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Synthesis Characterization CNS and Analgesic Studies of Methyl 4-[(1E)-3-(Cyclopropylamino)-2-(3-Methoxyphenyl)-3-Oxoprop-1-Eny] Benzoate

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ABSTRACT

Organic synthesis is applicable in everyday life. Organic synthesis is very important in medicinal chemistry. A literature review of the medicinal chemistry approach is briefly carried out. In this article, 4-formylbenzoic acid is treated with thionyl chloride to form methanol-4-formylbenzoate. The product obtained is treated with 3-methoxyphenylacetic acid to give product 2. Product 2 is treated with cyclopropylamine to give the final product. The final product is treated with CNS and analgesic studies and the result is obtained

Introduction

Organic synthesis is a special branch of chemical synthesis and deals with the deliberate construction of organic compounds. Organic molecules are often more complex than inorganic compounds, and their synthesis has developed into one of the most important branches of organic chemistry. Each step of synthesis involves a chemical reaction and reagents. The conditions for each step of the synthesis are designed to give an adequate yield of pure product with as few steps as possible. There may already be a method in the literature for making one of the first synthetic intermediates, and this method will usually be used rather than trying to "reinvent the wheel". However, most intermediates are compounds that have never been produced before, and these will normally be produced using general methods developed by methodology researchers. To be useful, these methods must provide high yields and be reliable for a wide variety of substrates. For practical applications, other barriers include industry standards for safety and cleanliness.

MATERIALS AND METHODS

INSTRUMENTS FOR NMR SPECTRA

The NMR sample is prepared in a thin-walled glass tube - NMR tube.

When placed in a magnetic field, NMR active nuclei (such as 1H) absorb electromagnetic radiation

In NMR, the transition from the more stable alignment A (with the field) to the less stable alignment B (against the field) occurs when the nucleus absorbs electromagnetic energy exactly equal to the energy separation between the states . This amount of energy is usually found in the radio frequency range. The condition for energy absorption is called the resonance state. It can be calculated as follows

There are three facts of NMR spectra that we will focus on: number and magnitude of signals, chemical shift, and spin-spin coupling.

Number and magnitude of signals

Let's see how an NMR spectrometer can distinguish between hydrogen nuclei and produce multiple signals. Magnetically equivalent hydrogen nuclei produce a single signal. These hydrogen nuclei experience the same local environment. For example, there are two sets of magnetically equivalent hydrogen in a molecule such as diethyl ether. The hydrogen labeled a is six magnetically equivalent methyl hydrogens, while the hydrogen labeled b is four magnetically equivalent methylene hydrogens. Note that the methyl (and) hydrogen are all placed next to the carbon containing two hydrogen atoms. In addition, all methylene (b) hydrogens are located near an oxygen atom and a carbon atom containing three hydrogen atoms.

Central nervous system

Central nervous system depressants in higher doses slow down normal brain functions, some CNS depressants can become general anesthetics

CNS depressants used to treat anxiety, panic, sleep disorders, acute stress reactions, and muscle spasms include drugs such as Valium, Librium, and Xanax. Most CNS depressants act on the brain by affecting the neurotransmitter gamma-aminobutyric acid (GABA). GABA's unique ways, it is through their ability to increase GABA activity that they produce a drowsy or calming effect that is beneficial for those who suffer from anxiety or sleep disorders. These drugs are also particularly dangerous when mixed with other drugs or alcohol; overdose can cause respiratory problems and lead to death. Although newer sleep medications such as ambient, lunesta, and sonasta---seem to have a reduced addiction and abuse risk.

Over-the-counter medications, such as some cough suppressants containing dextromethrophan (DXM), are also abused for their psychoactive effects inducing hallucinations and dissociative feelings. However, an overdose of DXM can also cause confusion, disorientation, motor disturbances, blurred vision and nausea, fast or irregular heartbeat, high blood pressure, and loss of consciousness. Tranquilizers and sedatives are examples of CNS depressants.

Barbiturates such as mephobarbital (Mebaral) and sodium pentobarbital (Nembutal) are used to treat anxiety and sleep disorders.

