Synthesis, Characterization and Docking studies of 2-Phenyl Indole derivatives as Antidepressant Agent

Nikita Devi[1], Navin Kumar[2], Amrita singh[3], Vibha tripath[4], Lakshman Chauhan[5] Ashok Kumar Yadav[6]

1. Assistant professor, Department of Pharmaceutical Chemistry, Babu Yugraj Singh College of Pharmacy, R2MF+273 Power House, Badhamau, Near Maleshemau, Ln E, Gomtinagar Extension, Sector 6, Gomti Nagar, Lucknow, Uttar Pradesh 226010
2. Assistant professor, Department of Pharmaceutical Chemistry, Mahatma Buddha College of Pharmacy, Singhai Road Nighasan, DIST.- Kheri 262903.
3. Research scholar, Department of Pharmaceutical Chemistry, Goel institute of pharmacy and sciences, Goel college, Faizabad Rd, near Indira Canal, Anora Kala, Lucknow, Uttar Pradesh 226028
4. Research scholar, Department of Modern Pharmaceutical Chemistry, Invertis Institute of pharmacy Invertis University, Rajau Paraspur, National Highway NH 30, Bareilly, Uttar Pradesh 243123
5. Research scholar, PhD in pharmacy, Monad University, N.H. 9, Delhi Hapur Road Village & Post Kastla, Kasmabad, Pilkhuwa, Uttar Pradesh 245304
6. Assistant professor, Department of Pharmaceutical Chemistry, Nova College Of Pharmacy, KH. no. 74 STP Road Behind Ganpati Vihar Colony, Khargapur, Gomti Nagar, Extention, Uttar Pradesh 226010

Abstract

In the present work a few 2-phenylindole derivatives have been synthesized and assessed for antidepressant potential. The synthesis was achieved in three steps where in the first two steps, aryl hydrazone is prepared by condensation of phenyl hydrazine and aromatic ketone followed by Fisher indole synthesis of indole via cyclization in the presence of acid catalyst. In the last step the nitrogen of the 2-phenyl indole is substituted with various alkyl groups. The IR spectra exhibited stretching vibration of at 1300-1100 cm^{-1}(C-N), 1500-1700 cm^{-1} (C=C), 3000-3200 cm^{-1} (C-H Ar) and 2600-3000 cm^{-1} (CH aliphatic). Similarly vibrations due to C-O (1000-1100 cm^{-1}), OH (3200-3500 cm^{-1}) and Nitro (1400-1500 cm^{-1}) were displayed. The antidepressant action of the synthesized compounds was testing using two animal models (FST and TST). The standard drug Fluoxetine and the test compounds **3p** and **3s** were found to decrease the immobility time in TST while the swimming frequency enhanced significantly.

Keywords

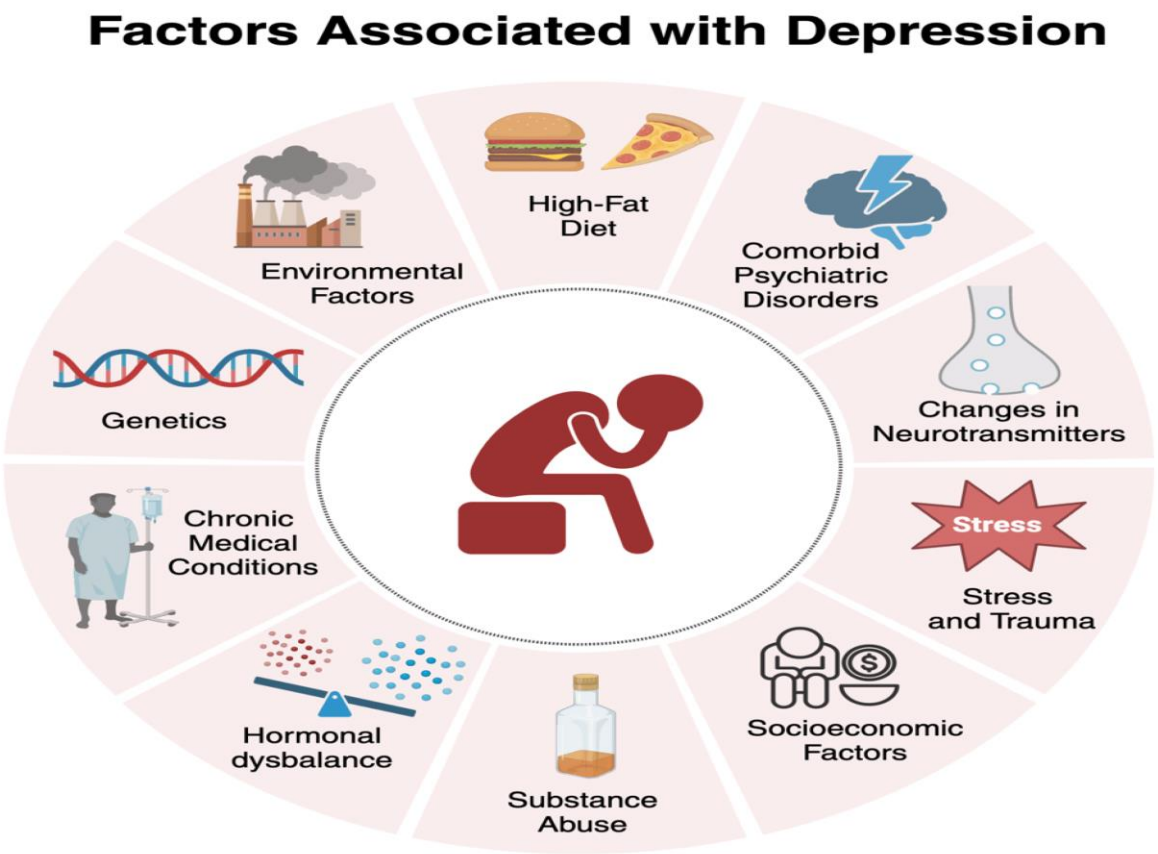
2-phenyl indole, antidepressant, forced swimming test, Fisher indole synthesis, tail suspension test

Introduction

Depression has been the most common psychiatric disorders. It is a heterogeneous disorder that has been characterized or classified in a variety of ways. Affective disorders are characterized basically by change of mood (depression or mania) more willingly than by thought disturbance [1] Depression is the initial expression and might vary from mild condition, adjoining on customariness to serve depression occasionally termed psychotic depression that may be accompanied by hallucination and delusions [2].

