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SYNTHESIS AND CHARACTERIZATION OF SOME NOVEL AZETIDINONE DERIVATIVES FOR ANTIDEPRESSANT ACTION

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ABSTRACT

A few unique substituted azetidinones were synthesized and evaluated for their potential as prospective new therapeutic molecules for the treatment of depression. All of the produced compounds were evaluated for the clarity of their structures. These chemicals' antidepressant trials revealed that they exhibited strong antidepressant effect. Three stages of SN_2 type substitution were used in the synthesis of the compounds. The stretching vibration peaks caused by C-N, C=O, and C=N were seen in the IR spectra of all the compounds at 1400-1000 cm-1, 1765-1645 cm-1, and 1690-1520 cm-1 (middle), respectively. The spectra also showed vibrations from the aromatic compounds C=C and C-H, C-H alkane, C-Cl (4e), CO (4d), C-H (methoxy), C-C (cycobutyl), and C=O. (cycobutyl). The test chemical 4d considerably enhanced the swimming frequency in FST. TST-like action was seen, and compounds 4a, 4b, 4c, and 4e did not perform as anticipated.

KEYWORDS

Antidepressant, forced swim test, synthesis, azetidinone, tail suspension test.

INTRODUCTION

One of the most prevalent psychiatric diseases, depression has been described and categorised in a variety of ways. Nowadays, the most often prescribed antidepressants, such as fluoxetine, imipramine, and desipramine, have been restricted due to possible side effects.

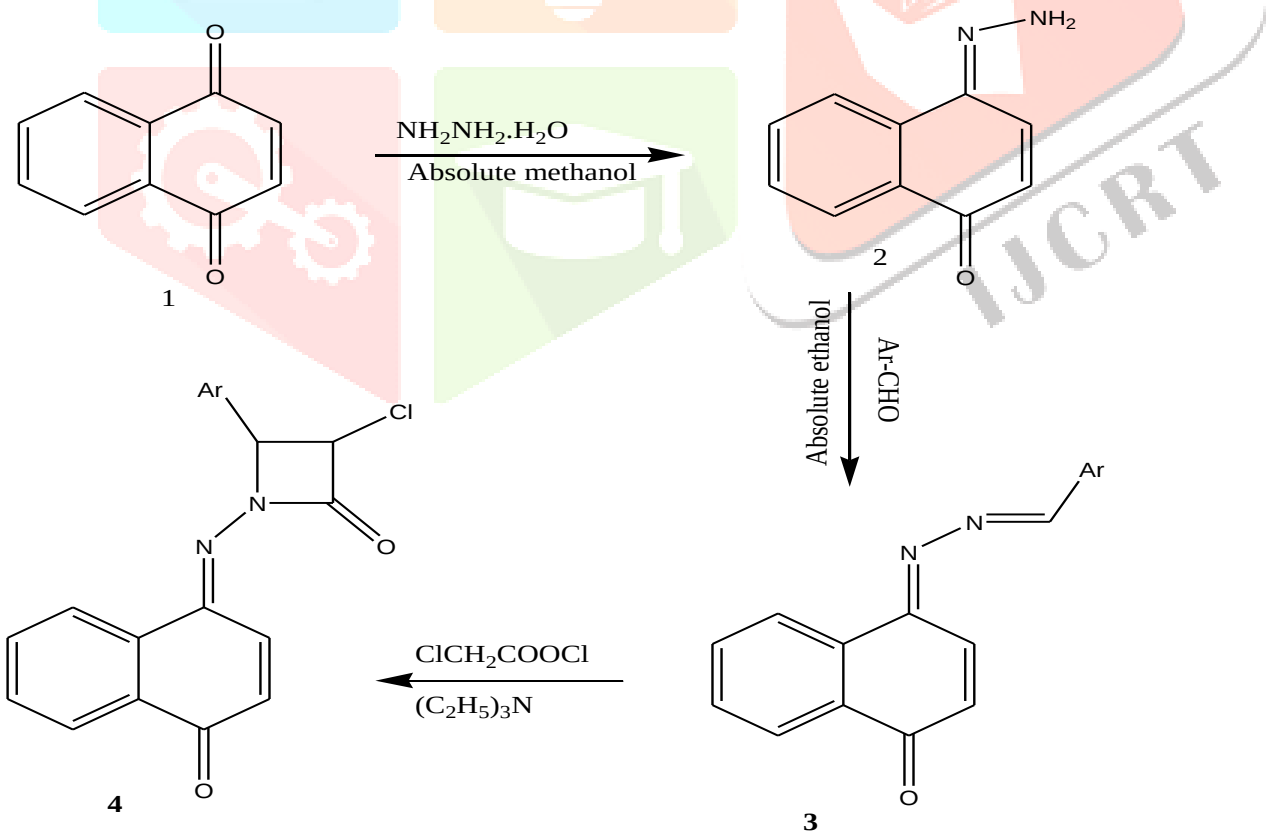
By utilising the strain energy associated with it, azetidin-2-one, a four-membered cyclic lactam (ß-lactam) skeleton, has been identified as an appealing target of modern chemical synthesis of several organic compounds. It has strong pharmacological and biological properties, including antimicrobial [1], antifungal

