"SYNTHESIS AND PHARMACOLOGIACAL EVALUATION OF SUBSTITUTED DIHYDROPYRIMIDINE DERIVATIVES AS AN ANTIHYPERTENSIVE AGENT"

A THESIS SUBMITTED TO

NIRMA UNIVERSITY

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF PHARMACY

IN

MEDICINAL CHEMISTRY

BY

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UNDER THE GUIDANCE OF

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APRIL 2010

CERTIFICATE

This is to certify that ***Mr. MUKESH J. VADHIYA*** *has prepared his thesis entitled "Synthesis and Pharmacological Evaluation of Substituted Dihydropyrimidine Derivatives as an Antihypertensive Agent", in partial fulfillment for the award of M. Pharm. degree of the Nirma University, under our guidance. He has carried out the work at the Department of Pharmaceutical Chemistry, Institute of Pharmacy, Nirma University.*

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DECLARATION

I declare that the thesis "Synthesis and Pharmacological Evaluation of Substituted Dihydropyrimidine Derivatives as an Antihypertensive Agent" has been prepared by me under the guidance of Dr. Anuradha K. Gajjar, Professor, and Mrs. Jignasa K. Savjani, Assistant Professor, Department of Pharmaceutical Chemistry, Institute of Pharmacy, Nirma University. No part of this thesis has formed the basis for the award of any degree or fellowship previously.

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There is a famous saying ***"Work is Worship"****. A slight turn of the key activates the self-starter that further sets the automobile engine roaring. Similarly, a bit of motivation puts a self-starter into action and it is such people who lend dynamism to organization.*

It affords me an immense pleasure to acknowledge with gratitude the help and guidance rendered to me by a host of people, whom, I owe a substantial measure for the completion of this dissertation

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Last but not least I bow my head and sincere acknowledge my deep sense of gratitude to my late Mamma, ***parents*** *for giving me an inner strength to face the ups and downs; and for showering her infinite compassions and blessings, which made me able to see this wonderful moment. I pray that she will always bless me and show me the right path.*

Finally sincere thanks to all those people who have directly or indirectly helped me in time of need.

"If I can see farther it is only because I stand on the shoulders of giants"

Date:

Place: Ahmedabad ***Vadhiya Mukesh***

Abstract

Hypertension is a worldwide diseases caused by several environmental factor as well as genetic factor. Some pyrimidine analogs were synthesized to be evaluated for their antihypertensive effect in animal experiments. Substituted Dihydropyrimidine ring is synthesized by a simple efficient procedure, the Biginelli Reaction. A series of acetoacetanilide synthesized by aniline derivative condensed with ethaylacetoacetate in presence of base. Acetoacetanilide was condensed with urea and aromatic aldehyde in ethanolic medium to give substituted dihydropyrimidine. The structure of synthesized compounds has been confirmed on the basis of their spectral (IR, Mass and NMR) data. The purity of the compounds was confirmed by TLC. All these compounds were evaluated for their *in vitro* activity in rat uterus smooth muscle by Drug Response Curve method. Compound MJV-$A_{26}M_4$, MJV-A_4N_3, MJV-A_4N_4, MJV-$A_{26}D_{34}$ exhibited good antihypertensive activity against Calcium channel with the reference standard Nifedipine.

1. INTRODUCTION TO ANTIHYPERTENSIVE AGENTS

2. EXPERIMENTAL WORK-1: SYNTHESIS ANCHARACTERIZATION OF NOVEL SUBSTITUTED DIHYDROPYRIMIDINE

3. EXPERIMENTAL WORK-II: ANTIHTYPERTENSIVE EVALUATION OF SUBSTITUTED DIHYDROPYRIMIDINE

4. SUMMARY

1.0 INTRODUCTION

1.1 Blood Pressure

Blood is carried from the heart to all parts of your body in vessels called arteries. Blood pressure is the force of the blood pushing against the walls of the arteries. Each time the heart beats (about 60-70 times a minute at rest), it pumps out blood into the arteries.[1]

Blood pressure is always given as these two numbers, the systolic and diastolic pressures. Both are important.[2]

1.1.1 Systolic pressure

Blood pressure is at its highest (120 mmHg.) when the heart beats, pumping the blood. This is called systolic pressure.

1.1.2 Diastolic pressures

Blood pressure is at its lowest (80 mmHg.), When the heart is at rest, between beats, your blood pressure falls. This is the diastolic pressure.

1.1.3 High blood pressure

High blood pressure is also known as hypertension. It is diagnosed when the blood pressure is 140/90 mmHg or higher. In determining blood pressure, both the systolic and the diastolic numbers are taken into consideration.[3]

In general, there are two major and four rarely found types of high blood pressure.

The two major types of hypertension found are

1) Primary hypertension: Primary hypertension has no known cause, and is found in most of the people.

2) Secondary hypertension: Secondary hypertension is basically caused by certain factors, and is sometimes very much curable.

A part from these two types of hypertension, there are some other rare types of hypertension as well. These are[4, 5]

A) Gestational Hypertension
B) Isolated Systolic Hypertension
C) White Coat Hypertension
D) Prehypertension
E) Preeclampsia
F) Resistant Hypertension
G) Malignant Hypertension.

A) Gestational Hypertension

Some pregnant women may experience gestational hypertension after the twentieth week of pregnancy. The hypertension is caught early, complications affecting the organs, such as the brain.

B) Isolated Systolic Hypertension

If your systolic blood pressure is too high, it's known as isolated systolic hypertension.

C) White Coat Hypertension

People who only experience high blood pressure at the doctor's office have "white-coat hypertension this condition doesn't require treatment other than self-monitoring at home.

D) Prehypertension

Prehypertension is not the same as hypertension. But blood pressure readings are higher than normal, but not high enough to be considered high blood pressure. In this hypertension systolic pressure of 120–139mmHg or a diastolic pressure of 80–89 mmHg.

E) Preeclampsia

Pregnant women with preeclampsia can experience decreased blood flow to vital organs. endothelial dysfunction decreases release of nitric oxide and other vasodilator substances, causing vasoconstriction, decreased rate of fluid filtration from the glomeruli into the renal tubules, impaired renal pressure natriuresis, and development of hypertension.[6]

F) Resistant Hypertension

Resistant hypertension is high blood pressure that does not respond to treatment. Specifically, resistant hypertension is defined as blood pressure that remains elevated the treatment goals despite administration of an optimal drug regimen that includes diuretics. Because some cases of high blood pressure are difficult to treat, and may require a combination of multiple drugs before control is established, high blood pressure cannot be called “resistant” until drug combination therapy has failed.[6]

G) Malignant Hypertension.

Malignant hypertension is blood pressure that is so high that it is actually causing damage to organs, particularly in the nervous system, the cardiovascular system, and/or the kidneys. One type of such damage is called papilledema, a condition in which the optic nerve leading to the eye becomes dangerously swollen, threatening vision.[6]

1.1.4 Low blood pressure

Low blood pressure refers to the fall in blood pressure below the normal accepted level. The normal accepted level of blood pressure is 120/80 mmHg. When the pressure exerted by blood against the walls of the blood vessels during and after each heart beat is much lower than the usual, it is considered as low blood pressure.[3, 7]

1.2 Pathophysiology, Biochemistry, and Genetics of Hypertension[8]

The pathophysiology of essential hypertension has been extensively studied over the last 50 years. Peripheral vascular resistance is usually increased in hypertensive individuals. Normally, the autonomic nervous system, kidneys, adrenal cortex, local hormones, and cytokines regulate vascular resistance. Failure of the normal regulation of vascular resistance leads to hypertension. The failure can theoretically occur in any part of the regulatory system.

Over activity of the sympathetic nervous system plays a major role in the development and maintenance of hypertension. The excessive activation of the renin–angiotensin system or enhanced sensitivity to its primary effectors, Angiotensin II, contributes to the development and maintenance of hypertension. The fact that inhibitors of the formation of Angiotensin II or its antagonists at the receptor level are highly useful antihypertensive drugs supports the likely involvement of RAS in the pathogenesis of hypertension.

Calcium ions are required for the contraction of vascular smooth muscle, excessive permeability of VSM cells to or altered sodium–calcium exchange may also be involved. Activation of Angiotensin II receptors leads to enhanced entry of calcium ions into VSM cells, so that the calcium and Angiotensin II hypotheses are not mutually exclusive.

Various biochemical abnormalities in vascular smooth muscle cells have been proposed to play a role in the development of essential hypertension, including:
(1) increased ratio of cyclic guanosine monophosphate/cyclic adenosine monophosphate
(2) Decreased basal adenylyl cyclase; and
(3) Altered activity of cyclic AMP-dependent protein kinase.
It is not clear whether any of these changes are consistently present in hypertensive individuals and whether they are causative or secondary to another abnormality in the biochemistry of vascular smooth muscle.

The estimate for the extent of genetic contributions to the pathogenesis of essential hypertension range from 30% to 50%. The studies have been failed, to identify one single gene responsible for essential hypertension. It appears that multiple candidate and susceptibility genes may contribute to the disease.

Candidate genes have been identified in the RAS. Genetic linkages between ACE and essential hypertension have been suggested. Polymorphisms of the Angiotensin II receptor gene have been related to differential responses to antihypertensive drugs and severe forms of essential hypertension were found to be associated with a specific defect in this gene. Mutations of subunits of the epithelial sodium-channel gene have been found in Ladle's syndrome that is known to be associated with increased renal reabsorption of sodium and hypertension. Linkages between adrenergic receptor genes and hypertension have been reported. B2-Adrenergic receptor gene, known to affect blood flow and arterial pressure, has been implicated in the genetics of essential hypertension.

It has been suggested that essential hypertension is caused by a combination of small quantitative changes in the expression of many susceptibility genes with the environmental factors. The mutations of susceptibility genes may also be responsible for the excessive sensitivity to salt and higher risk for hypertension in black Americans. Hypertension appears to be primarily responsible for the higher mortality of black Americans from heart disease, renal failure, and stroke.

1.2 Signs and Symptoms

Most people who have high blood pressure do not know they have it because they have no symptoms. Occasionally, some people may have a mild headache when their blood pressure is high. Advanced cases of hypertension may produce the following symptoms:[9]

- Severe headache
- Confusion
- Nausea
- Visual disturbances

1.4 Causes

There are two major types of hypertension: Primary and secondary.

1.4.1 Primary hypertension

Primary hypertension is by far the most common, making up more than 95% of all cases. Scientists don't know what causes primary hypertension, but a combination of factors may be involved, including:[10]

- Genetic factor
- Low levels of nitric oxide, a naturally occurring substance that makes blood vessels dilate
- Insulin resistance
- Obesity

1.4.2 Secondary hypertension

Secondary hypertension has an underlying cause, which may include:

- Kidney disorders
- Endocrine disorders, such as Cushing syndrome
- Obstructive sleep apnea (where breathing stops momentarily while you are asleep because your airway is obstructed)
- Chronic heavy alcohol use
- Long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen (Motrin, Advil) and naproxen (Aleve)
- Certain medications, including some birth control pills, pseudoephedrine, hormone replacement therapy, and steroids
- Use of cocaine, nicotine, or other stimulants or the herb licorice (*Glycyrrhiza glabra*) can cause or worsen existing hypertension.[11]

1.5 Risk Factors

The following factors increase an individual's risk for high blood pressure:

- Being overweight

- Not getting enough exercise
- Having a family history of hypertension
- Being African-American
- Abusing alcohol or smoking
- High sodium (salt) intake
- Stress
- Chronic conditions such as diabetes, kidney disease, or high cholesterol.[9, 11]

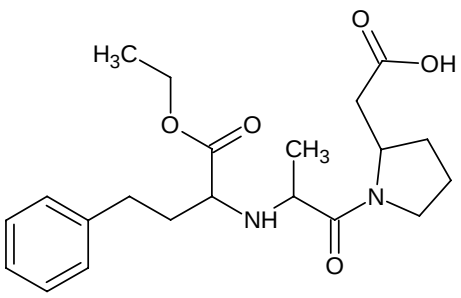
1.6 Anti Hypertensive Drugs and their Classification

Many different types of drugs are used, alone or in combination with other drugs, to treat high blood pressure. The major categories are: [12]

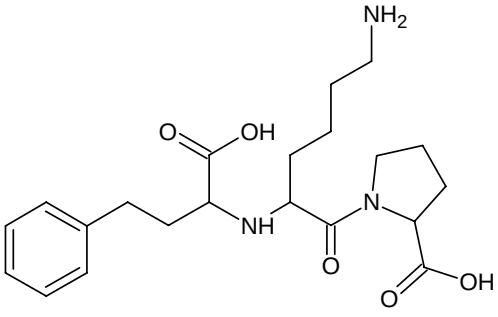
1.6.1 Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors work by preventing chemicals in the blood, angiotensin I, from being converted into a substance that increases salt and water retention in the body. These drugs also make blood vessels relax, which further reduces blood pressure.

Benazepril,	Captopril,
enalapril,	Fosinopril,
Lisinopril,	Perindopril,
quinapril,	ramipril,
trandolapril	



Enalapril



Lisinopril

1.6.2 Angiotensin II Receptor Blockers

These drugs act at a later step in the same process that ACE inhibitors affect. Like ACE inhibitors, they lower blood pressure by relaxing blood vessels. ·

Irbesartan,

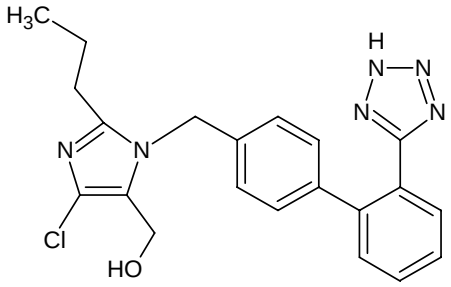
Olmesartan,

Valsartan,

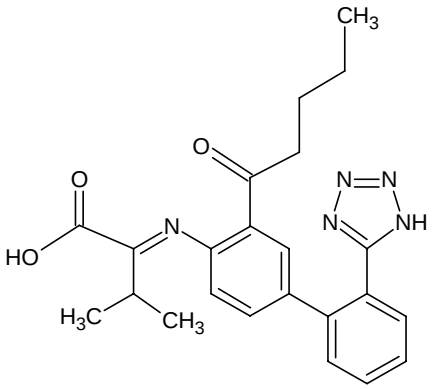
Losartan,

Telmisartan,

Eprosartan mesylate,



Losartan



Valsartan

1.6.3 Beta Blockers

Beta blockers affect the body's response to certain nerve impulses. This, in turn, decreases the force and rate of the heart's contractions, which lowers blood pressure. ·

Acebutolol,

Atenolol,

Betaxolol,

Carteolol,

Carvedilol,

Esmolol,

Labetalol,

Metoprolol,

Nadolol,

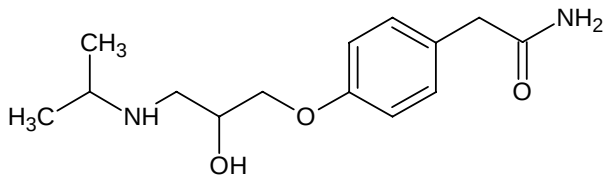
Nebivolol,

Penbutolol,

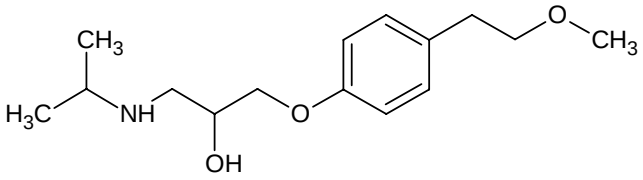
Pindolol,

Propranolol,

Sotalol,



Atenolol



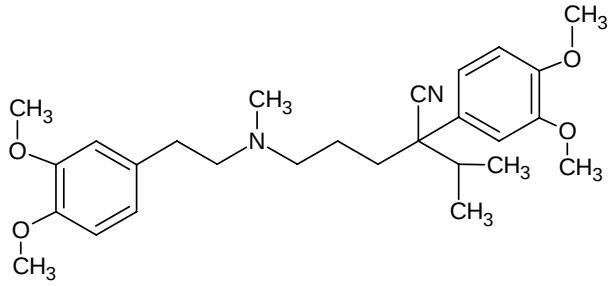
Metoprolol

1.6.4 Calcium Channel Blockers

Drugs in this group slow the movement of calcium into the cells of blood vessels. This relaxes the blood vessels and lowers blood pressure.

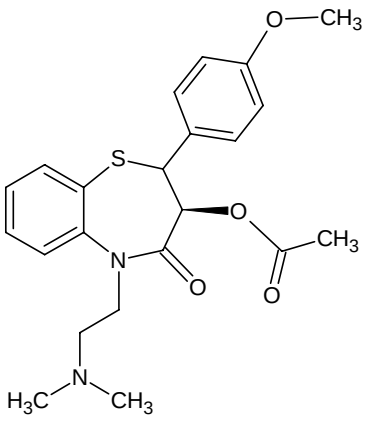
1.6.4.1 Arylalkylamines

Verapamil, Bepridil,



Verapamil

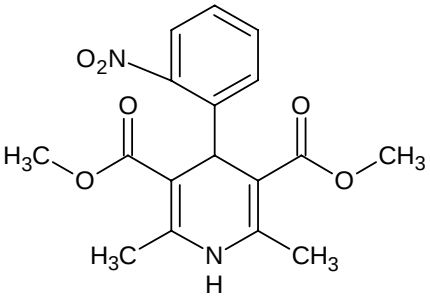
1.6.4.2 Benzothiazepines



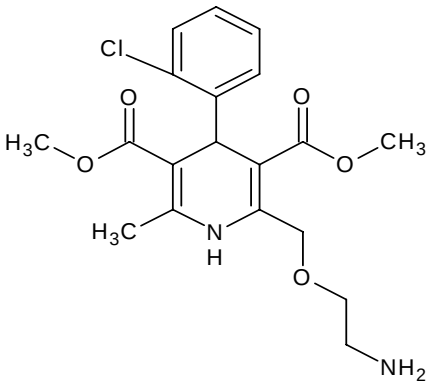
Diltiazem

1.6.4.3 1, 4-Dihydropyridine

Felodipine, Nifedipine,Amlodipine, Isradipine, Nicardipine, Nimodipine, Nisoldipine,



Nifedipine



Amlodipine

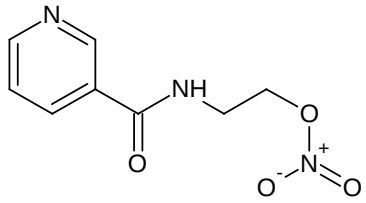
1.6.5 Blood Vessel Dilators (Vasodilators)

These drugs lower blood pressure by relaxing muscles in the blood vessel walls. ·

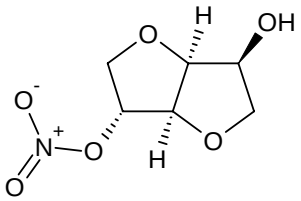
Amyl Nitrite, Glyceryltrinitrate,

Pentaerythritol tetranitrate, lsosorbide dinitrate,

lsosorbide mononitrate, Nicorandil,



Nicorandil



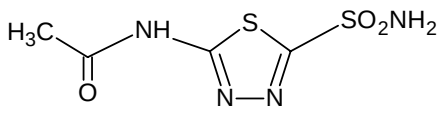
Isosorbide mononitrate

1.6.6 Diuretics

These drugs control blood pressure by eliminating excess salt and water from the body.

1.6.6.1 Carbonic Anhydrase inhibitors

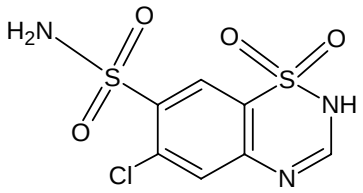
Acetazolamide, Methazolamide, Benzolamide, Ethoxzolamide



Acetazolamide

1.6.6.2 Benzothiadiazine Diuretics

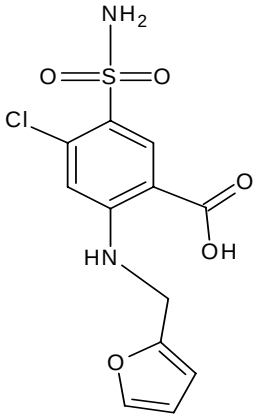
Chlorothiazide, Benzthiazide, Hydrochlorothiazide, Cyclopenthizide



Chlorothiazide

1.6.6.3 High Ceiling Diuretics

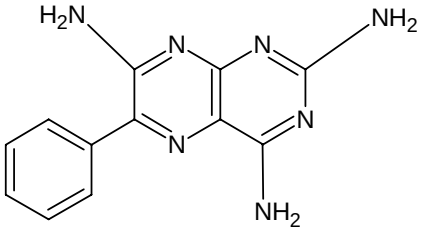
Bumetanide, Ethacrynic Acid, Azosemide, Furosemide



Furosemide

1.6.6.4 K^+ Sparing Diuretics

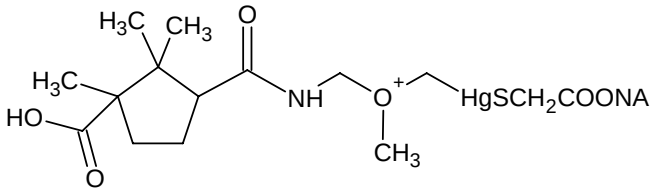
Triamterene, Amiloride, Azolimine and Clazolimine



Triamterene

1.6.6.5 Mercurial Diuretics

Meralluride, Sodium mercaptomerin, Chloromerodrin



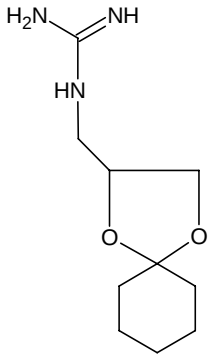
Sodium mercaptomerin

1.6.7 Nerve Blockers

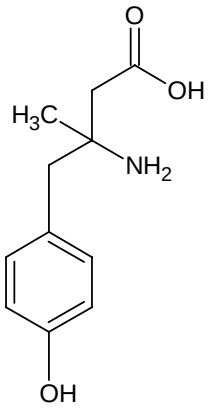
These drugs control nerve impulses along certain nerve pathways. This allows blood vessels to relax and lowers blood pressure.