Vilazodone, an indole containing drug has already been developed for treatment of depression [3]. Over the past decade several researchers have synthesized indole derivatives for the CNS effects including anticonvulsant, antianxiety and antidepressant. Recently, a few indole alkaloids viz. harman, harmol, harmine, harmalol, harmaline and mitragynine have been isolated and were found to possess good antidepressant action [4].

Owing to the growing interest in antidepressant potential of indole derivatives, it was envisioned to synthesize a few 2-phenylindole derivatives and evaluate them for antidepressant potential.



Depressive disorder (also known as depression) is a common mental disorder. It involves a depressed mood or loss of pleasure or interest in activities for long periods of time.

Depression is different from regular mood changes and feelings about everyday life. It can affect all aspects of life, including relationships with family, friends and community. It can result from or lead to problems at school and at work.

Depression can happen to anyone. People who have lived through abuse, severe losses or other stressful events are more likely to develop depression. Women are more likely to have depression than men.

An estimated 3.8% of the population experience depression, including 5% of adults (4% among men and 6% among women), and 5.7% of adults older than 60 years. Approximately 280 million people in the world have depression *(1)*. Depression is about 50% more common among women than among men. Worldwide, more than 10% of pregnant women and women who have just given birth experience depression *(2)*. More than 700 000 people die due to suicide every year. Suicide is the fourth leading cause of death in 15–29-year-olds.

Although there are known, effective treatments for mental disorders, more than 75% of people in low- and middle-income countries receive no treatment *(3)*. Barriers to effective care include a lack of investment in mental health care, lack of trained health-care providers and social stigma associated with mental disorders.

Depression results from a complex interaction of social, psychological, and biological factors. People who have gone through adverse life events (unemployment, bereavement, traumatic events) are more likely to develop depression. Depression can, in turn, lead to more stress and dysfunction and worsen the affected person's life situation and the depression itself.

Depression is closely related to and affected by physical health. Many of the factors that influence depression (such as physical inactivity or harmful use of alcohol) are also known risk factors for diseases such as cardiovascular disease, cancer, diabetes and respiratory diseases. In turn, people with these diseases may also find themselves experiencing depression due to the difficulties associated with managing their condition.

Prevention programmes have been shown to reduce depression. Effective community approaches to prevent depression include school-based programmes to enhance a pattern of positive coping in children and adolescents. Interventions for parents of children with behavioural problems may reduce parental depressive symptoms and improve outcomes for their children. Exercise programmes for older persons can also be effective in depression prevention

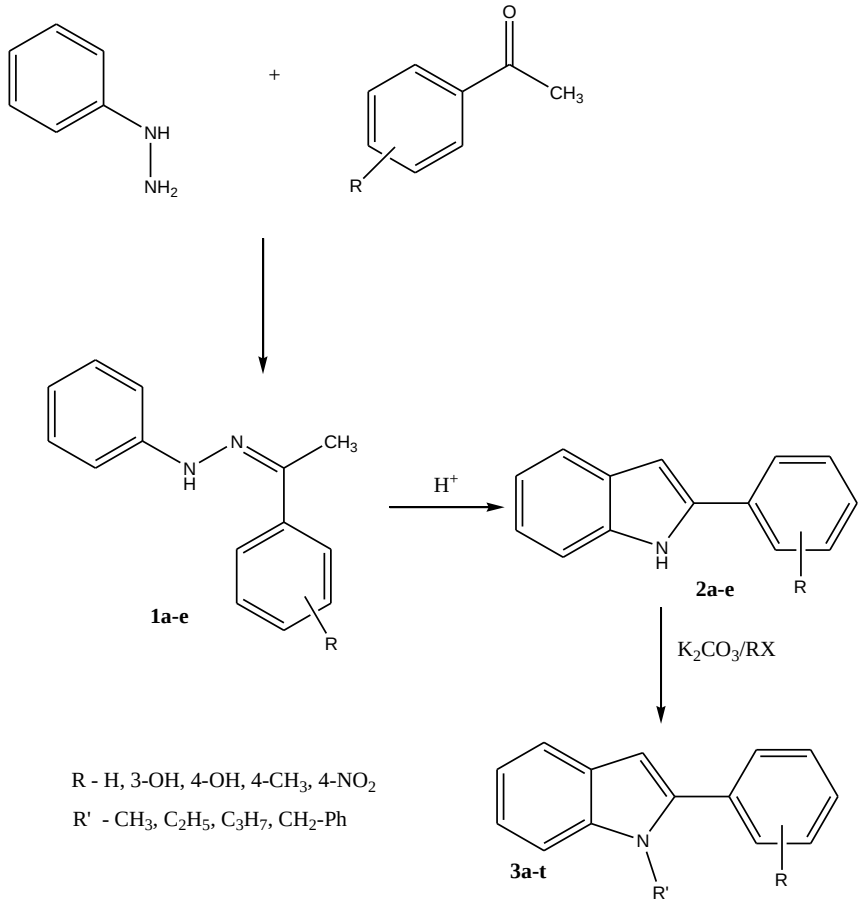
Material and Methods

Acetophenone, 3-hydroxy acetophenone, 4-hydroxy acetophenone, 4-methyl acetophenone, 4-nitro acetophenone, phenyl hydrazine, and polyphosphoric acid were obtained from Avra Chemicals. Methyl iodide, Iodoethane, iodopropane and phenethyl chloride were purchased from Sigma. Ethanol, methanol, glacial acetic acid, hydrochloric acid, acetone, chloroform and dimethyl sulfoxide were obtained from Rankem. Any other reagent used was of synthetic grade and used as procured. All glassware used were of Borosilicate grade, washed using chromic

acid cleaning mixture, rinsed with distilled water and dried in hot air oven (Biotechnics India) before using. Melting point are uncorrected and determined using open capillary.

