Turkish Online Journal of Qualitative Inquiry (TOJQI)
Volume 12, Issue 7,July 2021:3743-3750

Synthesis of Pyrazolopyrimidine derivatives and its Antidepressant activity

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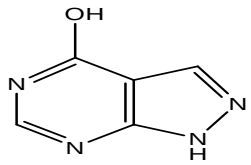
Abstract:

Antidepressants have a wide range of molecular mechanisms of action. Antidepressants are amphiphilic chemicals, which allow them to easily pass across the cell membrane and influence molecules on the outer and inner membrane surfaces, as well as cytoplasmic and nuclear molecules, Depressed persons may lose interest in once-pleasurable activities or experience cognitive problems (e.g., difficulty concentrating, remembering details, making decisions). They may think about or attempt suicide. Their weight might fluctuate considerably. Insomnia, excessive sleeping, sleep pattern changes (e.g., waking up in the middle of the night or early in the morning and being unable to fall asleep again), weariness, lack of energy, and aches, pains, or digestive disorders that are resistant to therapy may be present. Depressed mood is a normal reaction to some life experiences, a sign of many medical diseases (for example, Addison's disease, hypothyroidism), and a hallmark of several mental illnesses.

Keywords*: Digestive disorders, Addison's disease, Pyrazolopyrimidine derivatives.*

INTRODUCTION:

Pyrazolopyrimidines and similar fused heterocycles are being investigated for their possible bioactivity. The heterocyclic fusion of the pyrimidine and pyrazole rings resulted in the formation of pyrazolopyrimidines, structural analogues of the biogenic purine class. Pyrazolopyrimidines, with their broad spectrum of biological activities and numerous derivatives, have unquestionably high significance in the field of pharmaceutical and biotechnological sciences. e.g. (fig.1.1)



Allopurinol

Fig 1.1

The most commonly used antidepressants are **selective serotonin reuptake inhibitors (SSRI)**. In a depressed patient, there is a relative shortage of 5-HT in the serotonin neurone. The number of serotonin receptors, both presynaptic autoreceptors and postsynaptic receptors, is increased. The release of serotonin from synaptic knobs can be affected in two ways: first, positively by serotonin transporter

activity or availability of tryptophan (serotonin precursor), and second, negatively by activation of both presynaptic inhibitory receptors, 5-HT_{1B}aor $_2$-AR, and somatodendritic receptors, 5-HT_{1A}.

After acute administration of SSRI:

Because a significant portion of serotonin transporters are inhibited, serotonin lingers in extracellular space for a longer period of time. Serotonin levels rise mostly in the somatodendritic region as a result of this. Negative feedback is enhanced via inhibitory presynaptic and somatodendritic receptors, whereas both the frequency of action potential firing and the quantity of serotonin released from the presynaptic button are lowered.

After chronic treatment by SSRI:

Increased 5-HT induces inhibitory somatodendritic receptors to down-regulate and/or desensitise. It causes an increase in the frequency with which action potentials fire and an increase in the quantity of serotonin released into the synaptic cleft. When compared to the processes following acute SSRI treatment, the substantial increase in serotonin release at the axon terminal is delayed. This delay may explain why antidepressants do not have instant therapeutic effect.

Postsynaptic and presynaptic receptors are down-regulated and/or desensitised as 5-HT levels rise at the axon terminal. This desensitisation may help to mitigate the negative effects of SSRIs.