Guanabenz, Guanfacine

Guanadrel



Metyrosine



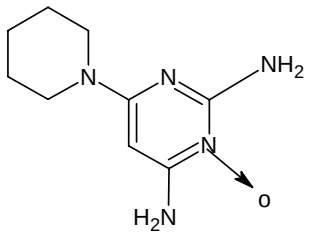
Guanadrel Metayrosine

1.6.8 K^+_{ATP} Channel Openers:

The hypotensive action of minoxidil was a significant advance in the treatment of hypertension, since the drug has proven to be efficacious in patients with the most severe and drug-resistant forms of hypertension.

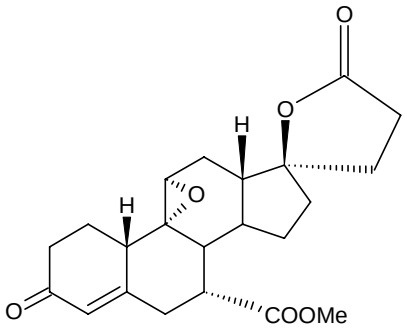
Minoxidil Lemakalim

Cromokalim Nicorandil



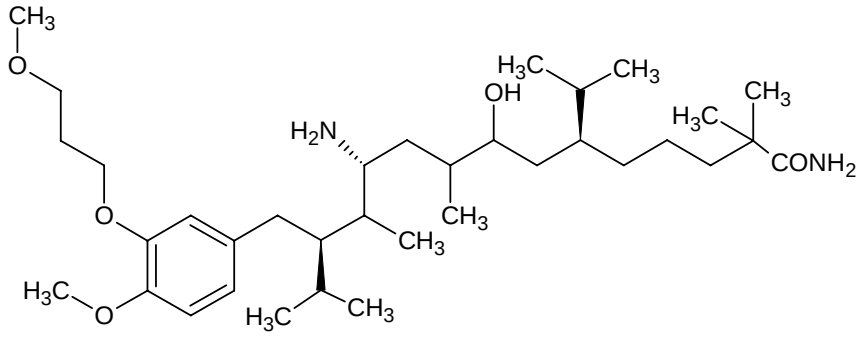
Minoxidil

1.7 Newer Antihypertensive agents



Eplerenone: K-sparing diuretics

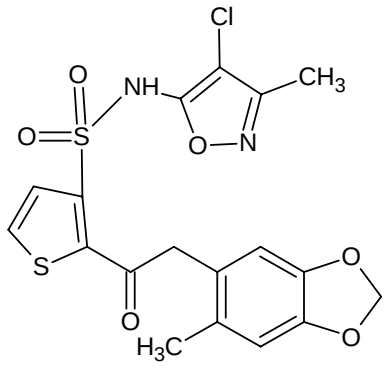
Eplerenone is more selective for mineralocorticoid receptors and has lower affinity for androgen and progesterone receptors than spironolactone. The antihypertensive activity of eplerenone was established in numerous clinical trials. Its efficacy was found to be independent of baseline aldosterone levels, age, race, or gender. In addition to its diuretic and antihypertensive effects, eplerenone has a cardioprotective effect: it prolongs survival in patients with heart failure secondary to myocardial infarction. [5]



Aliskiren: Rennin Inhibitor

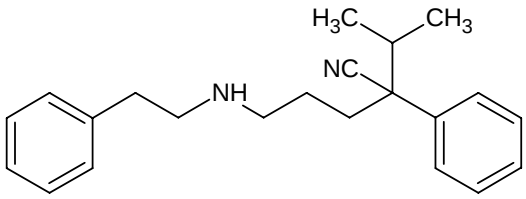
aliskiren is currently in advanced clinical evaluation. At 75,150, or 300 mg single doses, aliskiren effectively lowers ambulatory systolic pressure in hypertensive

patients and is well tolerated. Its effects appear to be synergistic with valsartan. It still remains to be shown that aliskiren can affect vascular pathology and reduce morbidity and mortality in cardiovascular disease.[5]



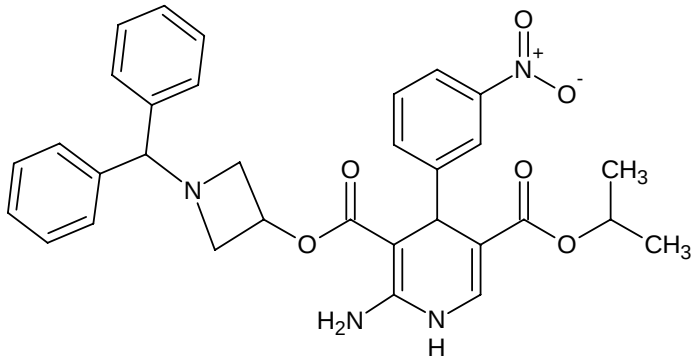
Sitaxsentan: endothelin antagonist

It has been proposed that in liver cirrhosis intrahepatic vascular tone increases due to an imbalance between increased sensitivity of hepatic blood vessels to endogenous vasoconstrictors and the reduced availability of NO.



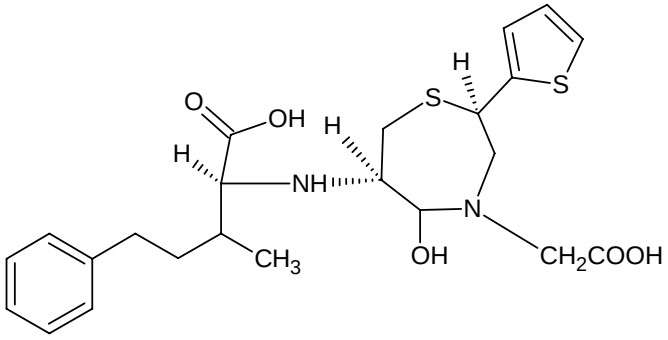
(S)-Emopamil: novel calcium channel blocker and serotonin S_2 antagonist

(S)-Emopamil is a novel calcium channel blocker of the phenylalkylamine class, with superior blood-brain permeability and potent serotonin S_2 antagonist activity.[13]



Azelnidipine: Novel Calcium Channel Blocker

Azelnidipine, a novel calcium channel blocker, could be a feasible antihypertensive regimen in terms of cerebral circulation in patients with ischemic white matter lesions.[14]



Temocaprilat : a Novel Angiotensin-Converting Enzyme Inhibitor[13]

1.8 Mechanism of action:

1.8.1 β Adrenergic Receptor Antagonists

Antagonism of β adrenergic receptors affects the regulation of the circulation through a number of mechanisms, including a reduction in myocardial contractility, heart rate, and cardiac output. An important consequence of using β adrenergic receptors is blockade of the β receptors of the juxtaglomerular complex, reducing renin secretion and thereby diminishing production of circulating angiotensin II. This action likely contributes to the antihypertensive action of this class of drugs, in concert with the cardiac effects.[15]

β Adrenergic receptor antagonists may lower blood pressure by other mechanisms, including alteration of the control of the sympathetic nervous system at the level of the CNS, altered baroreceptor sensitivity, altered peripheral adrenergic neuron function, and increased *prostacyclin* biosynthesis. Because all β adrenergic receptor antagonists are effective antihypertensive agents and (+)-propranolol, the inactive isomer that has little β adrenergic receptor blocking activity, has no effect on blood pressure, the antihypertensive therapeutic effect of these agents is undoubtedly related to receptor blockade.[16]

1.8.2 α_1 Adrenergic Antagonists

α_1 adrenergic receptor antagonists reduce arteriolar resistance and increase venous capacitance; this causes a sympathetically mediated reflex increase in heart rate and plasma renin activity. During long-term therapy, vasodilation persists, but cardiac output, heart rate, and plasma renin activity return to normal. Renal blood flow is unchanged during therapy with an α_1 receptor antagonist.

The α_1 adrenergic blockers cause a variable amount of postural hypotension, depending on the plasma volume. Retention of salt and water occurs in many patients during continued administration, and this attenuates the postural hypotension. α_1 Receptor antagonists reduce plasma concentrations of triglycerides and total LDL cholesterol and increase HDL cholesterol. These potentially favorable effects on lipids persist when a thiazide-type diuretic is given concurrently. The long-term consequences of these small, drug-induced changes in lipids are unknown.[17]

1.8.3 Ca^{2+} channel antagonists

Ca^{2+} channel blocking agents are an important group of drugs for the treatment of hypertension. Verapamil was the first clinically available calcium-channel blocker. Many other calcium entry blockers with a wide range of structures are now available. The largest group, including amlodipine, felodipine, isradipine, and nifedipine, are termed dihydropyridines.

Hypertension is generally the result of increased peripheral vascular resistance and contraction of vascular smooth muscle is dependent on the free intracellular concentration of Ca^{2+}, inhibition of transmembrane movement of Ca^{2+} through voltage-sensitive Ca^{2+} channels can decrease the total amount of Ca^{2+} that reaches intracellular sites.

Ca^{2+}-calmodulin-dependent activation of myosin light chain kinase, resulting in phosphorylation of myosin light chains, causes an increase in actin-myosin ATPase activity and contraction . Ca^{2+} channel blockers lower blood pressure by relaxing arteriolar smooth muscle and decreasing peripheral vascular resistance. As a consequence of a decrease in peripheral vascular resistance, the Ca^{2+} channel blockers evoke a baroreceptor-mediated sympathetic discharge.

1.8.4 Angiotensin-converting enzyme inhibitors

ACE inhibitors suppress Angiotensin II and aldosterone production, decrease sympathetic nervous system activity, and potentiate the effects of diuretics in heart failure. Angiotensin II levels frequently return to baseline values following chronic treatment with ACE inhibitors, due in part to production of Angiotensin II through ACE-independent enzymes such as chymase, a tissue protease.

ACE inhibitors are more potent arterial than venous dilators. In response to ACE inhibition, mean arterial pressure (MAP) may decrease or be unchanged; the change in MAP will be determined by the stroke volume response to after load reduction. Heart rate typically is unchanged, even when there is a decrease in systemic arterial pressure, a response that likely reflects a decrease in sympathetic nervous system activity in response to ACE inhibition. The decrease in left ventricular after load results in increased stroke volume and cardiac output. Venodilation results in decreases in right and left heart filling pressures and end-diastolic volumes.[18]

1.8.5 Vasodilators

Hydralazine causes direct relaxation of arteriolar smooth muscle. The mechanisms mediating this fall in intracellular calcium concentrations. Hydralazine-induced vasodilatation is associated with powerful stimulation of the sympathetic nervous system, likely due to baroreceptor-mediated reflexes, which result in increased heart rate and contractility, increased plasma renin activity, and fluid retention; all of these effects counteract the antihypertensive effect of hydralazine. Although most of the sympathetic activity is due to a baroreceptor-mediated reflex, hydralazine may stimulate the release of norepinephrine from sympathetic nerve terminals and augment myocardial contractility directly.[19]

1.8.6 K^+_{ATP} Channel Openers

Minoxidil is not active *in vitro* but must be metabolized by hepatic sulfotransferase to the active molecule, minoxidil *N-O* sulfate; the formation of this active metabolite is a minor pathway in the metabolic disposition of minoxidil. Minoxidil sulfate relaxes vascular smooth muscle in isolated systems where the parent drug is inactive. Minoxidil sulfate activates the ATP-modulated K^+ channel. By opening K^+ channels in smooth muscle and thereby permitting K^+ efflux, it causes hyperpolarization and relaxation of smooth muscle. [3]

1.8.7 Diuretics

Diuretics are drugs that increase the rate of urine flow; clinically useful diuretics also increase the rate of excretion of Na^+ and of an accompanying anion, usually Cl^-. NaCl in the body is the major determinant of extracellular fluid volume, and most clinical applications of diuretics are directed toward reducing extracellular fluid volume by decreasing total-body NaCl content. Mechanisms include activation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone axis, decreased arterial blood pressure, hypertrophy of renal epithelial cells, increased expression of renal epithelial transporters, and perhaps alterations in natriuretic hormones such as atrial natriuretic peptide. [20]

1.8.7.1 Thiazide diuretics

Some studies using split-droplet and stationary-microperfusion techniques have described reduction in proximal tubule reabsorption by thiazide diuretics; however, free-flow micropuncture studies have not consistently demonstrated increased solute delivery out of the proximal tubule following administration of thiazides. In contrast, micropuncture and in situ microperfusion studies clearly indicate that thiazide diuretics inhibit NaCl transport in the DCT. The DCT expresses thiazide binding sites and is accepted as the primary site of action of thiazide diuretics; the proximal tubule may represent a secondary site of action. [1]

1.9 Detail study of calcium channel and calcium channel blocker

1.9.1 Selectivity

Channels are generally either cation-selective or anion-selective. Cation-selective channels may be selective for Na^{+}, Ca^{2+} or K^{+}, or non-selective and permeable to all three. Anion channels are mainly permeable to Cl^{-}.

1.9.2 Types of calcium channel

There are four main routes by which Ca^{2+} enters cells across the plasma membrane: [2]

- voltage-gated calcium channels
- ligand-gated calcium channels
- store-operated calcium channels (SOCs)
- Na^{+}-Ca^{2+} exchange (can operate in either direction

1.9.2.1 Voltage-gated calcium channels

Voltage-activated calcium channels capable of allowing substantial amounts of Ca^{2+} to enter the cell when the membrane is depolarized. These voltage-gated channels are highly selective for Ca^{2+} and do not conduct Na^{+} or K^{+}; they are ubiquitous in excitable cells and allow Ca^{2+} to enter the cell whenever the membrane is depolarized, for example by a conducted action potential. There are five distinct subtypes of voltage-gated calcium channels: L, T, N, P and R.

L channels are particularly important in regulating contraction of cardiac and smooth muscle and N and P channels are involved in neurotransmitter and hormone release, while T channels mediate Ca^{2+} entry into neurons and thereby control various Ca^{2+}-dependent functions such as regulation of other channels, enzymes, etc. Clinically used drugs are, verapamil nifedipine and diltiazem.

1.9.2.2 Ligand-gated channels

Most ligand-gated cation channels are activated by excitatory neurotransmitters is relatively non-selective, and conducts Ca^{2+} ions as well as other cations. Most important in this respect is the glutamate receptor of the NMDA type, which has a particularly high permeability to Ca^{2+} and is a major contributor to Ca^{2+} uptake by postsynaptic neurons in the central nervous system. Activation of this receptor can readily cause so much Ca^{2+} entry that the cell dies, mainly through activation of Ca^{2+}-dependent proteases.

1.9.2.3 store-operated calcium channels

These are channels that occur in the plasma membrane and open to allow Ca^{2+} entry when the Endoplasmic reticulum stores are depleted. They are distinct from other membrane calcium channels, and belong to the large, recently discovered group of TRP (transient receptor potential) channels, which have many different functions. Like the ER and SR channels, they can serve to amplify the rise in Ca^{2+} resulting from Ca^{2+} release from the stores. So far, only experimental compounds are known to block these channels, but efforts are being made to develop specific blocking agents for therapeutic use as relaxants of smooth muscle.

1.9.2.4 Na^{+}-Ca^{2+} exchange

Active transport of Ca^{2+} outwards across the plasma membrane, and inwards across the membranes of the ER or SR, depends on the activity of a Ca^{2+}-dependent ATPase, similar to the Na^{+}/K^{+}-dependent ATPase that pumps Na^{+} out of the cell in exchange for K^{+}. Several subtypes of the Ca^{2+}-dependent ATPase have been cloned, but the physiological significance of this heterogeneity remains unclear. They have not been implicated in pharmacological responses, with the exception that thapsigargin specifically blocks the ER pump, causing loss of Ca^{2+} from the ER. Calcium is also extruded from cells in exchange for Na^{+}, by Na^{+}-Ca^{2+} exchange. E.g. dioxin.

1.9.3 Calcium Channel Blocker

The agents commonly called the calcium channel blockers comprise an increasing number of agents, including the prototypical verapamil, nifedipine, and diltiazem. These agents are a chemically and pharmacologically heterogeneous group of synthetic drugs, but they possess the common property of selectively antagonizing Ca^{++} movements that underlie the process of excitation–contraction coupling in the cardiovascular system. The primary use of these agents is in the treatment of angina, selected cardiac arrhythmias, and hypertension. Although the Ca^{++} channel blockers are potent vasodilating drugs, they lack the fluid-accumulating properties of other vasodilators and the persistent activation of the sympathetic and renin–angiotensin–aldosterone axes. A number of second-generation analogues are nifedipine, nimodipine, nicardipnicardipine, felodipine, nisoldipine, and amlodipine. Nimodipine has selectivity for the cerebral vasculature; amlodipine exhibits very slow kinetics of onset and offset of blockade; and felodipine and nisoldipine are vascular-selective 1,4-dihydropyridines.[19]

1.9.3.1 The Selectivity of Action of Calcium Channel Blockers

The activity of the Ca^{++} channel blockers increases with increasing frequency of stimulation or intensity and duration of membrane depolarization. This usedependent activity is consistent with a preferred interaction of the antagonists with the open or inactivated states of the Ca^{++} channel rather than with the resting state. This activity is not shared equally by all Ca^{++} blockers and so may provide a further basis for the therapeutic differences between them. For example, verapamil and diltiazem are approximately equipotent in cardiac and vascular smooth muscle, whereas nifedipine and all other agents of the 1, 4-dihydropyridine classes are significantly more active in

vascular smooth muscle.

Different members of the 1, 4-dihydropyridine class have different degrees of vascular selectivity. These differences are broadly consistent with the observation that verapamil and diltiazem act preferentially through the open channel state and nifedipine and its analogues act through the inactivated state.

Calcium channel antagonists have also proved to be invaluable as molecular probes with which to identify, isolate, and characterize calcium channels of the voltage-gated family. In particular, the 1, 4-dihydropyridines with their high affinity, agonist– antagonist properties, and selectivity have become defined as molecular markers for the L-type channel. Synthetic drugs of comparable selectivity and affinity to the 1, 4-dihydropyridines do not yet exist for the other channel types, T, N, P/Q, and R; these remain characterized by complex polypeptide toxins of the aga- andconotoxin classes. Neuronal pharmacology, including that of the central nervous system, is dominated by the N, P/Q, and R channels. This underscores the normally weak effect of L-channel antagonists on CNS function. Drugs that act at the N, P, and R channels with comparable selectivity and affinity to the 1, 4-dihydropyridines may be expected to offer major potential for a variety of CNS disorders, including neuronal damage and death from ischemic insults.

The Ca^{++} channel blockers also differ in the extent of their additional pharmacological properties. Verapamil and to a lesser extent diltiazem possess a number of receptor-blocking properties, together with Na^{+} and K^{+} channel–blocking activities, that may contribute to their pharmacological profile. Nifedipine and other 1, 4-dihydropyridines are more selective for the voltage-gated Ca^{++} channel, but they may also affect other pharmacological properties because their nonpolar properties may lead to cellular accumulation. Together with their channel-blocking properties, these properties may contribute contribute to the recently described antiatherogenic actions seen in experimental and clinical states.[19, 21]

1.9.3.2 Pharmacological effects on the cardiovascular system

Calcium channel–blocking drugs are clinically the most widely used compounds in this

very extensive class of pharmacological agents: amlodipine, diltiazem, isradipine, nifedipine, nicardipine, nimodipine, and verapamil.[19]

1.9.3.2.1 Vascular Effects

Vascular tone and contraction are determined largely by the availability of calcium from extracellular sources or intracellular stores. Drug-induced inhibition of calcium influx via voltage-gated channels results in widespread dilation and a decrease in contractile responses to stimulatory agents. In general, arteries and arterioles are more sensitive to the relaxant actions of these drugs than are the veins, and some arterial beds show greater sensitivity than others. Peripheral vasodilatation and the consequent fall in blood pressure are commonly accompanied by reflex tachycardia when nifedipine and its analogues are used; this is in contrast to verapamil and diltiazem, whose effects on peripheral vessels are accompanied by cardio depressant effects.[21]

1.9.3.2.2 Cardiac Effects

Calcium currents in cardiac tissues serve the functions of inotropy, pacemaker activity, and conduction at the atrioventricular node. In principle, the blockade of calcium currents should result in decreased function at these sites. In clinical use, dose-dependent depression is seen only with verapamil and diltiazem and not with nifedipine, reflecting mainly differences in the kinetics of their interaction at calcium channel. Characteristic cardiac effects include a variable slowing of the heart rate, strong depression of conduction at the A-V node, and inhibition of contractility, especially in the presence of preexisting heart failure.

1.9.3.3 Therapeutic applications

The calcium channel–blocking drugs have been investigated for an unusually wide number of clinical applications. Verapamil-induced improvement of diastolic function has proved to be beneficial in the treatment of hypertrophic cardiomyopathy.Vasodilatory properties of these drugs are used in the treatment of peripheral vasoconstrictive disorders and in relieving vasospasm following subarachnoid hemorrhage. There is ongoing interest in investigating protective effects on renal function and in the ability to reduce deleterious vascular changes in diabetes mellitus. Applications of CCBs are as follows.[21]

1.9.3.3.1 Hypertension

The calcium channel–blocking drugs are effective antihypertensive agents and enjoy widespread use as single medication or in combination. Their effectiveness is related to a decrease in peripheral resistance accompanied by increases in cardiac index. The magnitude of their effect is determined partly by pretreatment blood pressure levels; maximum blood pressure lowering generally is seen 3 to 4 weeks after the start of treatment. These drugs possess some distinct advantages relative to other vasodilators, including the following:

1. Their relaxant effect on large arteries results in greater compliance, which is beneficial in older persons.
2. Tolerance associated with renal retention of fluid does not occur; an initial natriuretic effect is often observed, especially with the nifedipine group of blockers.
3. Postural hypotension, Their antihypertensive efficacy is comparable to that of alpha-adrenergic blockers and angiotensin-converting enzyme inhibitors. The choice of a calcium channel blocker, especially for combination therapy, is largely influenced by the effect of the drug on cardiac pacemakers and contractility and coexisting diseases, such as angina, asthma, and peripheral vascular disease.[19, 21]

1.9.3.3.2 Ischemic Heart Disease

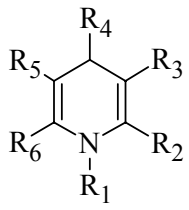
The effectiveness and use of calcium channel blockers in the management of angina

1.9.3.3.3 Cardiac Arrhythmias

The prominent depressant action of verapamil and diltiazem at the SA and A-V nodes finds use in specific arrhythmias. They are of proven efficacy in acute control and long-term management of paroxysmal supraventricular tachycardia.