The synthetic scheme (Scheme 1) for the synthesis of indoles was designed using the schemes reported earlier [5,6].

Scheme



General method for synthesis of substituted phenyl hydrazone

A mixture of 0.167 mol of appropriate acetophenone and 0.167 mol of phenyl hydrazine was prepared in ethanol (60 mL) and catalytic amount of glacial acetic acid was added. The mixture had been cooled at 0°C using an ice bath to obtain solid product. The product was filtered, washed with dilute HCl and then by rectified spirit. The product was recrystallized using ethanol and white product obtained was filtered and stored in air tight container.

General method for synthesis of substituted phenyl indole

0.15 mol of the substituted phenyl hydrazone was placed in a beaker containing excess of polyphosphoric acid (180 g). The mix was heated on a water bath, stirring the mixture and maintaining the temperature at 100-120°C for duration of 10 min. In the mixture was added

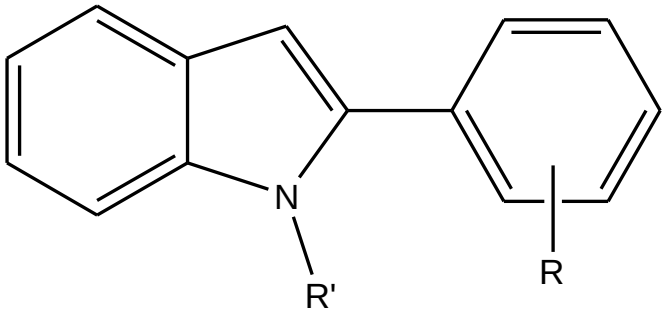
450 mL cold water and it was well stirred in order to dissolve the polyphosphoric acid completely. The solid obtained was filtered at pump and washed using ice-cold water several times to remove any trace of acid. The solid was refluxed with 300 mL of rectified spirit and a little amount of decolorizing charcoal was added to it and filtered. The filtrate was cooled to room temperature to obtain the white crystals of phenyl indole which were dried in desiccator over anhydrous calcium chloride and stored in air tight container.

General method for synthesis of N-alkyl substituted phenyl indole

A mixture of 3 mol of appropriate phenylindole, 6 mol of K_2CO_3 and 4 mol of the appropriate alkyl or aryl halide was prepared DMF (10 mL) and stirred at room conditions for 4 h using a magnetic stirrer. The reaction mix was then diluted with cold water and the solid obtained was filtered off, recrystallize from ethanol to obtain the N-alkyl substituted phenyl indole. TLC was performed using n-butanol: acetic acid: water (12:3:5) as the developing solvent and visualized in UV cabinet.

The synthesized compounds have been characterized by melting point, solubility and retention factor (R_f value) by TLC.

Table 1 Properties of Synthesized 2-phenyl indole derivatives



Code	Color	M.P (°C)	% Yield	R_f value	Molecular Mass (calculated)
3a	Yellow	172-174	70	0.42	207
3b	Brown	191-193	68	0.45	221
3c	Brown	204-206	62	0.56	235
3d	Yellow	169-173	64	0.67	297
3e	Yellow	211-214	61	0.41	223

3f	Brown	204-206	66	0.52	237
3g	Yellow	215-219	64	0.59	251
3h	Brown	217-220	65	0.53	313
3i	Brown	235-238	71	0.62	223
3j	Brown	231-233	62	0.66	237
3k	Yellow	248-251	60	0.65	251
3l	Yellow	244-246	62	0.51	313
3m	Yellow	272-274	58	0.43	221
3n	Yellow	269-271	55	0.45	235
3o	Yellow	261-264	57	0.49	249
3p	Yellow	271-275	54	0.43	311
3q	Yellow	243-245	61	0.70	252
3r	Yellow	249-251	63	0.70	266
3s	Yellow	237-240	60	0.71	280
3t	Yellow	257-260	60	0.67	342

Synthesized compounds

1-methyl-2-phenyl indole, (3a) **Yield** 70%, **Melting point** 172-174°C, **^{1}H NMR Spectra (δ, 300 MHz, DMSO):** 7.2-7.5 (H aromatic), 6.5 (H-pyrrole ring), 3.60 (H-methyl) **IR (KBr):** 3420.33 (C-H), 3161.06 cm^{-1} (CH Ar),2603.54 (-CH_2-), 1600-1700 cm^{-1} (C-C Ar), 1485.76 cm^{-1}(C=C), 1197.04 cm^{-1} (C-N)

1-ethyl-2-phenyl indole, (3b) Yield: *68%,* ***Melting point*** *191-192°C,* **^{1}H NMR Spectra (δ, 300 MHz, DMSO):** 7.4 (CH-Benzene), 7.3 (CH-Benzene), 7.2 (CH-Benzene), 2.5 (CH3), 7.0 (CH-Benzene), 7.1 (CH-Benzene) **IR (KBr):** 3114.3 cm^{-1} (CH Ar), 2928.74 (C-H stretch), 2599.84 (-CH_2-), 1550-1650 (C-C Ar), 1410.01 cm^{-1}(C=C), 1277.44 cm^{-1} (C-N)

1-propyl-2-phenyl indole, (3c) Yield:*62%,* **Melting point** 204-206°C, **^{1}H NMR Spectra (δ, 300 MHz, DMSO):** 7.4 (CH-Benzene), 7.3 (CH-Benzene), 7.2 (CH-Benzene), 2.5 (CH3), 7.0 (CH-Benzene), 7.1 (CH-Benzene) **IR (KBr):** 3164.62 cm^{-1} (CH Ar),2358.77 (-CH_2-), 1500-1650 cm^{-1} (C-C Ar), 1399.17 cm^{-1}(C=C), 1279.91 cm^{-1} (C-N)

