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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 to day to day life .Organic synthesis is very much importance in medicinal chemistry. A literature review is briefly conducted to medicinal chemistry approach. In this article 4-formyl benzoic acid is treated with thionyl chloride and methanol 4-formyl benzoate is formed. The product obtained is treated with 3-methoxy phenyl acetic acid and product 2 is obtained. The product 2 is treated with cyclopropyl amine and final product is formed. 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 is concerned with the intentional 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 a synthesis involves a chemical reaction and reagents. The conditions for each step of a synthesis are designed to give an adequate yield of pure product with as few steps as possible. A method may already exist in the literature for making one of the early synthetic intermediates, and this method will usually be used rather than an effort to "reinvent the wheel". However, most intermediates are compounds that have never been made before, and these will normally be made using general methods developed by methodology researchers. To be useful, these methods need to give high yields, and to be reliable for a broad range of substrates. For practical applications, additional hurdlesinclude industrial standards of safety and purity.

MATERIAL AND METHODS

INSTRUMENTATION FOR NMR SPECTRA

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

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

Bruker 300 MHz. Nuclear Magnetic Resonance (NMR) spectrometer

In NMR, transitions 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 that is exactly equal to the energy separation between the states (ΔE). This amount of energy is usually found in the radiofrequency range. The condition for absorption of energy is called the condition of resonance. It can be calculated as the following:

$$\Delta E=\frac{\gamma h}{2\pi}H = h\nu$$

h = Planck's constant; H= the strength of the applied magnetic field, H_o, at the nucleus; γ=the gyro magnetic ratio (a constant that is characteristic of a particular nucleus); ν=the frequency of the electromagnetic energy absorbed that causes the change in spin states

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

Number and Size of signals

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

Central nervous system

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

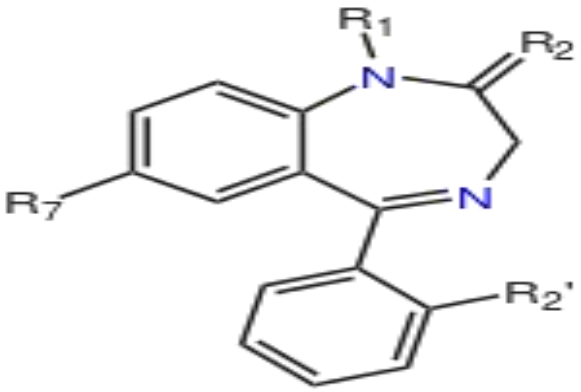
CNS depressant is used for the treatment of anxiety, panic, sleep disorders, acute stress reactions and muscle spasms, includes drugs such as valium, Librium and Xanax. Most CNS depressants act on the brain by affecting the neurotransmitter gamma aminobutyric acid (GABA). GABA unique ways, it is through their ability to increase GABA activity that they produce a drowsy or calming effect that is beneficial to that suffering room anxiety or sleep disorders. These drugs are also particulary dangerous when mixed with other medications or alcohol; overdose can cause breathing problems and lead to death. Although the newer sleep medications such as ambient, lunesta and sonasta---appear to have reduced dependence and abuse liabilities.

Over the counter medications such as certain cough suppressants containing dextromethrophan(DXM) are also abused for their psychoactive effects producing hallucinations and dissociative sensations. However, overdose of DXM can also produce confusion, disorientation, motor impairment, blurred vision and nausea, rapid or irregular heartbeat, high blood pressure and loss of consciousness. Transquilizers and sedatives are examples are examples of CNS depressants.

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

Benzodiazepines

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

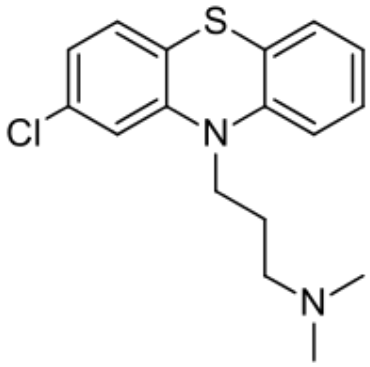


The core structure of benzodiazepines. "R" labels denote common locations of side chains, which give different benzodiazepines their unique properties.