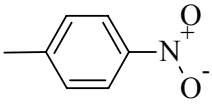
1.9.4 Structure activity relationship (SAR)

1, 4 dihydropyridines are dilators of coronary arteries. They are used in hypertension and angina.[22]



- First generation – Nifedipine, Nimodipine, Nivaldipine
- Second generation – Amlodipine, Felodipine, Isradipine, menidipine
- R_1 is H or a group with can be readily removed during metabolisam.
- R_2 and R_6, the best suited are lower alkyl group there is usually CH_3. But in amlodipine, R2 is replaced by aminoethayl ether.
- Amlodipine $R_2 = CH_2O(CH_2)_2NH_2$
- At physiological pH, amlodipine is more potent because of the R_2 group.
- If R2 is H or aryl group, then activity is decreases.
- Nifedipine $R_2 = R_6 = -CH_3$

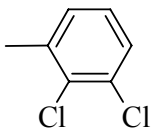
  $R_3 = R_5 = -COOCH_3$

  $R_4 =$ 

- R_3 and R_5 Best are ester groups. The alkyl components on the esters can be similar or different.
- Felodipine $R_2 = R_6 = -CH_3$

  $R_3 = –$ COOC2H5

  $R_5 =$ -COOCH3

  $R_4 =$ 

- The ester could be aliphatic, aryl or vary in degree of branching or saturation.
- Ester at R_3 and R_5 are responsible for duration of drug and vascular smooth muscle selectivity.
- R_4 phenyl group is required, could be mono or di-substituted.
- If it is mono substituted then ortho substitutes is more potent than meta substitutes, Para substitutes are inactive.
- If di-substitutions then ortho, meta – substitutes only electron withdrawing like NO_2, Cl, F, OCH_3 are disubstituted to give active molecules.
- Fourth position of ring is optically active and S enantiomers are more active than R.

1.10 References

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2.0 Aim and scope of the present work

Hypertension is a disorder of the cardiovascular system characterized by elevated arterial blood pressure. Hypertension is the primary cause of stroke and a risk factor for coronary heart disease, myocardial infarction, sudden cardiac death, cardiac failure, and renal insufficiency. . In these world millions of people are suffering from this treacherous disease and only few of them are aware about this disease and from these only 30 % are controlled only.

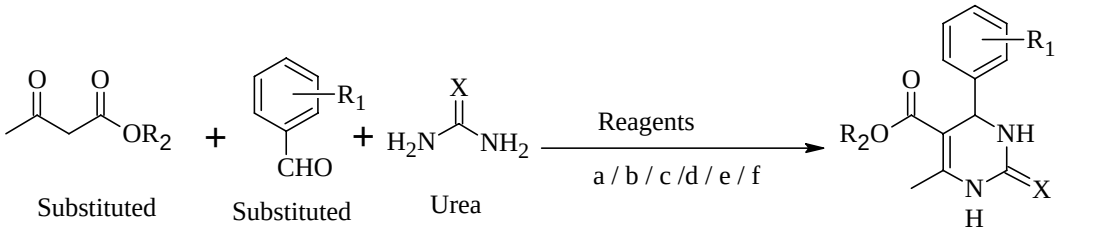
Until recently, many antihypertensive drugs are available in market. But these drugs also have some side effects. Now a day's Alfa and beta adrenergic antagonist are not used due to their side effects like orthostatic hypotension and vivid dreams (CNS effects). Also some of Calcium channel blockers (CCBs) does negative isotropic effects and depressed A-V nodal conduction. ACE inhibitors produce dry cough, also does proteinuria, glomerulonephritis. They are also contraindicated in bi or unilateral Renal Artery Disease. Some of anti-hypertensive's lack adequate physical chemical properties to permit oral absorption.

Some of the published articles on Dihydropyridines show good antihypertensive, calcium channel blocking, alfa-1a antagonism, and neuropeptide Y antagonism, antitumor and anti-inflammatory activities. Dihyropyrimidine is a bioisoster of Dihydropyridine which shows very good antihypertensive activity. So in order to make effective antihypertensive drugs and having minimum of side effects I was focused my work to make new derivatives of Dihydromidine-2-one and 2-thiones having amide linkage which increase the binding property of the drugs with the receptor.

2.1 Literature Review for the Synthetic Methods Available For Synthesis of Target Molecules

Dihydropyrimidine-2-ones and Dihydropyrimidine-2-thiones belong to an important class of heterocyclic compounds that have attracted organic chemist due to pharmacological and biological properties, such as antihypertensive activity, calcium channel blocking, alpha-1a-antagonism, neuropeptide antagonism, antitumor, antibacterial, and anti inflammatory activity. Recently, the batzelladine alkaloids contacting the dihydropyrimine-one-5-carboxylate core have been found to be potent HIV-gp-120-CD4 inhibitors. Due to importance of these compounds as synthons in organic synthesis, many synthetic methods for preparing such compounds have been developed based on the Biginelli reaction.[1, 2]

2.2.1 Synthesis of Dihydropyrimidine-2-one and Dihydropyrimidine-2-thione
2.2.2. from aldehyde, Urea or Thourea and Ethylacetoacetate



Substituted acetoacetate | Substituted Benzaldehyde | Urea | Substituted Dihydropyrimidine

R_2: -CH_3,-C_2H_5 R_1: -3-Cl,-4-Cl,-4-OCH_3,-4-OH,-2-Cl,-4-NO_2,-3-NO_2 X: S, O

Reagent a: tungastate sulfuric acid / Solvent - free

A mixture of benzaldehyde, ethylacetoacetate, urea and tungastate sulfuric acid were grounded in mortar with pestle for 10 minutes to obtain the desired product.[2]

Reagent b: Ps – AlCl3 / Ethanol, Reflux

A mixture of benzaldehyde, ethylacetoacetate, urea or thourea and Ps-$AlCl_3$ in ethanol was refluxed for 3 hours. After completion of reaction, hot ethanol was added to the mixture; The catalyst was filtered out and solid product was collected and wash with ether.[3]

Reagent c: 12.5 mol% ZnO / Solvent – free, 80^0C

A mixture of benzaldehyde, ethylacetoacetate, urea or thourea and ZnO was heated at 80^0C under stirring for the 19 minutes in ethanol. The reaction mixture was filtered to remove the catalyst, and filtered was poured into cold water. The solid product was obtained.[4]

Reagent d: 37% HCl / Ethanol

A mixture of benzaldehyde, ethylacetoacetate, urea or thourea and 37% HCl in Ethanol was refluxed for about 1 hour and kept for 24 hours for crystallization. The product was filtered, washed with 50% ethanol and recrystallized from ethanol.[5]

Reagent e: Glacial acetic acid / few drops of HCl

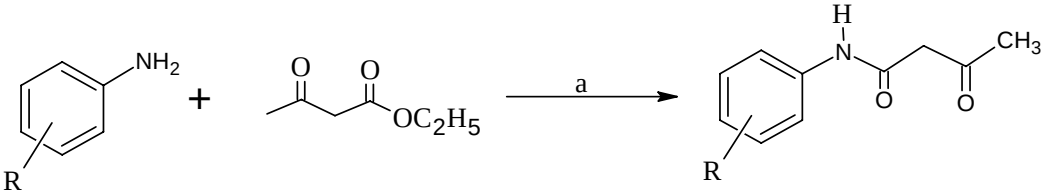
A mixture of benzaldehyde, ethylacetoacetate, urea or thourea and 20 ml of glacial acetic acid contacting a few drops concentrated hydrochloric acid was heated under for 8 hours. Reaction mixture allowed to stand approximately 3-4 hours to yield 52-65% of product.[5, 6]

Reagent f: VCl_3 / CH_2CN

A mixture of benzaldehyde, ethylacetoacetate, urea and a catalytic amount of VCl_3 (Vanadium (III) chloride) was added to each vessel which were then heated at acetonitrile reflux for 2 h. after which the completed reactions were taken out of the reaction. On cooling to room temperature the products precipitated out. The reaction mixtures were then poured onto crushed ice, and the solid product separated, filtered and recrystallized.

2.3 Synthetic Scheme Used For the Development of the Novel Substituted Dihydropyrimidine

Step 1 Ethaylacetoacetate on reaction with different aniline gives acetoacetanilide.[7, 8]

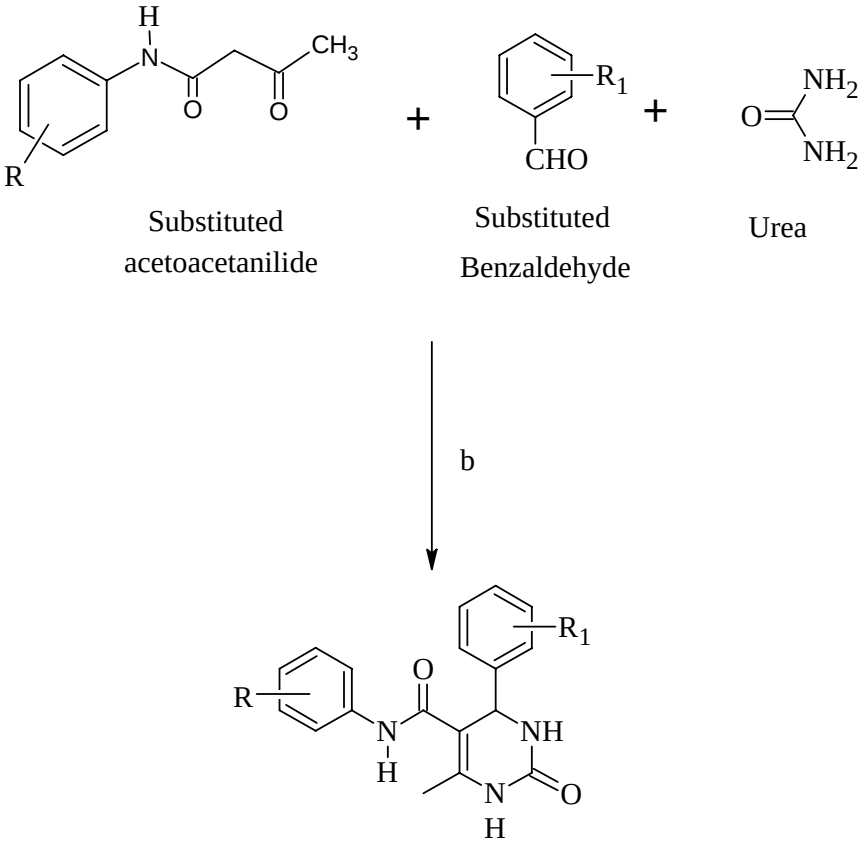


Substituted aniline Ethylacetoacetate Substituted acetoacetanilide

Reagents and conditions: a = KOH/NaOH, toluene, 115° C to 125°

Step 2A

When Substituted acetoacetanilide is refluxed with substituted aldehyde and Urea in presence of Ethanol and Conc HCl was gave N-(substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-4-(substitutedphenyl)-2-Oxo-pyrimidine-5-carboxamide derivatives.[3, 5, 9]



Substituted acetoacetanilide

Substituted Benzaldehyde

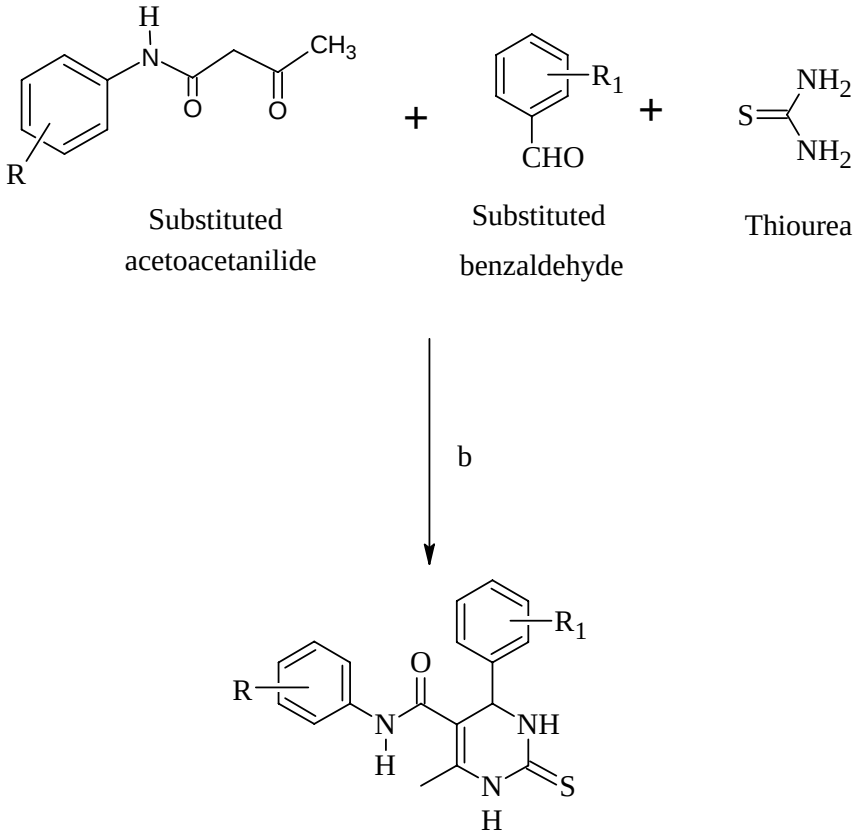
Urea

Substituted Dihydropyrimidine-2-one

Reagents and conditions: b = Ethanol, Conc. HCl, reflux 110° C to 120° C.

Step 2B

When Substituted acetoacetanilide is refluxed with substituted aldehyde and Urea in presence of Ethanol and Conc. HCl was gave N-(substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-4-(substitutedphenyl)-2-Thio-pyrimidine-5-carboxamide derivatives.[3, 6, 9]



Substituted Dihydropyrimidine-2-one

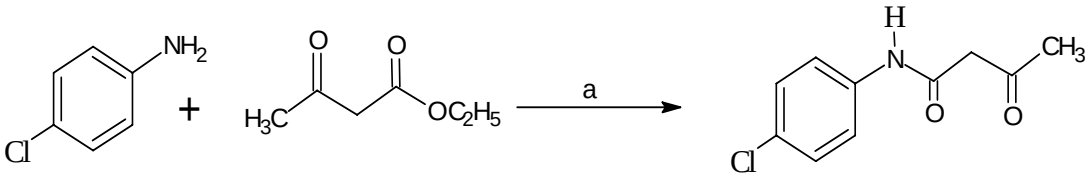
Reagents and conditions: c = Ethanol, Conc. HCl, reflux in water-bath

2.4 Synthesis of Intermediates

2.4.1 Synthesis of Substituted acetoacetanilide

2.4.1 (A) Synthesis of P-Chloro acetoacetanilide

Reaction



P-Chloro aniline Ethaylacetoacetate P-Chloro acetoacetanilide

Reagents and conditions: a = KOH/NaOH, toluene, 115° C to 125°

Requirements

Reagents	Mol. Weight (g/mol)	Quantity (g)	Mol	Mol ratio
Ethylacetoacetate	130.17	20.00	0.153	1.5
P-Chloro aniline	127.54	13.00	0.101	1

Procedure:

A mixture of P-Chloro aniline and ethyl acetoacetate was refluxed at 110° C in 40 ml of toluene and catalytic amount of KOH/NaOH. The completion of reaction was monitored with thin layer chromatography. After completion of reaction, toluene was distilled out. The residue was cooled at room temperature and was treated with ether and recrystalized with methanol. Product was dried with vacuum desiccators.[6]

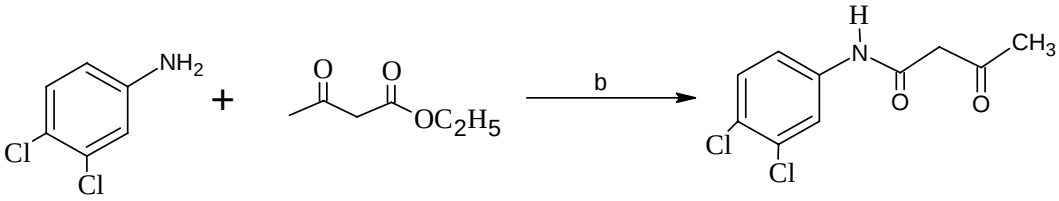
Solvent system used for TLC: Hexane: Ethylacetate (6:4)

Result

Product	Result
Percentage yield	70.52 %
R_f	0.4
Melting point	85 ^{o}C

2.4.1 B Synthesis of 3,4-dichloro acetoacetanilide

Reaction



3, 4-DiChloro aniline Ethylacetoacetate 3, 4-DiChloro acetoacetanilide

Reagents and conditions: b = KOH/NaOH, toluene, 115° C to 125°

Requirements

Reagents	Mol. Weight (g/mol)	Quantity (g)	Mol	Mol ratio
Ethylacetoacetate	130.17	20.00	0.153	1.5
3,4-DiChloro aniline	162.00	16.00	0.102	1

Procedure:

Same as 2.4.1 A

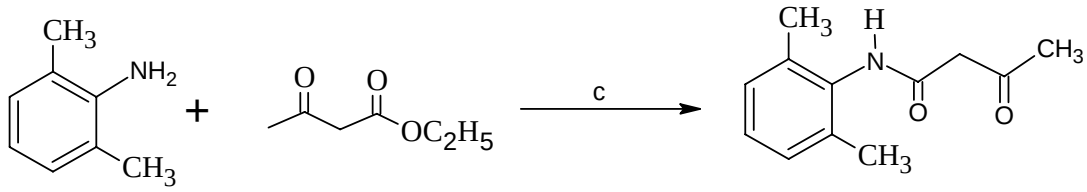
Solvent system used for TLC: Hexane: Ethylacetate (6:4)

Result

Product	Result
Percentage yield	65.35 %
R_f	0.45
Melting point	100 ^{o}C

2.4.1C Synthesis of 2, 6-dimethyl acetoacetanilide

Reaction



2, 6-dimethyl aniline Ethylacetoacetate 2, 6-dimethyl acetoacetanilide

Reagents and conditions: c = KOH/NaOH, toluene, 115° C to 125°

Procedure:

Same as 2.4.1 A

Requirements

Reagents	Mol. Weight (g/mol)	Quantity (g)	Mol	Mol ratio
Ethylacetoacetate	130.17	20.00	0.153	1.5
2,6-dimethyl aniline	121.17	12.35	0.102	1

Procedure

Same as 2.4.1 A

Solvent system used for TLC: Hexane: Ethylacetate (6:4)

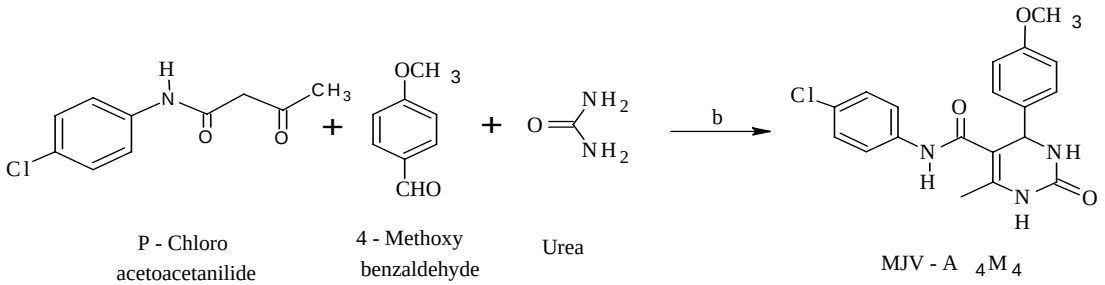
Result

Product	Result
Percentage yield	75.66 %
R_f	0.45
Melting point	150 ^{o}C

2.4.2 Synthesis of Substituted Dihydropyrimidine-2-one

2.4.2.1 A Synthesis of *N*-(4-chlorophenyl)-4-(4-methoxyphenyl)-6-methyl-2-oxo-1, 2, 3, 4- tetrahydropyrimidine-5-carboxamide (MJV-A_4M_4)

Reaction



P - Chloro acetoacetanilide | 4 - Methoxy benzaldehyde | Urea | MJV - A $_4$M$_4$

Reagents and conditions: b = Ethanol, Conc. HCl, reflux 110° C to 120° C.

Requirements

Reagents	Quantity(g)	Mol weight (g/mol)	Mol	Mol ratio
P-chloroacetoacetanilide	2.1	211.0	0.01	1
4 - Methoxybenzaldehyde	1.3	136.1	0.01	1
Urea	1.0	60.06	0.016	1.6

Procedure

Acetoacetanilide, aldehyde and urea were dissolved in ethanol and refluxed until clear solution was obtained. Few drops of conc. HCl was added to reaction mixture and was refluxed for the reaction was monitored with thin layer chromatography and after completion; the reaction mixture was allowed to cool. The solid separated was filtered & was recrystalized with DMF.

