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Synthesis, computational studies and pharmacological evaluation of some acetamides as serotonin antagonists

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ABSTRACT

*New acetamides (**4a-c**) linked with coumarin fragment were synthesized by chloroacetylation of some aminothiazoles and further treating with 7-hydroxy-4-methylcoumarin in the presence of anhydrous potassium carbonate in acetonitrile. The target compounds (**4a-c**) were evaluated for antiserotonergic activity by 5-HTP induced head twitches behavior in mice. The physicochemical similarity of the target compounds with respect to clozapine was assessed by calculating from a set of physiochemical properties using software programs. Compound **4b** demonstrated good similarity values with respect to the standard drug and has shown antiserotonergic activity.*

Key words: Aminothiazole, Acetamides, 7-Hydroxy-4-methylcoumarin, Computational studies and Serotonin antagonist.

INTRODUCTION

Serotonin (5-HT), a major neurotransmitter found in the central nervous system (CNS), is also present in many peripheral tissues. Its numerous biological functions are mediated by a variety of serotonin receptors [1-3]. In particular, 5-HT_2 mediate the actions of several drugs used in treating diseases such as schizophrenia, feeding disorders, depression, migraines, anxiety, and gastrointestinal dysfunctions [4, 5]. The 5-HT_{2A} receptor has been implicated as a therapeutic target for schizophrenia and depression. Representative 5-HT_{2A} antagonists include ketanserine, risperidone, aripiprazole and clozapine are used as antipsychotic drugs. Various acetamide and coumarin derivatives have been reported as dopamine and serotonin blocking activity [6, 7]. In view of these observations, we here in report the synthesis, computational studies of new acetamides linked with coumarin fragment and evaluated for antiserotonergic activity.

MATERIALS AND METHODS

Melting points of the synthesized compounds were determined by open capillary method and are uncorrected. The IR spectra of synthesized compounds were recorded in potassium bromide

discs on Perkin Elmer Spectrum RX1. The ^{1}H NMR spectra were recorded on a Bruker DRX-300 spectrophometer at 300 MHz in DMSO containing TMS as an internal standard. All reagents were of commercial quality and were used without further purification. The reaction's progress was monitored by thin-layer chromatography (TLC) using silica gel G and spots were visualized in an iodine chamber.

Synthesis

2-Chloro-N-(thiazole-2-yl) acetamide (2a)

Equimolar amounts of 2-aminothiazole **1** (0.05mole), chloroacetylchloride (0.05mole) and K_2CO_3 (0.05mole) in chloroform were refluxed for about 12 h. The mixture was filtered and solvent was washed with excess of water. The organic phase was dried (Na_2SO_4) and concentrated. The resulting residue was purified by crystallization from ethanol to afford compound **2a.** Yield: 48.0 %; m.p.: 148-150 ^{0}C; R_f: 0.77 (Hexane/EtOAc 1:2); IR (KBr) ν (cm-1): 3234 (NH Str) 2925 (CH Str) 1680 (C=O Str), 1414 (C=C Str) 1381 & 1266 (CN Str), 750 (C-Cl Str); ^{1}HNMR (300 MHz, DMSO-d_6, δ ppm): 8.48 (1H, NHCO), 6.62 & 7.49 (2H, CH in thiazole), 4.36 (2H, CH_2).

N-(Benzo[d]thiazol-2-yl)-2-chloroacetamide (2b)

Equimolar amounts of 2-aminobenzothiazole **1** (0.05mole), chloroacetylchloride (0.05mole) and K_2CO_3 (0.05mole) in chloroform were refluxed for about 12 h. The mixture was filtered and solvent was washed with excess of water. The organic phase was dried (Na_2SO_4) and concentrated. The resulting residue was purified by crystallization from ethanol to afford compound **2b.** Yield: 74.5 %; m.p.: 141-142 ^{0}C; R_f: 0.77 (Hexane/EtOAc 1:2); IR (KBr) ν (cm-1): 3406 (NH Str), 3049(CH Str Ar) 2928 (CH Str) 1647 (C=O Str), 1411 & 1237 (CN Str), 771 (C-Cl Str); ^{1}HNMR (300 MHz, DMSO-d_6, δ ppm): 8.1(1H, NHCO), 7.56- 7.9 (4H, Ar), 4.26 (2H, CH_2).

