REVIEW OF LITERATURE

CONGESTIVE HEART FAILURE

Congestive heart failure is a pathophysiological state, in which the circulatory system loses its resilience and is no longer able to increase cardiac output with the subsequent failure to meet demands of metabolizing tissue.\textsuperscript{25-27} It is characterized by impaired myocardial contractility leading to increase in systemic vascular resistance and activation of renin-angiotensin cascade.\textsuperscript{28} A poor blood supply resulting from CHF may cause the body organ system to fail and due to inadequate pumping of blood from heart, the blood 'backs up' behind the heart. This congestion can lead to fluid accumulation in the lungs, liver and body tissues. Over the time untreated CHF may affect virtually every organ in the body.\textsuperscript{29-32}

CHF can be broadly divided into various categories depending on the underlying heart condition present. Systolic dysfunction i.e. the strength (forward pumping function) of the heart may be impaired due to illnesses that cause heart muscle weakness or impairment of the ability of the heart to relax and contract. In some cases, although the pumping action of the heart may be intact, other factors due to abnormal demands of the body's tissues may make it difficult for the heart to supply an adequate blood flow and is called high output heart failure.\textsuperscript{1,6}

When the heart fails, the body responds with a series of compensatory mechanisms designed to restore the fall in cardiac output. However, as the disease progresses, they are overwhelmed by the progressive fall in contractility and contribute to worsening state of the heart. The circulatory system attempts to compensate for a failing cardiac output by a) dilation of the heart; b) hypertrophy and activation of the sympathetic nervous system, leading to increased heart rate; c) increased contractility, salt and water retention and d) raised venous pressure. Some causes of congestive heart failure are hypertension, heart valve
stenosis, cardiac myopathies and ischemic heart disease. Several other precipitating factors include respiratory infection, pulmonary embolism, hyperthyroidism, hypertension and cardiac arrhythmias, overexertion, excessive intake of sodium, excessive heat and humidity and emotional excesses. The symptoms of CHF among individuals also vary according to the particular organ systems involved and depending on the degree to which the rest of the body has 'compensated' for the heart muscle weakness. An early symptom of CHF is fatigue. As the disease progresses, fatigue is seen even at rest and breathlessness develops due to accumulation of fluid in the lungs and interstitial spaces and also may cause nausea, abdominal pain and decreased appetite.

**Diagnosis**

The diagnosis of CHF is most often a clinical one that is based on knowledge of the patient's pertinent medical history, a careful physical examination and selected laboratory tests. A thorough patient history may disclose the presence of one or more of the symptoms of CHF described above. A history of significant coronary artery disease, prior heart attack, hypertension, diabetes, or significant alcohol use can be clues. The physical examination is focused on detecting the presence of extra fluid in the body from breath sounds, leg swelling, or neck veins as well as carefully characterizing the condition of the heart i.e. pulse, heart size, heart sounds and murmurs.

Useful diagnostic tests include the electrocardiogram (ECG) and chest x-ray to explore the possibility of previous heart attacks, arrhythmias, heart enlargement and fluid in and around the lungs. Perhaps the single most useful diagnostic test is the echocardiogram, in which ultrasound is used to image the heart muscle, valvular structures and blood flow patterns. The echocardiogram is very helpful in diagnosing heart muscle weakness. In addition, the test can suggest possible causes for the heart muscle weakness, e.g., prior heart attack and severe valvular abnormalities. Virtually all patients in whom the diagnosis of CHF is suspected should ideally undergo echocardiography at some point.

Nuclear medicine studies assess the overall pumping capability of the heart and examine the possibility of inadequate blood flow to the heart muscle.
Heart catheterization allows the arteries to the heart to be visualized with angiography, using dye inside of the blood vessels that can be seen using x-ray methods. During catheterization the pressures in and around the heart can be measured and the heart's performance assessed. In rare cases, a biopsy of the heart tissue may be recommended to diagnose specific diseases. This biopsy can often be accomplished through the use of a special device that is inserted into a vein and maneuvered into the right side of the heart. Cardiovascular magnetic resonance (CMR) imaging has established itself as both a valuable clinical and research tool in this arena. Not only is CMR, the new gold standard for accurate and reproducible assessment of ventricular volumes and mass, but by using gadolinium contrast, underlying pathology can often be determined. In ischemic cardiomyopathy, a 'one stop' assessment can be made of function, perfusion and mass. Continuing advances such as myocardial tagging and the increasing availability of CMR mean that it will become an increasingly important and useful tool for clinicians looking after patients with cardiomyopathy and heart failure. The choice of tests depends on each patient's case and is based on the suspected diagnosis.

MANAGEMENT OF CONGESTIVE HEART FAILURE

The management of CHF involves: i) treatment of precipitating factors, ii) correction of the underlying causes such as hypertension and defective valves, iii) control of precipitating physical and mental factors, iv) use of vasodilators to reduce preload and afterload, control of fluid retention with diuretics and v) improvement of myocardial function by improvement of myocardial contractility with positive inotropes. The sites of action of various drugs used to treat CHF have been depicted in figure 1.

VASODILATORS

Angiotensin converting-enzyme (ACE) inhibitors and nitrates are used to treat CHF because they can decrease the workload of the overworked cardiac muscle. ACE inhibitors have been used for the treatment of hypertension for more
than 20 years and have also been extensively studied in the management of CHF. These medications block the formation of angiotensin II, a hormone with many potentially adverse effects on the heart and circulation in patients with heart failure. In multiple studies of thousands of patients, these drugs have demonstrated a remarkable improvement of symptoms, prevention of clinical deterioration and prolongation of survival. In addition, they have recently been shown to prevent the development of heart failure and heart attacks. The wealth of the evidence supporting the use of these agents in heart failure is so strong that ACE inhibitors are at least considered in all patients with heart failure, especially those with heart muscle weakness. Possible side effects of these drugs include...
nagging, dry cough, low blood pressure, worsening kidney function and electrolyte imbalances and rarely, true allergic reactions. When used carefully with proper monitoring, however, the majority of CHF patients tolerate these medications without significant problems.\textsuperscript{65-70} Some clinically useful ACE inhibitors include captopril (Capoten\textsuperscript{®} 1), enalapril (Vasotec\textsuperscript{®} 2), lisinopril (Vestril\textsuperscript{®, Prinivil\textsuperscript{®}}), benazepril (Lotensin\textsuperscript{®}) and ramipril (Altace\textsuperscript{®}).\textsuperscript{71} For those patients who are unable to tolerate the ACE inhibitors, an alternative group of drugs, called the angiotensin receptor blockers (ARBs), may be used.\textsuperscript{72} These drugs act on the same hormonal pathway as the ACE inhibitors, but instead block the action of angiotensin II at its receptor site directly. A small early study on one of these agents suggested a greater survival benefit in elderly CHF patients as compared to an ACE inhibitor.