[3, 9]

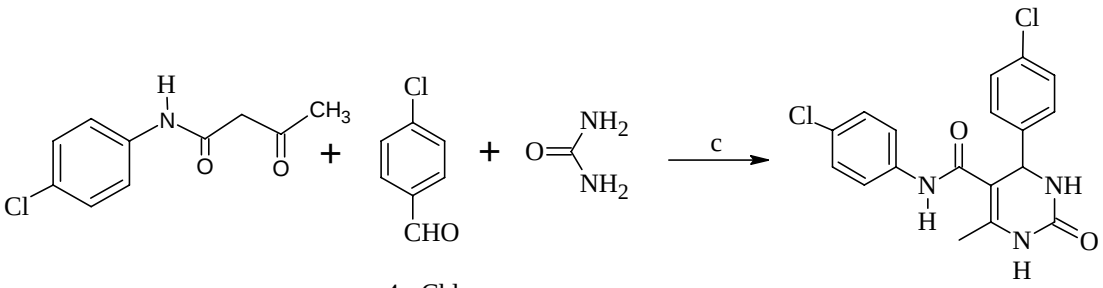
Solvent system used for TLC: Chloroform: Methanol (9:1)

Result

Product	Result
Percentage yield	45.56%
R_f	0.60
Melting point	278^0C

2.4.2.1 B Synthesis of *N*, 4-bis (4-chlorophenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (MJV-A_4A_4)

Reaction



P - Chloro acetoacetanilide | 4 - Chloro benzaldehyde | Urea | MJV - A_4A_4

Reagents and conditions: b = Ethanol, Conc. HCl, reflux 110° C to 120° C.

Requirements

Reagents	Quantity(g)	Mol weight (g/mol)	Mol	Mol ratio
P-chloroacetoacetanilide	2.1	211.0	0.01	1
4 – Chlorobenzaldehyde	1.4	140.56	0.01	1
Urea	1.0	60.06	0.016	1.6

Procedure

Same as 2.4.2 A

Compound was purified by Column chromatography in 85 % Ethyl acetate in Hexane.

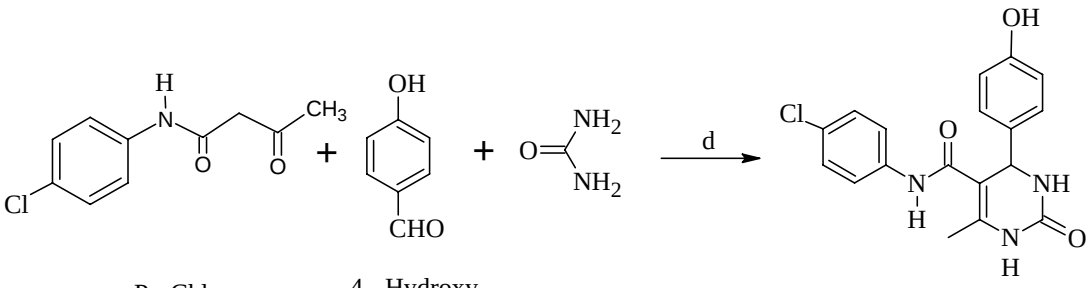
Solvent system used for TLC: Chloroform: Methanol (9:1)

Result

Product	Result
Percentage yield	40.68%
R_f	0.80
Melting point	210^0C

2.4.2.1 C Synthesis of *N*-(4-chlorophenyl)-4-(4-hydroxyphenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (MJV-A_4H_4)

Reaction



P - Chloro acetoacetanilide | 4 - Hydroxy benzaldehyde | Urea | MJV - A_4H_4

Reagents and conditions: b = Ethanol, Conc. HCl, reflux 110° C to 120° C.

Requirements

Reagents	Quantity(g)	Mol weight (g/mol)	Mol	Mol ratio
P-chloroacetoacetanilide	2.1	211.0	0.01	1
4 – Hydroxy benzaldehyde	1.2	122.12	0.01	1
Urea	1.0	60.06	0.016	1.6

Procedure

Same as 2.4.2 A

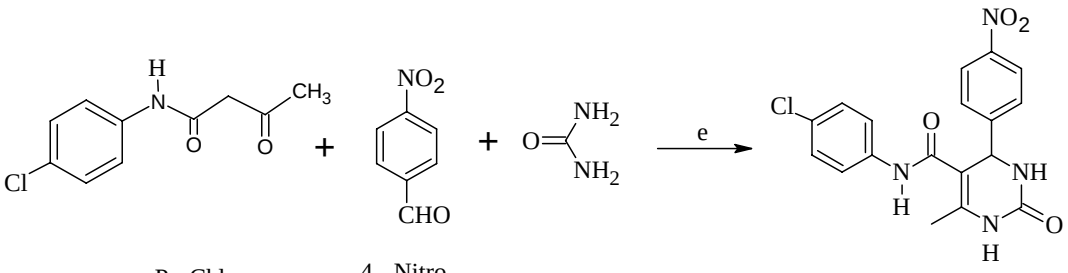
Solvent system used for TLC: Chloroform: Methanol (9:1)

Result

Product	Result
Percentage yield	35.89%
R_f	0.29
Melting point	288^0C

2.4.2.1 D Synthesis of *N*-(4-chlorophenyl)-6-methyl-4-(4-nitrophenyl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (MJV-A_4N_4)

Reaction



P - Chloro acetoacetanilide | 4 - Nitro benzaldehyde | Urea | MJV - A_4N_4

Reagents and conditions: b = Ethanol, Conc. HCl, reflux 110° C to 120° C.

Requirements

Reagents	Quantity(g)	Mol weight (g/mol)	Mol	Mol ratio
P-chloroacetoacetanilide	2.1	211.0	0.01	1
4 – Nitro benzaldehyde	1.5	151.11	0.01	1
Urea	1.0	60.06	0.016	1.6

Procedure

Same as 2.4.2 A

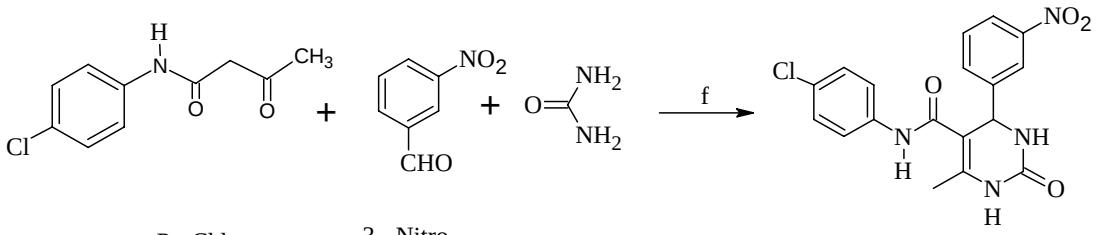
Solvent system used for TLC: Chloroform: Methanol (9:1)

Result

Product	Result
Percentage yield	50.65%
R_f	0.72
Melting point	298^0C

2.4.2.1 F Synthesis of 4-(3-chlorophenyl)-*N*-(4-chlorophenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (MJV-A_4N_3)

Reaction



P - Chloro acetoacetanilide | 3 - Nitro benzaldehyde | Urea | MJV - A_4N_3

Reagents and conditions: f = Ethanol, Conc. HCl, reflux 110° C to 120° C.

Requirements

Reagents	Quantity(g)	Mol weight (g/mol)	Mol	Mol ratio
P-chloroacetoacetanilide	2.1	211.0	0.01	1
3 – Nitro benzaldehyde	1.5	151.11	0.01	1
Urea	1.0	60.06	0.016	1.6

Procedure

Same as 2.4.2 A

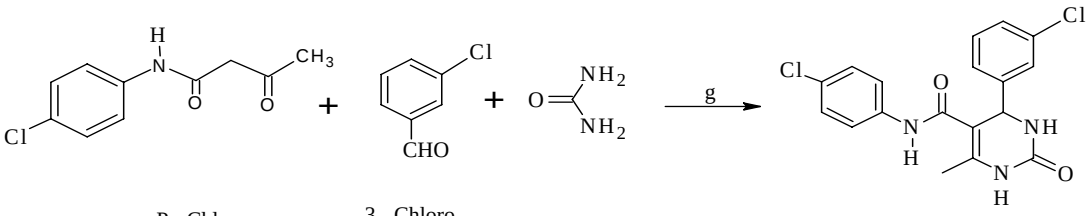
Solvent system used for TLC: Chloroform: Methanol (9:1)

Result

Product	Result
Percentage yield	32.78%
R_f	0.75
Melting point	244^0C

2.4.2.1 F Synthesis of 4-(3-chlorophenyl)-*N*-(4-chlorophenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (MJV-A_4A_3)

Reaction



P - Chloro acetoacetanilide | 3 - Chloro benzaldehyde | Urea | MJV - A $_4$A$_3$

Reagents and conditions: g = Ethanol, Conc. HCl, reflux 110° C to 120° C.

Requirements

Reagents	Quantity(g)	Mol weight (g/mol)	Mol	Mol ratio
P-chloroacetoacetanilide	2.1	211.0	0.01	1
3 – Chloro benzaldehyde	1.4	140.56	0.01	1
Urea	1.0	60.06	0.016	1.6

Procedure

Same as 2.4.2 A

Compound was purified by Column chromatography in 85 % Ethyl acetate in Hexane.

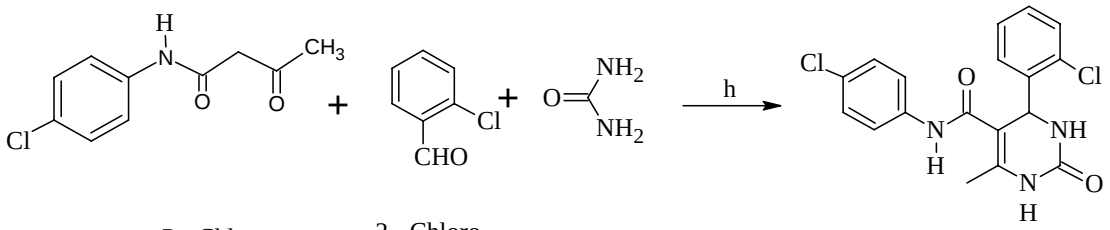
Solvent system used for TLC: Chloroform: Methanol (9:1)

Result

Product	Result
Percentage yield	42.78%
R_f	0.50
Melting point	234^0C

2.4.2.1 G Synthesis of 4-(2-chlorophenyl)-*N*-(4-chlorophenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (MJV-A_4A_2)

Reaction



P - Chloro acetoacetanilide | 2 - Chloro benzaldehyde | Urea | MJV - A_4A_2

Reagents and conditions: g = Ethanol, Conc. HCl, reflux 110° C to 120° C.

Requirements

Reagents	Quantity(g)	Mol weight (g/mol)	Mol	Mol ratio
P-chloroacetoacetanilide	2.1	211.0	0.01	1
2 – Chloro benzaldehyde	1.4	140.56	0.01	1
Urea	1.0	60.06	0.016	1.6

Procedure

Same as 2.4.2 A

Compound was purified by Column chromatography in 85 % Ethyl acetate in Hexane.

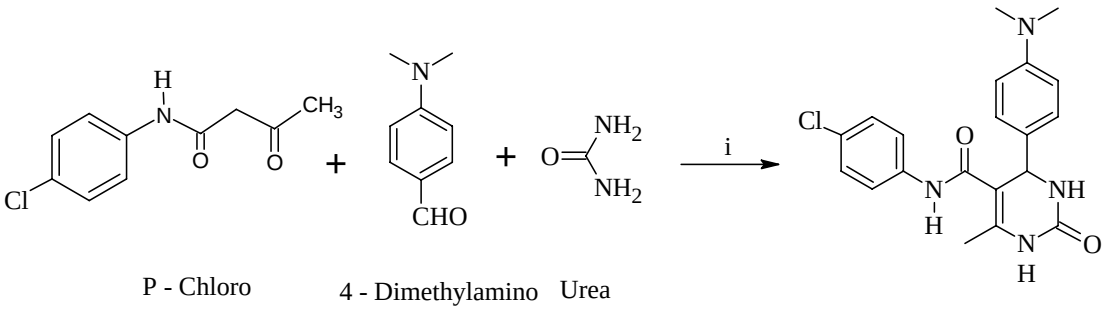
Solvent system used for TLC: Chloroform: Methanol (9:1)

Result

Product	Result
Percentage yield	60.78%
R_f	0.59
Melting point	230^0C

2.4.2.1 H Synthesis of *N*-(4-chlorophenyl)-4-[4-(dimethylamino) phenyl]-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (MJV-A_4D_4)

Reaction



P - Chloro acetoacetanilide | 4 - Dimethylamino benzaldehyde | Urea | MJV - A_4D_4

Reagents and conditions: i = Ethanol, Conc. HCl, reflux 110° C to 120° C.

Requirements

Reagents	Quantity(g)	Mol weight (g/mol)	Mol	Mol ratio
P-chloroacetoacetanilide	2.1	211.0	0.01	1
4 – Dimethylamino benzaldehyde	1.4	149.18	0.01	1
Urea	1.0	60.06	0.016	1.6

Procedure

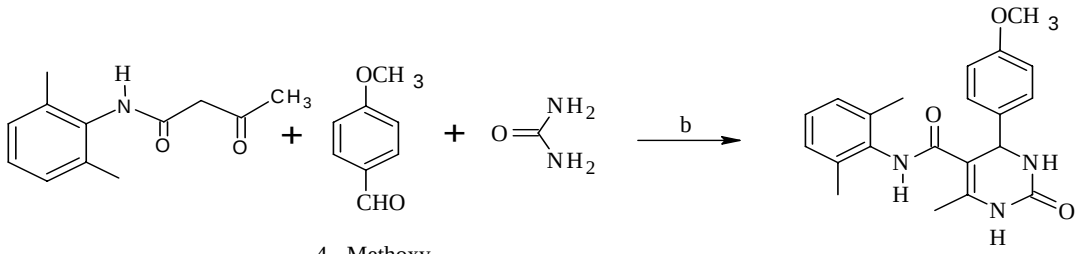
Same as 2.4.2.1 A

Solvent system used for TLC: Chloroform: Methanol (9:1)

Result

Product	Result
Percentage yield	38.78%
R_f	0.65
Melting point	> 300^0C

2.4.2.2 A Synthesis of *N*-(2,6-dimethylphenyl)-4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (MJV-$A_{26}M_4$)
Reaction



2,6 - Dimethyl acetoacetanilide | 4 - Methoxy benzaldehyde | Urea | MJV - A $_{26}$M$_4$

Reagents and conditions: b = Ethanol, Conc. HCl, reflux 110° C to 120° C.

Requirements

Reagents	Quantity(g)	Mol weight (g/mol)	Mol	Mol ratio
2,6 – Dimethylacetoacetanilide	2.0	205.25	0.01	1
4 – Methoxy benzaldehyde	1.3	136.14	0.01	1
Urea	1.0	60.06	0.016	1.6

Procedure

2, 6 – Dimethyl acetoacetanilide, 4-Methoxybenzaldehyde and urea were dissolved in ethanol and refluxed until clear solution was obtained. Few drops of con HCl was added to reaction mixture and was refluxed for 8 hr. The reaction was monitored with thin layer chromatography and after completion; the reaction mixture was allowed to cool. The solid separated was filtered. Solid product was recrystalized with DMF. Product was dried with vacuum desiccators.[3, 9]

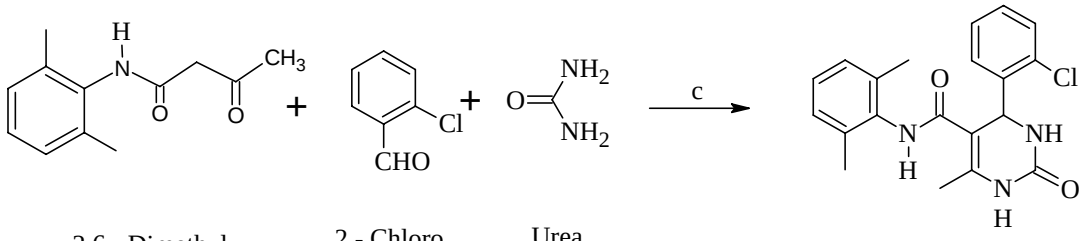
Solvent system used for TLC: Chloroform: Methanol (9:1)

Result

Product	Result
Percentage yield	47.78%
R_f	0.70
Melting point	290^0C

2.4.2.2 B Synthesis of 4-(2-chlorophenyl)-*N*-(2, 6-dimethylphenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (MJV-$A_{26}A_2$)

Reaction



2,6 - Dimethyl acetoacetanilide | 2 - Chloro benzaldehyde | Urea | MJV - $A_{26}A_2$

Reagents and conditions: c = Ethanol, Conc. HCl, reflux 110° C to 120° C

Requirements

Reagents	Quantity(g)	Mol weight (g/mol)	Mol	Mol ratio
2,6 – Dimethylacetoacetanilide	2.0	205.25	0.01	1
2 – Chloro Benzaldehyde	1.4	140.56	0.01	1
Urea	1.0	60.06	0.016	1.6

Procedure

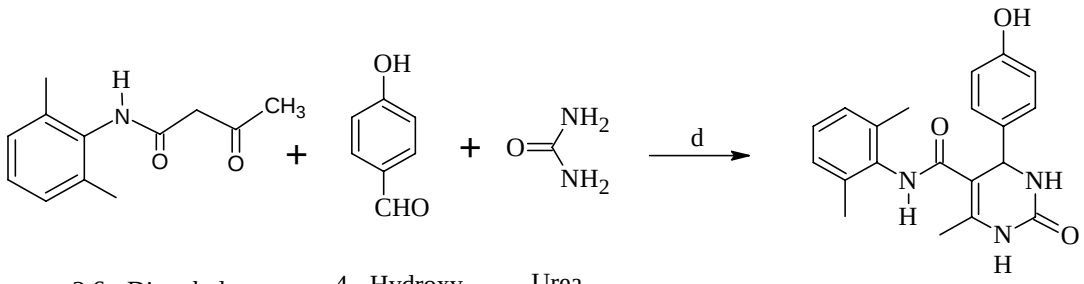
Same as 2.4.2.2 A

Solvent system used for TLC: Chloroform: Methanol (9:1)

Result

Product	Result
Percentage yield	65.90%
R_f	0.62
Melting point	250^0C

2.4.2.2 C Synthesis of *N*-(2, 6-dimethylphenyl)-4-(4-hydroxyphenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (MJV-$A_{26}H_4$)
Reaction



2,6 - Dimethyl acetoacetanilide | 4 - Hydroxy benzaldehyde | Urea | MJV - $A_{26}H_4$

Reagents and conditions: d = Ethanol, Conc. HCl, reflux 110° C to 120° C.

Requirements

Reagents	Quantity(g)	Mol weight (g/mol)	Mol	Mol ratio
2,6 – Dimethylacetoacetanilide	2.0	205.25	0.01	1
4 – Hydroxy benzaldehyde	1.2	122.12	0.01	1
Urea	1.0	60.06	0.016	1.6

Procedure

Same as 2.4.2.2 A

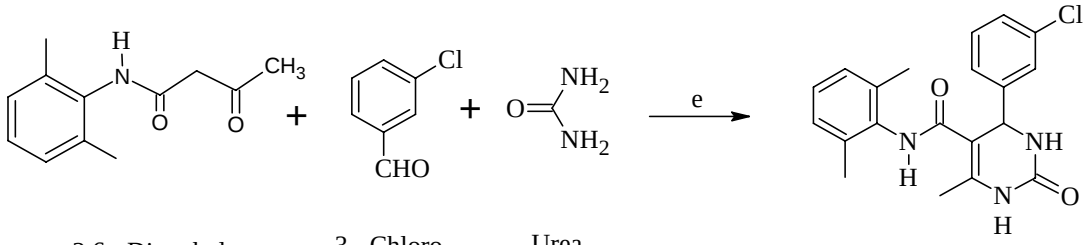
Solvent system used for TLC: Chloroform: Methanol (9:1)

Result

Product	Result
Percentage yield	31.64%
R_f	0.75
Melting point	> 300^0C

2.4.2.2 D Synthesis of 4-(3-chlorophenyl)-*N*-(2, 6-dimethylphenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (MJV-$A_{26}A_3$)

Reaction



2,6 - Dimethyl acetoacetanilide | 3 - Chloro benzaldehyde | Urea | MJV - $A_{26}A_3$

Reagents and conditions: e = Ethanol, Conc. HCl, reflux 110° C to 120° C.

Requirements

Reagents	Quantity(g)	Mol weight (g/mol)	Mol	Mol ratio
2,6 – Dimethylacetoacetanilide	2.0	205.25	0.01	1
3 – Chloro benzaldehyde	1.4	140.56	0.01	1
Urea	1.0	60.06	0.016	1.6

Procedure

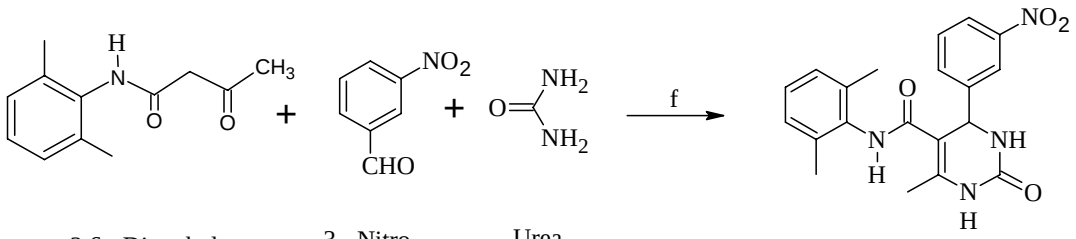
Same as 2.4.2.2 A

Solvent system used for TLC: Chloroform: Methanol (9:1)

Result

Product	Result
Percentage yield	54.76%
R_f	0.87
Melting point	290^0C

2.4.2.2 E Synthesis of *N*-(2, 6-dimethylphenyl)-6-methyl-4-(3-nitrophenyl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (MJV-$A_{26}N_3$)
Reaction



2,6 - Dimethyl acetoacetanilide | 3 - Nitro benzaldehyde | Urea | MJV - $A_{26}N_3$

Reagents and conditions: f = Ethanol, Conc. HCl, reflux 110° C to 120° C.