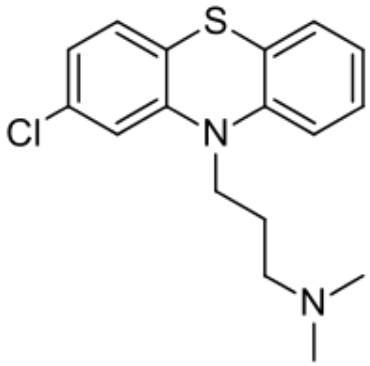
Benzodiazepines

Various benzodiazepines, such as diazepam, chlordiazepoxide HCl (Librium), and alprozolam (Xanax), which may be prescribed to treat anxiety, acute stress reactions, and panic attacks. Benzodiazepines that have a more sedating effect, such as estazolam, may be prescribed for the short-term treatment of sleep disorders

There are many CNS depressants, and most in the brain similarly affect the neurotransmitter gamma-aminobutyric acid (GABA). Neurotransmitters are brain chemicals that facilitate communication between brain cells. GABA works by reducing brain activity. Although different classes of CNS depressants work in unique ways, ultimately it is their ability to increase GABA activity that produces a drowsy or sedative effect. Despite these beneficial effects for those suffering from anxiety or sleep disorders, barbiturates and benzodiazepines can be addictive and should only be used as prescribed. CNS depressants should not be combined with any drugs or substances that cause drowsiness, including prescription pain relievers, certain over-the-counter cold and allergy medications, or alcohol, when combined they can slow breathing or slow the heart and breathing, which can be deadly.

Chlorpromazine

Chlorpromazine is the oldest antipsychotic. The molecular structure is 3-(2-chlorophenothiazin-10-yl)-N,N-dimethylpropan-1-amine. Chlorpromazine was the first drug developed with a specific antipsychotic effect. Its use has been described as the single greatest advance in psychiatric treatment, dramatically improving the prognosis of patients in psychiatric hospitals worldwide. It was the prototype for the phenothiazine class, which later expanded to include several other substances. Chlorpromazine acts on various receptors in the central nervous system and has anticholinergic, antidopaminergic, antihistaminic and antiadrenergic effects. Its anticholinergic properties cause constipation, sedation, hypotension and relieve nausea. It also has anxiolytic (anxiety-relieving) properties. Its antidopaminergic properties can cause extrapyramidal symptoms such as akathisia (restlessness), dystonia, and parkinsonism. Chlorpromazine inhibits clathrin-mediated endocytosis. It is often given in an acute state as a syrup, which has a faster onset of action than Chlorpromazine



Structure of Chlorpramazine

Pharmacodynamics and central effects

Chlorpromazine is a very potent antagonist of dopamine D2 receptors and similar receptors such as D3 and D5. Unlike most other drugs of this genre, it also has a high affinity for D1 receptors. Blocking these receptors causes reduced binding of neurotransmitters in the forebrain, resulting in many different effects. Dopamine, unable to bind to the receptor, causes a feedback loop that causes dopaminergic neurons to release more dopamine. Therefore, when taking the drug for the first time, patients experience an increase in the activity of dopaminergic nerve activity.

Eventually, dopamine production in neurons will drop substantially and dopamine will be removed from the synaptic left. At this point neural activity is greatly reduced, continuous blockade or receptors only increase this effect. Chlorpromazine acts as an antagonist at various postsynaptic receptors.

dopamine receptors (subtypes D1, D2, D3, and D4), which account for its various antipsychotic properties on productive and nonproductive symptoms; in the mesolimbic dopamine system accounts for the antipsychotic effect, while blockade in the nigrostriatal system produces extra-pyramidal effects.

Serotonin receptors (5-HT1 and 5-HT2) with anxiolytic and anti-aggressive properties, as well as alleviation of extrapyramidal side effects, but also leading to weight gain, drop in blood pressure, sedation and ejaculation difficulties

Histamine receptors (H1 receptors responsible for sedation, antiemetic effect, vertigo, drop in blood pressure and weight gain)

Alpha1 and alpha 2 - Adrenergic receptors (antisympathomimetic properties, lowering of blood pressure, reflex tachycardia, vertigo, sedation, hypersalivation, sexual dysfunction

M1 and M2 muscarinic acetylcholine receptors (causing anticholinergic symptoms such as dry mouth, blurred vision, constipation, tachycardia side effects)

Peripheral effects

Chlorpromazine is an antagonist of H1 receptors (anti-allergic effects). H2 receptors (formation of gastric juice and 5-HT receptors (anti-allergic/gastrointestinal action) Chlorpromazine is often referred to as a "dirty drug", where as an atypical antipsychotic, amisulpride acts e.g. only on central D2 and D3 receptors and is therefore a "Clean drug".