1-phenethyl-2-phenyl indole, (3d) **Yield** 64%**Melting point** 169-173°C, **^{1}H NMR Spectra (δ, 300 MHz, DMSO):** 7.4 (CH-Benzene), 7.3 (CH-Benzene), 7.2 (CH-Benzene), 2.5 (CH3), 7.0 (CH-Benzene), 7.1 (CH-Benzene), **IR (KBr):** 3084.72 cm^{-1} (CH Ar),2924.71, 2856.44 (C-H), 1500-1700 cm^{-1} (C-C Ar), 1472.76 cm^{-1}(C=C), 1241.09 cm^{-1} (C-N)

1-methyl-3'-hydroxy-2-phenyl indole (3e) **Yield** 61% **Melting point** 212-214°C, **^{1}H NMR Spectra (δ, 300 MHz, DMSO): ^{1}HNMR:** 7.63, 7.85 (HC=CH), 7.37-7.91 (C-H Ar), 5.21 (C-OH) **IR (KBr):** 3082.69 (Ar-H), 1500-1750 cm^{-1} (C-C Ar), 1412.70 (-C=C-), 1341.84 (O-H bending), 1248.06 (-C-N)

1-ethyl-3'-hydroxy-2-phenyl indole (3f) **Yield:** 66% **Melting point:** 204-206°C, **1H NMR Spectra** (□, 300 MHz, DMSO): 6.6-7.3 (H Aromatic), 6.5 (H- pyrrole ring), 4.99 (H- hydroxy), 3.9 (H- CH2), 1.5 (H- CH3) **IR (KBr):** 3368.40 cm-1 (O-H), 1145.36 cm-1 (C-N), 1022.53 (C-O)

1-propyl-3'-hydroxy-2-phenyl indole, (3g) **Yield** 65% **Melting point** 215-219°C, ^{1}H NMR Spectra (δ, 300 MHz, DMSO): 7.4 (CH-Benzene), 7.3 (CH-Benzene), 7.2 (CH-Benzene), 2.5 (CH3), 7.0 (CH-Benzene), 7.1 (CH-Benzene) IR (KBr): 3422.56 (O-H), 3173.91 (C-H Ar), 2602.47 (C-H), 1500-1650 cm^{-1} (C-C Ar), 1474.58 (C=C), 1244.74 (C-N), 1067.55 (C-O)

1-benzyl-3'-hydroxy-2-phenyl indole, (3h) **Yield** 65% **Melting point** 217-219°C, **^{1}H NMR Spectra (δ, 300 MHz, DMSO):** 7.4 (CH-Benzene), 7.3 (CH-Benzene), 7.2 (CH-Benzene), 2.5 (CH3), 7.0 (CH-Benzene), 7.1 (CH-Benzene) **IR (KBr):** 3410.90 (O-H), 3121.21 (C-H Ar), 2602.10 (C-H), 1500-1650 cm^{-1} (C-C Ar), 1481.52 (C=C), 1282.15 (C-N), 1069.29 (C-O)

1-methyl-4'-hydroxy-2-phenyl indole, (3i) **Yield** 71% **Melting point** 225-238°C, **^{1}H NMR Spectra (δ, 300 MHz, DMSO):** 7.4 (CH-Benzene), 7.3 (CH-Benzene), 7.2 (CH-Benzene), 2.5 (CH3), 7.0 (CH-Benzene), 7.1 (CH-Benzene) **IR (KBr):** 3431.73 (O-H), 3165.33 (C-H Ar), 2599.71 (C-H), 1500-1700 cm^{-1} (C-C Ar), 1482.00 (C=C), 1275.40 (C-N), 1065.27 (C-O)

1-ethyl-4'-hydroxy-2-phenyl indole, (3j) **Yield** 62% **Melting point** 231-233°C, **^{1}H NMR Spectra (δ, 300 MHz, DMSO):** 7.4 (CH-Benzene), 7.3 (CH-Benzene), 7.2 (CH-Benzene), 2.5 (CH3), 7.0 (CH-Benzene), 7.1 (CH-Benzene) **IR (KBr):** 3422.70 (O-H), 3172.38 (C-H Ar), 2604.85 (C-H), 1500-1650 cm^{-1} (C-C Ar), 1406.44 (C=C), 1279.55 (C-N), 1063.27 (C-O)

1-propyl-4'-hydroxy-2-phenyl indole, (3k) **Yield** 60% **Melting point** 248-250°C, **^{1}H NMR Spectra (δ, 300 MHz, DMSO):** 6.7-7.4 (H Aromatic), 6.5 (H – pyrrole ring), 5.0 (H –hydroxy), 3.86 (H –CH_2), 1.8 (H – CH_2), 0.95 (H – CH_3) **IR (KBr):** 3242.62 (O-H), 3119.15 (C-H Ar), 2979.33 (C-H), 1500-1650 cm^{-1} (C-C Ar), 1478.10 (C=C), 1398.01 (O-H bending), 1299.78 (C-N), 1091.14 (C-O)

1-benzyl-4'-hydroxy-2-phenyl indole, (3l) **Yield** 62% **Melting point** 244-246°C, **^{1}H NMR Spectra (δ, 300 MHz, DMSO):** 7.4 (CH-Benzene), 7.3 (CH-Benzene), 7.2 (CH-Benzene), 2.5 (CH3), 7.0 (CH-Benzene), 7.1 (CH-Benzene) **IR (KBr):** 3240.81 (O-H), 3119.55 (C-H Ar), 2981.44 (C-H), 1500-1650 cm^{-1} (C-C Ar), 1484.01 (C=C), 1396.53 (O-H bending), 1294.08 (C-N), 1092.37 (C-O)