Requirements

Reagents	Quantity(g)	Mol weight (g/mol)	Mol	Mol ratio
2,6 – Dimethylacetoacetanilide	2.0	205.25	0.01	1
3 – Nitro benzaldehyde	1.5	151.11	0.01	1
Urea	1.0	60.06	0.016	1.6

Procedure

Same as 2.4.2.2 A

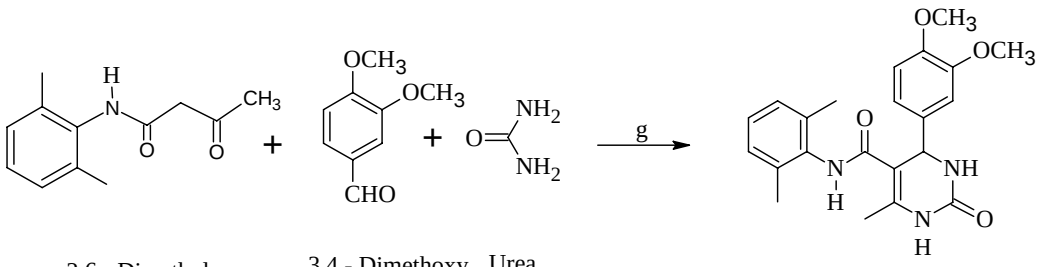
Solvent system used for TLC: Chloroform: Methanol (9:1)

Result

Product	Result
Percentage yield	39.36%
R_f	0.32
Melting point	268^0C

2.4.2.2 F Synthesis of *N*-(2, 6-dimethylphenyl)-6-methyl-4-(3, 4-dimethoxyphenyl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (MJV-$A_{26}D_{34}$)

Reaction



2,6 - Dimethyl acetoacetanilide

3,4 - Dimethoxy benzaldehyde

Urea

MJV - $A_{26}D_{34}$

Reagents and conditions: g = Ethanol, Conc. HCl, reflux 110° C to 120° C.

Requirements

Reagents	Quantity(g)	Mol weight (g/mol)	Mol	Mol ratio
2,6 – Dimethylacetoacetanilide	2.0	205.25	0.01	1
3,4 – Dimethoxy benzaldehyde	1.6	166.17	0.01	1
Urea	1.0	60.06	0.016	1.6

Procedure

Same as 2.4.2.2 A

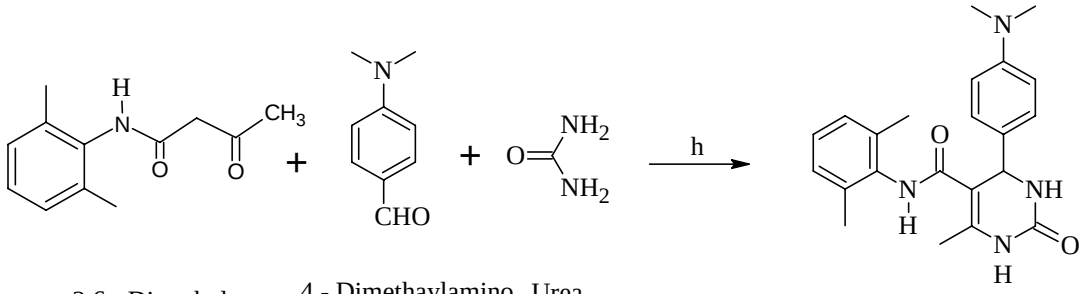
Solvent system used for TLC: Chloroform: Methanol (9:1)

Result

Product	Result
Percentage yield	46.96%
R_f	0.70
Melting point	> 300^0C

2.4.2.2 F Synthesis of *N*-(2, 6-dimethylphenyl)-6-methyl-4-(4-dimethylaminophenyl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (MJV-$A_{26}D_4$)

Reaction



2,6 - Dimethyl Acetoacetanilide

4 - Dimethaylamino benzaldehyde

Urea

MJV - $A_{26}D_4$

Reagents and conditions: h = Ethanol, Conc. HCl, reflux 110° C to 120° C.

Requirements

Reagents	Quantity (g)	Mol weight (g/mol)	Mol	Mol ratio
2,6 – Dimethylacetoacetanilide	2.0	205.25	0.01	1
4 – Dimethylamino benzaldehyde	1.4	149.18	0.01	1
Urea	1.0	60.06	0.016	1.6

Procedure

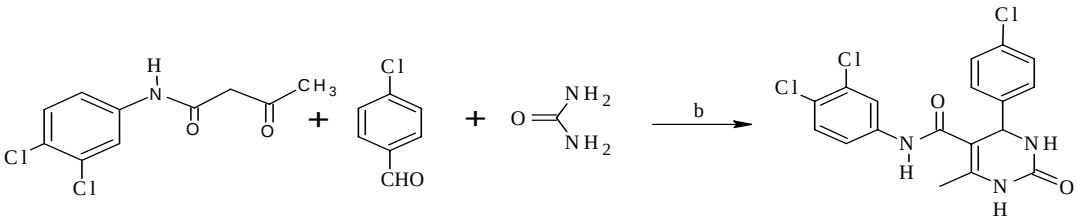
Same as 2.4.2.2 A

Solvent system used for TLC: Chloroform: Methanol (9:1)

Result

Product	Result
Percentage yield	39.86%
R_f	0.72
Melting point	> 300^0C

2.4.2.3 A Synthesis of 4-(4-chlorophenyl)-*N*-(3, 4-dichlorophenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (MJV-$A_{26}A_4$)
Reaction



3,4 - Dichloro acetoacetanilide | 4 - Chloro benzaldehyde | Urea | MJV - A 34 A 4

Reagents and conditions: b = Ethanol, Conc. HCl, reflux 110° C to 120° C.

Requirements

Reagents	Quantity(g)	Mol weight (g/mol)	Mol	Mol ratio
3,4–Dichloro acetoacetanilide	2.4	246.08	0.01	1
4-Chloro benzaldehyde	1.4	140.56	0.01	1
Urea	1.0	60.06	0.016	1.6

Procedure

3,4–Dichloro acetoacetanilide, 4-Chloro benzaldehyde and urea were dissolved in ethanol and refluxed until clear solution was obtained. Few drops of conc. HCl was added to reaction mixture and was refluxed in water-bath for 8 hr.. The reaction was monitored with thin layer chromatography and after completion; the reaction mixture was allowed to cool. The solid separated was filtered. Solid product was recrystalized with DMF. Product was dried with vacuum desiccators.[3, 9]

Compound was purified by Column chromatography in 85 % Ethyl acetate in Hexane.

Solvent system used for TLC: Chloroform: Methanol (9:1)

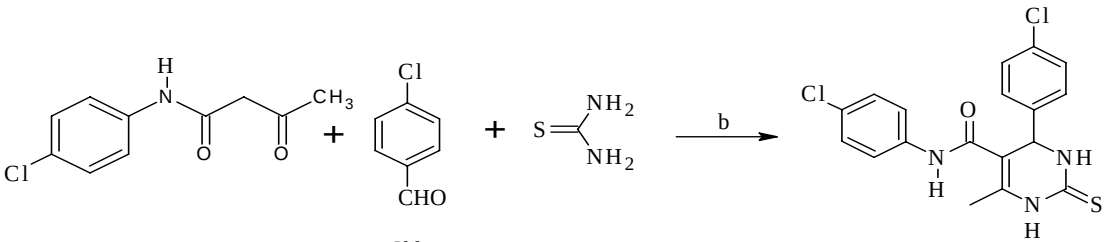
Result

Product	Result
Percentage yield	45.80%
R_f	0.85
Melting point	240^0C

2.4.3 Synthesis of Substituted Dihydropyrimidine-2-thione

2.4.3A Synthesis of *N*, 4-bis (4-chlorophenyl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (MJV-TA$_4$A$_4$)

Reaction



P - Chloro acetoacetanilide | 4 - Chloro benzaldehyde | Thiourea | MJV -TA $_4$A$_4$

Reagents and conditions: b = Ethanol, Conc. HCl, reflux in water-bath.

Requirements

Reagents	Quantity(g)	Mol weight (g/mol)	Mol	Mol ratio
P - Chloroacetoacetanilide	2.1	211.0	0.01	1
4-Chloro benzaldehyde	1.4	140.56	0.01	1
Thiourea	1.1	76.12	0.015	1.5

Procedure

P-Chloro Acetoacetanilide, 4-Chloro benzaldehyde and Thiourea were dissolved in ethanol and refluxed in water-bath until clear solution is obtained. Few drops of con HCl was added to reaction mixture and was refluxed in water-bath. The reaction was monitored with thin layer chromatography and after completion; the reaction mixture was allowed to cool. The solid separated was filtered. Solid product was recrystalized with DMF.[3, 9]

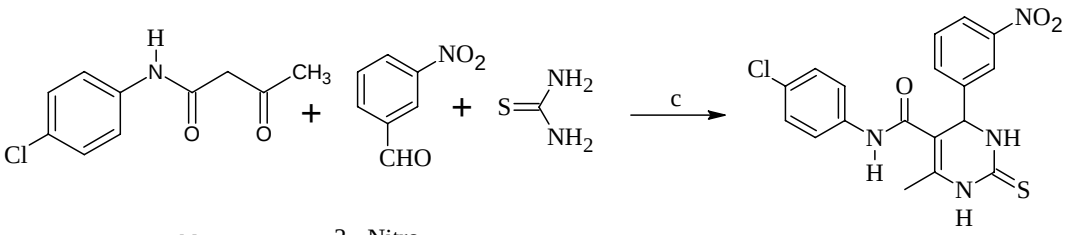
Solvent system used for TLC: Chloroform: Methanol (9:1)

Result

Product	Result
Percentage yield	36.80%
R_f	0.75
Melting point	250^0C

2.4.3 B Synthesis of *N*, 4-bis (4-chlorophenyl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (MJV-TA$_4$N$_3$)

Reaction



P - Chloro acetoacetanilide | 3 - Nitro benzaldehyde | Thiourea | MJV -TA_4N_3

Reagents and conditions: c = Ethanol, Conc. HCl, reflux in water-bath.

Requirements

Reagents	Quantity(g)	Mol weight (g/mol)	Mol	Mol ratio
P - Chloroacetoacetanilide	2.1	211.0	0.01	1
3-Nitro benzaldehyde	1.5	151.11	0.01	1
Thiourea	1.1	76.12	0.015	1.5

Procedure

Same as 2.4.3 A

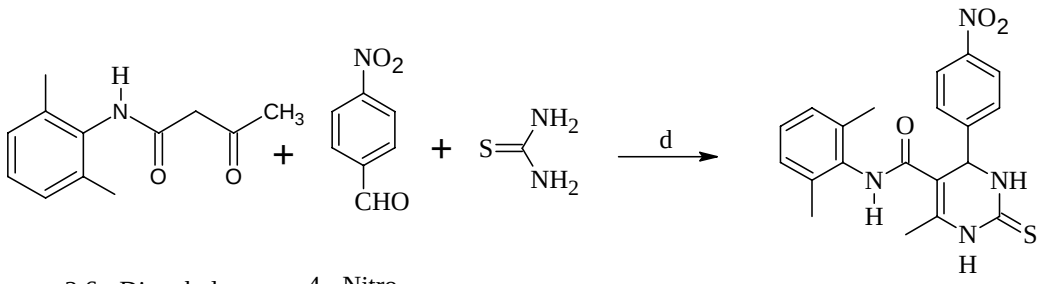
Solvent system used for TLC: Chloroform: Methanol (9:1)

Result

Product	Result
Percentage yield	35.60%
R_f	0.66
Melting point	245^0C

2.4.3 C Synthesis of *N*, 4-bis (4-chlorophenyl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (MJV-TA_4N_3)

Reaction



2,6 - Dimethyl acetoacetanilide | 4 - Nitro benzaldehyde | Thiourea | MJV -$TA_{26}N_3$

Reagents and conditions: d = Ethanol, Conc. HCl, reflux in water-bath.

Requirements

Reagents	Quantity(g)	Mol weight (g/mol)	Mol	Mol ratio
2,6 – Dimethaylacetoacetanilide	2.1	205.25	0.01	1
4-Nitro benzaldehyde	1.5	151.11	0.01	1
Thiourea	1.1	76.12	0.015	1.5

Procedure

Same as 2.4.3 A

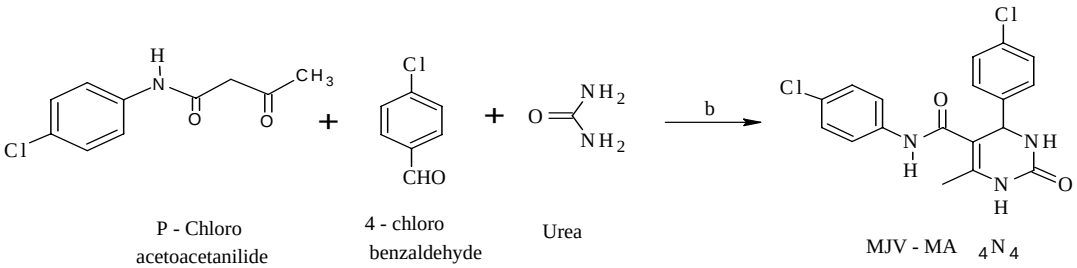
Solvent system used for TLC: Chloroform: Methanol (9:1)

Result

Product	Result
Percentage yield	30.60%
R_f	0.60
Melting point	238^0C

2.4.4 Microwave Assisted Synthesis of Substituted Dihydropyrimidine-2-one

2.4.4.1 A Synthesis of *N*-(4-chlorophenyl)-6-methyl-4-(4-nitrophenyl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (MJV-MA_4N_4)
Reaction



P - Chloro acetoacetanilide | 4 - chloro benzaldehyde | Urea | MJV - MA $_4$N$_4$

Reagents and conditions: b = AcOH/EtOH 3:1, FeCl3, 10-20 min

Requirements

Reagents	Quantity(g)	Mol weight (g/mol)	Mol	Mol ratio
P - Chloroacetoacetanilide	2.1	211.0	0.01	1
4 – Chloro benzaldehyde	1.5	140.56	0.01	1
Urea	0.6	60.06	0.01	1

Procedure

Equimolar amounts of benzaldehyde, ethyl acetoacetate, and urea react were reacted in presence of Lewis acid ($FeCl_3$, catalysis) to yield corresponding dihydropyrimidine. Utilizing single-mode microwave irradiation, the reaction can be carried out on a 4.0 mmol scale in AcOH(glacial acetic acid)/EtOH 3:1 at 120 °C within 10 min, compared to 3-4 h using conventional thermal heating, providing dihydropyrimidine in 88% isolated yield. [10, 11]

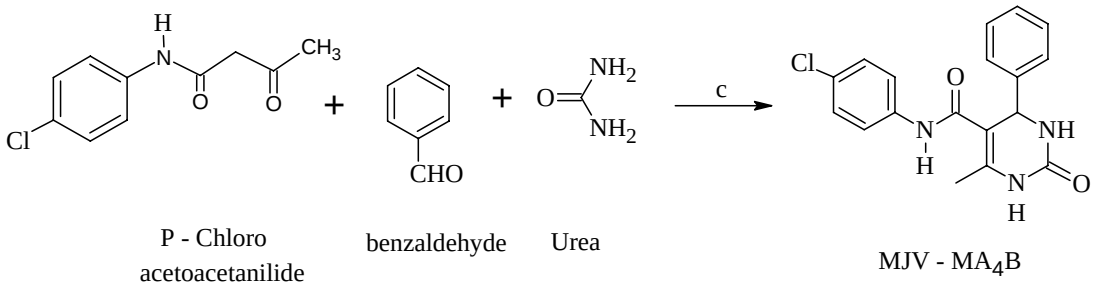
Solvent system used for TLC: Chloroform: Methanol (9:1)

Result

Product	Result
Percentage yield	56.60%
R_f	0.67
Melting point	165^0C

2.4.4.2 A Synthesis of *N*-(4-chlorophenyl)-6-methyl-2-oxo-4-phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (MJV-MA$_4$B)

Reaction



P - Chloro acetoacetanilide | benzaldehyde | Urea | MJV - MA_4B

Reagents and conditions: c = AcOH/EtOH 3:1, FeCl3, 10-20 min

Requirements

Reagents	Quantity(g)	Mol weight (g/mol)	Mol	Mol ratio
P - Chloroacetoacetanilide	2.1	211.0	0.01	1
Benzaldehyde	1.0	106.12	0.01	1
Urea	0.6	60.06	0.01	1

Procedure

Same as 2.4.4.1 A

Solvent system used for TLC: Chloroform: Methanol (9:1)

Result

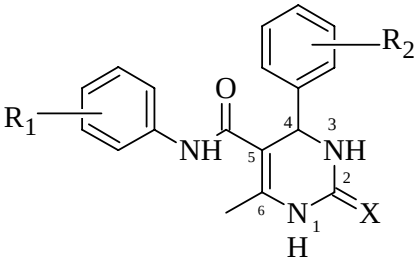
Product	Result
Percentage yield	62.30%
R_f	0.65
Melting point	180^0C

2.5 Result and Discussion

In order to obtain effective antihypertensive agents, new substituted Dihydropyrimidine compounds were successfully synthesized. Dihydropyrimidine

ring system was synthesized by Biginelli reaction. A series of total 21 compounds was prepared having dihydropyrimidine moiety which are mentioned in Table 2.1.

Table 2.1 List of Target Compounds with IUPAC Name



Common Structure

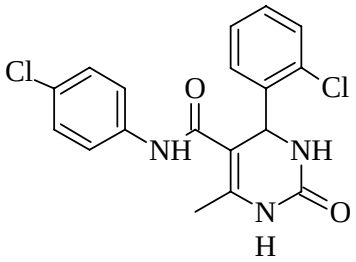
Compound Code No.	R1	R2	X	IUPAC Name
MJV-A_4M_4	4-Cl	4-OCH_3	O	*N*-(4-chlorophenyl)-4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4- tetrahydropyrimidine-5-carboxamide
MJV-A_4A_4	4-Cl	4-Cl	O	*N*,4-bis(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
MJV-A_4H_4	4-Cl	4-OH	O	*N*-(4-chlorophenyl)-4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
MJV-A_4N_4	4-Cl	4-NO_2	O	*N*-(4-chlorophenyl)-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
MJV-A_4N_3	4-Cl	3-NO_2	O	4-(3-chlorophenyl)-*N*-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
MJV-A_4A_3	4-Cl	3-Cl	O	4-(3-chlorophenyl)-*N*-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
MJV-A_4A_2	4-Cl	2-Cl	O	4-(2-chlorophenyl)-*N*-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

MJV-A_4D_4	4-Cl	4-diCH_3-NH_2	O	*N*-(4-chlorophenyl)-4-[4-(dimethylamino)phenyl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
MJV-$A_{26}M_4$	2,6-diCH_3	4-OCH_3	O	4-(2-chlorophenyl)-*N*-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
MJV-$A_{26}A_2$	2,6-diCH_3	2-Cl	O	4-(2-chlorophenyl)-*N*-(2,6-dimethylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
MJV-$A_{26}H_4$	2,6-diCH_3	4-OH	O	*N*-(2,6-dimethylphenyl)-4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
MJV-$A_{26}A_3$	4-Cl	3-Cl	O	4-(3-chlorophenyl)-*N*-(2,6-dimethylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
MJV-$A_{26}N_3$	4-Cl	2-Cl	O	*N*-(2,6-dimethylphenyl)-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
MJV-$A_{26}D_{34}$	4-Cl	4-diCH_3-NH_2	O	*N*-(2,6-dimethylphenyl)-6-methyl-4-(3,4-dimethoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
MJV-$A_{26}D_4$	2,6-diCH_3	4-OCH_3	O	*N*-(2,6-dimethylphenyl)-6-methyl-4-(4-dimethylaminophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
MJV-$A_{34}A_4$	2,6-diCH_3	2-Cl	O	4-(4-chlorophenyl)-*N*-(3,4-dichlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
MJV-TA_4A_4	4-Cl	4-Cl	S	*N*,4-bis(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
MJV-TA_4N_3	4-Cl	3-NO_2	S	*N*,4-bis(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
MJV-$TA_{26}N_3$	2,6-diCH_3	3-NO_2	S	*N*,4-bis(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
MJV-MA_4N_4	4-Cl	4-NO_2	O	*N*-(4-chlorophenyl)-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

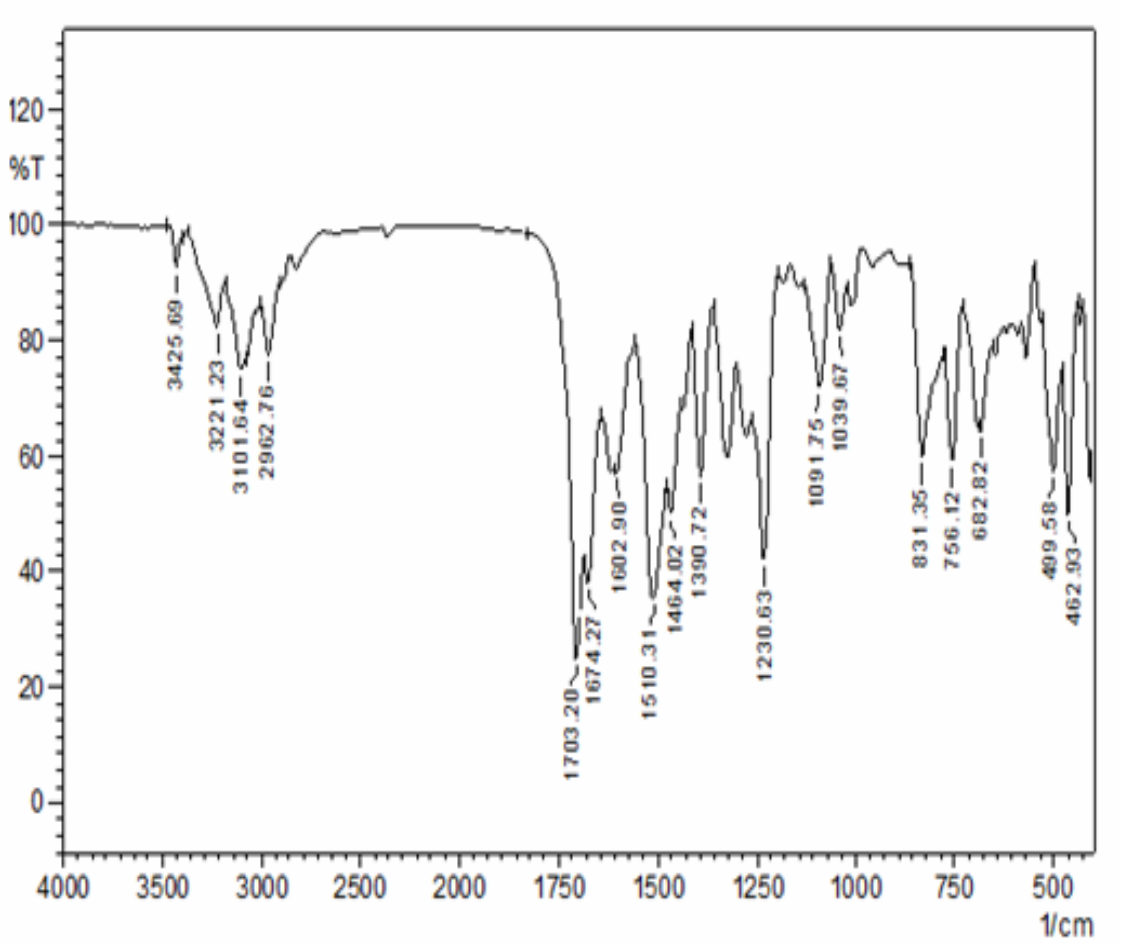
MJV-MA_4B	4-Cl	H	O	*N*-(4-chlorophenyl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide

The structures of the novel synthesized compounds of substituted Dihydropyrimidine series were elucidated by IR, ^{1}H NMR, and MASS spectroscopic tools. The summery of physical data and spectral analysis data of the synthesized compounds shown in Table 4.1

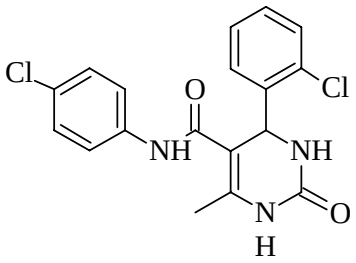
Summary of IR Spectral Data of novel MJV-A_4A_2 compounds



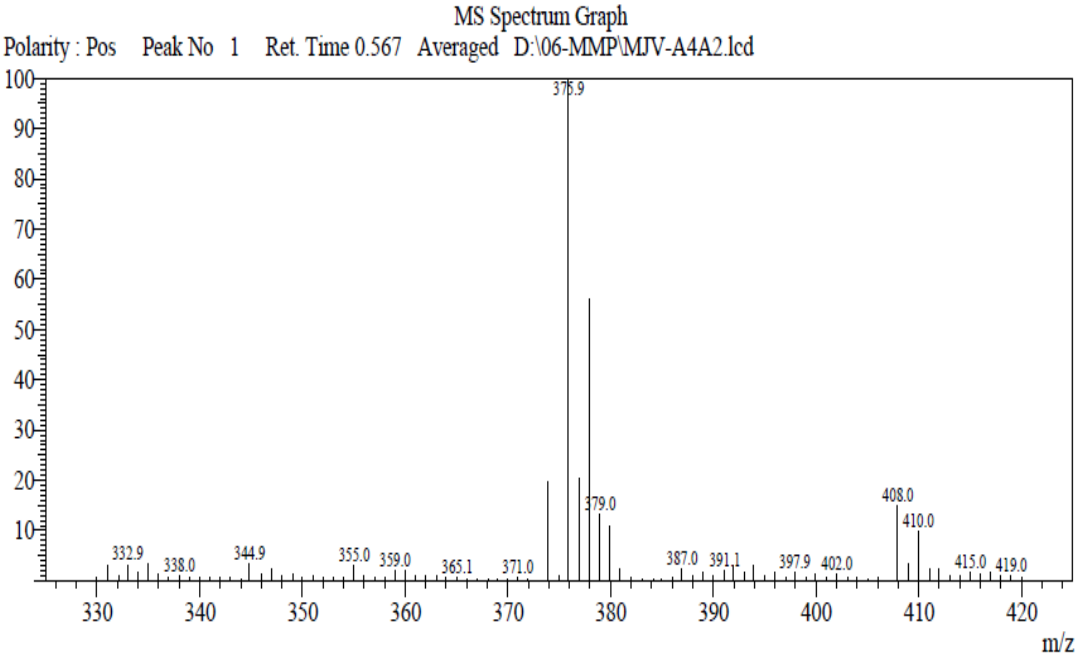
MJV - A_4A_2



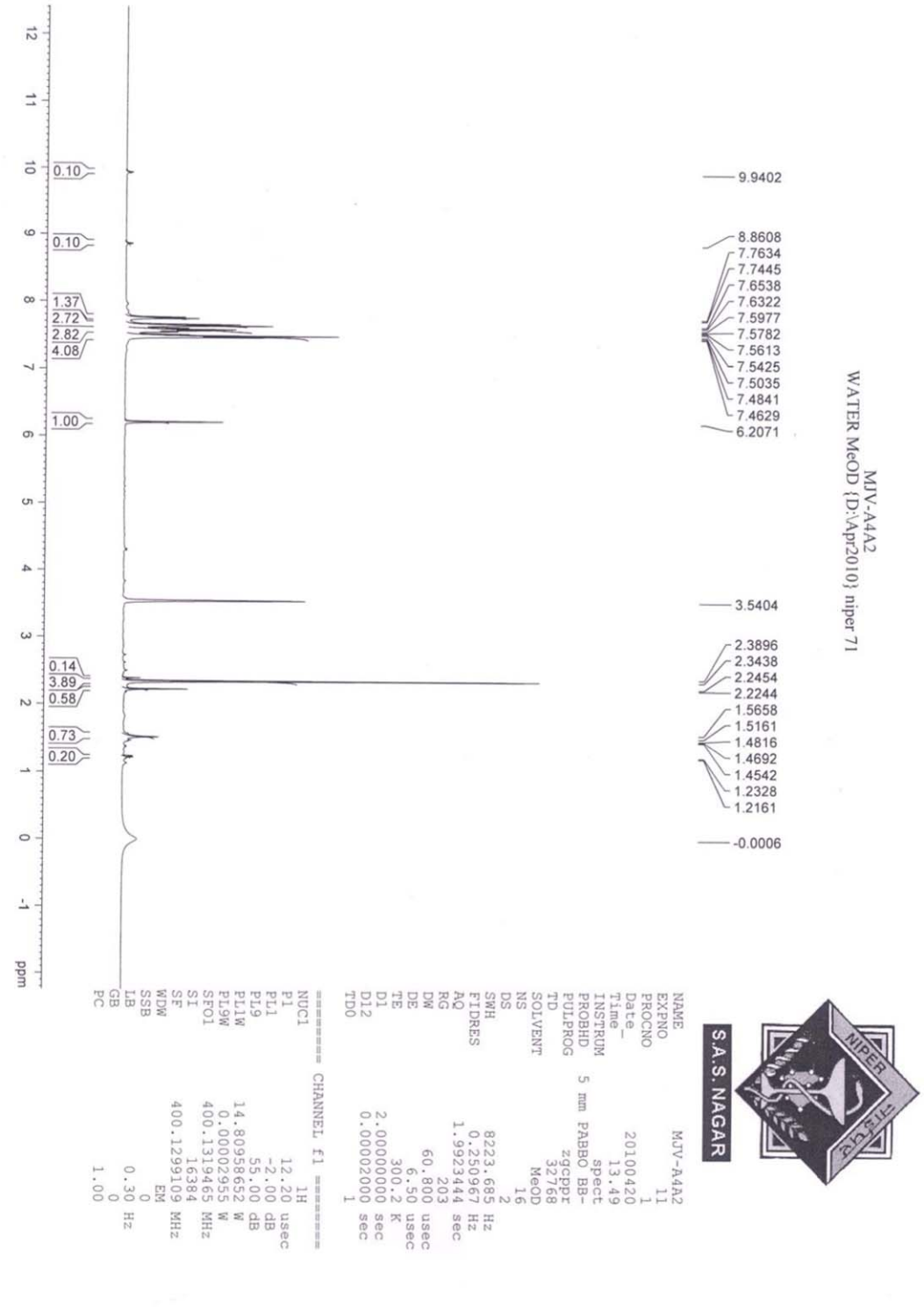
Summary of Mass Spectral Data of novel MJV-A_4A_2 compounds



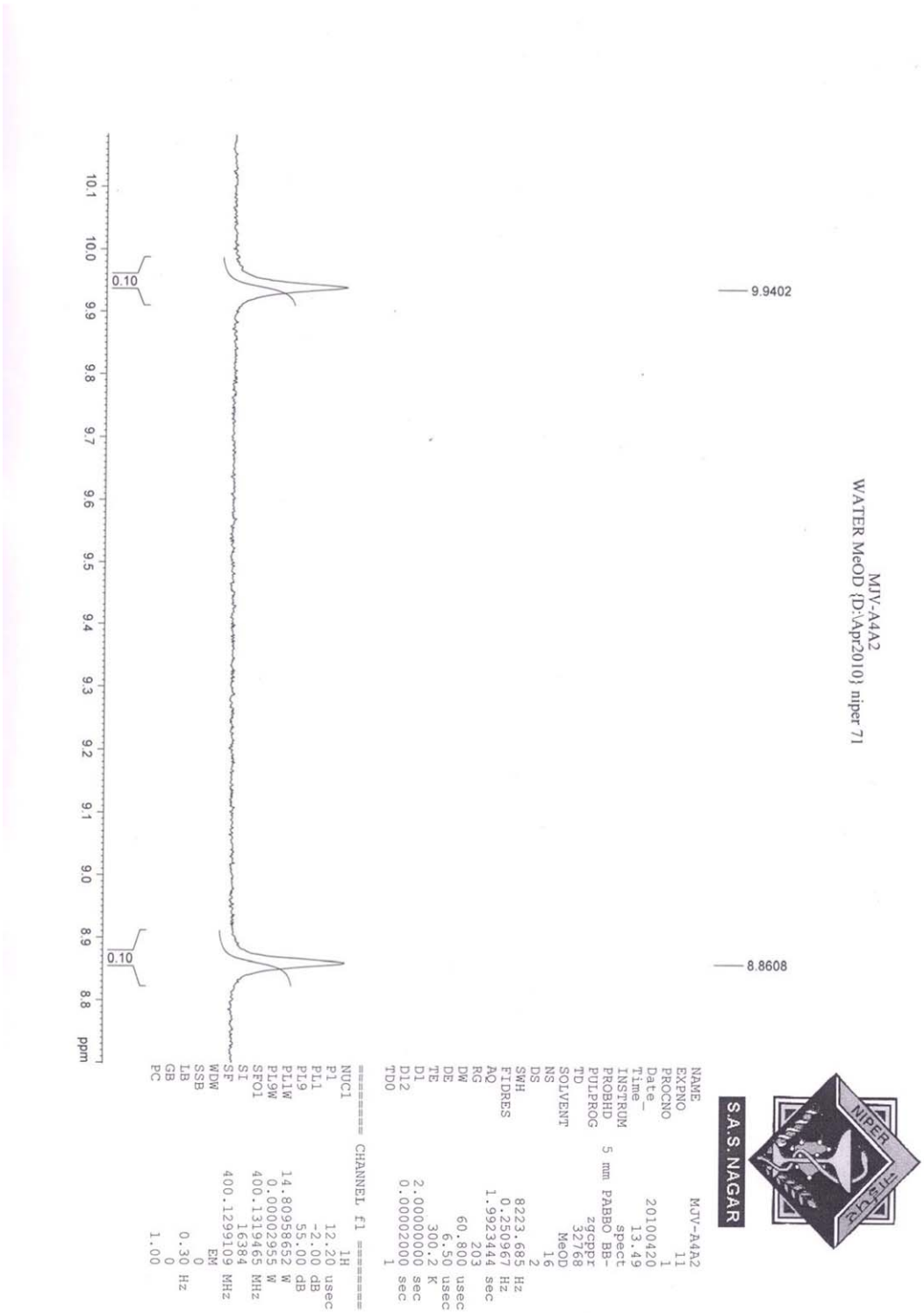
MJV - A_4A_2



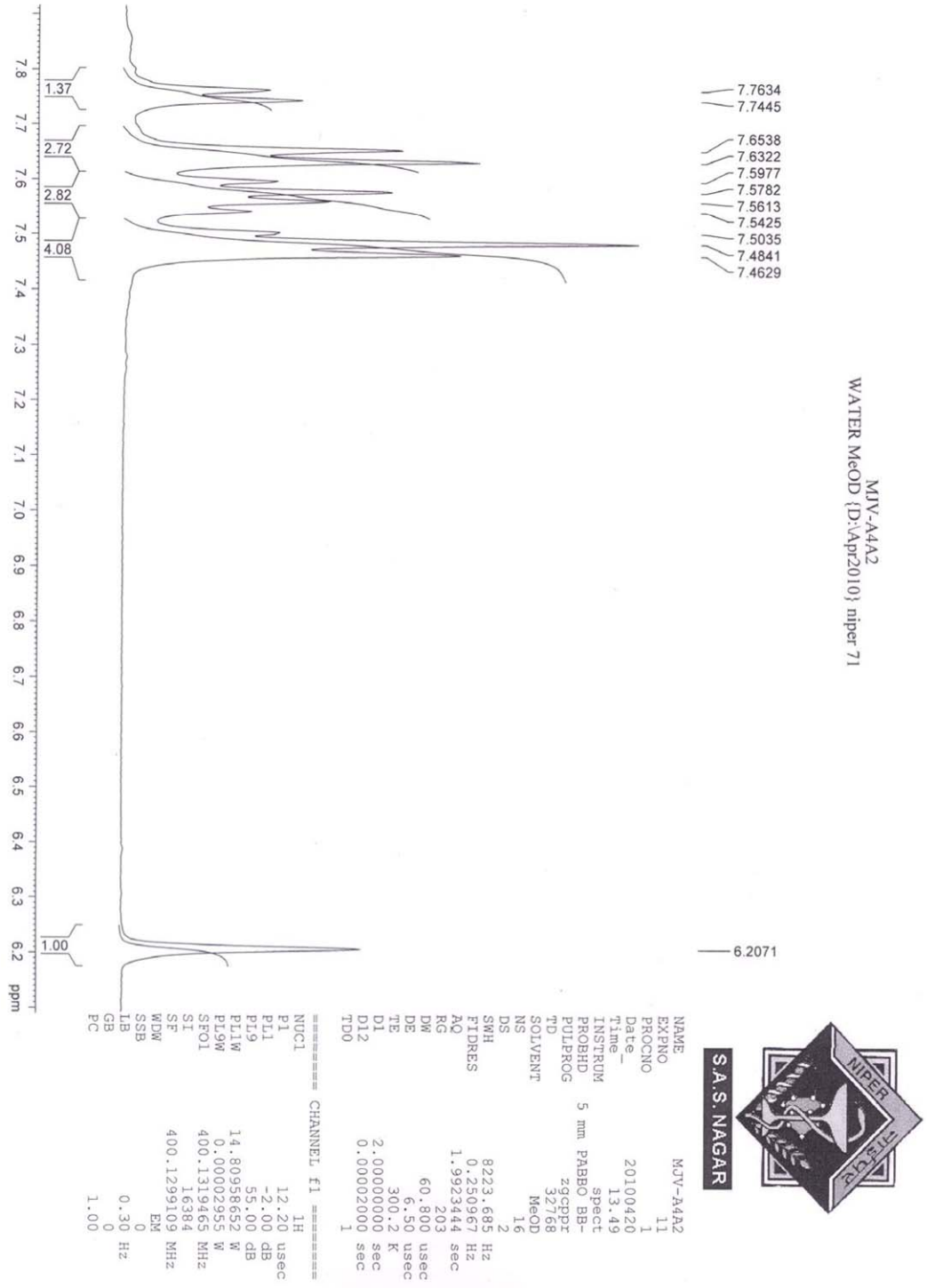
Summary of ^{1}H NMR Spectral Data of novel MJV-A_4A_2 compounds



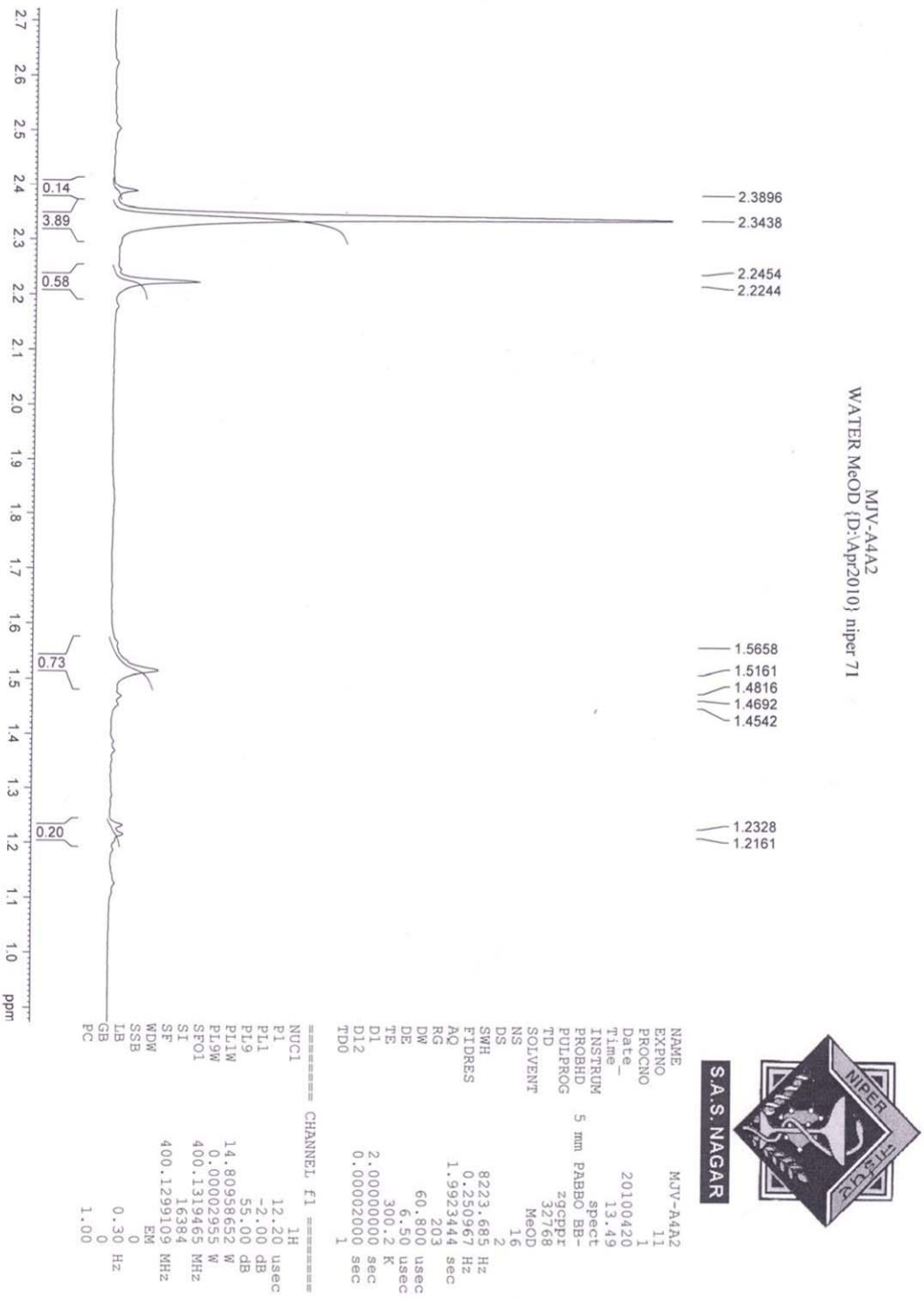
Summary of ^{1}H NMR Spectral Data of novel MJV-A_4A_2 compounds



Summary of ^{1}H NMR Spectral Data of novel MJV-A_4A_2 compounds



Summary of ^{1}H NMR Spectral Data of novel MJV-A_4A_2 compounds



Spectral analysis of synthesized compounds by IR Spectroscopy

Functional group	Spectral data (KBr, Cm^{-1})				
	Compound Code				
	MJV-A_4A_2	**MJV- TA_4N_3**	**MJV- A_4A_4**	**MJV- A_4H_4**	**MJV-$A_{26}N_3$**
-N-H(stretch)	3425.69	3425.69	3408.33	3331.18	3416.05
-C-H(sp^2 stretch)	3101.64	3279.10	3259.81	3217.37	3236.66
-C-H(sp^3 stretch)	2962.76	-	-	2845.10	-
-C=O (stretch)	1674.64	1672.34	1635.69	1664.69	1674.27
-C-N (stretch)	1390.72	1323.21`	1323.21`	1321.28`	1350.22
-N-H (bending)	1510.31	1502.60	1514.17	1535.69	1525.74
-C=S(stretch)	-	1242.20	-	-	-

Spectral analysis of synthesized compounds by ^{1}H NMR & Mass Spectroscopy

Compound Code	Molecular Weight	1H NMR(WaterMeOD,δ,ppm)	ESI-MS(m/z)
MJV- A_4A_2	376.23	7.43-7.65(m,8*H* aromatic protons) 8.86(s, 1*H* NH of pyrimidine) 9.94(s, 1*H* NH of pyrimidine) 6.20(s, 1*H* NH of amide) 2.34(s, 3*H*. CH_3, aliphatic) 7.74(d, 1*H* of CH of pyrimidine)	M+2(m/z)= 378.2 M+4(m/z)= 380.0
MJV- $A_{34}A_4$	410.68	-	M+2(m/z)= 412.6 M+4(m/z)= 414.2 M+6(m/z)= 416.6

2.6 References

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3.1 Introduction

Pharmacological evaluation is a crucial thing to ensure the activity of the compounds. In this era, the prevalence of heart diseases has increased to a great extent. Antihypertensive agents are among the most commonly used to treat the variety of heart diseases. Literature review revealed that substituted Dihydropyrimidine containing compounds show different biological activities. These compounds are also evaluated for their antihypertensive activities.

There are various *in vivo* and *in vitro* methods are available for evaluation of antihypertensive activity. Synthesized compounds were evaluated for their antihypertensive activity against calcium channel.