Analgesic

A drug that relieves pain without blocking the conduction of nerve impulses

Analgesics are classified by the mechanism of their pain-relieving effect on a receptor in the brain that inhibits pain impulses that inhibit prostaglandin synthesis.

Antipyretics also have mild analgesic activity.

The most common group of compounds used as antipyretics and analgesics include salicylates, aniline and aminophenol analogues, pyrazolones and quinoline derivatives. Although these heterogeneous groups of compounds are analgesics, they have no addictive properties. Their analgesic use is limited to mild pain such as headache and backache.

Analgesia is an ill-defined unpleasant sensation that is usually developed by external or internal noxious substances

Analgesics are divided into two

Opioid analgesics

Opiate Analgesics- The word opiates refers to products derived from the poppy. The term opioid is used to refer to all naturally occurring, semi-synthetic and synthetic drugs that have a morphine-like effect through pain relief and depression (like morphine) inducing sleep.

Non-opioid analgesic

Non-opioid analgesics that do not interact with opioid receptors and relieve pain without CNS depression (ex salicylates and related compounds). A painful reaction in experimental animals can be induced by the application of noxious (unpleasant) stimuli, such as

I Thermal (radiant heat as a source of pain)

II Chemical (irritants such as acetic acid and bradykinin) a

III Physical pressure (tail compression)

Tail-flicking methods (tail-pulling from radiant heat) using an analgesiometer and hot plate method etc. are commonly used in the laboratory.

Mechanism of action of analgesics

Although these drugs have different chemical structures, they have qualitatively similar analgesic effects. According to the current unified concept of the action of NSAIDs in inflammatory pain and fever. Arachidonic acid (AA) is released from the phospholipid fraction of the cell membrane. AA is then converted to prostaglandins (PG) by the cyclooxygenase pathway (Cox-I and Cox-2).

There are steps

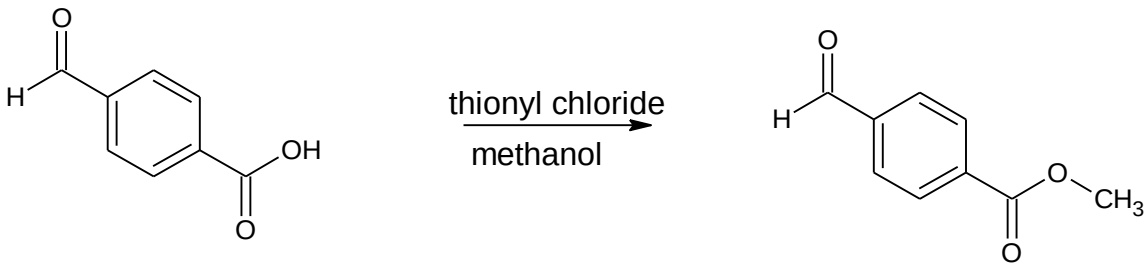
1) Oxidation of AA to hydroxyl endoperoxide a

2) Its subsequent reduction transformed into the primary prostaglandin PGE2, PGF2, PGD2, PGI2 and TXA2

Although Cox-1 and Cox-2 are structurally very similar, there are clear biochemical differences between them. Even then, they both use the same thing