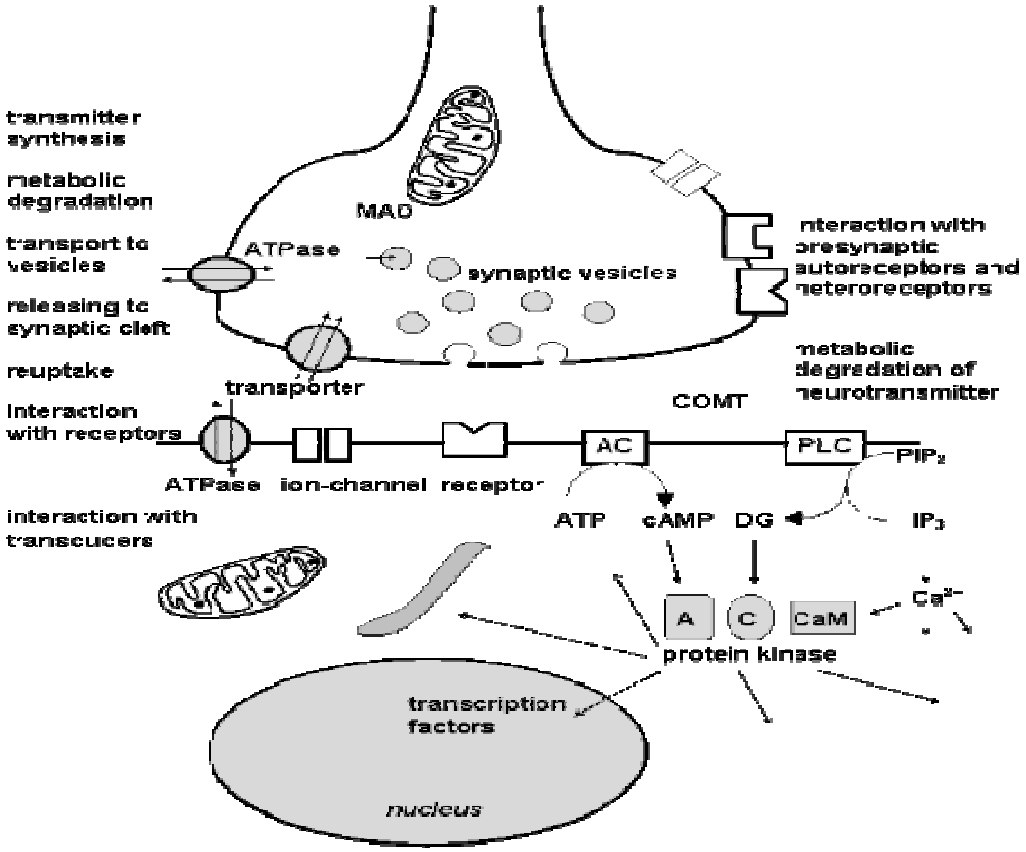


Fig: 1.2. Mechanisms of antidepressants action

Table 1. Classification of antidepressants based on acute pharmacological action

Inhibitors of neurotransmitter catabolism	**Monoamine oxidase inhibitors (IMAO)**
Reuptake inhibitors	Serotonin reuptake inhibitors (SRI) Norepinephrine reuptake inhibitors (NRI) Selective SRI (SSRI) Selective NRI (SNRI) Serotonin/norepinephrine (dual) inhibitors (SNRI) Norepinephrine and dopamine reuptake inhibitors (NDRI) Serotonin 2A antagonist/reuptake inhibitors (SARI)
Agonists of receptors	$5\text{-}HT_{1A}$
Antagonists of receptors	α_2-AR, $5\text{-}HT_2$
Inhibitors or stimulators of other components of signal transduction	G proteins, adenylyl cyclase (AC), phospholipase (PL), protein kinase (PK), phosphatase, atpase, phospholipid dependent proteins, transcription factors, Second and Third messengers

General categories of antidepressants agents

Illnesses featuring depression

1)Psychiatric syndromes: Major depressive disorder (MDD), sometimes known as "major depression" or "clinical depression," is a condition in which a person has a gloomy mood or a lack of interest or pleasure in practically all everyday activities for at least two weeks and these symptoms are not caused by a medical ailment. Dysthymia is a persistent sad mood state with symptoms that do not reach the intensity of a severe depressive episode. [1]

2) Non-psychiatric illnesses: Depressed mood can be caused by a variety of viral illnesses and physiological issues. For example, mononucleosis (glandular fever), which can be caused by two distinct viral infections, frequently produces symptoms that resemble a depressed mental disease; and sadness is frequently one of the first indications of hypothyroidism (reduced activity of the thyroid gland). Despair caused by life events may create a harmful feedback loop, and therefore a self-fulfilling prophecy, in which unhappy memories trigger greater depression, all while impairing the patient's ability to problem solve and take initiative.[2]