1-methyl-4'-methyl-2-phenyl indole, (3m) **Yield** 58% **Melting point** 272-274°C, ^{1}H NMR Spectra (δ, 300 MHz, DMSO): 7.4 (CH-Benzene), 7.3 (CH-Benzene), 7.2 (CH-Benzene), 2.5 (CH3), 7.0 (CH-Benzene), 7.1 (CH-Benzene) IR (KBr): 3113.84 (C-H Ar), 2943.23 (C-H), 1500-1650 cm^{-1} (C-C Ar), 1461.21 (C=C), 1282.19 (C-N)

1-ethyl-4'-methyl-2-phenyl indole, (3n) **Yield** 58% **Melting point** 272-274°C, **^{1}H NMR Spectra (δ, 300 MHz, DMSO):** 7.4 (CH-Benzene), 7.3 (CH-Benzene), 7.2 (CH-Benzene), 2.5 (CH3), 7.0 (CH-Benzene), 7.1 (CH-Benzene), **IR (KBr):** 3115.03 (C-H Ar), 2975.67, 2809.17 (C-H), 1500-1650 cm^{-1} (C-C Ar), 1455.01 (C=C), 1289.03 (C-N)

1-propyl-4'-methyl-2-phenyl indole, (3o) **Yield** 57% **Melting point** 261-264°C, **^{1}H NMR Spectra (δ, 300 MHz, DMSO):** 7.4 (CH-Benzene), 7.3 (CH-Benzene), 7.2 (CH-Benzene), 2.5 (CH3), 7.0 (CH-Benzene), 7.1 (CH-Benzene), **IR (KBr):** 3116.49 (C-H Ar), 2978.17 (C-H), 1500-1650 cm^{-1} (C-C Ar), 1455.11 (C=C), 1293.21 (C-N)

1-benzyl-4'-methyl-2-phenyl indole, (3p) **Yield** 54% **Melting point** 271-274°C, **^{1}H NMR Spectra (δ, 300 MHz, DMSO):** 7.0-7.4 (H Aromatic), 6.5 (H – pyrrole ring), 2.4 (H – methyl), 4.18 (H – CH_2), 3.01 (H – CH_2), **IR (KBr):** 3118.09 (C-H Ar), 2978.51 (C-H), 1500-1650 cm^{-1} (C-C Ar), 1455.11 (C=C), 1295.29 (C-N)

1-methyl-4'-nitro-2-phenyl indole, (3q) **Yield** 54% **Melting point** 271-274°C, **^{1}H NMR Spectra (δ, 300 MHz, DMSO):** 7.1-7.4 (H Aromatic), 8.25 (H adjacent to NO_2), 3.6 (H – methyl), **IR (KBr):** 3116.02 (C-H Ar), 2978.17, 2809.22 (C-H), 1500-1650 cm^{-1} (C-C Ar), 1525.49 (N-O), 1454.47 (C=C), 1285.93 (C-N)

1-ethyl-4'-nitro-2-phenyl indole, (3r) **Yield** 58% **Melting point** 272-274°C, **^{1}H NMR Spectra (δ, 300 MHz, DMSO):** 7.4 (CH-Benzene), 7.3 (CH-Benzene), 7.2 (CH-Benzene), 2.5 (CH3), 7.0 (CH-Benzene), 7.1 (CH-Benzene), **IR (KBr):** 3091.09 (C-H Ar), 2930.15 (C-H), 1500-1650 cm^{-1} (C-C Ar), 1498.08 (N-O), 1449.44 (C=C), 1309.18 (C-N)

1-propyl-4'-nitro-2-phenyl indole, (3s) **Yield** 58% **Melting point** 272-274°C, ^{1}H NMR Spectra (δ, 300 MHz, DMSO): 7.4 (CH-Benzene), 7.3 (CH-Benzene), 7.2 (CH-Benzene), 2.5 (CH3), 7.0 (CH-Benzene), 7.1 (CH-Benzene), IR (KBr): 3207.03 (C-H Ar), 3050.22, 2642.96 (C-H), 1500-1700 cm^{-1} (C-C Ar), 1486.73 (N-O), 1431.75 (C=C), 1271.41 (C-N)

1-benzyl-4'-nitro-2-phenyl indole, (3t) **Yield** 61% **Melting point** 212-214°C, **^{1}H NMR Spectra (δ, 300 MHz, DMSO):** 7.4 (CH-Benzene), 7.3 (CH-Benzene), 7.2 (CH-Benzene), 2.5 (CH3), 7.0 (CH-Benzene), 7.1 (CH-Benzene), **IR (KBr):** 3145.29 (C-H Ar), 3045.74, 2940.43 (C-H), 1500-1650 cm^{-1} (C-C Ar), 1478.51 (N-O), 1397.26 (C=C), 1207.85 (C-N)

Pharmacological Study

Animal

The *in vivo* antidepressant action of the synthesized compounds was performed in male albino mice of weight between 25–30 g by Forced Swim Test (FST) and Tail Suspension Test (TST) methods. The protocol was approved from the Institutional Animal Ethical Committee (IAEC).

The animal had been segregated and kept in polyacrylic cages in the animal house of the institute under standard conditions (14 h light/10 h dark; 27±2°C; % RH 44-56%) with free right to use standard diet and potable water *ad libitum* for a week.

Animal were grouped in 7 groups of 6 animals in each for conducting the procedures. Group I (control) was administered normal saline, group II, III, IV,V & VI were administered 40 mg/kg (i.p) of the test compounds, whereas group VII served as positive control and was administered with fluoxetine, 10 mg/kg (i.p).

Forced Swim Test [7]

The synthesized compounds and fluoxetine were suspended in DMSO and injected intraperitoneally (0.05 mL per 20 g body weight), 30 minutes prior to the test. To determine the effect of the test compound mice were individually kept in a glass cylinder (25 cm high and 10 cm wide) filled with water (22-25°C) up to 10 cm of the cylinder. Each mouse was allowed to swim 6 min during the test, and the duration of inaction or immobility was noted down during the final 4 min of the test. The time spent by the mouse floating in the water without struggling and making only those movements necessary to keep its head above water was regarded as the immobility period.