[2], anti-inflammatory [3], antitubercular [4], anticancer [5], and cytotoxic [6] effects. Azetidinone has also been used in several attempts to create novel antidepressant compounds, according to reports [7,8].

The use of a simple nitrogen bearing heterocycle like azetidinone as a component of a larger molecule was hypothesised to be able to present antidepressant action and may also inculcate properties favourable for interaction with the enzymes involved in depression in light of the aforementioned limitations and growing demand for antidepressant drugs.

MATERIALS AND METHODS

The solubility, yield, physical features, melting point, and spectral characteristics of the azetidinone derivatives were all characterised. The melting points are uncorrected and were established using a melting point equipment. Mass and proton NMR spectra were obtained using a Jeol apparatus, whereas IR spectra were captured using a Bruker spectrophotometer. In order to determine the purity (reaction completeness) of the intermediate products, the solvent solution for the compound utilised for TLC was Methanol: Ethyl Acetate in the ratios of 4:6 for the desired products and 8:2 / 7:3. Azetidinone synthesis was based on a publication by Malviya et al. [9], which was then modified. Compounds were synthesised in accordance with the plan shown in Scheme 1.



Scheme 1 Scheme of the synthesis of Azetidinone Derivatives

Synthesis of (E)-4-hydrazononaphthalen-1(4H)-one (2)

The mixture of hydrazine hydrate (99%, 5.05 g, 1.1 mol) and napthoquinone (15.08 g, 0.1 mol) in 100 ml of 100% methanol was refluxed for one hour before being cooled to room temperature. Filtered and dried hydrazone crystals that precipitated out. To get pure hydrazone, the crude product was recrystallized using ethanol.

Synthesis of Substituted (E)-4-(2-methylenehydrazono)naphthalen-1(4H)-one (3a-e)

A substituted aromatic aldehyde (0.01 mol) and a few drops of glacial acetic acid were added to a solution of compound 2 (0.01 mol) in ethanol (60 mL). After that, the mixture was refluxed for 7-8 hours. The surplus ethanol was removed by distillation, and the residual fluid was cooled by being poured over crushed ice and then put through a filter. 70% ethanol was recrystallized to produce the obtained crude product.

Synthesis of (E)-3-chloro-1-(4-oxonaphthalen-1(4H)-ylideneamino)azetidin-2-one (4a-e)

1, 4-Dioxane was used to dissolve a combination of Schiff base (3a-f) (0.01 mol) and triethylamine (0.02 mol) (15 mL). At room temperature for 20 minutes, parts of a chloroacetyl chloride (0.02 mol) solution were added to this. After being heated under reflux for three hours, the reaction mixture's contents were left at room temperature for 48 hours before being dumped into ice-cold water. The resultant solid was filtered, rinsed with water several times, and then crystallised again using ethanol at a 70% concentration.