N-(4-(Benzo[d]thiazol-2-yl) phenyl)-2-chloroacetamide (2c)

Equimolar amounts of 2-(4-aminophenyl) benzothiazole **1** (0.05mole), chloroacetylchloride (0.05 mole) and K_2CO_3 (0.05 mole) in acetone were refluxed for about 12 h. The mixture was filtered and solvent was removed under reduced pressure and washed with water to afford **2c.** Yield: 74.0 %; m.p.: 150-155 ^{0}C; R_f: 0.77 (Hexane/EtOAc 1:1); IR (KBr) ν (cm-1): 3310(NH Str) 3010 (CH Str) 2939 (CH Str) 1680 (C=O Str), 1311 & 1222 (CN Str), 739 (C-Cl Str); ^{1}HNMR (300 MHz, $CDCl_3$ δ): 9.01 (1H, CONH), 8.21- 7.26 (8H, Ar), 4.35 (2H, CH_2).

General method for the preparation of various derivatives (4a-c)

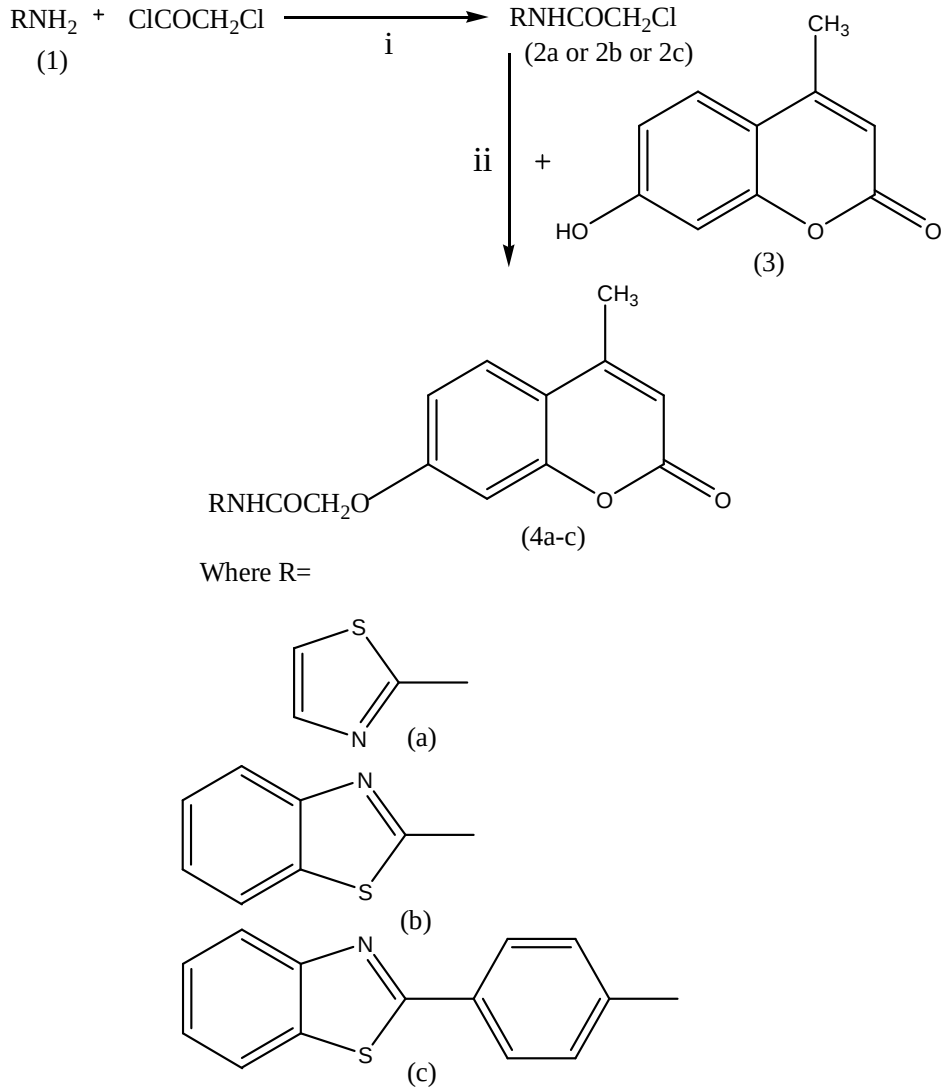
Equimolar amounts of 7-hydroxy-4-methylcoumarin **3** and anhydrous K_2CO_3 in dry acetonitrile were refluxed for 3h, then the compound **2a or 2b or 2c** was added and reaction mixture was further refluxed on water bath with continuous stirring for 24 hr. After cooling, the reaction mixture was filtered and solvent was removed under reduced pressure. Resulting residue was washed with water and recrystallized from ethanol to afford **4a-c**.