Experimental section

Synthesis of Methyl-4-formyl benzoate

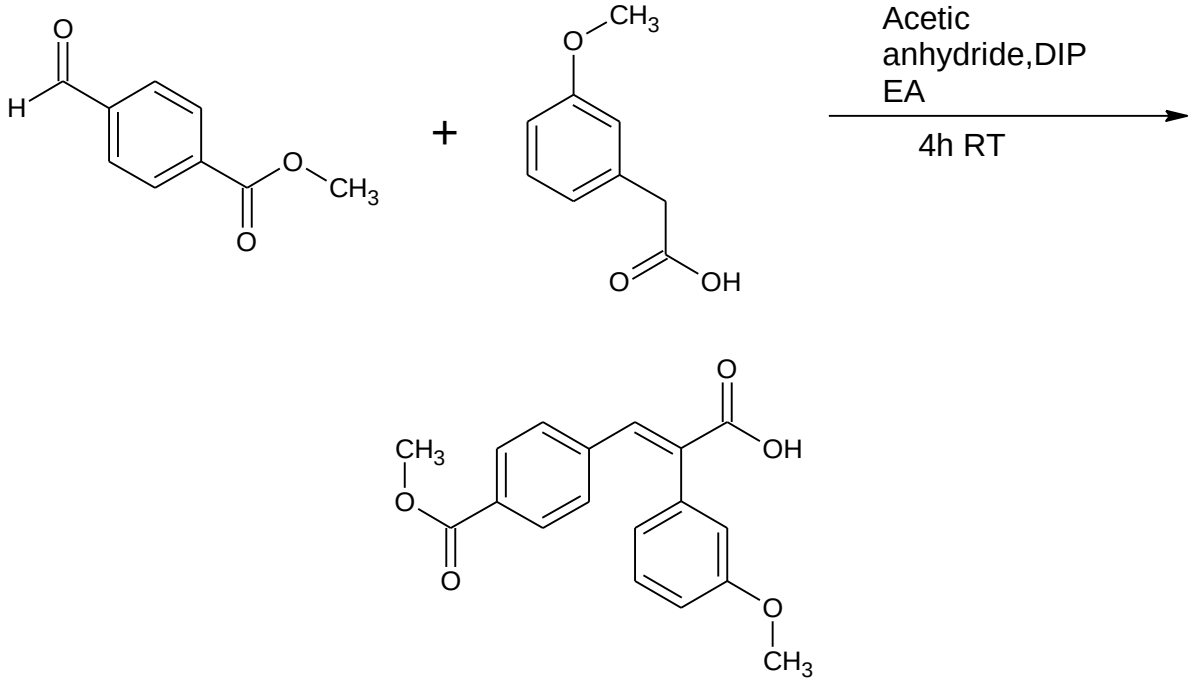


To a solution of (20g 13.3mol) 4-formyl benzoic acid in 60ml of methanol at room temperature (38ml 53.3 mmol) thionyl chloride became added in small quantities with steady stirring. The response temperature became raised from 30 to 65^{O}C and it was maintained on the equal temperature all through the addition. The response turned into monitored via TLC and stirred for 2hours. After completion of the reaction extra thionyl chloride was eliminated on buchi rotavapour and poured to an excess of ice. Sonicated this response aggregate for 10 minutes to gain yellow solid filtered below vacuum washed with 50 ml bloodless water and dried (19.3 g 88.9%yield)

^{1}H NMR (DMSO-d_6) ppm; 3.9(3H, S, -OCH_3), 8.03-8.05(2H, d, Ar-H),8.15-8.17 (2H ,d,Ar-H) 10.12 (1H,s,-CHO)

Mass spectra calculated M 164.05 observed (M+1) 165

Synthesis of (2*E*)-3-[4-(methoxycarbonyl)phenyl]-2-(3-methoxyphenyl)prop-2-enoic acid