There are many CNS depressants and most on the brain similarly they affect neurotransmitter gamma-amino butyric acid(GABA). Neurotransmitters are brain chemicals that facilitate communication between brain cells. GABA works by decreasing 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 calming effect. Despite these beneficial effects for people suffering from anxiety or sleep disorders, barbiturates and benzodiazepines can be addictive and should be used only as prescribed. CNS depressants should not be combined with any medication or substance that causes sleepiness, including prescription pain medicines, certain over the counter cold and allergy medications or alcohol if combined they can slow breathing or slow both the heart and respiration, which can be fatal

Chlorpromazine

Chlorpromazine is the oldest antipsychotic drug. The molecular structure is 3-(2-chlorophenothiazin-10-yl)-N,N-dimethylpropan-1-amine. Chlorpromazine was the first drug developed with specific antipsychotic action. Its use has been described as the single biggest advance in psychiatric treatment, dramatically improving the prognosis of patients in psychiatric hospitals world-wide. It was the prototype for the phenothiazine class which later grew to comprise several other agents. Chlorpromazine works on a variety of receptors in the central nervous system producing anticholinergic,antidopaminergic,antihistaminic and antiadrenergic effects. Its anticholinergic properties cause constipation, sedation,hypotension and relieve nausea. Its also has anxiolytic (anxiety relieving) properties. Its antidopaminergic properties can cause extrapyrimidal symptoms such as akathisa(restlessness), dystonia and Parkinosonism. Chlorpromazine inhibits clathrin-mediated endocytosis. It is often administered in acute settings as syrup which has a faster onset of action than tablets



Structure of Chlorpramazine

Pharmacodynamics and central effects

Chlorpromazine is a very effective antagonist of D_2 dopamine receptors and similar receptors such as D_3 and D_5. Unlike most other drugs of this genre, it also has a high affinity for D_1 receptors. Blocking these receptors cause diminished neurotransmitter binding in the forebrain, resulting in many different effects. Dopamine, unable to bind with a receptor, cause a feedback loop that causes dopaminergic neurons to release more dopamine. Therefore, upon first taking the drug patients will experience an increase in activity of dopaminergic neural activity.

Eventually, dopamine production of the neurons will drop substantially and dopamine will be removed from the synaptic left. At that point, neural activity decreases greatly, the continual blockade or receptors only compounds this effect. Chlorpromazine acts as an antagonist on different postsynaptic receptors.

Dopamine receptors (Subtypes D_1,D_2,D_3 and D_4) which account for its different antipsynoptic properties on productive and unproductive symptoms; in the mesolimbic dopamine system accounts for the antipsychotic effect whereas the blockade in the nigrostraiatal system produces the extra pyramidal effects.

Serotonin receptors (5-HT_1 and 5-HT_2) with anxiolytic, and antiaggresive properties as well as an attenuation of extrapyrimidal side effects, but also leading to weight gain, fall in blood pressure, sedation and ejaculation difficulties

Histamine receptors (H_1 receptors accounting the sedation,antiemetic effect, vertigo, fall 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

M_1 and M_2 muscarinic acetylcholine receptors (causing anticholinergic symptoms such as dry mouth, blurred vision, constipation, tachycardia side effects)

Peripheral effects

Chlorpromazine is an antagonist to H1 receptors (antiallergic effects). H_2 receptors (forming of gastric juice and 5-HT receptors (antiallergic/gastrointestinal actions) Chlorpromazine is often referred to as a "dirty drugs" , where as the atypical antipsychotic amisulpride, for example, acts only on central D2 and D3 receptors and is therefore a "Clean drug".

Analgesic

Drug that relieves pain without blocking the conduction of nerve impulses

Analgesics are classified by the mechanism of their pain relieving act on receptor in brain to inhibit pain impulses on which inhibit the systhesis of prostaglandins

The antipyretic agents also have mild analgesic activity.

Amongst the most common group of compounds used as antipyretic, analgesics are salicylates,aniline and aminophenol analogues, pyrazolones and quinoline derivatives. Though these heterogeneous groups of compounds are analgesics, they have no addictive properties. Their analgesic use is limited to mild aches and pains like headache and backache.