2-(4-Methyl-2-oxo-2H-chromen-7-yloxy)-N (thiazol-2-yl) acetamide (4a)

Yield: 33%; m.p.: 95-100^{0}C; R_f: 0.80 (Hexane/EtOAc 1:2); IR (KBr, νcm^1): 3380 (NH Str), 3020 (CH Str, Aromatic), 2924, (CH Str, Aliphatic), 1628 (C=O Str), 1218 (CN Str), 1031 (C-O-C Str); ^{1}HNMR (300 MHz, DMSO-d6, δ ppm): 8.47 (1H, NHCO), 7.42 & 6.37 (2H, CH in thiazole), 7.73- 6.23 (4H Aromatic), 4.89 (2H, CH_2), 2.42 (3H, CH_3).

N-(Benzo[d]thiazol-2-yl)-2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetamide (4b)
Yield: 54%; m.p.: 145-150^{0}C; R_f: 0.86 (Hexane/EtOAc 1:2); IR (KBr, νcm^1): 3400 (NH Str), 3022 (CH Str, Aromatic), 2932(CH Str, Aliphatic), 1616 (C=O Str), 1217 (CN Str), 1031 (C-O-C Str); ^{1}HNMR (300 MHz, DMSO-d6, δ ppm): 8.90 (1H, NHCO), 8.18- 6.23 (8H, Aromatic), 4.65 (2H, CH_2), 2.46 (3H, CH_3).

N-(4-(Benzo[d]thiazol-2-yl) phenyl)-2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetamide (4c)
Yield: 38%; m.p.: 192-196^{0}C; R_f: 0.85 (Hexane/EtOAc 1:2); IR (KBr, νcm^1): 3408 (NH Str), 3021 (CH Str Ar), 2927(CH Str, Ali), 1666 (C=O Str), 1217 (CN Str), 1024 (C-O-C Str); ^{1}HNMR (300 MHz, DMSO-d6, δ ppm): 9.23 (1H, NHCO), 8.14-6.45 (12H, Aromatic), 3.17 (2H, CH_2), 2.18 (3H, CH_3).



Scheme 1. Synthesis of the target compounds. Reagents and condition :(i) $CHCl_3$ or Acetone, Anhydrous K_2CO_3, reflux (ii) Acetonitrile, Anhydrous K_2CO_3 and KI.

Computational Studies

Computation of physicochemical properties

A set of molecular parameters was computed for the target compounds as well as standard drug clozapine using Chem3D Ultra version 11.0 and values are shown in Table 1. The important molecular parameters for antipsychotics are log P and topological polar surface area. Literature review suggested that TPSA is a measure of a molecule's hydrogen bonding capacity and its

value should not exceed certain limit if the compound is intended to be CNS active. Two differing limits have been proposed: van de Waterbeemed et al [8] suggested a limit of 90 A^2, where, Kelder et al [9] suggested 60-70 A^2. The TPSA value for test compounds was well within the limit (41.99-52.33 A^2) which shows that these compounds have a potential to effectively cross the blood brain barrier. Further, lipophilicity correlates positively with BBB penetration and the log P value for test compounds was very close to the marketed drug (2.108- 4.657).

Table 1. Calculation of molecular properties for target compounds and standard drug

Comp. Code	Log P	M.W[a]	M.R[b]	SAS[c] (A^2)	MSA[d] (A^2)	SEV[e] (A^3)	TPSA[f]	MTI[g]	WI[h]	OV[i]
4a	2.108	316.33	81.532	517.912	272.043	230.319	41.99	8393	1197	1.4971
4b	3.585	366.39	97.456	578.202	309.947	265.31	41.99	13939	1931	1.5522
4c	4.657	442.49	123.654	717.081	381.464	324.621	52.33	26577	3626	1.6700
Cloz[j]	3.71	326.82	94.58	508.991	259.124	215.892	30.87	8127	1082	1.4889

[a]Molecular weight; [b]Molar refractivity; [c]Connolly solvent accessible surface area; [d]Connolly molecular surface area; [e]Connolly solvent excluded volume; [f]Topological polar surface area; [g]Molecular topological index; [h]Wienner index, [i]Ovality; [j]Clozapine

Similarity calculations:

The physicochemical similarity of the target compound was calculated with respect to clozapine and shown in Table 2. Firstly, the distance d_i of a particular target compound j to drug molecule e.g., clozapine was calculated by the formula:

$$d_i^2 = \sum_{j=1}^{n} (1-Xi,j\ /Xi,std)^2\ /n$$

Where, $X_{i,j}$ is the value of molecular parameter 'i' for compound 'j', $X_{i,std}$ is the value of the same molecular parameter for the standard drug, e.g., clozapine. Then, the similarity of compound 'j' to the standard drug was calculated as:

Similarity (%) = (1-R) x 100. Where R =$\sqrt{d^2}$ is the quadratic mean (root mean square), a measure of central tendency [10].