(2*E*)-3-[4-(methoxycarbonyl)phenyl]-2-(3-methoxyphenyl)prop-2-enoic acid

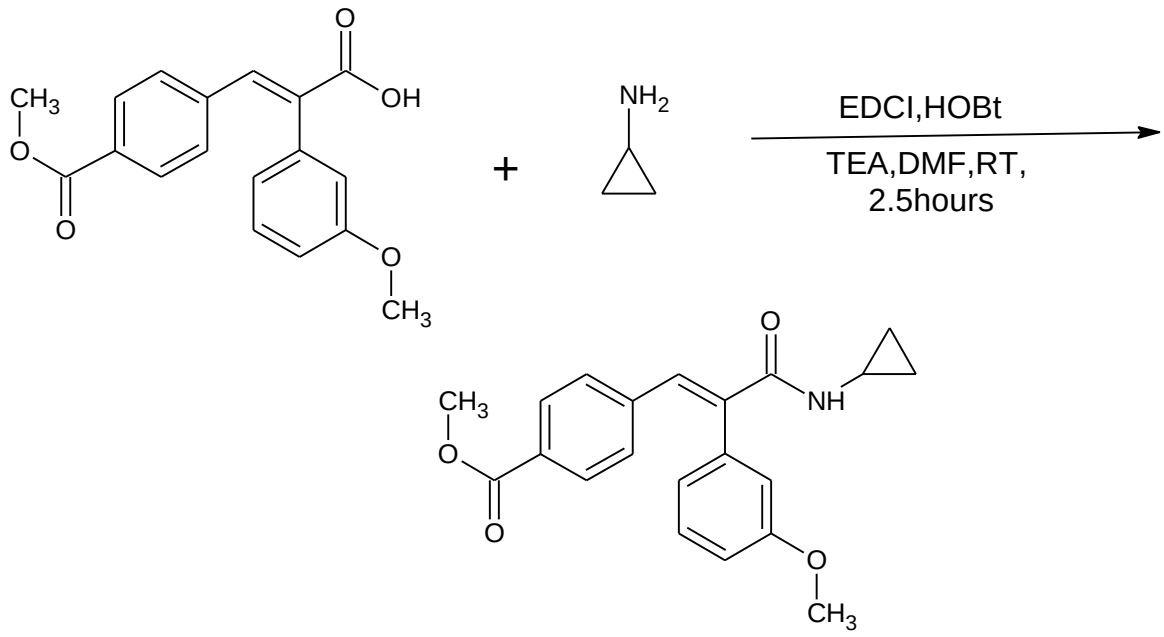
Procedure

Add 20 ml acetic anhydride, (5 g 3 mmol) 3methoxyphenylacetic acid and (4.9 g 3 mmol) methyl 4formylbenzoate (10.5 ml 6.0 mmol) to the DIPEA m ixture in small portions with constant stirring at room temperature. After completion of analysis of the reaction by TLC, the reaction mixture was coole d to 5°C. To the cold reaction mixture was added 5 ml of concentrated HCl in an attempt to gain strength. A yellow solid formed, diluted with 10 ml of water and vacuum filtered, washed with 30 ml of water and dried. The crude product was dissolved in 20 ml of 7:3 DCM/hexane. After cooling in the r efrigerator overnight, drain and dry. After cooling in the refrigerator overnight, filter and dry (5.7g, 60.5% yield)

^{1}H NMR (DMSO-d_6) ppm 3.7 (3H s, -OCH_3), 3.8 (3H s,OCH_3), 6.70 (2H m =CH and Ar-H) 6.92-6.95 (1H ,m, Ar-H),7.19-7.21 (2H m Ar-H), 7.26-7.30 (1H , m, Ar-H) 7.74-7.78 (3H m Ar-H) 12.9 (1H s –COOH)

Mass spectra calculated M 311 observed M+1 312

Synthesis of methyl 4-[(1*E*)-3-(cyclopropylamino)-2-(3-methoxyphenyl)-3-oxoprop-1-en-1-yl]benzoate(product III)



^{1}H NMR (DMSO-d_6) ppm 0.50-0.53 (2H , m, CH_2), 0.62-0.66 (2H, m, -CH_2) 2.7-2.77 (1H ,m –CH) 3.68 (3H, s, OCH_3) 3.80(3H s.OCH_3) 6.68 (2H, m ,=CH and Ar-H) 6.92-6.94 (1H ,m Ar-H), 7.14 (2H, d, Ar-H) , 7.25-7.30 (2H, m, Ar-H), 7.74 (2H, d, Ar-H), 7.85 (1H, s, -NH)

Mass spectra calculated M 351,observed M+1 352

Procedure

(2E)-3-[4-methoxycarbonyl)phenyl]-2-[3-(methoxycarbonyl)phenyl]acrylic acid (4g 1.28mmol) EDCI (4.89g, 2.56mmol) and HOBt (1.72g, 1 .28mmol) mixture was added to cyclopropylamine (0.89ml, 1.28mmol) in DMF (20ml), then TEA (5.35ml, 3.84mmol) was added dropwise with constant stirring. After 2.5 hours, the reaction mixture wa s poured into cold water (100 ml) and the reaction was monitored by TLC. Light yellow color formed, vacuum filtered, washed with 20 ml cold water a nd dried (4.11 g, yield 91.53%)