However, a larger follow-up study failed to demonstrate the superiority of the ARBs over the ACE inhibitors. Further studies are underway to explore the use of these agents in CHF both alone and in combination with the ACE inhibitors. Possible side effects of these drugs are similar to those associated with the ACE inhibitors, although the dry cough is much less common. Examples of ARBs are losartan (Cozaar\textsuperscript{®, 3}), candesartan (Atacand\textsuperscript{®}), telmisartan (Micardis\textsuperscript{®}), valsartan
Nitrates directly relax vascular muscle and cause a decrease in blood pressure and a pooling of blood in the veins. These two actions also decrease preload and afterload. Nitrates are used to treat more severe CHF.75-79

DIURETICS

These are often an important component of the treatment therapy of CHF to prevent or alleviate the symptoms of fluid retention. By promoting the flow of fluid through the kidneys, these drugs help keep fluid from building up in the lungs and other tissues. Although they are effective in relieving symptoms such as shortness of breath and leg swelling, they have not been demonstrated to positively impact long term survival. Nevertheless, diuretics remain key in preventing deterioration of the patient's condition thereby requiring hospitalization.80-85 During hospitalization, diuretics are often administered intravenously because the ability to absorb oral diuretics may be impaired.86 Potential side effects of diuretics include dehydration, electrolyte abnormalities, particularly low potassium levels, hearing disturbances and low blood pressure. Such electrolyte disturbances may make patients susceptible to serious heart rhythm disturbances, therefore, supplements are recommended along with diuretic therapy. Various examples of diuretics include furosemide (Lasix®, 4), hydrochlorothiazide, bumetanide (Bumex®), torsemide (Demadex®) and metolazone (Zaroxolyn®). Spironolactone (Aldactone®) has been used for many years as a relatively weak diuretic in the treatment of various diseases. Among other actions, this drug blocks the action of the hormone aldosterone, which has many theoretical detrimental effects on the heart and circulation in CHF. The release of aldosterone is stimulated in part by angiotensin II. In patients taking ACE inhibitors
however, there is an 'escape' phenomenon in which aldosterone levels can increase despite low levels of angiotensin II. Medical researchers have recently found that a weak diuretic like spironolactone can improve the survival rate of patients with CHF.\textsuperscript{87} Although the doses used in the study were relatively small, it has been theorized that the benefit of the drug was in its ability to block the effects of aldosterone rather than its relatively weak action as a diuretic. Possible side effects of this drug include elevated potassium levels and breast tissue growth called gynecomastia in males.\textsuperscript{86,90}

**CARDIOTONIC (INOTROPIC) AGENTS**

Cardiotonic agents are the drugs that act on myocardium and increase the force of contraction (positive inotropic effect) of heart without concomitant increase in myocardial oxygen demand. The increase in the force of contraction of myocardium leads to increased cardiac output, decreased heart size, venous pressure, blood volume, diuresis and relief of edema in patients with heart failure.\textsuperscript{1,6}

*Biochemical basis*

The force of contraction of heart is generated by the interaction between two proteins, actin and myosin, which can form cross-bridges. This interaction is regulated by binding of Ca\textsuperscript{2+} to troponin.\textsuperscript{91-95} The cascade or sequence of events between extracellular stimulation and contraction of cardiac muscle cell are depicted in figure 2.\textsuperscript{96}

Since the initial designation of cyclic adenosine 3',5'-monophosphate (cAMP, 5) as second messenger,\textsuperscript{96} details of its various intracellular actions...
have been extensively studied and characterized.

Stimulation of either β₁-adrenergic receptors (a) or H₂-histaminergic receptors (b) activates the catalytic component (f) of the adenylate cyclase complex through close association of these cell surface receptors with the cell membrane bound adenylate cyclase regulatory component (d). Since this enzyme system is responsible for the conversion of ATP to cAMP, its activation results in increased cellular concentration of cAMP. Higher intracellular cAMP concentrations lead to greater interactions of cAMP with the regulatory subunit of protein kinase (h), which in turn, increases its catalytic activity and causes enhanced phosphorylation (i) of various cellular proteins. Phosphorylation of specific proteins associated with the Ca²⁺ channel in the sarcolemma enhances the slow channels responsiveness to voltage activation and prolongs the gate (j) open time, which results in greater influx of Ca²⁺. The entering Ca²⁺ is thought to act as a trigger for release of intracellular Ca²⁺ stored in the sarcoplasmic reticulum (k). This releases Ca²⁺ and subsequently causes contraction through
direct interaction with the contractile proteins (I). Phosphorylation (i) of specific proteins associated with the sarcoplasmic reticulum (k) allows for a more rapid and increased reuptake of Ca\textsuperscript{2+} after a contractile event has occurred. Thus, when intracellular cAMP levels are raised, both the rate of contraction and the rate of relaxation are increased. Two important regulatory systems are also depicted in figure 2. At least one consequence of stimulating muscarinic cholinergic receptors (c) is to decrease the conversion of ATP to cAMP\textsuperscript{97} through association of these receptors with an inhibitory component (e) of the adenylate cyclase complex. Similarly, the degradative enzyme phosphodiesterases (g), e.g., PDE3 decreases intracellular cAMP by converting it to 5'-AMP.

From this cascade there are several points of access, for which increases in the end product cardiac muscle contraction can be attempted. As these pathways have become elaborated, attention has shifted from approaches involving interaction with cell surface receptor systems to mechanisms involving specific interaction with the various intracellular components. Regulation of intracellular calcium in cardiac myocytes by various inotropes has been depicted in figure 3.\textsuperscript{98}

