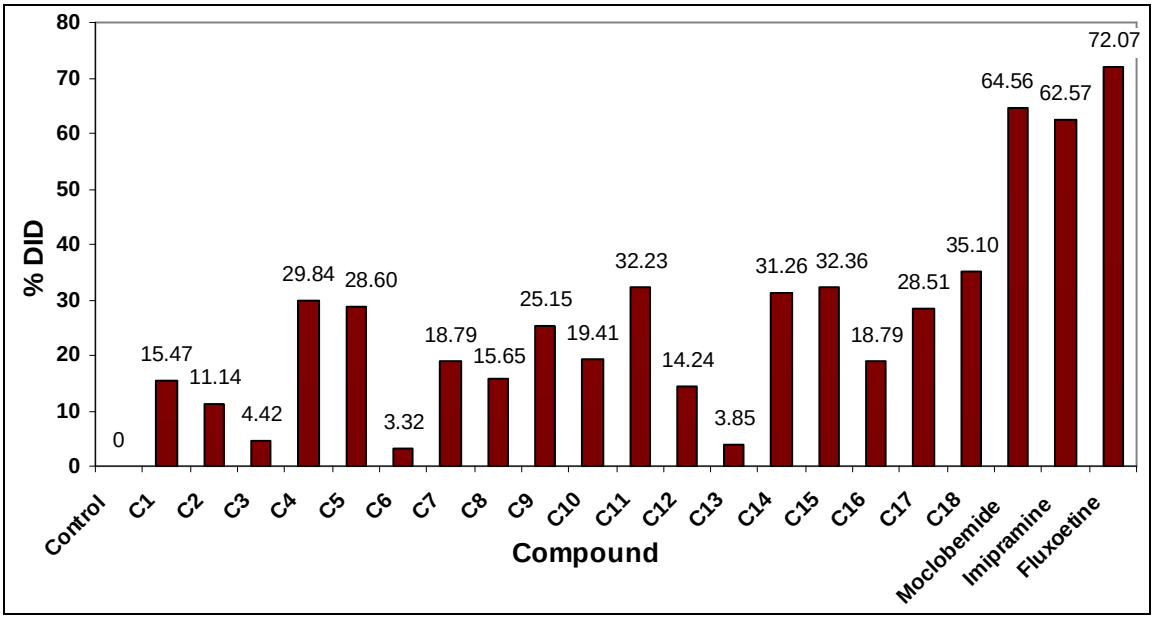
Moclobemide	-	80.1 ± 12.2*	64.56
Imipramine	-	84.6 ± 9.1*	62.57
Fluoxetine	-	63.17 ± 10.3*	72.07
Control	-	226.2 ± 8.0	-

n = 6; Data were analyzed by one-way ANOVA followed by Dunnett's test;
[a] Dose of standard and test drugs: 30 mg/kg; [ns] non-significant compared to control;
** $p < 0.05$ versus control*

Pharmacology

During pharmacological evaluation, only few of the synthesized compounds exhibited moderate antidepressant activity in tail suspension test, with many exhibiting weak activity (Table 1). None of the test compound caused considerable decrease in immobility duration as compared to standard drugs. However, within the series, halogen substitution (Cl, Br) at any position of phenyl ring had a favorable influence on activity as seen in **C_4, C_5, C_9, and C_{15}**. From %DID values of **C_2**, **C_7** and **C_{12}**, it can be said that methyl substitution on the phenyl ring doesn't influence antidepressant activity of its unsubstituted analogue **C_1**. On the other hand, methoxy substitution, as in **C_3** and **C_{13}** virtually reduces antidepressant activity to nil. Effect of electron withdrawing nitro group on the activity depends upon the position of substitution with *m*-nitro **C_{11}** amongst one of the most active test compound. Replacement of phenyl ring in **C_1** with benzyl **C_{17}** or cyclohexyl **C_{18}** enhances activity substantially; **C_{18}** being the most active of all the test compounds. Graph of %DID values against compounds tested is shown in Figure 2.

Figure 2: Plot of % DID against compounds tested



On the whole, it is quite evident that impressive antidepressant activity of previously reported 2-(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylthio)-*N*-(substituted phenyl)acetamides [12], was decreased by several folds when the chain length of acyl group in acetamides was increased by one carbon

atom to give presently studied 3-(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylthio)-*N*-(substituted phenyl)propionamides.

CONCLUSION

The main aim of this research work was to evaluate the effect of increased chain length of acyl group on the antidepressant activity of previously reported 2-(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylthio)-*N*-(substituted phenyl)acetamides. Accordingly, a new series of 3-(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylthio)-*N*-(substituted phenyl)propionamides was synthesized and characterized using modern tools of structure confirmation. The antidepressant activity of synthesized compounds was evaluated in TST. All the synthesized compounds showed only moderate to weak antidepressant activity. Thus, to conclude, increasing chain length of acyl group in acetamide derivatives by one carbon atom to form the present series adversely affected their antidepressant profile, rendering some of the them almost inactive.

Acknowledgements

One of the authors (S.M.S.), is indebted to Council of Scientific and Industrial Research (CSIR), New Delhi, for awarding him Senior Research Fellowship. Authors are grateful to Dr. R. A. Joshi and Dr. (Mrs.) R. R. Joshi, National Chemical Laboratory (NCL), Pune for their valuable help. Assistance of Indian Institute of Technology-Bombay, Mumbai in performing spectral analysis is also duly acknowledged.

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