CNS STUDY

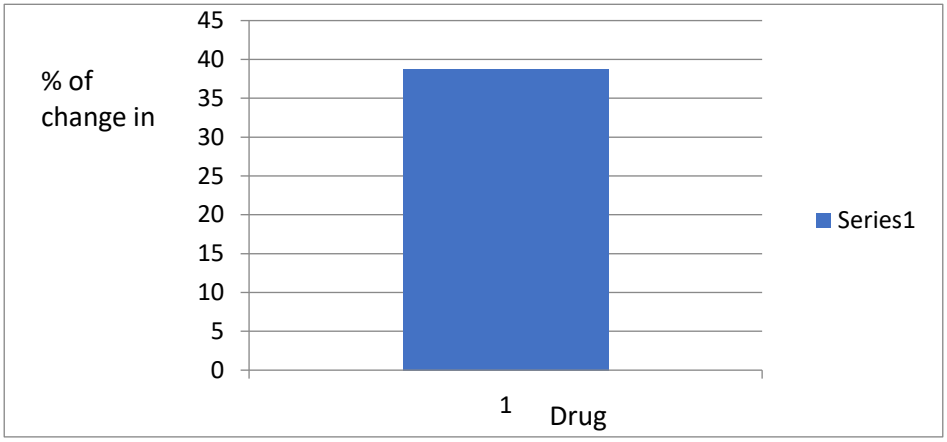
The CNS activity was studied using albino mice through oral route using canula insertion via mouth. The scores from the digital actophotometer were tabulated before and after drug administration. The mean % score for a group was plotted as chart likewise the tables and chart for dose of drug (30 mg/10 ml) were drawn.

Then from the mean values and chart the dose dependence of the synthesized compound was studied and it shows positive result. All the above facts can be observed using the following table and chart.

CNS stimulant activity of caffeine

Animals body weight(g)	Drug	Dose mg/kg	Actophotometer activity in 10 min		
			Before treatment	After treatment	% Change in activity
36.18	caffiene	30 mg/10 ml	190	240	26.31
34.28			240	280	16.66
35.10			242	350	44.62
35.93			192	300	56.25
36.55			240	360	50.00
Mean					38.76