Figure 3. Effects of inotropic therapy on intracellular calcium handling in cardiac myocytes.
Depolarization of membrane by action potential leads to opening of voltage-gated L-type calcium (Ca\(^{2+}\)) channels, which allows entry of small amount of Ca\(^{2+}\) into cell. Through coupling mechanism between L-type Ca\(^{2+}\) channel and sarcoplasmic reticulum (SR) release channels (ryanodine receptors), larger amount of Ca\(^{2+}\) is released, which activates myofilaments, leading to contraction. During relaxation, Ca\(^{2+}\) is accumulated back into SR by SR Ca\(^{2+}\)-ATPase pump (SERCA2a) and extruded extracellularly by sarcolemmal Na\(^+\)/Ca\(^{2+}\) exchanger.\(^{96,99}\) Many sarcolemmal receptors affect calcium handling in cardiac myocytes. Agonists through G proteins increase adenyl cyclase (AC) activity, which results in cAMP production. This results in activation of protein kinase A (PKA), which leads to phosphorylation of L-type calcium channels, allowing increase in calcium entry, phosphorylation of phospholamban, increasing SERCA2a activity and phosphorylation of troponin I, which decreases sensitivity of myofilaments to Ca\(^{2+}\). Phosphorylation effects of PKA induce greater release of calcium from SR and faster relaxation. Digoxin inhibits Na\(^+\), K\(^+\)-ATPase pump, which increases intracellular Na\(^+\). This results in increase in intracellular Ca\(^{2+}\) via Na\(^+\)/Ca\(^{2+}\) exchanger, which leads to enhanced Ca\(^{2+}\) loading of SR and increase in Ca\(^{2+}\) release. Phosphodiesterase inhibitors block breakdown of cAMP, which increases its intracellular level and activates PKA. Calcium sensitizers increase sensitivity of myofilaments to Ca\(^{2+}\), enhancing myofilament activation for any concentration of Ca\(^{2+}\). Vesnarinone prolongs action potential duration through modulation of K\(^+\) channels, thereby prolonging opening of L-type calcium channels and increasing Ca\(^{2+}\) entry. Through gene transfer of SERCA2a, modified phospholamban (mPL), or antisense phospholamban (asPL), SR ATPase activity can be increased, which enhances SR Ca\(^{2+}\) content, inotropic and lusitropic state. At level of cardiomyocyte, several stimuli, including endothelin-1 (ET-1), phenylephrine and angiotensin are involved in development of hypertrophy through Gq-coupled receptors. They induce activation of phospholipase C (PLC) and diacylglycerol (DAG), which increases levels of inositol triphosphate (IP3). IP3 induces release of calcium from SR. Increased cytosolic calcium induces mitogen-activated protein...
kinases (MAPK) and activates calcineurin and caspase that contribute to apoptosis.\textsuperscript{98,100,101}

The use of inotropic drugs in heart failure has always been controversial, since it is not clear whether the damaged heart needs rest or stimulation. Inodilation i.e. the combination of positive inotropic and vasodilating therapy, conceptually should be an ideal form of heart failure treatment. The orally inactive inodilator drugs, such as \(\beta\)-agonists, dopaminergic compounds, have not been generally accepted for the treatment of heart failure. The combined \(\beta\)-1 and \(\beta\)-2 agonists do not afford long-term clinical efficacy and also may lead to serious ventricular arrhythmias. Moreover dopaminergic compounds, that besides dopamine-1 and dopamine-2 activation also act through \(\beta\)-receptor stimulation, do not consistently improve the patient’s clinical condition. The inodilation by way of increasing cAMP may not be the right approach in some cases, at least not in advanced heart failure, in which cAMP-dependent inotropic activity is significantly diminished. In contrast, clinical efficacy may be present when partial PDE inhibitors that also act through calcium sensitization, such as pimobendan, are administered to patients with mild to moderate or moderately severe heart failure. Moreover, adverse events may be less at the lower dose level at which, consequently, the degree of PDE inhibition is reduced. Calcium-sensitizing properties may afford an alternative, more economical way to improve contractile force in failing hearts. Hence, agents that combine calcium sensitization with a relatively low degree of PDE inhibition may well be the inodilators of choice, in particular in mild to moderate failure.\textsuperscript{102-106}

Since the present research work is focused on the development of cardiotonic drugs, the literature pertaining to various classes of cardiotonic agents has been extensively studied. Broadly cardiotonic agents can be classified into i) cardiac glycosides and ii) nonglycoside cardiotonics.
CARDIAC GLYCOSIDES

Cardiac glycosides such as digoxin (6) and digitoxin (7) have been used for over 200 years in the management of CHF\textsuperscript{15-23} and till today are most widely prescribed drugs for the treatment of this disease.\textsuperscript{107,108}

The glycosides are obtained from dried leaves of foxglove, *Digitalis purpurea* (digitoxin) or *Digitalis lanata* (digitoxin and digoxin) and from seeds of *Strophanthus gratus* (ouabain). Cardiac glycosides are the combination of an aglycone or genin and one to four sugars. The aglycone is chemically similar to bile acids and to steroids, such as adrenocortical and sex hormones and constitutes the pharmacologically active portion of glycosides. The normal cyclopentanoperhydrophenanthrene nucleus is characteristic of genin portion of all the members of both classes. Digitalis compounds are characterized by a cis/trans/cis steroidal skeleton with an \(\alpha,\beta\)-unsaturated lactone (gammabutyrolactone) in the 17\(\beta\)-position, a 14\(\beta\)-hydroxyl group and a 3\(\beta\)-hydroxyl group, the latter usually linked to one or more sugar rings. The first three moieties are considered essential for inotropic activity, while the sugar portion is responsible for the pharmacokinetics of the compounds. The sugar modifies the water and lipid solubility of the glycoside molecules and thus affects their potency and duration of action.\textsuperscript{109} The cardiac glycosides can be divided into two major classes, cardenolides and bufadienolides, with a major five
membered and six membered unsaturated lactone ring at 17-position of the steroid nucleus, respectively. Prototype of cardenolides is digitoxigenin (aglycone of 7) and that of bufadienolides is bufogenin (8).

Cardiac glycosides exhibit their inotropic effect by inhibiting Na\(^+\), K\(^+\)-ATPase enzyme and inhibit pumping of Na\(^+\) out of the cell, which in turn leads to increased intracellular Na\(^+\) concentration and subsequent increase in Na\(^+\)/Ca\(^2+\) exchange. The increased intracellular Ca\(^2+\) concentration is associated with increased contraction.\(^{110,111}\)

Unfortunately, the low therapeutic index resulting in toxicity of cardiac glycosides, limits their usefulness as cardiotonic drugs. Their use is further complicated by their propensity to cause life threatening arrhythmias and marked variations in individual sensitivity.\(^{112,113}\) Most investigators engaged in Na\(^+\), K\(^+\)-ATPase research agree that the toxic effects of the glycosides, like their positive inotropic actions are intimately related to their binding to the Na\(^+\) pump.\(^{114}\) The beneficial effects of digitalis in congestive heart failure include increased myocardial contractile force and stroke volume and there is decrease in end-systolic ventricular volume, ventricular wall and ventricular filling tension. Among the thousands of analogues of cardiac glycosides synthesized, no significant improvement in therapeutic ratio has been achieved.\(^{115,116}\)

A large number of semisynthetic nonglycosidic agents with similar positive inotropic effects have been synthesized. They have same mechanism like cardiac glycosides. These include erythrophleum alkaloids like cassaine,
chlorpromazine, ethacrinic acid, vandate etc., but all have toxicity problem like cardiac glycosides.\textsuperscript{117-119}

**NONGLYCOSIDE CARDIOTONIC AGENTS**

To find a nonglycoside ‘digitalis replacement’, several chemical classes of nonglycoside compounds have been screened and further exploited for positive inotropic properties on the basis of their pharmacological mechanism of action.