Analgesic is an ill-defined unpleasant sensation usually evolved by external or internal noxious

Analgesics are classified into two

Opiod analgesics

Opiod analgesics- The word opiates refers to the products obtained from the opium poppy. The term opiod is used to denote all naturally occurring, semi synthetic and synthetic drugs which have a morphine like action via relief from pain and depression of them (Such as morphine) induce sleep

Non Opioid analgesic

Non-opioid analgesics which do not interact with opioid receptors and relieve pain without depression of the CNS (ex salicylates and related compounds). Painful reaction in experiment animals can be produced by applying noxious (unpleasant) stimuli such as.

I Thermal (radiant heat as a source of pain)

II Chemical (irritant such as acetic acid and bradykinin) and

III Physical pressure (tail compression)

In the laboratory commonly used procedures are Tail-flicking (tail-withdrawal from the radiant heat) method using analgesiometer and hot plate method etc

Mechanism of action of analgesic drugs

Though these drugs have different chemical structure, they produce qualitatively similar analgesic effects. According to the current unify concept of NSAID action during inflammatory pain and fever. Arachidonic acid (AA) is liberated from phospholipids fraction of the cell membrane. AA is then converted via,cyclo oxygenase (Cox-I and Cox-2) pathway to prostaglandin (PGs).

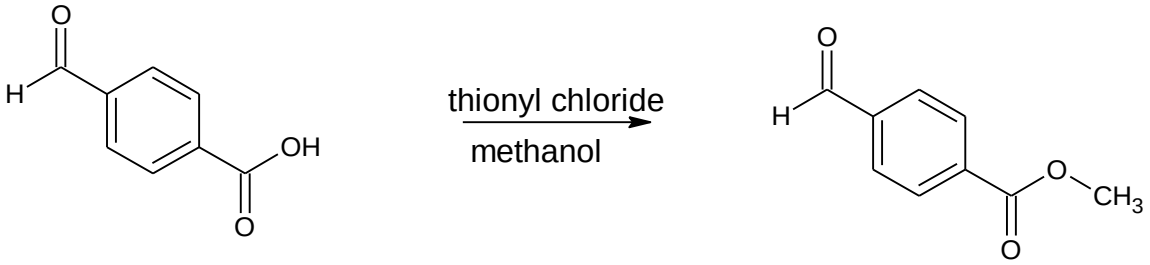
The steps are

1) Oxidation of AA to the hydroxyl endoperoxide and
2) Its subsequent reduction transformed into the primary prostaglandin PGE_2,PGF_2,PGD_2,PGI_2 and TXA_2