(E)-3-chloro-1-(4-oxonaphthalen-1(4H)-ylideneamino)-4-phenylazetidin-2-one1H, 4a

^{1}H NMR Spectra (δ, 300 MHz, DMSO): 6.696-8.202 (CH-Aromatic), 4.222 (O-H); IR (KBr): 3800-3600 cm^{-1} (O-H), 3000-2900 cm^{-1} (C-C cyclic), 1600-1700 cm^{-1} (C-C Ar), 3100-3000 cm^{-1} (CH Ar), 1500 cm^{-1} (C=N), 1400-1000 cm^{-1} (C-N), 1100-1020 (C-Cl)

(E)-3-chloro-4-(4-nitrophenyl)-1-(4-oxonaphthalen-1(4H)-ylideneamino)azetidin-2-one, 4b

^{1}H NMR Spectra (δ, 300 MHz, DMSO): 6.722-8.111 (CH-Aromatic), 4.494 (O-H); IR (KBr): 3800-3600 cm^{-1} (O-H), 3000-2900 cm^{-1} (C-C cyclic), 1600-1700 cm^{-1} (C-C Ar), 3100-3000 cm^{-1} (CH Ar), 1500 cm^{-1} (C=N), 1400-1000 cm^{-1} (C-N), 1100-1020 (C-Cl)

(E)-3-chloro-4-(2-nitrophenyl)-1-(4-oxonaphthalen-1(4H)-ylideneamino)azetidin-2-one, 4c

^{1}H NMR Spectra (δ, 300 MHz, DMSO): 6.722-8.111 (CH-Aromatic), 4.494 (O-H); IR (KBr): 3800-3600 cm^{-1} (O-H), 3000-2900 cm^{-1} (C-C cyclic), 1600-1700 cm^{-1} (C-C Ar), 3100-3000 cm^{-1} (CH Ar), 1500 cm^{-1} (C=N), 1400-1000 cm^{-1} (C-N), 1100-1020 (C-Cl)

(E)-3-chloro-4-(4-methoxyphenyl)-1-(4-oxonaphthalen-1(4H)-ylideneamino)azetidin-2-one, 4d

^{1}H NMR Spectra (δ, 300 MHz, DMSO): 7.261-7.799 (CH-Aromatic), 1.564-1.666 (CH_3); IR (KBr): 3000-2900 cm^{-1} (C-C cyclic), 1600-1700 cm^{-1} (C-C Ar), 3100-3000 cm^{-1} (CH Ar), 1500 cm^{-1} (C=N), 1400-1000 cm^{-1} (C-N), 1100-1020 (C-Cl)

(E)-3-chloro-4-(4-chlorophenyl)-1-(4-oxonaphthalen-1(4H)-ylideneamino)azetidin-2-one, 4e

^{1}H NMR Spectra (δ, 300 MHz, DMSO): 7.024-8.207 (CH-Aromatic), 3.897-3.928 (NH_2); IR (KBr): 3000-2900 cm^{-1} (C-C cyclic), 1600-1700 cm^{-1} (C-C Ar), 3100-3000 cm^{-1} (CH Ar), 1500 cm^{-1} (C=N), 1400-1000 cm^{-1} (C-N), 1100-1020 (C-Cl)

Evaluation of antidepressant action [10,11]

Male albino mice weighing 25–30 g were used to test the synthetic compounds' in vivo antidepressant activity using the FST and TST methods. The institutional animal ethical committee gave its approval to the present study's protocol.

In the institute's animal house, the animals were kept in groups and housed in poly acrylic cages that measured 38 by 23 by 10 cm. For acclimatisation before and during the experiments, the animals were kept in cages with a maximum of four animals each, under standard laboratory conditions with a natural light and dark cycle (14 h light/10 h dark), relative humidity (RH) of 44-56%, and free access to a standard diet (Golden Feeds, India).

For the purpose of conducting the study, the animals were split into 7 groups of six each. Groups II, III, IV, V, & VI received 40 mg/kg (i.p.) of the test chemicals, while Group VII acted as the positive control and received fluoxetine at a dose of 10 mg/kg. Group I received normal saline (i.p)as the reference.