Depression and neurotransmitters

Depression is linked to changes in brain chemicals (neurotransmitters) that aid in nerve cell communication, such as serotonin, dopamine, and norepinephrine. Physical disorders, genetics, personality, substance misuse, food, hormonal changes, medicines, age, brain traumas, seasonal/light cycle changes, and social conditions can all alter the levels of these neurotransmitters (e.g. lack of social support).[3]Blood tests for TSH and thyroxine to rule out hypothyroidism; basic electrolytes and serum calcium to rule out a metabolic disruption; and a complete blood count with ESR to rule out a systemic infection or chronic illness. Subjective cognitive complaints are common in persons who are sad, but they can also indicate the beginnings of a dementing ailment, such as Alzheimer's disease.[4][5]

Methods for evaluation of antidepressant activity

Forced Swimming Test in Rats.

Techniques was first described by **Porsolt et al. (1977).**[6]
In glass cylinders containing water animals were placed in individually. Two swimming sessions were held (an initial 15-min pretest followed 24 h later by a 5-min test).

For a 5-minute interval, the total length of immobility was assessed. When the animal stayed passively floating in the water, it was deemed immobile.

CMS. Willner et al. (1992) created it for rats, while Kopp et al. (2013) recently modified it for mice. (1999).[7,8]

The CMS procedure entails the successive administration of a number of minor stressors, including as restraint, forced swimming, water deprivation, and pairing with another stressed animal, each for a period of 2 to 24 hours, in a schedule that lasts 3 weeks and is repeated afterward. In persistently stressed rats, body weight growth was reduced, giving a meaningful assessment of a depressive symptom.

Effects on Muscle Tone in Mice: Horizontal Wire Test.

Individual mice were taken by the tail and allowed to hold a horizontally strung wire (20 cm above the bench level, 2 mm in diameter, and 15 cm in length) using their forepaws. The failure to grab the wire with the forepaws or the failure to actively grab the wire with at least one hindpaw within 5 seconds is measured. Probit analysis may be used to obtain ED50 values.

Effects on Motor Coordination in Mice: Rotarod Test.

The device was a plastic cylinder (4 cm in diameter) that rotated at a rate of 4 rotations per minute. Mice are put on the rotating rotarod after sixty or 120 minutes of medication delivery orally. During the 2-minute interval that followed, there was a fall from the rotarod. Probit analysis may be used to obtain ED50 values.

Elevated plus maze test:

Passive Avoidance Test.

Effects on Mice Learning and Memory:

The device was a two-compartment black and white box divided by a "guillotine" door. The white compartment (10x10x12 cm) is modest, lighted by a 100-W lamp, and has a plastic floor. The dark container is rather spacious (22.5x16x12 cm) and has a steel grid bottom that is linked to a continuous current shock generator. Mice were placed in the tiny light container sixty minutes after being given medications orally. Entrance inside the dark box normally takes less than 30 seconds and is penalised with an electric footshock (0.75 mA, 2 sec) (trial 1). After returning to its home cage, the mouse is put in the light compartment and permitted to explore the box 24 hour's later (trial 2). Animals that stayed in the lit box for more than 60 seconds were thought to recall the assignment. The percentage of animals avoiding the dark chamber was therefore used to calculate retention.

Effects on Spontaneous Locomotor Activity in Mice: Actophotometer:A square, transparent Plexiglas box (22x27x10 cm) fitted with infrared beams and sensors device actophotometer is utilised for testing. It should be kept in sound-proof cabinets. The total number of beams traversed during a 10-minute period was used to calculate horizontal locomotor activity. Animals were placed separately in the centre of the device 60 minutes after being given a vehicle or several test medicines orally. The activity of the locomotor system may be tracked.