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

Experimental section

Synthesis of Methyl-4-formyl benzoate

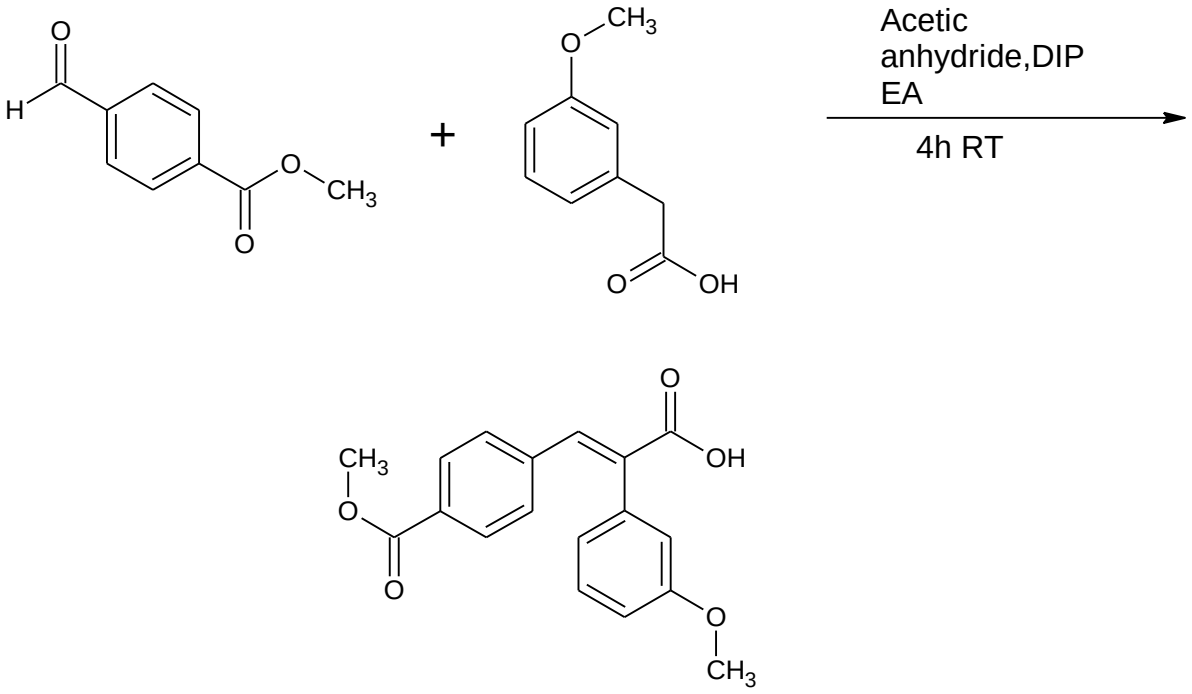


To a solution of (20g 13.3mol) 4-formyl benzoic acid in 60ml of methanol at room temperature (38ml 53.3 mmol) thionyl chloride was added in small portions with constant stirring. The reaction temperature was raised from 30 to 65^{O}C and it was maintained at the same temperature during the addition. The reaction was monitored by TLC and stirred for 2hours. After completion of the reaction excess thionyl chloride was removed on buchi rotavapour and poured to an excess of ice. Sonicated this reaction mixture for 10 minuted to obtain yellow solid filtered under vacuum washed with 50 ml cold 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

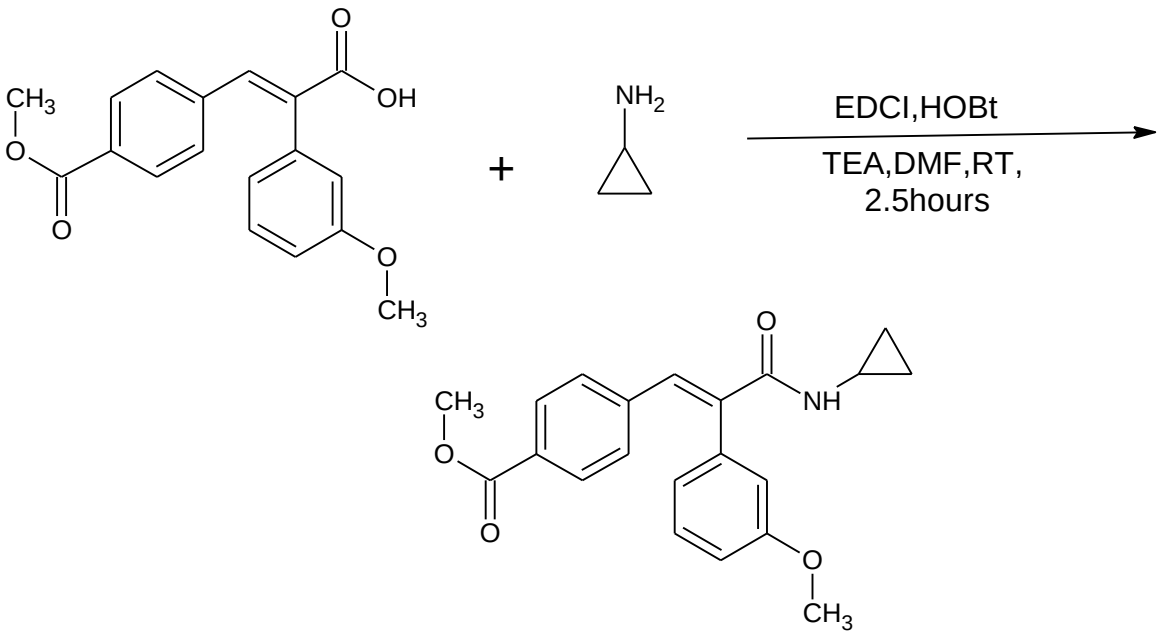
Procedure

To a mixture of 20ml acetic anhydride, (5g 3mmol) 3-methoxyphenylacetic acid and (4.9g 3mmol) methyl-4-formyl benzoate (10.5ml 6.0mmol) DIPEA was added in small portions at room temperature with constant stirring. After the completion of the reaction as monitored by TLC, the reaction mixture was cooled to 5^{o}C. To this cold reaction mixture 5ml con Hcl was added with vigorous stirring. Yellow solid formed diluted with 10ml water and filtered under vacuum washed with 30ml water dried. The crude product dissolved in 20ml 7:3 DCM/HEXANE. After an overnight cooling in refrigerator it was filtered and dried. After an overnight cooling in refrigerator it was filtered and dried (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