**\(\beta\)-ADRENERGIC STIMULANTS**

Direct \(\beta\)-adrenergic stimulants cause an increase in force (inotropic) and rate (chronotropic) of contraction of cardiac muscle, leading to an increase in cardiac output work and myocardial oxygen consumption.\textsuperscript{120,121} Catecholamines are the prototype of this class of cardiotonic agents.

The positive inotropic action of catecholamines, e.g., nor-epinephrine, epinephrine and isoproterenol is accompanied by either tachycardia or vasotrophic activities, which limit the use of these agents in treatment of patients with heart failure.\textsuperscript{122} Although, these drugs are orally inactive, but have shown promise by intravenous route for short duration of infusion and are useful as inotropes when such therapy is required. The most commonly used \(\beta\)-adrenergic stimulants used for CHF are dobutamine (9), butopamine (10) and prenalterol (11). However, their use in congestive heart failure, which requires long-term oral administration, seems precluded by the tachyphylaxis and unwanted peripheral vasoconstriction that generally becomes apparent after their continued intravenous administration,
as disease progresses.\textsuperscript{123,124} Although bioavailability problems of \( \beta \)-agonists can be solved, pharmacological tolerance due to \( \beta \)-receptors downregulation and modulation of ventricular arrhythmias upon chronic administration appear to limit their use. Collectively these findings suggest that \( \beta \)-adrenoceptor agonists would be less effective as positive inotropic agents for the long term treatment of chronic cardiac failure.\textsuperscript{125,126}

**PHOSPHODIESTERASE 3 (PDE3) INHIBITORS**

Inhibitors of cardiac phosphodiesterase of type 3 are the most important among the nonglycoside cardiotonics. Cyclic 3',5'-adenosine monophosphate (cAMP) and cyclic 3',5'-guanosine monophosphate (cGMP) regulate a myriad of cellular functions in all cell types including cardiovascular system. The cAMP and cGMP are ubiquitous intracellular second messengers, which regulate many prominent cellular processes such as secretion, contraction, metabolism and growth. The increase in their intracellular levels by PDE inhibition (Figure 4) represents a useful strategy for eliciting a variety of pharmacological effects.\textsuperscript{127-130}

![Figure 4. Catalytic hydrolysis of cAMP and cGMP to 5'-AMP and 5'-GMP by phosphodiesterases.](image-url)
There are at least 11 different families of mammalian phosphodiesterases PDE1-PDE11, most of which contain more than one gene product. Each phosphodiesterase family and even phosphodiesterases within a family, can display different substrate specificity, kinetic behavior, allosteric regulation, subcellular localization, regulation by endogenous inhibitors and activators and susceptibility to phosphorylation. Phosphodiesterase enzymes hydrolyze the 3'-ribose phosphate bond of cAMP and cGMP to form biologically inert 5'-nucleotide monophosphates (Figure 4). The members of the PDE3 family are known as cGMP-inhibited PDEs (cGI-PDEs). These enzymes bind both cAMP and cGMP with high affinity at the active site but cAMP is hydrolyzed 4-10 times higher than cGMP.

The possible significant roles of PDE3 are in platelet aggregation, regulation of blood pressure and regulation of insulin secretion. At present, for this PDE family two different gene products have been identified i.e. PDE3A and PDE3B. These two isoforms are encoded by different genes that show a high degree of homology within the catalytic domain of the protein, except for a poorly conserved region of 44 amino acids that represents an insertion unique to the PDE3 family. The PDE3A cDNAs were originally isolated from heart tissue, but the mRNA can be detected by Northern analysis or in situ hybridization in myocardium, vascular and non-vascular smooth muscle, megakaryocytes, epithelium, oocytes and a subset of neurons. In contrast, PDE3B cDNAs were initially isolated from adipose tissue, but the message can also be detected by northern analysis or in situ hybridization in hepatocytes, kidney epithelium, T-cells, spermatocytes and embryonic neuroepithelium. PDE3B is one of the predominant cAMP-hydrolysing activities present in adipose tissue and in isolated adipocytes and is associated with induction of lipolysis in vitro as well as in vivo. Hence PDE3B inhibitors have a combination of metabolic properties that suggests their utility for the treatment of obesity. At present the PDE inhibitors belong to second class of drugs that act as cardiotonic agents. Interest in selective inhibitors of PDE3 as inotropes, vasodilators and antithrombotic agents has been extensive.
As initial enthusiasm about β-adrenergic approaches diminished, the industry began to search for a ‘non-glycosidic’, ‘non-catechol’ (non-adrenergic) digitalis replacements for the treatment of CHF.143 The intensity of efforts to design novel inotrops was augmented upon the discovery and clinical development of amrinone (12), a bipyridine and it was the first breakthrough that occurred nearly three decades ago. Subsequently, amrinone was found to have side effects like thrombocytopenia and gastrointestinal disturbances and then it was replaced by milrinone (13), which has higher therapeutic potency. Infact, it appears that amrinone, the parent or prototype compound is responsible for igniting the development of PDE3 inhibitors.143,144 PDE3 inhibitors can be of particular use for the treatment of CHF because of their mixed inotropic-vasodilator profile, which can lead to reduced afterload on heart. From chemistry point of view, PDE3 inhibitors may be divided into various classes.