Synthesis of Pyrazolopyrimdine derivatives:

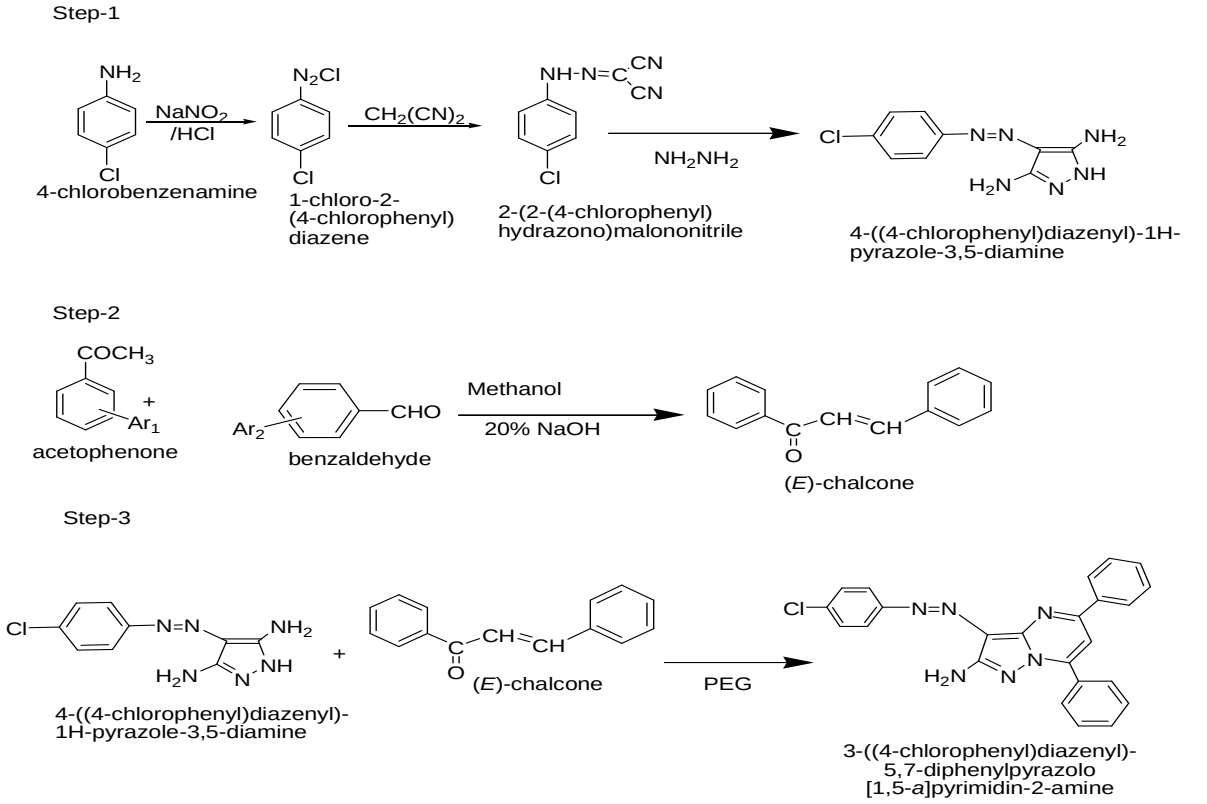


Fig 1.3

Material and methods:

Animals

Mice (20-25gm) both sex

Standard drug

Chlorpromazine (30mg/kg BW)

Control

0.1% CarboxyMethyl Cellulose (CMC) solution

Experimental procedure

Activity was performed by the instrument Photoactometer [9]
The locomotor activity (ability of mental wakefulness or alertness) [10] was measured by using an Photoactometer. The animal's movement disrupts a light beam falling on a photocell, at which a count is recorded and displayed digitally.