To a mixture of (2E)-3-[4-methoxycarbonyl) phenyl)-2-[3-(methoxycarbonyl)phenyl] acrylic acid(4g 1.28 mmol) EDCI (4.89g,2.56 mmol) and HOBt(1.72g,1.28 mmol) in DMF (20 ml) cyclopropylamine (0.89ml 1.28 mmol) was added followed by TEA (5.35 ml, 3.84 mmol) dropwisee with constant stirring. Reaction was monitored by TLC after a 2.5h reaction mixture was poured into ice cold water(100 ml) The pale yellow solid was formed filtered under vacuum, washed with 20ml cold water dried(4.11g 91.53% yield)

CNS STUDY

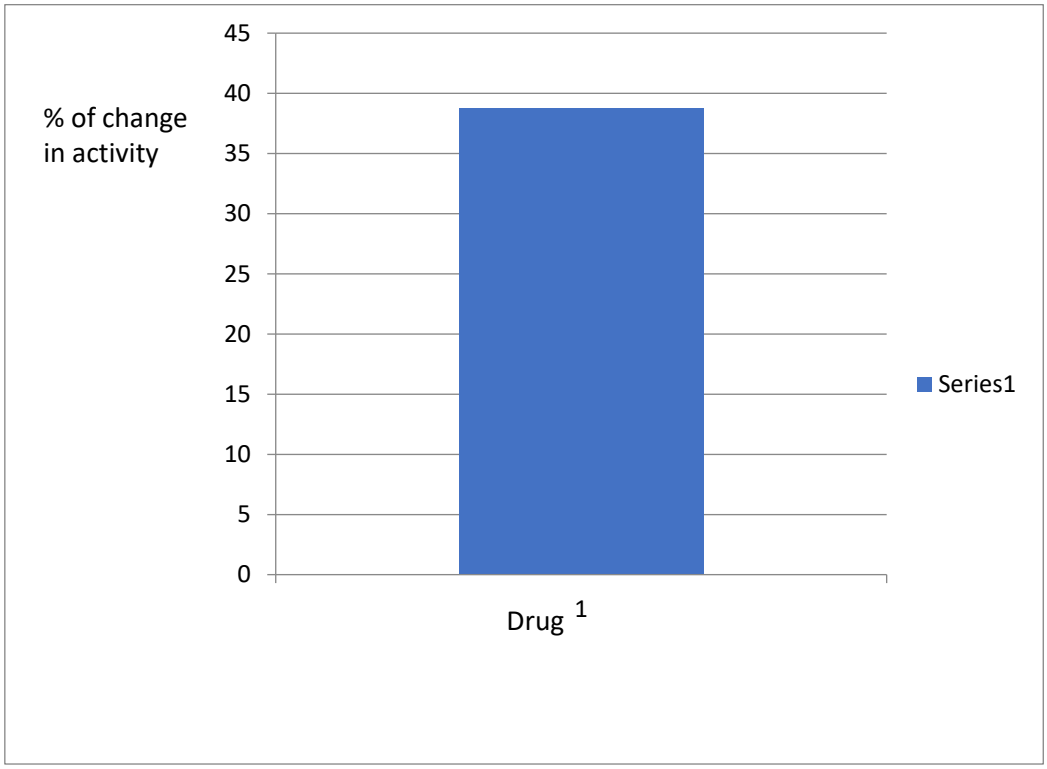
The CNS activity was studied using albino mice through oral route using canula insertion via mouth. The scores from the digital actophotometer were tabulated before and after drug administration. The mean % score for a group was plotted as chart likewise the tables and chart for dose of drug (30 mg/10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