2-PYRIDONES

Amrinone (12) and milrinone (13) are the prototypical agents of this class of PDE3 inhibitors. Amrinone, 5-amino-[3,4'-bipyridine]-6-one, has both positive inotropic and vasodilator properties and it was the first non-steroidal, non-

\begin{align*}
(12) & R = N, R_1 = H, R_2 = NH_2 \\
(13) & R = N, R_1 = CH_3, R_2 = CN \\
(14) & R = CH, R_1 = CH_3, R_2 = NH_2
\end{align*}

catecholamine type inodilator discovered with mechanism of action quite different from digitalis glycosides and β-adrenergic agonists. The relative contributions of inotropic and vasodilatory activity to the clinical effects of amrinone have been extensively reviewed.145-150
Amrinone (12) causes significant increase in cardiac contractile force, coronary blood flow, oxygen uptake and total cardiac work with no significant changes in heart rate and an increase in the efficiency of heart. The vasorelaxant action of amrinone does not involve adenosine 3',5' cyclic monophosphate (cAMP) or involve guanosine 3',5' cyclic monophosphate (cGMP) but may include an inhibition of Ca\(^{2+}\) influx through receptor or L-operated Ca\(^{2+}\) channels, although it does not directly affect intracellular Ca\(^{2+}\) release.\(^{151}\) However, this drug suffers from major side effects like thrombocytopenia, gastrointestinal disturbances and arrhythmias. Later on milrinone (13), which is chemically 1,6-dihydro-2-methyl-6-oxo-[3,4'-bipyridine]-5-carbonitrile was synthesized and it showed 20-50 times more potency than 12. Milrinone was developed in same series as amrinone and initially appeared to have overcome some of the unfavorable effects of amrinone including blood dyscrasias and short elimination half-life.\(^{152-158}\)

APP 201-533 (14) is another analogue of amrinone, which has been reported to produce positive inotropic actions in experimental animals. Positive inotropic and electrophysiological effects of 14 can be explained due to an increase of cardiac cAMP.\(^{159,160}\)

A series of 5-aryl-3,4-dihydropyridin-2(1H)-ones, structurally related to 12 were prepared in order to develop new cardiotonic agents. Pharmacological
assays showed that 6-methyl-5-[(4-methylsulfonyl)phenyl]-2-oxo-1,2-dihydro-
pyridine-3-carbonitrile (15) has a remarkable cardiotonic effect and produces a 
selective inhibition of PDE3/PDE1, isolated from cat heart.\textsuperscript{161}

Pyridones of general formula 4-alkyl(aryl)-6-aryl-3-cyano-2(1H)-pyridinones were synthesized and target compounds were evaluated for their 
cardiotonic activity using the spontaneously beating atria model from reserpine 
treated guinea pigs. Among this series, 3-cyano-6-(3,4-dimethoxyphenyl)-4-(4-
hydroxyphenyl)-2(1H)-pyridinone (16) displayed the best pharmacological profile 
and also selectivity for increasing the force of contraction (108.7±6.7% change 
over control) rather than the frequency rate (40.8±5.3% change over control) at 
5 x 10^{-4} \text{M}.\textsuperscript{162}

One milrinone analogue with better pharmacological profile has been 
marketed in the name of E-1020 (loprinone hydrochloride) (17). The PDE3 
inhibitor 17 has positive inotropic and vasodilating effects. Clinically, 17 appears 
to have a positive inotropic effect that depends on the extent of myocardial 
perfusion.\textsuperscript{163}

The ionization and partitioning behavior of a number of inotropic pyridine-
2(1H)-one derivatives and their relation with the pharmacological activity was also studied. Based on the CZE-determined pKa values, intramolecular electronic interactions were precisely assessed. The results revealed the importance of the acidity in understanding pyridone/hydroxypyridine tautomerism. Octanol/water partition coefficients encode for tautomerism as well and a comparison between experimental and calculated partition data helped to detect the 'oxo' tautomers as the most relevant forms from a pharmacodynamics point of view. This physicochemical study carried out on a set of milrinone-related compounds with a different degree of cardiotonic activity brings evidence that a high fraction of the neutral species at physiological pH predominantly in the more polar pyridone tautomer is required for a good positive inotropism.164

Another milrinone analogue (±)-1,2-dihydro-5-[4-[2-hydroxy-3-[4-(2-methoxyphenyl)-1-piperazinyl]propoxy]phenyl]-6-methyl-2-oxo-3-pyridinecarbonitrile (BDF 8634; saterinone, 18) was synthesized at Beiersdorf AG (Hamburg, Germany). Saterinone (18) is a PDE3 inhibitor of the bipyridine type with an A₁-adrenoceptor antagonistic moiety. Chemically, it resembles milrinone (13) and urapidil (19). Saterinone (18) has a concentration dependent positive inotropic effect on the isolated guinea pig papillary muscle and a potent antagonistic effect at
vascular \( \alpha_1 \)-adrenoceptors. The EC\(_{50} \) for its positive inotropic effect was found to be \( 3.2 \times 10^{-6} \) M and it was associated with an elevation of myocardial cAMP content and was not mediated by either \( \beta \)-adrenoceptors or \( H_2 \)-histaminergic receptors. In homogenates of guinea pig right ventricles, the hybrid compound 18 inhibited PDE.\(^{165} \) The effects of 18 were compared with those of 3-isobutyl-1-methylxanthine (IBMX) and milrinone (13) and was found more potent than milrinone as a positive inotrope, while the maximum obtainable effect of 18 was only half that of milrinone. However, increase in the rate of contractions of spontaneously beating right guinea pig atria induced by 18 was only half as pronounced as that caused by isoproterenol at concentrations producing a similar positive inotropic effect.\(^{165} \)

In another study, the enantiomeric forms of 18 were investigated using \textit{in vitro} and \textit{in vivo} models in laboratory animals.\(^{166} \) Both \( R \) and \( S \) forms exhibited equipotent inotropic activity in the guinea pig papillary muscle and were also as potent as racemic mixture. However, \( R \)-18 exhibited a greater maximal obtainable effect than the related compounds. Even the phosphodiesterase inhibiting activity in the guinea pig myocardium was also same for enantiomers as well as racemic forms. Thus the enantiomers of 18 did not display enantioselectivity for inotropic and PDE3 inhibitory effects \textit{in vitro}, nor for cardiotonic effects \textit{in vivo}.\(^{166} \) There is a slight enantioselectivity at \( \alpha_1 \)-adrenoceptor in receptor binding studies, but this is reduced to biological irrelevant magnitude in functional studies \textit{in vitro} and \textit{in vivo}.\(^{167} \)

Milrinone analogues, such as 6-substituted-3-acetyl-5-acylpyridin-2(1H)-ones and 7-substituted-3-acetyl-7,8-dihydro-2,5(1H,6H)-quinolinediones, in which the cyano group was replaced by the acetyl function, have also been prepared.\(^{168} \) The compounds did not induce any inotropic effect in preliminary pharmacological investigation as compared to reference compound, milrinone.