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

Tail Suspension Test [7]

The synthesized compounds and fluoxetine were dispersed in DMSO and injected intraperitoneally (0.05 mL per 20 g body weight), 30 minutes prior to the test. To determine the effect of the test compound mice were suspended by tail using clamp (2 cm from the tip of the tail) in a box (25 × 25 × 30 cm) with the head 5 cm from the bottom. Minimal background noise was maintained and the test was done in dark room. The total time of keeping animals suspended by tail was 6 minutes, and the duration of inaction or immobility was noted during

the final 4 minutes of the test. Animal was considered immobile when they hung completely motionless.

Results and Discussion

Synthesis

In the first two steps, aryl hydrazone is prepared by condensation of phenyl hydrazine and aromatic ketone followed by Fisher indole synthesis of indole via cyclization in the presence of acid catalyst. In the last step the nitrogen of the phenyl indole is substituted with various alkyl groups.

Twenty derivatives of indole were synthesized using five aromatic acetophenones and four alkyl halides. The compounds were characterized by using TLC and IR. NMR and mass spectral study was carried out on five compounds in order to assure the formation of proper products. The result of the yield, melting point and R_f value of the synthesized compound were depicted in the Table 1. All the compounds were found to be insoluble in water and dimethyl formamide whereas only partially soluble in methanol. The compounds were easily soluble in chloroform.

CNS depressant action

The antidepressant action of the synthesized compounds was testing using two animal models and the results obtained are depicted in Figure 1 and 2. The immobility time was recorded and statistically analyzed using one way ANOVA followed by Dunnett's multiple comparison test.

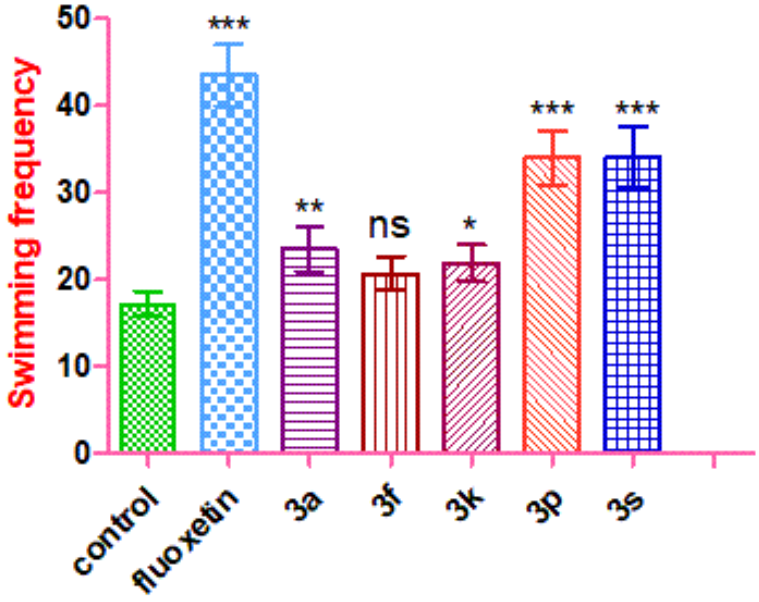


Figure 1 Effect of test compounds (40mg/kg) and Fluoxetine (10mg/kg) on swimming frequency of mice in TST. *p<0.05, **p<0.01, ***p<0.001, ns –not significant; Values are represented as mean ± SD, (n = 6)

As it can be seen from Figure 5.1 the swimming frequency for the compounds **3p** and **3s** was much higher than the control group and was comparable to that of Fluoxetine at a dose on 10mg/kg. On the other hand the results obtained by compounds **3a, 3f** and **3k** were not as significant suggesting the importance of presence of hydrophobic substitution on the phenyl ring.

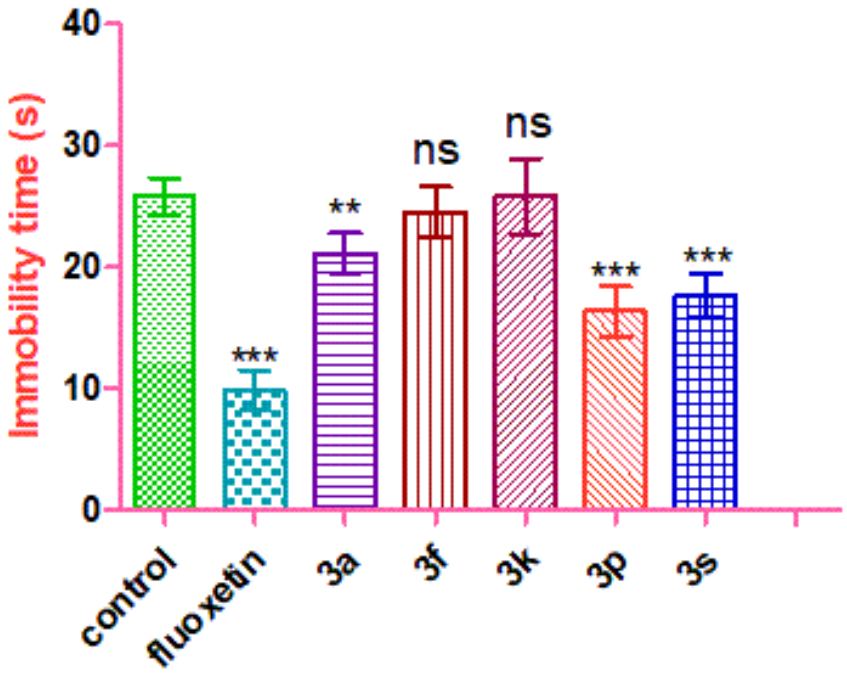


Figure 2 Effect of test compounds (40mg/kg) and Fluoxetine (10mg/kg) on immobility time of mice in TST. **p<0.05, ***p<0.001, ns-not significant, Values are represented as mean ± SD, (n = 6)

As it can be seen from Figure 5.1 and 5.2 that Fluoxetine and test compounds **3p** and **3s** improved the swimming frequency and decreased the immobility times indicating the role do hydrophobic substitution at the 2-phenyl ring. It was also evident that the presence of hydroxyl substitution on the 2-phenyl ring of indole was detrimental to antidepressant action.