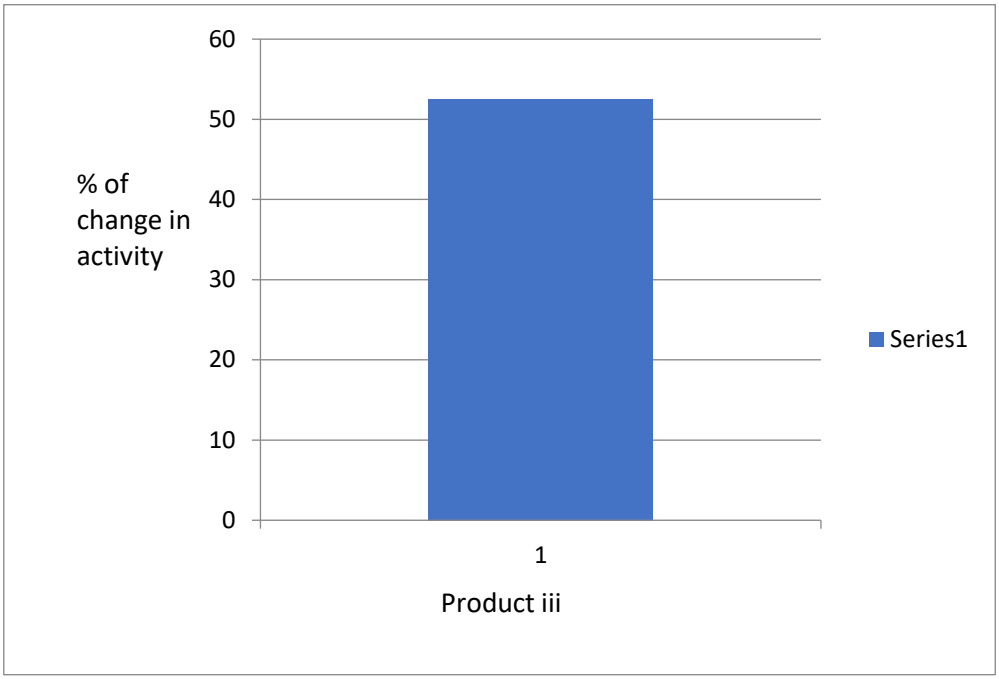
CNS stimulant activity of caffeine



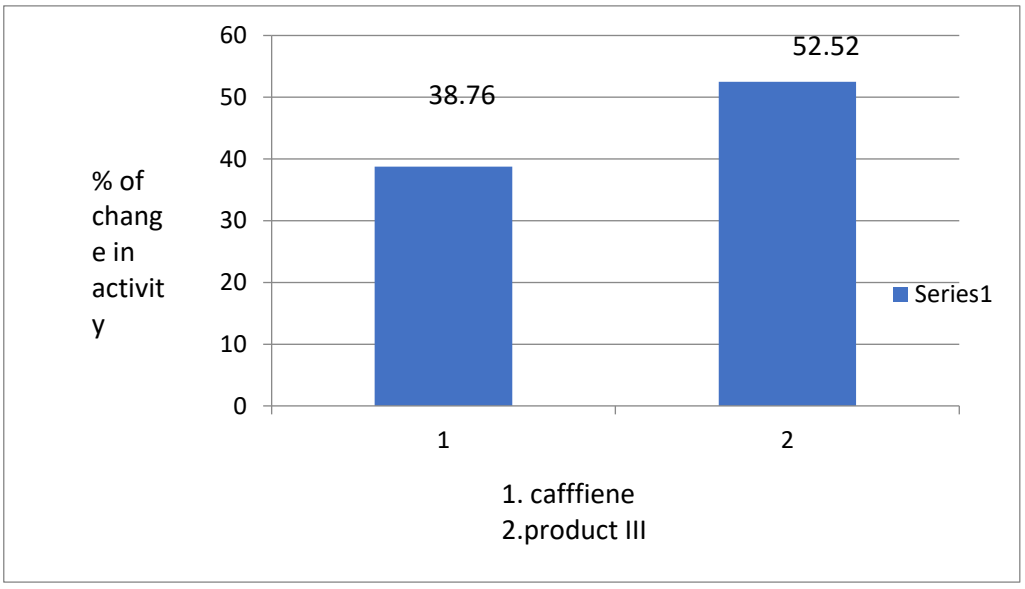
CNS study of product III

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)