Molecular modeling studies on 2-pyridone derivatives have supported a possible correlation between positive inotropic response and selective PDE inhibition, coming out from the finding that these substances mimic the structural and electronic features of cAMP at the enzyme active binding site. It was assumed that agonists and antagonists compete for a common receptor site.\(^{169} \)
In a series of 1,6-naphthyridin-2(1H)-ones, reported as novel inhibitors of cAMP PDE3, modification of the carbonyl group of medorinone (20) or N-methylation at N-1 resulted in a dramatic loss of enzyme activity. Absence of the C-5 methyl group of 20 or its shift to other positions also led to reduced activity.

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\text{(20)}
\]

However, substitution at C-5 by a wide variety of substituents showed improvement of enzyme activity and some were even more potent than milrinone.\(^{170}\)

The success with 2-pyridones prompted the researchers to synthesize and evaluate pyrimidone derivatives for inotropic and chronotropic effects. It was observed that this class of agents demonstrated a varying degree of vasodilator effects concomitant with increases in ventricular contractility. A major component of their inotropic effect is mediated by the inhibition of cardiac PDE3. Of these, 21 was found to be the most potent inhibitor of PDE3.\(^{171}\)

**INDOLE DERIVATIVES**

The 5H-pyridazino[4,5-b]indoles, 22 and 23, with a planar topology, a dipole with an adjacent acidic proton and a basic hydrogen-acceptor site opposite the dipole have been prepared. These compounds have some resemblance to carbazeram and other similar agents with cardiotonic activity. Some of these compounds possess inotropic activity with a complementary effect.
as inhibitors of platelet aggregation. Hydrazino derivative of 22 is the novel indole with activities both as inhibitor of PDE4 and as selective inhibitor of TXA₂ (thromboxane-A₂) synthetase.¹⁷²

Pharmacological actions such as effect on force of contraction, beating frequency and cyclic nucleotide PDE activity of 4-(4'-n-butylaniline)-7,8-dimethoxy-5H-pyrimido[5,4-b]indole (B11, 24) were investigated in isolated cardiac tissue preparations using amrinone as standard drug.¹⁷³ The indole derivative 24 produced a concentration dependent positive inotropic and positive chronotropic responses in guinea pig atrial tissues and the potency was greater than that of amrinone. Activities of PDE1-4 from dog heart ventricle and PDE4 from guinea pig heart ventricle were also inhibited by 24, nonselectively. It was concluded that 24 possesses potent positive inotropic activity in guinea pig atria and the effect is probably mediated by a non-selective inhibition of PDE activity.¹⁷³

QUINAZOLIN-2-ONES

Of this class Ro 13-6438 (25), a chloroquinazolin-2-one derivative, was the first agent reported with cardiotonic activity. The Possible mechanism involved in the positive inotropic activity of 25 was studied. It was observed that
the positive inotropic response to 25 of the isolated guinea pig papillary muscle was accompanied by inhibition of myocardial cyclic AMP PDE activity and elevation of intracellular cyclic AMP levels. Apparently, the elevated cAMP levels resulting from the induced inhibition of PDE enhanced the slow inward Ca\(^{2+}\) current. The compound 25 produced a concentration dependent increase in the upstroke velocity, overshoot and duration of slow action potentials evoked in partially depolarized papillary muscles.\(^{174}\)

Investigations on pharmacological properties of a novel, potent inhibitor of cAMP phosphodiesterase, \(N\)-cyclohexyl-\(N\)-methyl-4-(7-oxy-1,2,3,5-tetrahydro-imidazo[2,1b]quinazolin-2-one)butyramide (lixazinone, RS-82856, 26), revealed it as a useful agent to increase cardiac output in the treatment of congestive heart failure.\(^{175}\)

Hybridization of structural elements of the PDE inhibitors 26 and anagrelide with complementary features of other PDE inhibitor cardiotonic agents led to the design and synthesis of new compounds like 27 and 28. Pharmacological evaluation of these compounds showed that structures possessed negligibly enhanced activities over the parent heterocyclic system and remained significantly inferior to lixazinone in all respects. This difference is ascribed to the absence of the \(N\)-cyclohexyl-\(N\)-methylbutyramidyl-4-oxy side chain of 26, which
may function as an effective surrogate for selected characteristics of the adenine

\[
\begin{align*}
(27) & \quad (28)
\end{align*}
\]

portion of cAMP.\(^{176,177}\)

Oxime derivative R 79595 (29) represents a novel class of compounds with PDE inhibitory and positive inotropic actions. The \(E\) isomer of 29 was found nearly 100 fold more potent than the \(Z\) isomer.\(^{178}\)

A related series of alkyl aryl pyrrolone derivatives was designed by making use of rolipram (30), a known PDE4 inhibitor,\(^{129}\) as a lead structure and was guided by a model which describes the features required for potent inhibition

\[
\begin{align*}
(29) & \quad (30)
\end{align*}
\]

of the cardiac isoenzyme. The compounds 31 and 32 displayed good activity as inhibitors of the cardiac and brain cAMP PDE isoenzymes and positive inotropic activity in ferret papillary muscle. Selected compounds were further examined in an \textit{in vivo} hemodynamic model and 32 was identified as a potent and selective
positive inotropic agent and inhibitor of cardiac cAMP PDE.\textsuperscript{179}

\begin{center}
\begin{tikzpicture}
  \node[draw] (c) {\textbf{(31)}\hspace{1cm}\textbf{(32)}};
  \node[draw, above] at (c) {MeO} edge[->] (c);
  \node[draw, below] at (c) {MeO} edge[->] (c);
  \node[draw, above] at (c) {\textbf{\textcolor{red}{\texttt{N}}}} edge[->] (c);
  \node[draw, left] at (c) {\textbf{\textcolor{red}{\texttt{CH}}}} edge[->] (c);
  \node[draw, above] at (c) {\textbf{\textcolor{red}{\texttt{O}}}} edge[->] (c);
  \node[draw, left] at (c) {\textbf{\textcolor{red}{\texttt{CH}}}} edge[->] (c);
  \node[draw, above] at (c) {\textbf{\textcolor{red}{\texttt{CH}}}} edge[->] (c);
  \node[draw, above] at (c) {\textbf{\textcolor{red}{\texttt{CH}}}} edge[->] (c);
\end{tikzpicture}
\end{center}

QUINOLINONE DERIVATIVES

Based on a pharmacophore analysis, a series of cardiotonic quinolin-2(1H)-one derivatives was designed and compared with amrinone for inotropic and chronotropic activities. Among these, vesnarinone (33), a recently introduced cardiotonic agent showed the best profile as a potential drug for the treatment of congestive heart failure, having greater positive inotropic activity than amrinone.\textsuperscript{180,181}

\begin{center}
\begin{tikzpicture}
  \node[draw] (c) {\textbf{(33)}};
  \node[draw, above] at (c) {MeO} edge[->] (c);
  \node[draw, below] at (c) {MeO} edge[->] (c);
  \node[draw, above] at (c) {\textbf{\textcolor{red}{\texttt{N}}}} edge[->] (c);
  \node[draw, above] at (c) {\textbf{\textcolor{red}{\texttt{O}}}} edge[->] (c);
\end{tikzpicture}
\end{center}

This (1-piperazinyl)-2-(1H)-quinolinone derivative exhibited dual concentration dependent effects on the spontaneous beating rate (SBR) of the SA nodes.\textsuperscript{180,181} Several recent studies have also shown the utility of 33 in the treatment of cancer.\textsuperscript{182,183}

A tetrahydroisoquinolinone derivative MS-857 (34) produced a significant and dose-dependent increase in cardiac contractility with relatively small changes.