Forced Swim Test

The synthetic substances and fluoxetine were dissolved in DMSO and administered intraperitoneally to each mouse 30 minutes before the test in a standard volume of 0.05 mL per 20 g body weight. Mice were each placed in a glass cylinder (25 cm high, 10 cm in diameter) that was 10 cm high and filled with water (22–25°C) to detect the effect of the test substance. During the test, each mouse was permitted to swim for 6 minutes, and the final 4 minutes of the test were used to monitor and record the duration of immobility. The immobility period was defined as the time the mouse floated in the water without exerting any effort and just making the movements required to keep its head above water.

The animals were dried using tower and returned back to their housing conditions.

Tail Suspension Test

The synthetic substances and fluoxetine were dissolved in DMSO and administered intraperitoneally to each mouse 30 minutes before the test in a standard volume of 0.05 mL per 20 g body weight. In a box of 25 by 25 by 30 cm, with the head positioned 5 cm from the floor, mice were each separately suspended by their tails using clamps, to measure the impact of the test substance. There was very little ambient noise, and the testing was done in a completely dark room. The duration of immobility was tracked and recorded for the final 4 minutes of the test, which involved suspending all animals for a total of 6 minutes. Only when mice hang passively and motionlessly were they deemed to be immovable.

The animals were used only once for this test.

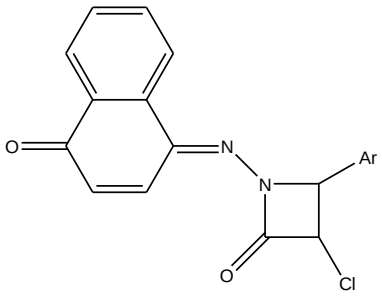
Statistical Analysis

Pharmacological study outcomes were presented as mean S.D. Graph Pad Prism 5 project software was used to perform a one-way analysis of variance (ANOVA) on the data before performing a Dunnett's multiple comparison test. When the result has a P-value of 0.05 or below (P0.05) compared to the control, the result was deemed statistically significant.

RESULTS AND DISCUSSION

The optimal strategy shown in Scheme 1 was used to perform the synthesis. The yield, melting point, and molecular weight of the synthesized chemical are shown in Table 1, while the solubility profile is shown in Table 2. Five derivatives of azetidinone were produced and studied using TLC, IR, and NMR. The synthetic scheme has also been used to previously synthesize indole azetidinone based compounds as antidepressants [7].

Table 1 Properties of Synthesized Compounds



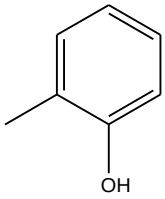
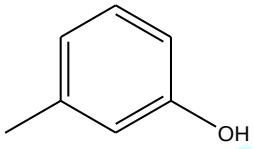
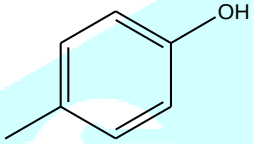
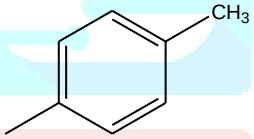
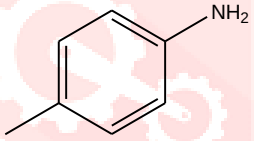
Code	----Ar	Color	M.P (˚C)	% Yield	Molecular weight (Calculated)
4a		Yellow	172-174	71	352.7
4b		Brown	191-193	71	352.7
4c		Brown	204-206	75	352.7
4d		Yellow	169-173	66	350.8
4e		Yellow	211-214	69	351.8

Table 2 Solubility profile of the synthesized compounds

Comp. Name	Solubility Profile			
	Water	**Methanol**	**$CHCl_3$**	**Acetone**
4a	Insoluble	Partially Soluble	Freely Soluble	Freely Soluble
4b	Insoluble	Partially Soluble	Freely Soluble	Freely Soluble
4c	Insoluble	Partially Soluble	Freely Soluble	Freely Soluble
4d	Insoluble	Partially Soluble	Partially Soluble	Freely Soluble
4e	Insoluble	Partially Soluble	Partially Soluble	Freely Soluble