3.2 Measurement of Antihypertensive activity

In Vitro Calcium channel blocking properties of amlodipine in vascular smooth muscle is due to vascular Dihydropyrimidine receptors.[1, 2]

3.3 Calcium antagonism in the isolated Rat Uterus

3.3.1 Purpose and rationale

Contraction of Uterus is induced by adding potassium chloride & calcium chloride to the organ bath containing slightly modified Dejalon buffer. Test drugs with calcium channel blocking activity have a relaxing effect.[3, 4]

3.3.2 Procedure

Rat of either sex weighing 300g ware sacrificed with an overdose of pentobarbital sodium. The chest cavity was opened and the descending uterus was rapidly removed and placed in a beaker of oxygenated dejalon buffer at 37 °C. The content of calcium chloride was slightly diminished in the deJalon resulting in the following composition:

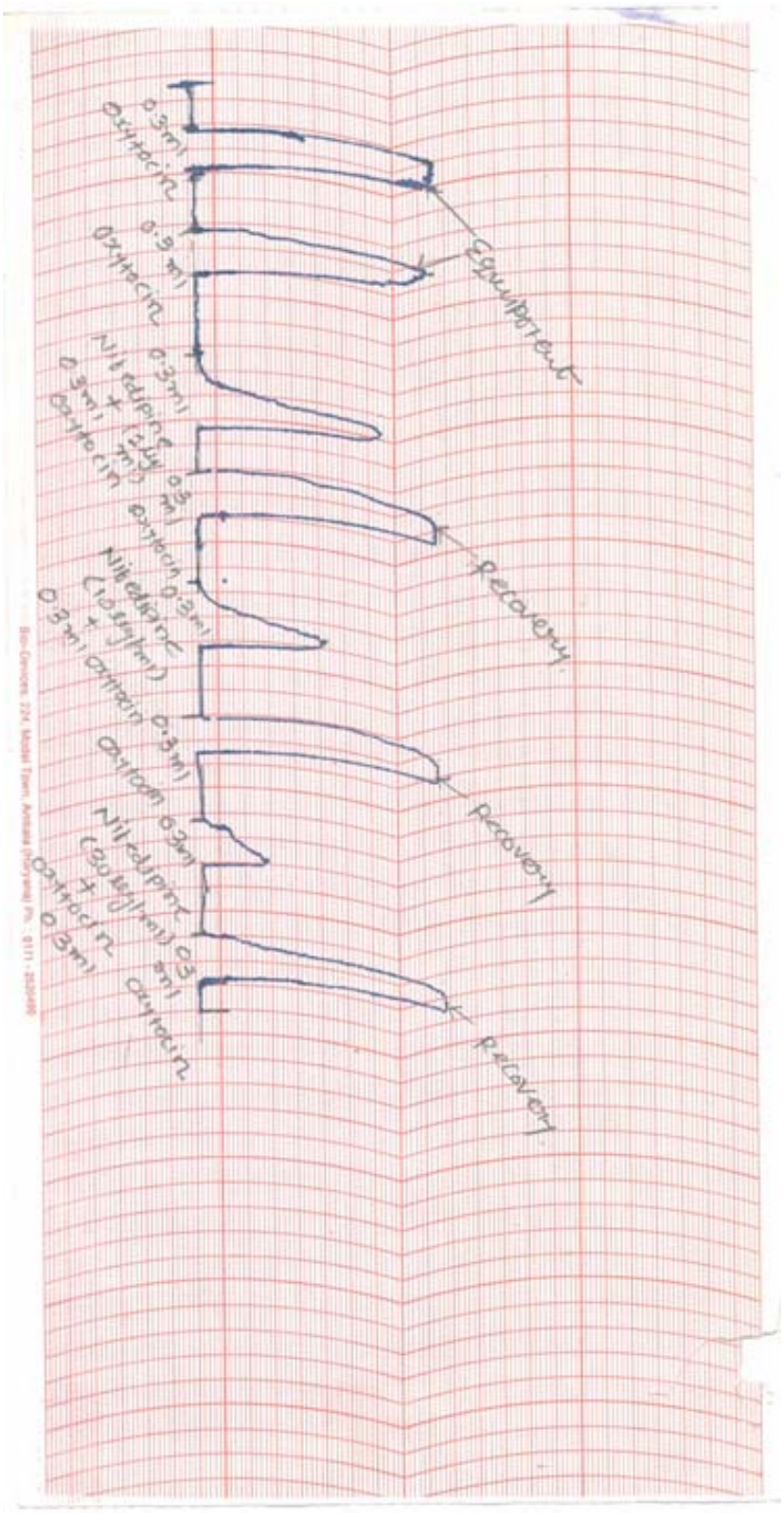
- NaCl 9gm
- KCl 0.350gm
- $CaCl_2 \cdot 2\ H_2O$ 0.003gm
- $NaHCO_3$ 0.5gm
- Dextrose 0.5gm

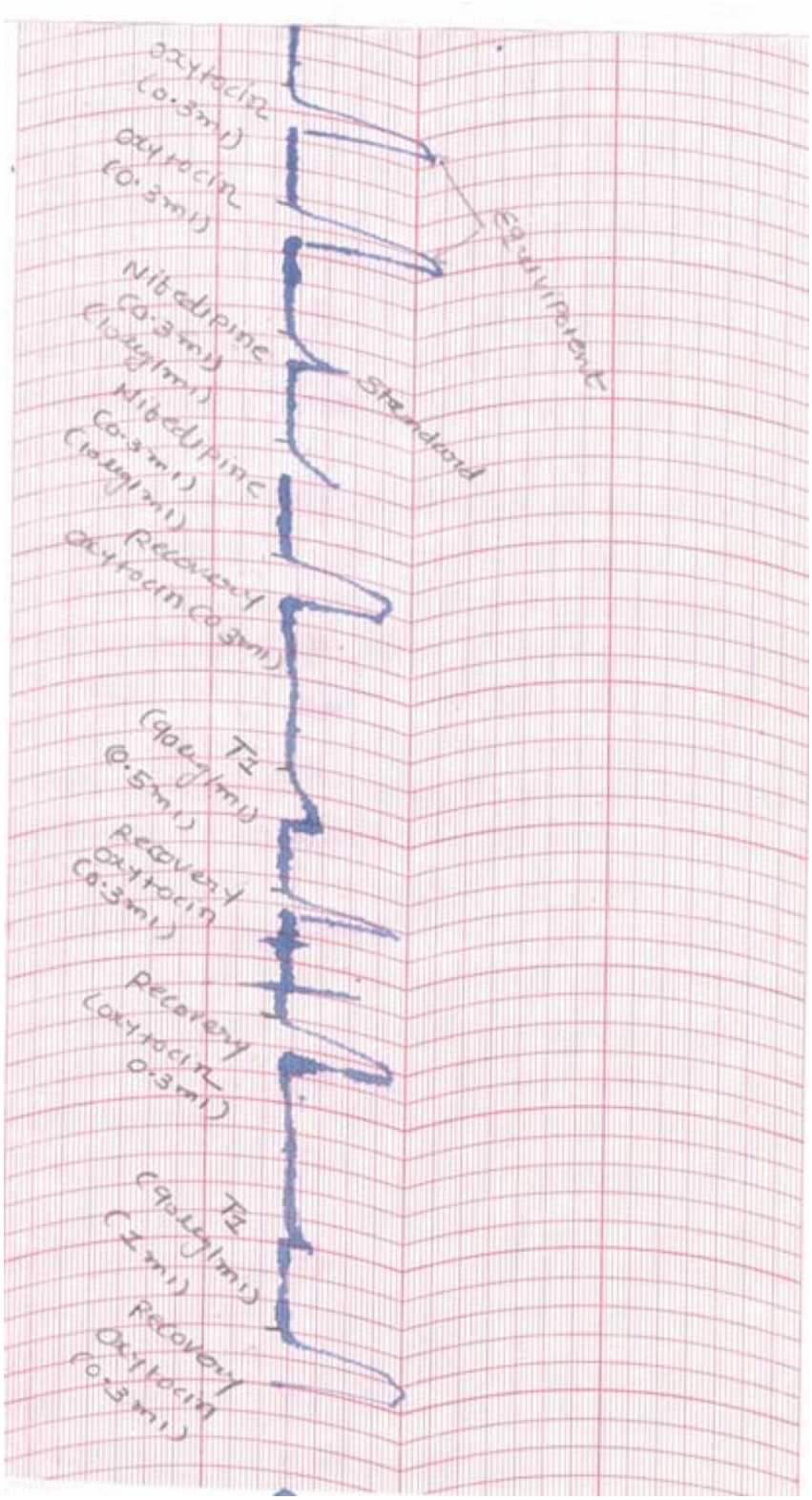
• EDTA 0.013 mol

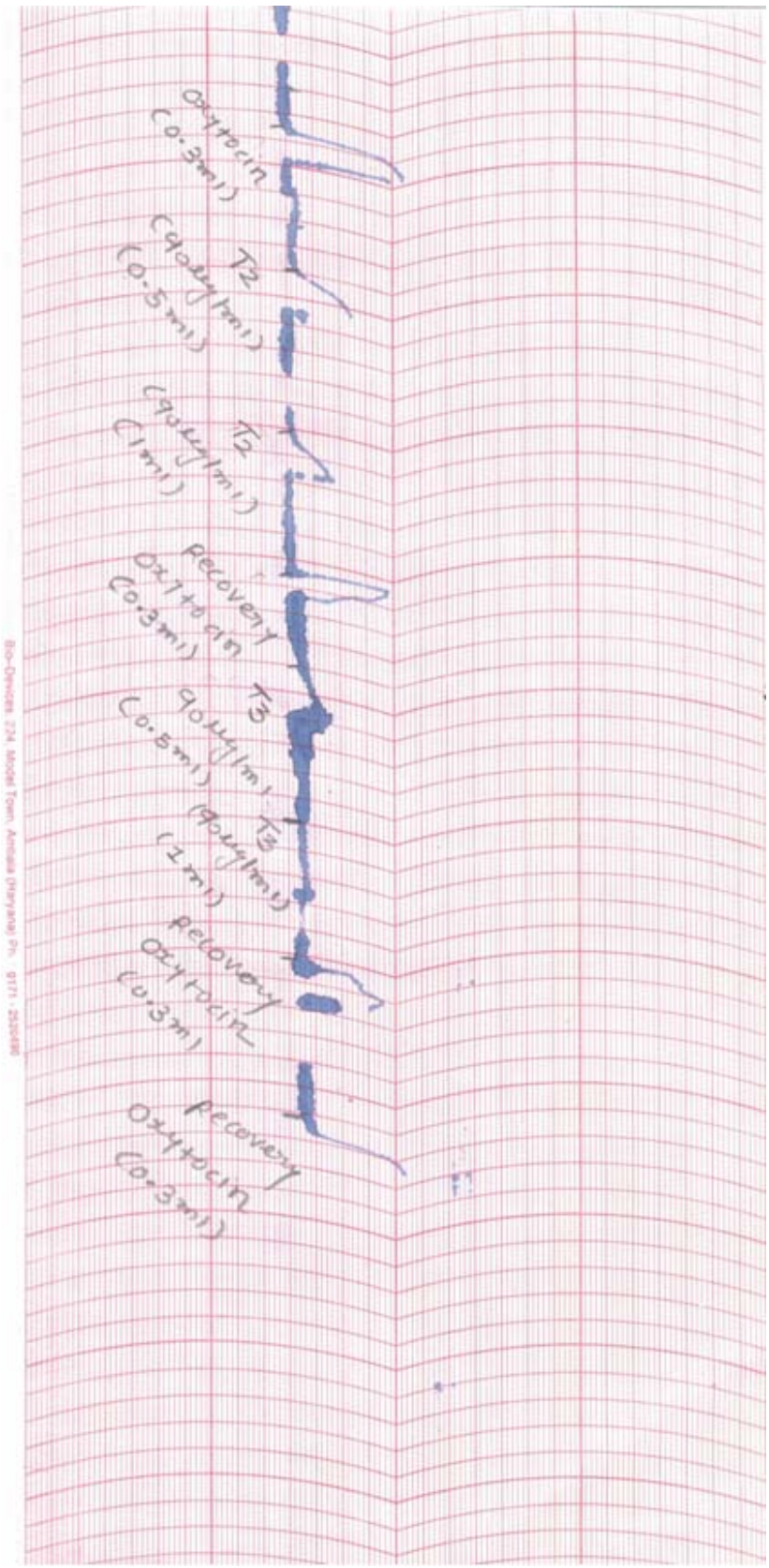
The tissue was then transferred to a dish containing fresh oxygenated, warmed De Jalon solution. Fat and loose connective tissue ware carefully removed while keeping the tissue moist with the solution. Each is mounted in a 20 ml tissue bath which contains the oxygenated warmed De Jalon solution. Initial tension was set at1.0 g. The tissue is allowed to incubate over a period of 2 h, during which time the De Jalon solution was changed every 15 min. Also during this time, tension was maintained at 1.0 g. Just prior to the end of the 2 h equilibration period, the De Jalon solution is changed again and the tissue was allowed to stabilize at 1.0 g tension. A sustained contraction is then generated by addition of either 4 M CaCl2. Twenty min after addition of the agonist, the test was added so that the final concentration in the bath is 1 × 10–5 M. The percent relaxation reading was taken 30 min after addition of the test drug. If at least 30% relaxation occurs, an accumulative concentration-relaxation curve was established. There was a 30 min period Of time between the addition of each concentration of test compound. [3,4]

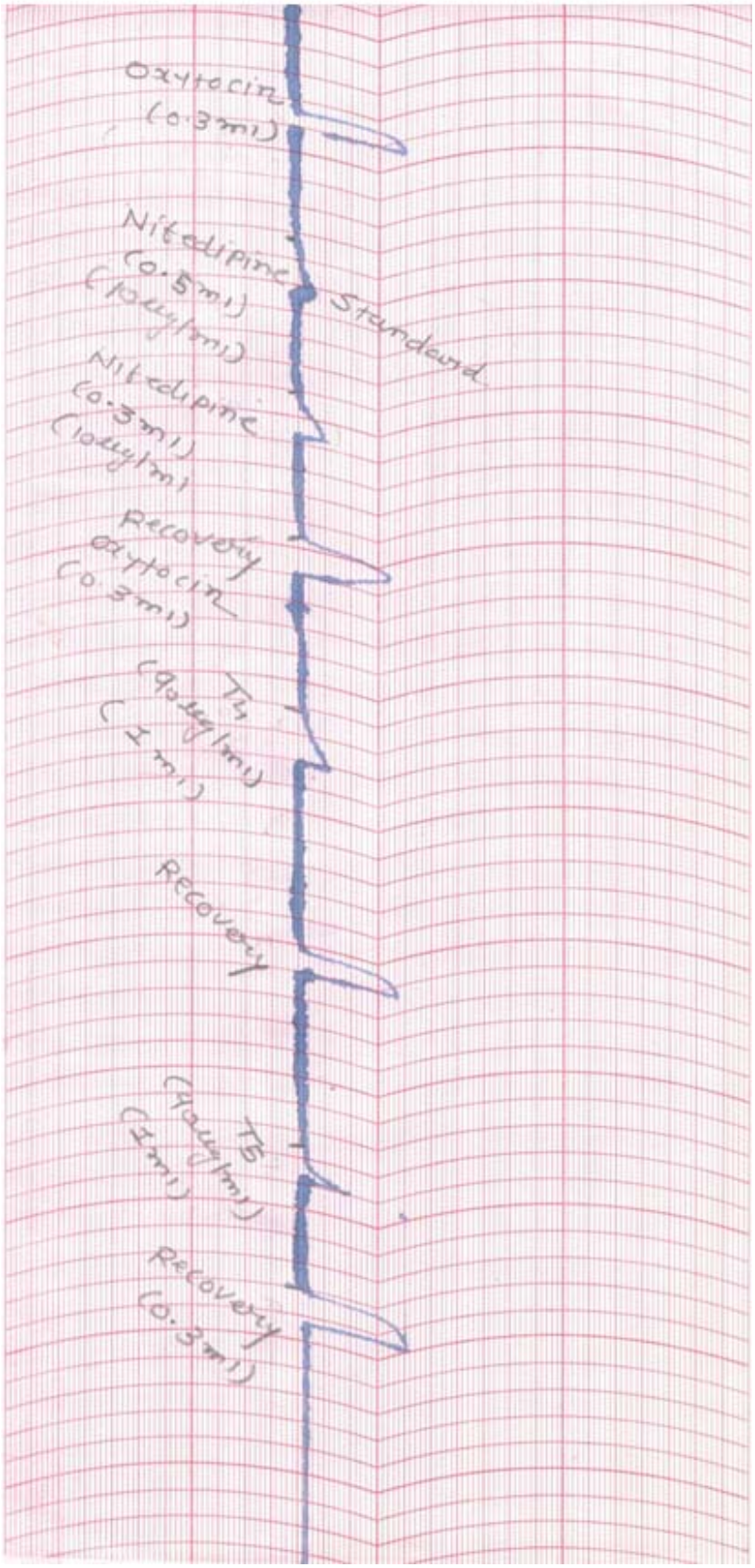
3.3.3 Evaluation

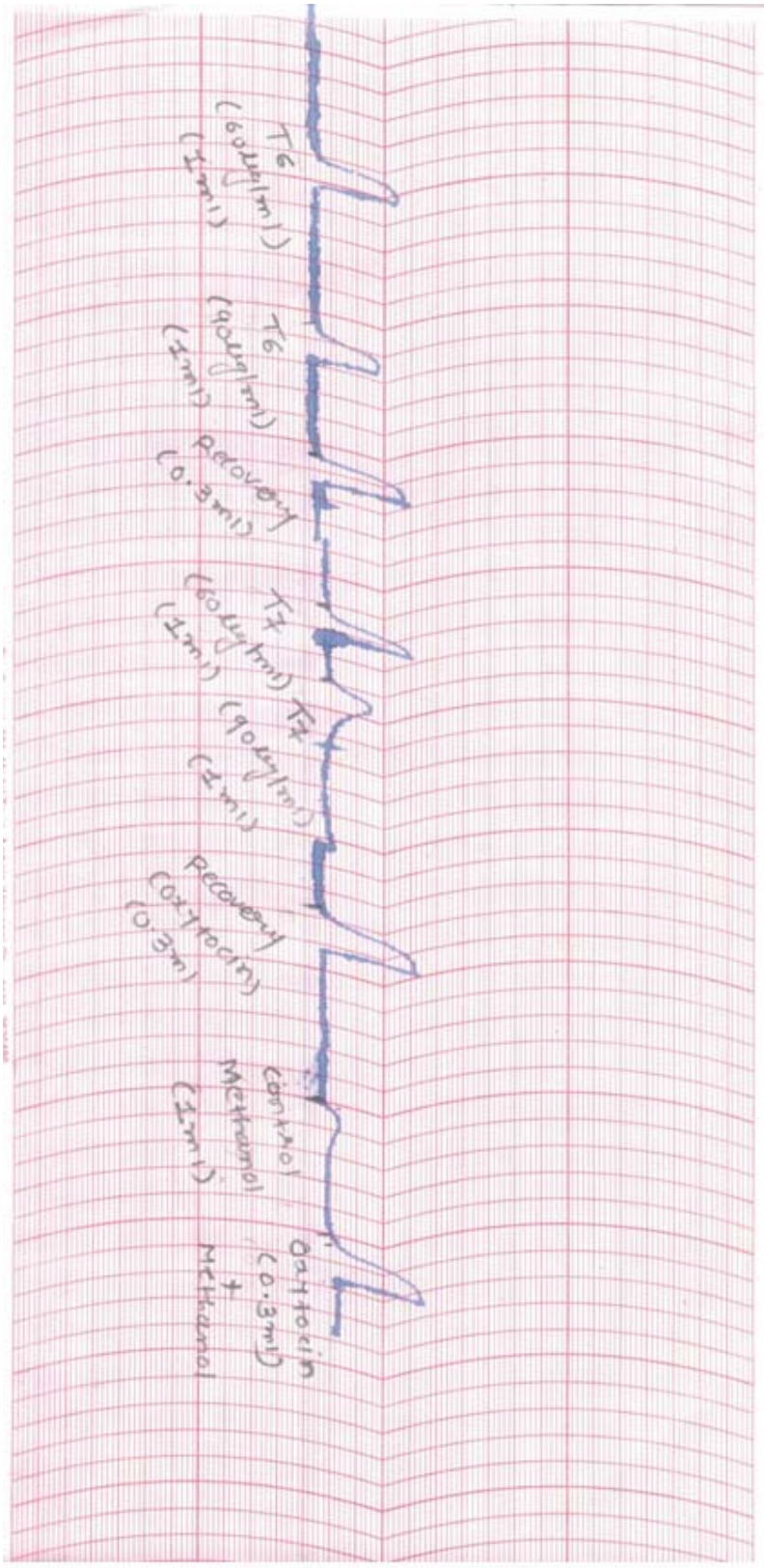
Active tension was calculated for the tissue at the time point just prior to the addition of the test compound and also at the point 30 min after the addition of each concentration of test compound. Active tension is defined as the difference between the generated tension and the baseline tension. The percent relaxation from the predrug, precontracted level was calculated for each concentration of test compound. An *IC*50 is calculated by linear regression analysis. [3, 4]