28
in heart rate and blood pressure. No arrhythmias and no changes in animal behavior occurred. After chronic oral administration, 34 completely retained its activities, indicating lack of tachyphylaxis. The compound also inhibited PDE3 selectively.\textsuperscript{184}

Cilostamide (35) chemically, \textit{N}-cyclohexyl-\textit{N}-methyl-4-(1,2-dihydro-2-oxo-6-quinolyloxy)butyramide, is one of the most potent and selective PDE3 inhibitor reported till date with IC\textsubscript{50} value of ~ 30 nm. It also exhibited good activity when tested in rabbit and canine ventricular muscle.\textsuperscript{185}

Cilostazol (36) is another quinolinone type PDE3 inhibitor that has recently been approved by the Food and Drug Administration (FDA) for the treatment of intermittent claudication. Its efficacy is presumed to be due to its vasodilatory and platelet activation inhibitory activities. Because of its PDE3 inhibitory activity, however, the possibility that cilostazol (36) exerts positive cardiac inotropic effects is a safety concern. In a new study, effects of 36 on intracellular cAMP levels in platelets, cardiac ventricular myocytes and coronary smooth muscle cells have been compared with milrinone.\textsuperscript{186} Both produced a concentration-dependent increase in the cAMP level in rabbit and human platelets with similar potency and were also equally effective in inhibiting human platelet aggregation and increased coronary flow equally in rabbit hearts. The results showed that although, 36 and 13 both inhibit PDE3, cilostazol preferentially acts on vascular
elements (platelets and flow). This unique profile of cilostazol is consistent with its beneficial and safe clinical outcomes in patients with intermittent claudication.\textsuperscript{186-188} The cardiac effects of OPC-13015, a metabolite of 36 with about seven fold higher PDE3 inhibition, were similar to 36.

**IMIDAZOLE DERIVATIVES**

Enoximone (37) and piroximone (38) belong to the imidazoline class of PDE3 inhibitors.\textsuperscript{189} In a series of 4-aryl-1,3-dihydro-2H-imidazol-2-one, substitution

\begin{align*}
\text{CH}_3\text{S}-\text{CH}=\text{CH}_2 & \quad \text{HN-CH}_2\text{NH} \\
\text{HN-CH}_2\text{NH} & \quad \text{O} \\
\text{HN-CH}_2\text{NH} & \quad \text{O}
\end{align*}

of 4-methylthiobenzyl (37) or 4-pyridyl (38) afforded compounds of greatest inotropic potency. Both are highly potent inodilators with dual inotropic and vasodilatory activities, which are not accompanied by changes in myocardial oxygen demand. An inotropic dose of 37 increases the level of cAMP in the isolated, blood perfused dog papillary muscle owing to its selective inhibition of the one isoform of phosphodiesterase from the dog heart that is inhibited by cGMP.\textsuperscript{190,191}

Imidazole substituted derivatives 39 and 40 were found to be highly potent positive inotropic agents in a series of 4-alkyl-1,3-dihydro-5-[(1H-imidazolyl)]-benzoyl]-2H-imidazol-2-ones. A wide range of inotropic and cAMP PDE inhibitory
potencies were observed in this series. Substitution on the imidazolyl moiety
being the major determinant of activity.\textsuperscript{192}

Several 2-imidazolidinones (41) and 2-imidazolidinethiones (42) have also
been reported as potent cardiotonic agents. Alkylation of 41 produced potent

\[
\begin{align*}
\text{(41) } R &= O \\
\text{(42) } R &= S
\end{align*}
\]

compounds, whereas that of 42 resulted in weak activity.\textsuperscript{193}

A new series of hybrid molecules, \( p \)-substituted 4-benzoyl-5-alkyl-2-
imidazolones, were prepared by combining the structural features of
imidazolone-type PDE inhibitor enoximone and guanidine-type histamine \( H_2 
\)
receptor agonists.\textsuperscript{194} The compounds were screened for positive inotropic activity
in the isolated electrically stimulated guinea pig papillary muscle and for inhibition
of PDE3 isolated from guinea pig heart. The cardiotonics obtained proved to be
either PDE3 inhibitors, some of them surmounting up to 3-fold the potency of

\[
\begin{align*}
\text{(43)}
\end{align*}
\]

enoximone or pharmacological hybrids, combining both PDE3 inhibitor and
histamine \( H_2 \) receptor agonist activities. These hybrids were the most potent
positive inotropic substances at the papillary muscle, probably due to their
synergistic mechanism of action. The compound 43 with moderate PDE3
inhibition and histamine \( H_2 \) agonist activity was about 2 and 10 times more potent
than enoximone at the papillary muscle.\textsuperscript{194}

In another study, substituted 2,2'-bi-1\textit{H}-imidazoles and related analogues were synthesized and evaluated for inotropic activity.\textsuperscript{195} Structure-activity relationship studies based on a nonclassical bioisosteric approach indicated the necessity of a cyano group on one of the imidazole rings and an acidic -NH to obtain the desired pharmacological profile. 4(5)-Cyano-2,2'-bi-1\textit{H}-imidazole (44)

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {R};
\node (b) at (0.5,0) {N};
\node (c) at (1,0) {N};
\node (d) at (0.5,0.5) {R};
\node (e) at (0.5,-0.5) {R};
\node (f) at (0.5,0) {CN};
\draw (a) -- (b) -- (c) -- (d) -- (e);
\end{tikzpicture}
\end{center}

(44) $R = \text{H}$

(45) $R = \text{CH}_3$

was the most potent inotropic agent of the series. It is a good inhibitor of PDE type IV, isolated from dog heart, with potency similar to that of amrinone. Replacement of acidic -NH with methyl as in 45 resulted in loss of activity.\textsuperscript{195}