Table 2. Similarity values of target compounds with respect to the standard drug

Comp. code	Similarity[ab](in %) to Clozapine
4a	85.43
4b	58.43
4c	- 22.62

[a](1 - R) X 100 where R = Quadratic mean (Root mean square mean).

[b]Calcd. from physicochemical properties: Molecular weight; Molar refractivity; Connolly solvent accessible surface area; Connolly molecular surface area; Connolly solvent excluded volume; Topological polar surface area; Molecular topological index; Wiener index.

Preliminary pharmacological evaluation for antipsychotic effect:

All the target compounds were subjected to preliminary pharmacological evaluation to determine their ability to antagonize 5-hydroxy tryptophan (5-HTP) induced head twitches behavior in albino mice [11, 12]. Prior permission of the Animal Ethics Committee was obtained and all experiments were conducted according to the approved protocol. Clozapine was employed as a standard (positive control). The results from the pharmacological evaluation of the target compounds at 60 mg/kg, i.p, are depicted graphically in Figure 1. Statistical analysis of the

results in the test group was done by comparison with the results in the control group employing one way ANOVA. Level of significance was fixed at $p<0.05$.

Antagonism of 5-Hydoxytryptophan (5-HTP) induced head twitches

Swiss albino mice in the control group (n=6) was injected with pargyline (75 mg/kg, i.p.) in order to prevent the rapid degradation of 5-HTP. Thirty minutes later, the test compound (60 mg/kg, i.p.) was administered. After a further 30 min., the mice received 5-HTP (50 mg/kg, i.p.).The mice were returned to the test cages and then head twitches were assessed at 10 min. intervals for 30 min., starting 20 min. after the 5-HTP treatment. Head twitches were monitored using the following scoring system, 0-absent, 1-moderate, 2-marked (Fig. 1). A maximum of 8 score is possible. An observer made all observations unaware of the specific drug treatments.

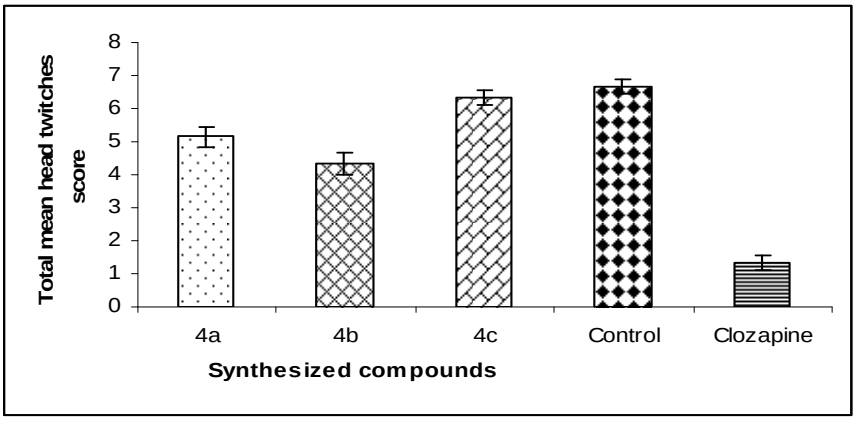


Figure 1. The effect of synthesized compounds (4a-c) on the 5-HTP induced head twitches behavior. Each column represents the mean ± SEM of total head twitches score for group of six mice assessed at 10-min intervals for 30 min, starting 20 after the 5-HTP treatment. A score of 8 is the maximum possible. All values statistically significant with respect to control at $p<0.05$

RESULTS AND DISCUSSION

The target compounds (**4a-c**) were synthesized as outlined in scheme 1. The purity of the compounds was monitored by TLC and the structure of the compounds was deduced on the basis of spectroscopic methods. A set of molecular parameters and physicochemical similarity of the target compounds was calculated with respect to the clozapine and values are shown in Table 1 and 2 respectively. The compounds **4a** and **4b** showed good structural similarity with respect to clozapine but compound **4c** did not shown similarity with respect to clozapine. The results from the pharmacological evaluation of the target compounds were showed significant reduction in inhibition of 5-hydroxy tryptophan (5-HTP) induced head twitches behavior (Fig.1).

CONCLUSION

We have synthesized new acetamides (**4a-c**) and evaluated for antiserotonergic activity. Among the compounds, **4b** exhibited significant inhibition of 5-hydroxy tryptophan (5-HTP) induced head twitches behavior probably by inhibition of 5-HT_2 receptor and showed good structural similarity with respect to clozapine. Moreover, log P and TPSA values suggested that this compound has the potential to penetrate the blood brain barrier and might be useful as serotonin antagonist.

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