FT-IR, 1H-NMR, and mass spectral analyses of the compounds were used to confirm the compounds. The compounds' structures were clarified using mass, 1HNMR, and IR spectroscopy. Stretching vibration peaks owing to C-N, C=O, C=N, and C-Cl were present in the IR spectra of all the compounds at 1400-1000 cm-1, 1765-1645 cm-1, 1690-1520 cm-1 (medium), and 1100-1020 cm-1, respectively. The spectra also showed vibrations from the aromatic compounds C=C and C-H, C-H alkane, C-O & O-H (4a, 4b, 4c), C-H (alkyl), C-C (cycobutyl), and C=O. (cycobutyl). The acquired ^{1}HNMR spectra showed the aliphatic CH and aromatic CH peaks at 2-3.3 ppm and 6.7-7.2 ppm, respectively.

CNS depressant action

Two animal models were used to assess the synthetic compounds' ability to treat depression, and the results are shown in Figures 1 and 2. One-way ANOVA and Dunnett's multiple comparison test were used to statistically examine the immobility time and swimming frequency.

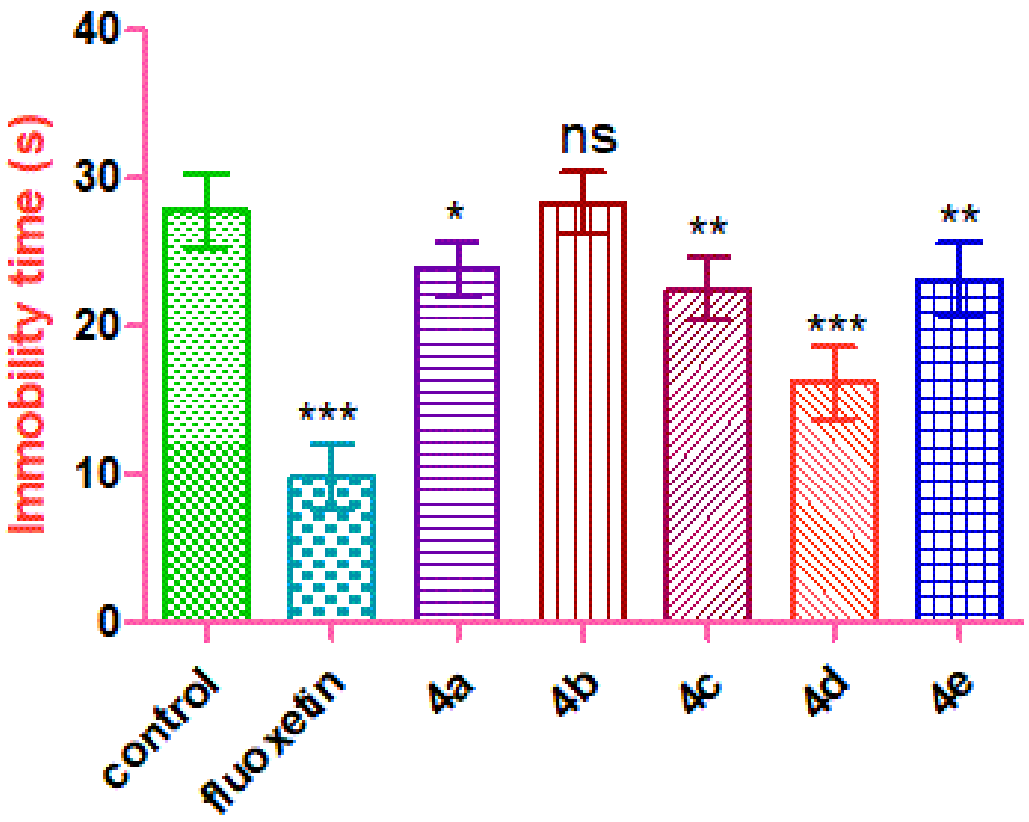


Figure 1 Effect of test compounds 4a-4e (40mg/kg) and fluoxetine (10mg/kg) on immobility time of mice in TST. *p<0.05, **p<0.01, ***p<0.001, ns-not significant. Values are represented as mean ± SD, (n = 6)

Figure 1 illustrates that the immobility period for compound 4d was much shorter than that of the control group and was on par with that of fluoxetine at a dose of 10 mg/kg. While the results of compound 4b were determined to be non-significant in contrast to the control group, those of compounds 4a, 4c, and 4e were not as effective as expected (p0.05). This shows that the phenyl ring's hydrophilic substitutes were harmful to the antidepressant effect.