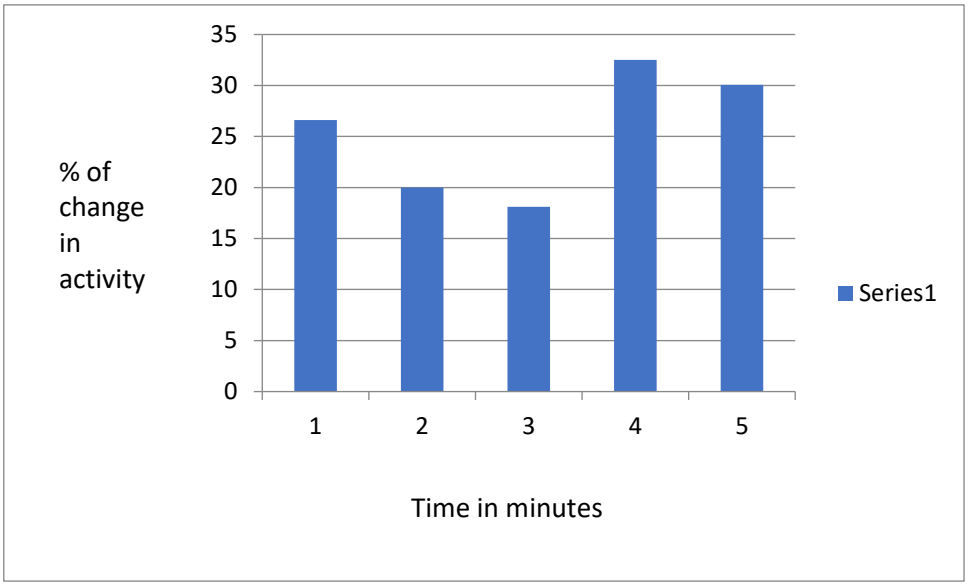
ANALGESIC ACTIVITY:

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 article 4-formyl benzoic acid is treated with thionyl chloride and methanol 4-formyl benzoate is formed. The product obtained is treated with 3-methoxy phenyl acetic acid and product 2 is obtained. The product 2 is treated with cyclopropyl amine and final product is formed. The final product is

treated with CNS activity it shows stimulant activity the central nervous system stimulant activity is increased by 52.52 and shows 30.07% good analgesic activity.

References

(1) Kervinen, K.; Korpi, H.; Leskela, M.; Repo, T. *J. Mol. Catal. A: Chem.* **2003**, *203*, 9–19.

(2) Chaube, V. D.; Shylesh, S.; Singh, A. P. *J. Mol. Catal. A: Chem.* **2005**, *241*, 79-87.

(3) Mukherjee, S.; Samanta, S.; Roy, B. C.; Bhaumik, A. *Appl. Catal.,* **2006**, *301*, 79

(4) Singha, U. G.; Williams, R. T.; Hallamb, K. R.; Allen, G. C. *J. Solid State Chem.***2005**, *178*, 3405–3413.

(5) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147–4154..(6) Hosseini, M.; Mertens, S. F. L.; Ghorbani, M.; Arshadi, M. R. *Mater. Chem. Phys.***2003**, *78*, 800–808.

(6) Emregul, K. C.; Atakol, O. *Mater. Chem. Phys.* **2003**, *82*, 188–193.

(7) Emregul, K. C.; Kurtaran, R.; Atakol, O. *Corros. Sci.* **2003**, *45*, 2803–2817.

(8) Yurt, A.; Balaban, A.; Ustun Kandemir, S.; Bereket, G.; Erk, B. *Mater. Chem. Phys.***2004**, *85*, 420–426.

(9) Ashassi-Sorkhabi, H.; Shaabani, B.; Seifzadeh, D. *Appl. Surf. Sci.* **2005**, *239*, 154–164.

(10) Ashassi-Sorkhabi, H.; Shaabani, B.; Seifzadeh, D. *Electrochim. Acta* **2005**, *50*, 3446–3452.

(11) Emregul, K. C.; Abdulkadir Akay, A.; Atakol, O. *Mater. Chem. Phys.* **2005**, *93*, 325–329.

(12) Yurt, A.; Bereket, G.; Kivrak, A.; Balaban, A.; Erk, B. *J. Appl. Electrochem.* **2005**,*35*, 1025–1032.