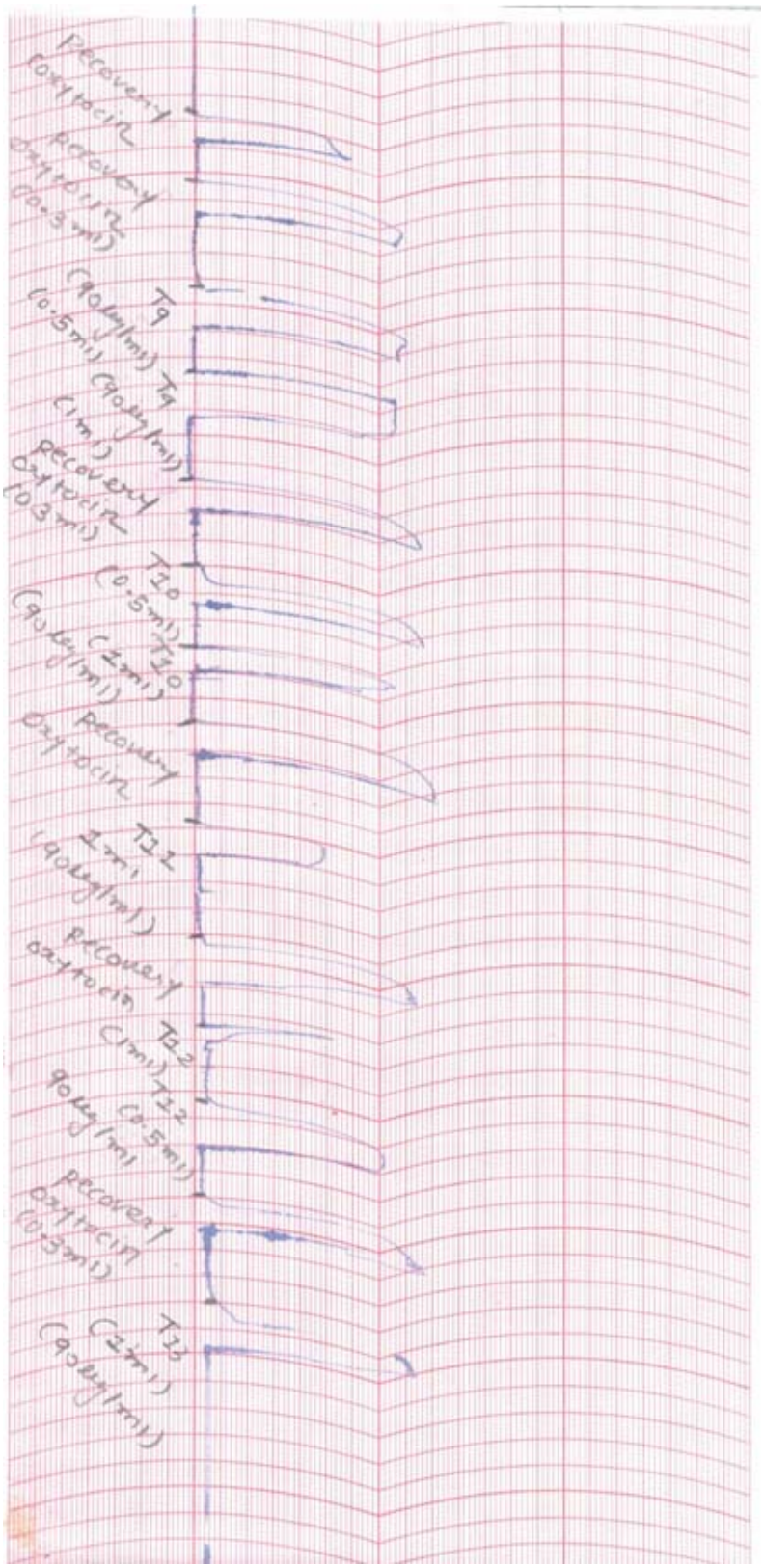

0.3ml Oxytocin
0.3 ml Oxytocin
Nilediprine 0.3ml + 0.3ml Oxytocin
Nilediprine (10 µg/kg/min) + 0.3ml Oxytocin
Nilediprine (30 µg/kg/min) + 0.3ml Oxytocin
Equilibrium
Recovery
Recovery
Recovery
Recovery
Oxygen 0.3ml

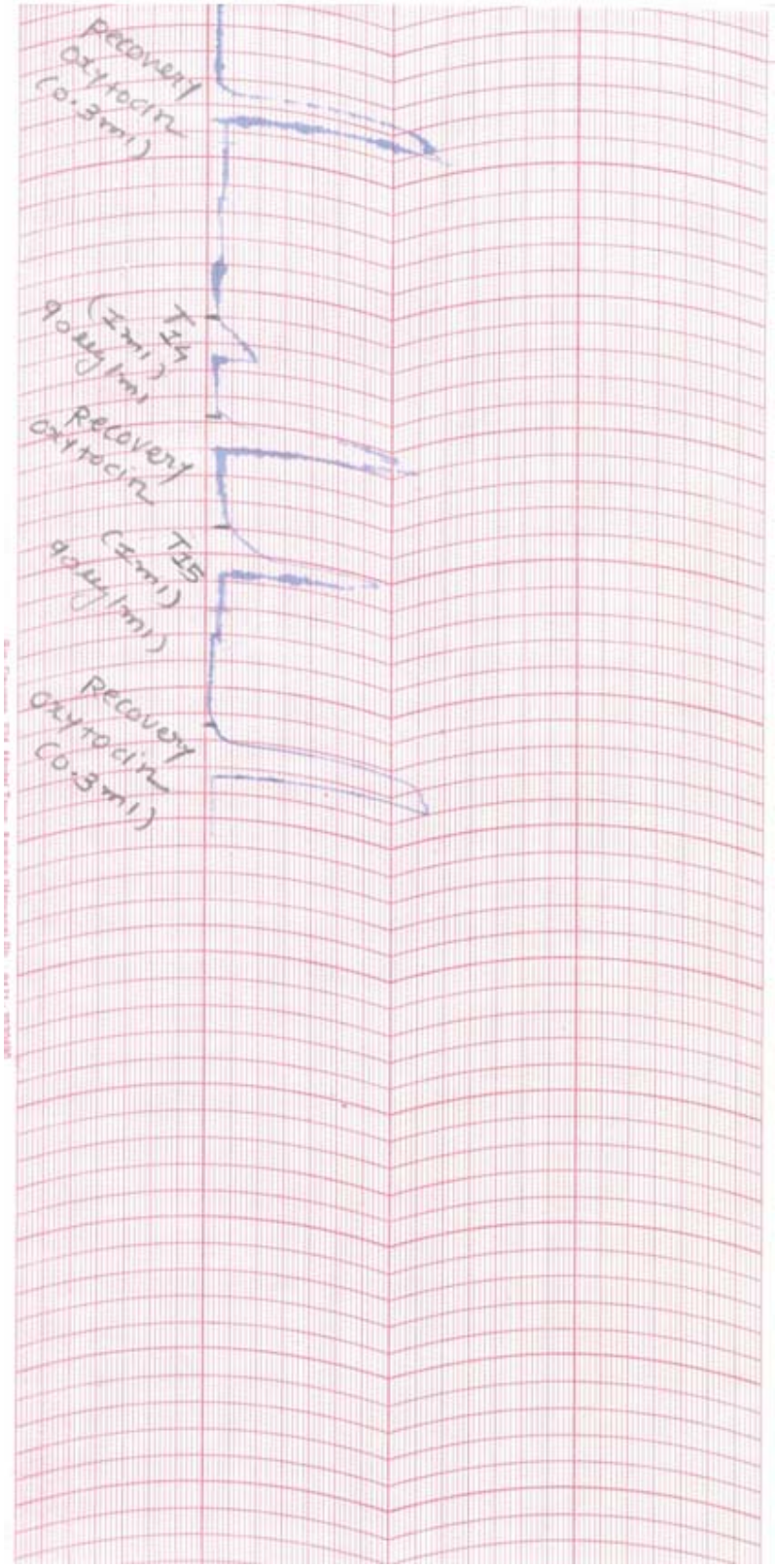

Oxytocin (0.3ml)
Oxytocin (0.3ml)
Nifedipine (0.3ml) (10µg/ml)
Nifedipine (0.3ml) (10µg/ml)
Recovery Oxytocin (0.3ml)
(90µg/ml) T2 @0.5ml)
Recovery Oxytocin (0.3ml)
Recovery (Oxytocin 0.3ml)
(90µg/ml) T2 (2ml)
Recovery Oxytocin (0.3ml)
Equivalent
Standard


Oxytocin
(0.3ml)
T2
Quabain
(0.5ml)
T2
Quabain
(1ml)
Recovery
Oxytocin
(0.3ml)
T3
Quabain
(0.5ml)
T3
Quabain
(1ml)
Recovery
Oxytocin
(0.3ml)
Recovery
Oxytocin
(0.3ml)


Oxytocin
(0.3ml)
Nifedipine
(0.5ml)
(10dyl/ml)
Standard
Nifedipine
(0.3ml)
(10dyl/ml)
Recovery
Oxytocin
(0.3ml)
(40dyl/ml)
(1ml)
Recovery
(40dyl/ml)
(1ml)
Recovery
(0.3ml)


T6
(60μg/ml)
(1ml)
T6
(90μg/ml)
(1ml)
Recovery
(0.3ml)
T7
(60μg/ml)
(1ml)
T7
(90μg/ml)
(1ml)
Recovery
(Oxytocin)
(0.3ml)
Control
Methanol
(1ml)
Oxytocin
(0.3ml)
+
Methanol


Recovery
Bacitracin
(0.5ml)
T9
(0.5ml)
(90µg/ml)
T9
(1ml)
(90µg/ml)
Recovery
Bacitracin
(0.5ml)
T10
(0.5ml)
(90µg/ml)
T10
(2ml)
(90µg/ml)
Recovery
Bacitracin
T12
2ml
(90µg/ml)
Recovery
Bacitracin
T12
(1ml)
T12
(0.5ml)
90µg/ml
Recovery
Bacitracin
(0.5ml)
T12
(2ml)
(90µg/ml)


Recovery
Oxytocin
(0.3ml)
TIS
(2ml)
Recovery
Oxytocin
TIS
(2ml)
Recovery
Oxytocin
(0.3ml)

3.4 Calculation

% Inhibition = [(H – h) / H] (100)

H: The heights of control (Oxytocin)

h: The heights of Test in presence of Control

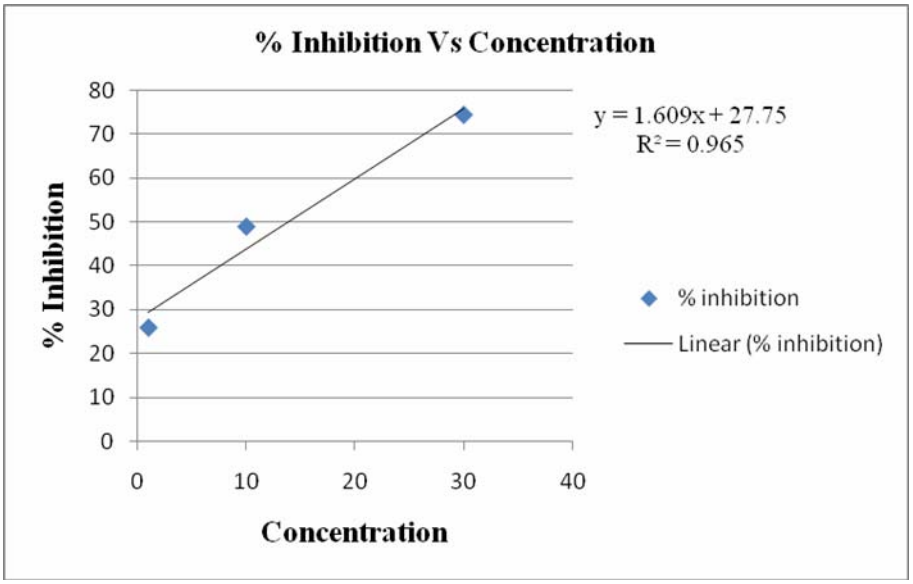
Concentration of standard nifedipine Solution : 1 µg/ml, 10 µg/ml and 30 µg/ml

Concentration of Test Solution : 90 µg/ml

Table 3.1 Percentage inhibition of test compounds.[5]

Compound code	Dose (ml)	Control (cm) (H)	Test (cm) (h)	% Inhibition
MJV-A_4A_2	0.3	2.6	0.24	90.76
MJV-A_4N_3	0.3	2.6	0.72	72.30
MJV-A_4M_4	0.3	2.0	0.24	88.00
MJV-A_4N_3	0.3	2.0	0.15	92.50
MJV-$A_{26}A_2$	0.3	2.1	0.30	85.71
MJV-A_4M_4	0.3	2.2	0.42	80.90
MJV-$A_{26}A_3$	0.3	2.0	0.30	85.00
MJV-$A_{34}A_4$	0.3	2.1	0.30	85.71
MJV-$A_{26}H_4$	0.3	4.7	1.17	75.10
MJV-A_4N_4	0.3	4.5	1.11	75.33
MJV-A_4H_4	0.3	4.7	0.75	84.04
MJV-TA_4A_4	0.3	4.2	0.75	82.14
MJV-$A_{26}D_{34}$	0.3	4.7	1.20	74.46
MJV-MA_4N_4	0.3	4.6	0.24	94.78
MJV-$A_{26}M_4$	0.3	3.9	1.17	70.00
Std. 1	0.3	4.7	3.50	25.86
Std. 2	0.3	4.7	2.40	48.93
Std. 3	0.3	4.7	1.20	74.46

Calculation of IC_{50} of Nifedipine



y = 1.609x + 27.75

50 = 1.609x + 27.75

x = 13.8284

Concentration (µg/ml) = 13.82 IC_{50} of Nifedipine

Calculation of IC_{50} of Test compound

1) For % inhibition of 90.76 of test compound:

90 µg/ml Concentration of test compound ≈ 39.16 µg/ml of Nifedipine (From std curve)

IC_{50} of Nifedipine = 13.86 µg/ml

Then, IC_{50} of test compound = 31.78 µg/ml

IC_{50} of test compound is 31.78

Table 3.2 IC_{50} value of test compounds

Sample	Dose (µg/ml)	IC_{50} (µg/ml)
MJV-A_4A_2	0.3	31.78
MJV-A_4N_3	0.3	44.95
MJV-A_4M_4	0.3	33.24
MJV-A_4N_3	0.3	30.93
MJV-$A_{26}A_2$	0.3	34.55
MJV-A_4M_4	0.3	37.68
MJV-$A_{26}A_3$	0.3	34.98
MJV-$A_{34}A_4$	0.3	34.55
MJV-$A_{26}H_4$	0.3	42.29
MJV-A_4N_4	0.3	42.09
MJV-A_4H_4	0.3	35.57
MJV-TA_4A_4	0.3	36.82
MJV-$A_{26}D_{34}$	0.3	42.87
MJV-MA_4N_4	0.3	29.87
MJV-$A_{26}M_4$	0.3	47.40
Std.	0.3	13.82

3.5 Results and Discussion

The synthesized compounds show good antihypertensive activity against calcium channel. Synthesized compounds were shown good antihypertensive activity against L- type's calcium channel but still they were somewhat less potent than the standard. All compounds ware weakly active against calcium channel as compare to standard drug.

MJV- $A_{26}M_4$ (4-(2-chlorophenyl)-*N*-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide), MJV-A_4N_3 (4-(3-chlorophenyl)-*N*-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide), MJV-$A_{26}H_4$ (*N*-(2,6-dimethylphenyl)-4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide), MJV-A_4N_4 (*N*-(4-chlorophenyl)-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide), MJV-$A_{26}D_{34}$ (*N*-(2,6-dimethylphenyl)-6-methyl-4-(4-dimethylaminophenyl)-2-oxo-1,2,3,4 -tetrahydropyrimidine-5-carboxamide) are good active against *calcium channel* than any other compounds.

MJV-MA_4N_4 (*N*-(4-chlorophenyl)-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide), MJV-A_4N_3 (4-(3-chlorophenyl)-*N*-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide), MJV A_4M_4 (*N*-(4-chlorophenyl)-4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide) show moderate to low activity against calcium channel.

Amongst all drug MJV- $A_{26}M_4$ (4-(2-chlorophenyl)-*N*-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide), MJV-A_4N_3 (4-(3-chlorophenyl)-*N*-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide) show good calcium channel blocking activity.

3.6 References

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2. Sanguinetti MC; Kass Rs., *Voltage- dependent block of calcium channel current in the calf cardiac purkinje filter by dihydropyrimidine calcium channel antagonists.* Circ Res, 1984. **55**: p. 336-348.
3. Vogel Gerhard H.; Vogel wolfgang H.;Vogel wolfgang F. *Drug Discovery And Evaluation, Pharmacology Assays,*.
4. Burges R.A.;Gardiner D.G.;Gwlit M.;Higgins A.J.;Blackburn K.J.;Campbell S.F., Journal of cardiovascular pharmacology, 1987. **9**: p. 110-118.
5. Dr. Goyal R.K.;Dr. Mehta A.A., *Practicals in Pharmacology*. 2006, B.S. Shah Prakashan. p. 97.

4. 1 Summary

The aim of therapy is reduction of blood pressure to within the normal range. Hypertension is secondary to a known organic disease, such as renovascular disease or pheochromocytoma.

There are three general approaches to the pharmacological treatment of primary hypertension. The first involves the use of diuretics to reduce blood volume. The second employs drugs that interfere with the renin–angiotensin system, and the third is aimed at a drug-induced reduction in peripheral vascular resistance, cardiac output, or both. A reduction in peripheral vascular resistance can be achieved directly by relaxing vascular smooth muscle with drugs known as vasodilators or indirectly by modifying the activity of the sympathetic nervous system.

The directly acting vasodilators, with the exception of calcium channel antagonists and sympathetic nervous system depressants.

Thiazide diuretics are not the drugs of choice in patients with renal insufficiency. Diuretics probably should not be used because they further elevate plasma renin. β adrenergic blocking agents should be avoided in patients with reactive airway disease (asthma). α_1 adrenergic receptor antagonist's doxazosin as monotherapy for hypertension increased the risk for developing congestive heart failure. ACE inhibitors that result from inhibiting angiotensin II-related functions also occur with AT_1 receptor antagonists. These include hypotension, hyperkalemia, and reduced renal function, including that associated with bilateral renal artery stenosis and stenosis in the artery of a solitary kidney. Minoxidil fluid and salt retention, cardiovascular effects, and hypertrichosis.

All Ca^{2+} channel blockers are effective when used alone for the treatment of mild to moderate hypertension. There is an urgent need for new antihypertensive agents. Extensive research is going in the direction to develop new targets which can be exploited to design and develop new antihypertensive agents. With the advantage of modern technologies like genomics, proteomics and high throughput screening assays, discovery of novel targets and novel molecules has been made possible. Some of these molecules have advanced to successive clinical trials.

Intense investigation is being carried out on pyrimidine compounds owing to their wide spectrum of activity. The different classes of pyrimidine compounds are 1, 2-dihydropyrimidine; 1, 2, 3, 4- tetrahydropyrimdine. Among the different pyrimidines, 1, 2, 3, 4-tetrahydropyrimidine represent the most therapeutically active class of compounds and have wide range of biological activities. In the recent years many article shows that pyrimidine containing compounds give good antihypertensive activity.

Prompted by these observations, as a part of present study aimed at developing new biologically active substituted dihydropyrimidine were synthesized. The target molecules were synthesized according to the steps reported in literature and all the reaction steps were optimized in context of present study.

Intermediates, different substituted acetoacetanilide were obtained by reaction of different aniline derivative with ethaylacetoacetate. Reaction of these different acetoacetanilide with different aryl aldehyde and urea or thourea in presence of ethanol and HCl gave Substituted dihydropyrimidine.

The structures of the synthesized compounds were established by ^{1}H NMR, MASS and IR spectroscopic techniques. The data of the physical characterization of the compounds ware given below in table.

Table 4.1 Physical characterization of synthesized compounds

Compound code	Molecular formula	Molecular Weight (g/mol)	Melting Point (^{o}C)	% Yield	R_f value
MJV-A_4M_4	$C_{19}H_{18}ClN_3O_3$	371.81	278	45.56	0.60
MJV-A_4A_4	$C_{18}H_{15}Cl_2N_3O_2$	376.23	210	40.68	0.80
MJV-A_4H_4	$C_{18}H_{16}ClN_3O_3$	357.79	288	35.89	0.29
MJV-A_4N_4	$C_{18}H_{15}ClN_4O_4$	386.78	298	50.65	0.72
MJV-A_4N_3	$C_{18}H_{15}ClN_4O_4$	386.78	244	32.78	0.75
MJV-A_4A_3	$C_{18}H_{15}Cl_2N_3O_2$	376.23	234	42.78	0.50
MJV-A_4A_2	$C_{18}H_{15}Cl_2N_3O_2$	376.23	230	60.78	0.59
MJV-A_4D_4	$C_{20}H_{21}Cl_2N_4O_2$	384.85	> 300	38.78	0.65
MJV-$A_{26}M_4$	$C_{21}H_{23}N_3O_3$	365.42	290	47.78	0.70
MJV-$A_{26}A_2$	$C_{20}H_{20}ClN_3O_2$	369.84	250	65.90	0.62
MJV-$A_{26}H_4$	$C_{20}H_{21}N_3O_3$	351.39	> 300	31.64	0.75
MJV-$A_{26}A_3$	$C_{20}H_{20}ClN_3O_2$	369.84	290	54.76	0.87
MJV-$A_{26}N_3$	$C_{20}H_{20}N_4O_4$	380.39	268	39.36	0.32
MJV-$A_{26}D_{34}$	$C_{22}H_{25}N_3O_4$	395.45	> 300	46.96	0.70
MJV-$A_{26}D_4$	$C_{22}H_{25}N_4O_2$	378.46	> 300	39.86	0.72
MJV-$A_{34}A_4$	$C_{18}H_{14}Cl_3N_3O_2$	410.68	240	45.80	0.85
MJV-TA_4A_4	$C_{18}H_{15}Cl_2N_3OS$	392.30	250	36.80	0.75
MJV-TA_4N_3	$C_{18}H_{15}Cl_2N_4O_3S$	402.85	245	35.60	0.66
MJV-$TA_{26}N_3$	$C_{20}H_{20}N_4O_3S$	396.46	238	30.60	0.60
MJV-MA_4A_4	$C_{18}H_{15}ClN_4O_4$	386.78	210	56.60	0.67
MJV-MA_4B	$C_{18}H_{15}ClN_3O_2$	341.79	180	62.30	0.65