Docking Study

The docking of the energy minimized structures was performed on MOA enzyme using Shrodinger software (trial version). The fit of the molecule in the grid was studied and the docking score was obtained. Compound 3p exhibited the most prominent binding energy comparable to the reference structure harmine (Figure 5.1). The binding site involved interaction of benzene rings with amino acid Tyrosine 69 and Phe 208 in the compound 3p (Figure 1).

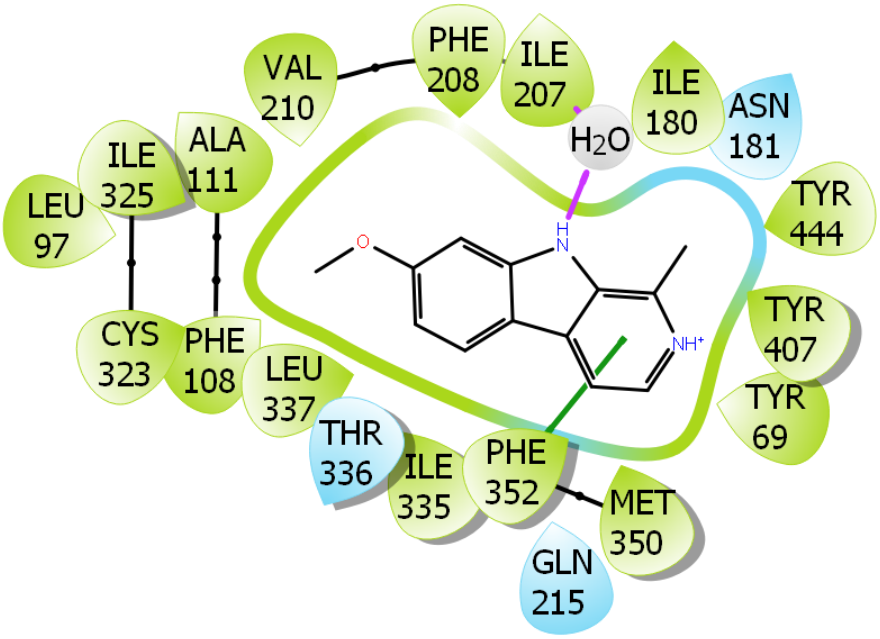


Figure 5.1 Interaction of reference compound with MOA

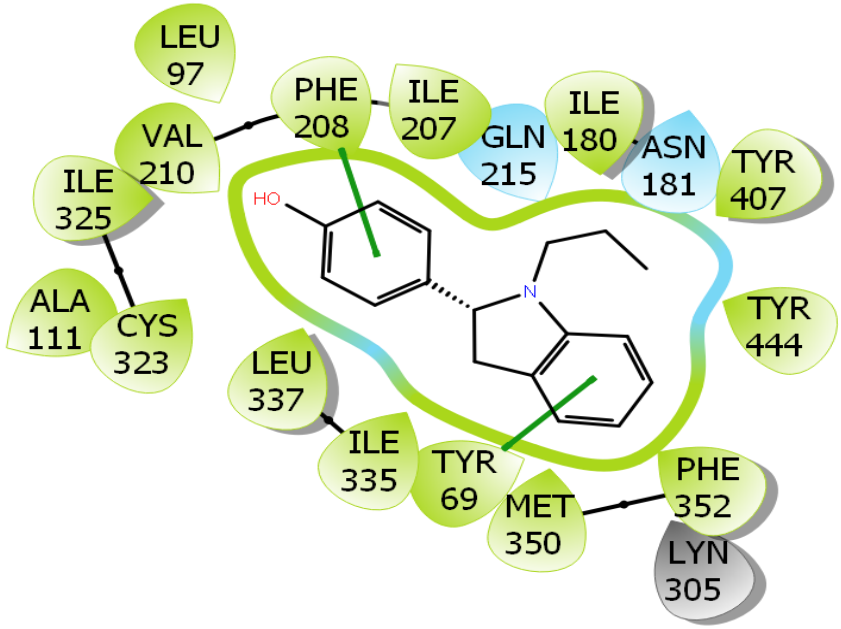


Figure 5.2 Interaction of compound 3p with MOA

Conclusion

The present work focused on synthesizing 2-phenyl indole derivatives possessing antidepressant potential. The synthesized compounds with diverse substitution pattern were able to exhibit antidepressant action. Further studies on new compounds of similar structure would be carried out in order to derive a relation between the structure and activity of the nucleus.