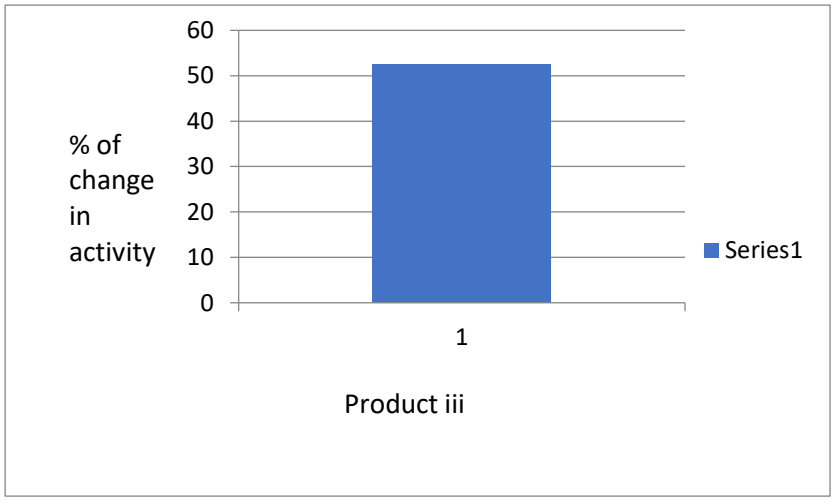
CNS stimulant activity of caffeine



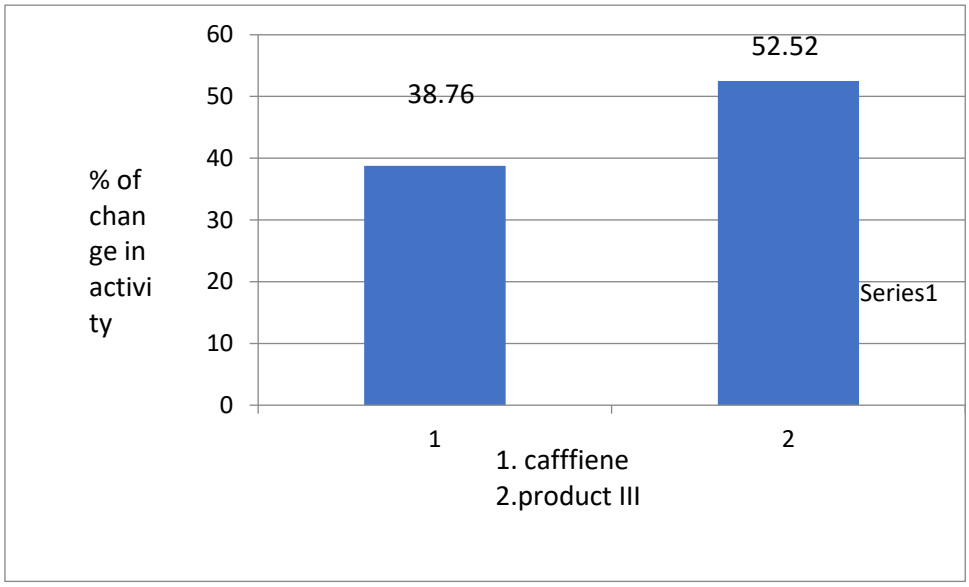
CNS study of product III

Animals body weight(g)	Drug	Dose mg/kg	Actophtometer activity in 10 min		
			Before treatment	After treatment	% Change in activity
36.18	Product III	30 mg/10 ml	170	300	64.70
34.28			225	275	10.66
35.10			214	310	75.23
35.93			164	294	45.12
36.55			203	284	63.54
				Mean	51.85

CNS activity of product III



Comparion of caffeine with product III (30mg/10ml)



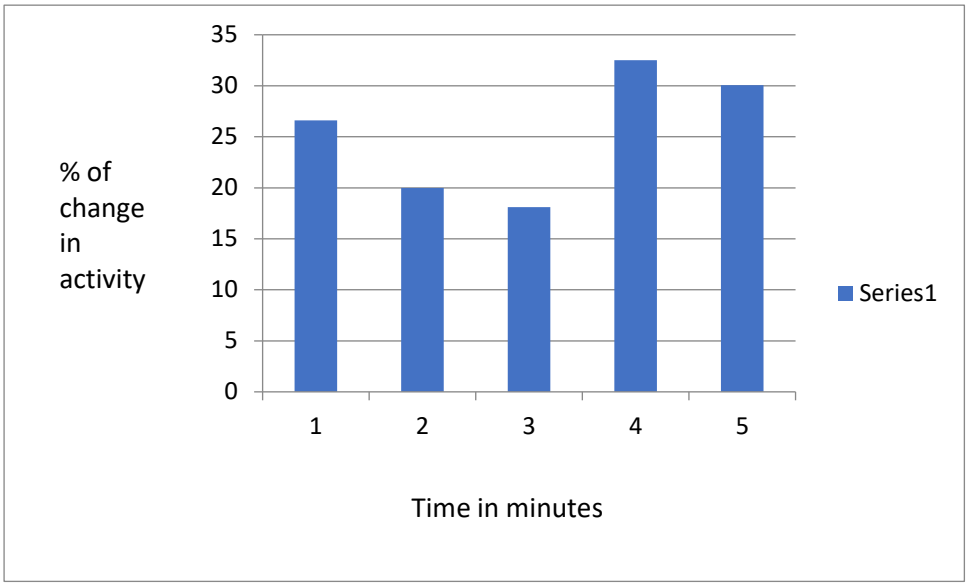
ANALGESIC ACTIVITY:

The doses of Schiff base Cu (II) Complex are prepared with a concentration of 20mg/ 10ml. The doses were given depending upon the body weight of the animal.

Analgesic activity of Product III

Animal body weight(g)	**Drug and dose**	**Basal reading (Seconds)**					**Reaction time after treatment (Seconds)**				
		1	2	3	4	5	15	30	60	90	120
34.83	**Control 1ml saline**	1	1	2	1	1	2	1	1	1	1
31.45		1	1	1	2	1	1	1	1	2	1
30.19		1	1	1	1	1	1	1	1	2	1
	Mean	1.00	1.00	1.33	1.33	1.00	1.33	1.00	1.00	1.66	1.00
29.18	**Test Product III (20 mg in 10 ml)**	1	2	2	1	2	2	2	3	4	4
25.16		1	1	2	2	1	3	3	3	5	4
27.56		1	1	1	1	1	3	3	3	4	4
	Mean	1.00	1.33	1.66	1.33	1.33	2.66	2.66	3.00	4.33	4.00
		% of analgesic activity					26.6	20	18.1	32.5	30.07

% of Analgesic activity of product III



Conclusion

In this paper, 4-formylbenzoic acid is treated with thionyl chloride to produce methanol 4-formylbenzoate. Treatment of the obtained product with 3-methoxyphenylacetic acid gives product 2. Product 2 is treated with cyclopropylamine to form the final product. The final product is treated with CNS activity, which shows a 52.52% increase in central nervous system stimulating activity and a good analgesic activity of 30.07%.

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