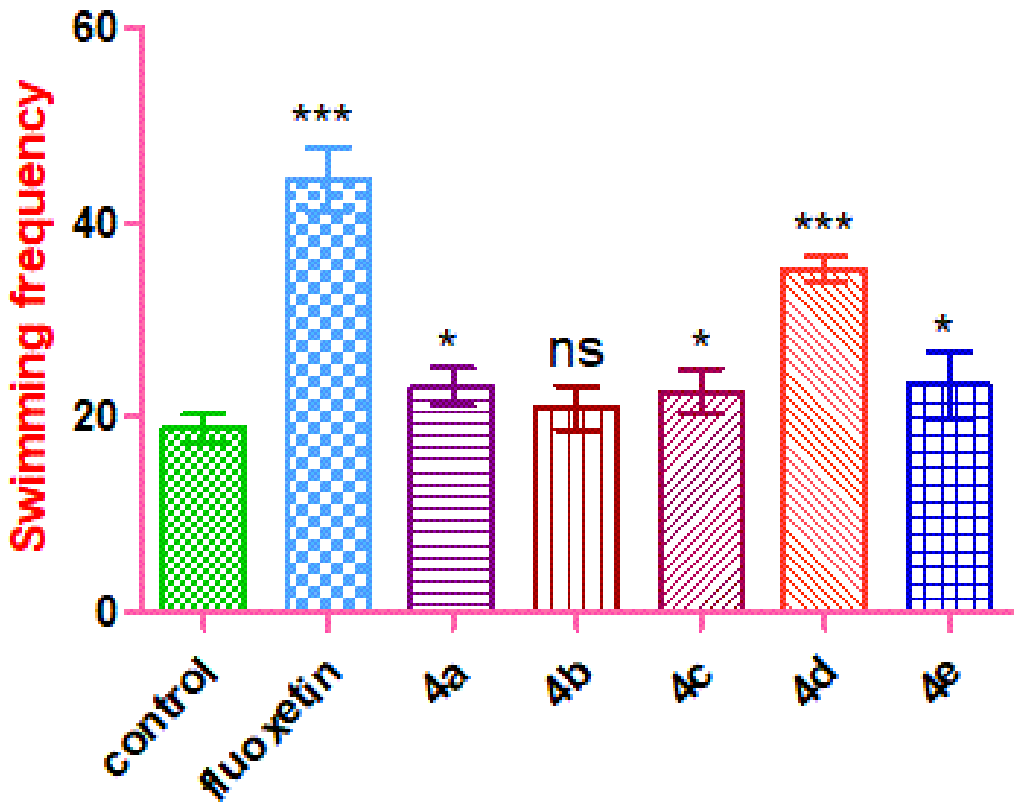


Figure 2 Effect of test compounds 4a-4e (40mg/kg) and fluoxetine (10mg/kg) on swimming time of mice in FST. *p<0.05, ***p<0.001, ns-not significant, Values are represented as mean ± SD, (n = 6)

Figures 1 and 2 show that the reference medicine fluoxetine and the test chemical 4d considerably enhanced the swimming frequency in FST. TST-like action was seen, and compounds 4a, 4b, 4c, and 4e did not perform as anticipated.

In their attempt by Malviya et al [9], they established the importance of the substitution on the aromatic ring attached to 4-position the azetidin-2-one moiety, which was again convincingly utilized for improvement of activity in the current compounds.

CONCLUSION

The goal of the current research was to create fresh azetidinone compounds with possible antidepressant properties. The synthetic compounds that have a variety of substitution patterns could operate as an antidepressant. To establish a connection between the structure and activity of the nucleus, additional research on novel substances with comparable structures will be conducted.

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