References

1. World Health Organization. “Depression: let’s talk” says WHO, as depression tops list of causes of ill health [press release]; 2017. https://www.who.int/news-room/detail/30-03-2017--depression-let-s-talk-says-who-as-depression-tops-list-of-causes-of-ill-health assessed on 08/04/2020
2. World Health Organization. Depression [fact sheet]; 2018. https://www.who.int/news-room/fact-sheets/detail/depression assessed on 08/04/2020
3. Grover S, Dutt A, Avasthi A. An overview of Indian research in depression. Indian Journal of Psychiatry. 2010; 52(S1): S178-S188
4. NHS Choices. Clinical Depression; 2016. https://www.nhs.uk/conditions/clinical-depression assessed on 08/04/2020
5. Furniss BS, Hannaford AJ, Smith PWG, Tatchell AR. Vogels Textbook of Practical Organic Chemistry. 5th edition; pp 1161
6. Mishra R, Mishra B, Moorthy NSHN. Synthesis and antimicrobial evaluation of some 3,4-dihydropyrimidine-2-one derivatives. Trends in Applied Sciences Research, 2008; 3(2): 203-208.
7. Malviya M, Mishra B, Korde B. Antidepressant molecules: Synthesis and evaluation of novel azetidinone compounds. Journal of Pharmacology and Biomedicine, 2021; 5(2): 286-294.
8. Varghese B., et al. “Unveiling a versatile heterocycle: pyrazoline–a review”. RSC Advances 7.74 (2017): 46999-47016.
9. Ju Y., et al. “Aqueous N-heterocyclization of primary amines and hydrazines with dihalides: microwave-assisted syntheses of N-azacycloalkanes, isoindole, pyrazole, pyrazolidine, and phthalazine derivatives”. The Journal of organic chemistry 71.1 (2006): 135-141.
10. Lellek V., et al. “An Efficient Synthesis of Substituted Pyrazoles from One-Pot Reaction of Ketones, Aldehydes, and Hydrazine Monohydrochloride”. Synlett 29.8 (2018): 1071-1075.
11. Alex K., et al. “Zinc-catalyzed synthesis of pyrazolines and pyrazoles via hydrohydrazination”. Organic Letters 10.12 (2008): 2377-2379.
12. Yang MN., et al. “Synthesis of dihydropyrazoles via ligand-free Pd-catalyzed alkene aminoarylation of unsaturated hydrazones with diaryliodonium salts”. Organic Letters 19.19 (2017): 5208-5211.\
13. Cho CH., et al. “Solution-phase parallel synthesis of a multi-substituted benzo [b] thiophene library”. Journal of Combinatorial Chemistry 11.5 (2009): 900-906.
14. Wang Z., et al. “Synthesis of 5- (trifluoromethyl) pyrazolines by formal [4+ 1] annulation of fluorinated sulfur ylides and azoalkenes”. Organic letters 20.4 (2018): 934-937.
15. Cui SL., et al. “Facile access to pyrazolines via domino reaction of the Huisgen zwitterions with aziridines”. Organic Letters 10.1 (2008): 13-16.
16. Chen M., et al. “Copper-catalyzed diamination of alkenes of unsaturated ketohydrazones with amines”. Organic Letters 20.3 (2018): 510-513.

17. Shaikh, M.U.; Jadhav, G.R.; Kale, R.P.; Chate, A.V.; Nagargoje, D.R.; Gill. C.H. Synthesis and antimicrobial screening of some novel 2-(5-(4-(1H benzo[d][1,2,3]triazol-1-yl)phenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenol incorporated by triazole moiety. J. Heterocyclic Chem., 2014, 51, 513-517.
18. Ovais, S.; Pushpalatha, H.; Reddy, G.B.; Rathore, P.; Bashir, R.; Yaseen, S.; Dheyaa, A.; Yaseen, R.; Tanwar, O.; Akthar, M.; Samim, M.; Javed, K. Synthesis and biological evaluation of some new pyrazoline substituted benzenesulfonylurea/thiourea derivatives as anti-hyperglycaemic agents and aldose reductase inhibitors. Eur. J. Med. Chem., 2014, 80, 209-217.
19. Patel, P.A.; Bhadani, V.N.; Bhatt, P.V.; Purohita D.M. Synthesis and biological evaluation of novel chalcone and pyrazoline derivatives bearing substituted vanillin nucleus. J. Heterocyclic Chem., 2014, DOI 10.1002/jhet.
20. Jadhav, S.Y.; Shirame, S.P.; Kulkarni, S.D.; Patil, S.B.; Pasale, S.K.; Bhosale R.B. PEG mediated synthesis and pharmacological evaluation of some fluoro substituted pyrazoline derivatives as anti-inflammatory and analgesic agents. Bioorg. Med. Chem. Lett., 2013, 23, 2575-2578.
21. Wang, H.H.; Qiu, K.M.; Cui, H.E.; Yang, Y.S.; Luo, Y.; Xing, M.; Qiu, X.Y.; Bai, L.F.; Zhu, H.L. Synthesis, molecular docking and evaluation of thiazolyl-pyrazoline derivatives containing benzodioxole as potential anticancer agents. Bioorgan. Med. Chem., 2013, 21, 448-455.
22. Desai, N.C.; Joshi, V.V.; Rajpara, K.M.; Vaghani, H.V.; Satodiya, H.M. Synthesis of quinoline-pyrazoline based thiazole derivatives endowed with antimicrobial activity. Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem., 2013a, 52, 1191-1201.
23. ElShora AI: Crystal and molecular structure of 3-hydrazino-1-hydrazinothio-carbonyl pyrazoline (TNT3). Egyptian Journal of Science 2000; 23: 251-54.
24. Li JT, Zhang XH and Lin ZP: An improved synthesis of 1, 3, 5-triaryl-2-pyrazolines in acetic acid aqueous solution under ultrasound irradiation. Beilstein Journal of Organic Chemistry 2007; 3: 1860-97.
25. Kelekci NG, Koyunoglu S, Yabanoglu S, Yelekci K, Ozgen O, Ucar G, Erol K, Kendi E and Yesilada A: New pyrazoline bearing 4-(3H)-quinazolinone inhibitors of monoamine oxidase: Synthesis,biological evaluation and structural determinants of MAO-A and MAO-B selectivity. Bioorganic and Medicinal Chemistry 2008; 22: 23 25.
26. Havrylyuk D, Zimenkovsky B, Vasylenko O, Zaprutko L, Gzella A and Lesyk R: Synthesis of novel thiazolone-based compounds containing pyrazoline moiety and evaluation of their anticancer activity. European Journal of Medicinal Chemistry 2008; 42: 1-9.
27. Sobhia HR, Yaminib Y, Esrafili A and Adiba M: Extraction and determination of 2 pyrazoline derivatives using liquid phase microextraction based on solidification of floating organic drop. Journal of Pharmaceutical and Biomedical Analysis 2008; 45: 316-20.