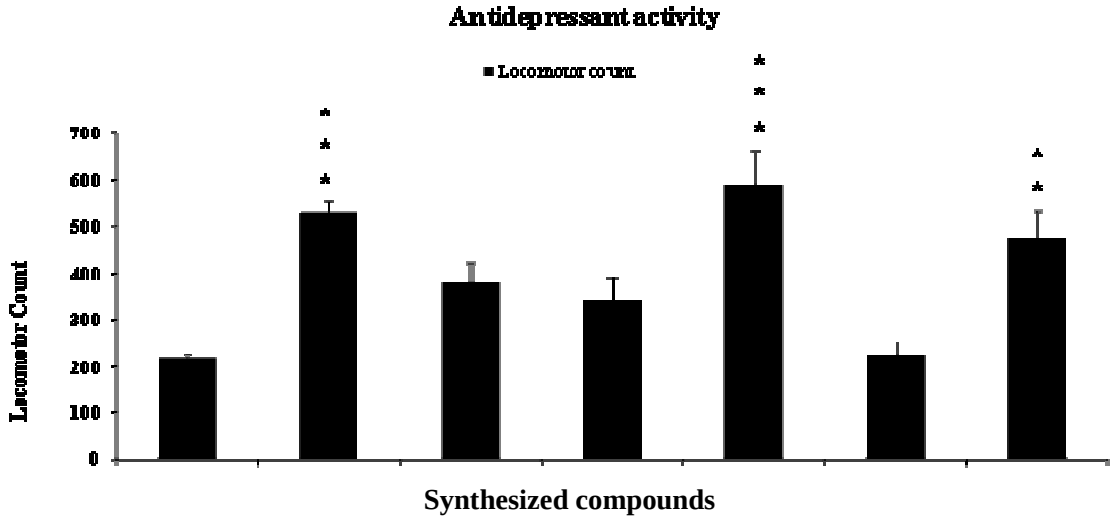
Mice were weighed (20-25gm) and divided into five different groups containing 6 animals each.

1. Dose selected for test and standard drug was 30mg/Kg BW. Drugs were suspended in 0.1% CMC solution.
2. All animals were acclimatized for a period of 10 min before starting the experiment.
3. Basal counts were taken for all animals individually for 10minutes.
4. Drugs were administered through oral route and after 60 minutes locomotor counts were recorded. The locomotor activity was measured for a period of 10 min.
5. Percentage of activity was calculated by the formula:
6.

$$\text{Percentage activity} = 1 - \left(\frac{\text{Locomotor count after drug}}{\text{Locomotor count before drug}} \right) \times 100$$

Table 2: Locomotor count for antidepressant activity

Group	Dose (mg/kg)	Mean Locomotor count		
		Before Drug	After Drug	Antidepressant activity (%)
Control	0.1 % CMC	262.83 ± 6.25	220.16 ± 18.77	--
Std (Chlorpromazine)	30	247.16 ± 18.09	530.16 ± 22.27	53.17***
PP_1	30	292.00 ± 46.83	343.33 ± 43.30	24.25
PP_2	30	211.16 ± 26.27	379.16 ± 51.47	35.16
PP_3	30	264.00 ± 35.09	615.16 ± 80.37	52.35***
PP_4	30	182.83 ± 25.49	224.16 ± 28.50	18.44
PP_5	30	241.66 ± 35.79	472.00 ± 61.98	44.29**



Statistical analysis Data were analyzed by One-Way ANOVA followed by Tukey's t-test using computerized Graph Pad Instat version 5.04 (Graph Pad software)

Result and Discussion:

This thesis deals primarily with the synthesis of heterocyclic compounds, particular pyrazolopyrimidine derivatives. In recent years, considerable attention has been paid to their syntheses which undeniably play a significant choice of synthetic strategy and development of new classes of therapeutically active compounds. As Pyrazolopyrimidine derivatives are well established in literature as important biologically active heterocyclic compounds. These derivatives are the subject of many research studies due to their widespread potential biological activities. A considerable amount of research activity is directed towards a potent, more specific and less toxic compounds. We had planned to incorporate different substitutions on parent molecule in our synthesized series of Pyrazolopyrimidine derivatives and evaluate them for different biological activities to search the potent compounds.

Aim of the proposed research work was to synthesize novel Pyrazolopyrimidine derivatives and evaluation of their biological activities and its Toxicity. All the newly synthesized derivatives were tested *in-vivo* and *in-vitro* in order to evaluate their pharmacological activity. Antidepressant activity was performed by instrument photoactometer by assessing locomotor activity of animals and compound **PP3** and **PP5** have shown significant antidepressant activity.

Conclusions:

In this article, a simple and efficient method for synthesizing some novel pyrazolopyrimidine incorporating the pyrazole moiety in good yields and high purity was achieved. Our synthesized compounds were elucidated depending on different spectroscopic techniques. Further studies are being conducted to acquire more information about biological activities such as antimicrobial, or antifungals to study quantitative structure-activity relationships (QSAR).

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