\section*{BENZIMIDAZOLE DERIVATIVES}

Sulmazole (AR-L 115 BS, \textbf{46}) was one of the chosen compound from a large series of benzimidazoles synthesized by Diederen \textit{et al.}\textsuperscript{196} It displayed cardiotonic as well as vasodilator activities in heart failure model and also showed good PDE3 inhibition.\textsuperscript{199} Structural requirements necessary for optimal inotropic activity in this series of molecules, containing a heterocyclic ring fused
to 2-phenylimidazole, were investigated. It was observed that the 2-phenylimidazo[4,5-\textit{c}]pyridines (Isomazole, \textbf{47}) were generally 5-10 folds more potent than analogues 2-phenylimidazo[4,5-\textit{b}]pyridines (\textbf{46}).\textsuperscript{198} In addition, the [4,5-\textit{c}] isomer possessed superior oral activity and longer duration of action than
Further pharmacological studies on 46 and 47 exhibited that they are weak inhibitors of PDE3 and their inotropic activity is unlikely to be due to PDE3 inhibition.\textsuperscript{197} Removal of methyloxythio group of 46 and 47 in another series of imidazopyridines resulted in compounds 48 and 49, respectively, which were significant PDE inhibitors of the cGMP specific isoenzyme PDE5.\textsuperscript{199}

Studies on several classes of imidazopyridines like 50 and 51, revealed that the relationship heterocycle-phenyl-imidazole is of critical importance for positive inotropic activity and is accompanied by varying degrees of cAMP PDE inhibitory activity. Compounds with imidazole substituents consistently showed greater activity.\textsuperscript{200}

Various "A" ring substituted analogues of sulmazole and isomazole were prepared and evaluated for inotropic activity.\textsuperscript{201} Electron releasing substituents, such as methoxy and amino, were better tolerated than lipophilic or electron-
withdrawing groups. The 6-position of sulmazole appeared to be the most tolerant towards substituents and a methoxy substituent was best tolerated at the 4-position of isomazole. Thus, 6-aminosulmazole (52) and 4-methoxyisomazole (53) displayed the most potent inotropic effects in vivo.

A structurally related series of 6-pyridinylimidazo[2,1-b]thiazoles and thiazolines were prepared and tested for their positive inotropic activity. Among them the compounds 54 and 55 exhibited a significant positive inotropic activity, when compared with amrinone (12). The compounds exhibited PDE3 inhibition and also increased Ca\(^{2+}\) availability to the contractile proteins.\(^{202}\)

Various methylthiophenylimidazo[2,1-b]thiazoles (56) and thazolines (57) analogous to sulmazole were synthesized and screened for their inotropic activity. The results show that the saturated derivatives were more active than the corresponding unsaturated ones. The compound 57 showed the same strong positive inotropic activity as the analogue imidazo[2,1-b]thiazole bearing a 2,4-dimethoxyphenyl group in position 6. Both cleavage of methyl group and sulphur oxidation gave rise to a drop in activity. The compounds were believed to act by same mechanism as that of sulmazole.\(^{203}\)

**FLAVONOIDS**

Two tested flavonoids, quercetin (58) and apigenin (59), both showed cardiotonic effects on the isolated toad heart perfusion system; however, their action was different from that of isoprenaline sulfate and was not associated with
β-receptors but phosphodiesterase enzyme. The PDE-inhibitory activity of 58 was highest of all the flavonoids tested and was 15-fold greater than that of 1-methyl-3-isobutylxanthopterin, a known potent PDE inhibitor. The inhibitory effect of these tested flavonoids on cAMP-PDE was much greater than that on cGMP-PDE. Thus, the cardiotonic action of flavonoids is probably the result of their inhibitory effects on cardiac cAMP-PDE.

PYRIDAZINONES

The first synthesis of pyridazin-3(2H)-one was achieved by Bistryki et al. in 1899. Since then 4,5-dihydro-3(2H)-pyridazinone ring system has attracted much attention as the nucleus of potential therapeutic utility. The chemical, biological and pharmacological aspects of pyridazin-3(2H)-ones have been extensively reviewed. These compounds are particularly important due to their antihypertensive, platelet aggregation inhibitory and antithrombotic, analgesic and cardiotonic effects.

A number of 6-phenyl-4,5-dihydro-3(2H)-pyridazinones have been synthesized and examined for hypotensive activity in the normotensive rats. Considerable activity in this area has been observed for a variety of substituents on the phenyl moiety. The compounds containing acetamido and cyano groups combined with a methyl group at position 5 exhibited potent and long lasting hypotensive activity and SK&F-93741 (60) and 61 were the most active ones in the series. The pyridazinone 60 emerged as potent inodilator in cats in both in vivo and in vitro studies with good PDE inhibition profile. It was observed that PDE3 inhibitory potency is associated with overall planar topology of the phenyl
pyridazinone moiety and the presence of two electronegative centers. Further Coates et al. prepared 1,4-bis(3-oxo-2,3-dihydropyridazin-6-yl)benzene and related bis(azinone) derivatives and it was found that bis(azinone) of 60 was more potent than the parent molecule.\textsuperscript{217} R-isomer (methyl at C-5 of pyridazinone with $R$ configuration) of 60 is an established drug by the name OR-1896 and has been reported as a calcium sensitizier for the treatment of congestive heart failure.\textsuperscript{218, 219}

In comparison with milrinone, RS-1893 (62), an orally active pyridazinone was found about 20 times more active venous and arterial vasodilator with cardiotonic activity.\textsuperscript{220}

The pyridazinone derivative zardaverine (63) is a potent bronchodilator both \textit{in vivo} and \textit{in vitro} and exerts a positive inotropic action on heart muscle \textit{in vitro}. The actions of 63 are mediated via inhibition of PDE activity. It

\[
\text{MeO} \\
\text{F}_2\text{HCO} \\
\text{N} \\
\text{N} \\
\text{O}
\]

(63)

inhibited the cGMP-inhibited PDE3 from human platelets and the rolipram-inhibitable PDE4 from canine trachea and human polymorphonuclear (PMN)
Zardaverine (63) is a mixed inhibitor of PDE3 and PDE4 isoenzymes. In another study, imidazolyl substituted 6-phenyl-3(2H)-pyridazinones were synthesized and investigated for positive inotropic activity. Among the series, a compound Imazodan (CI-914, 64) produced substantial increase in myocardial contractility. Alkyl substitution of the imidazole moiety did not offer any advantage, whereas substitution of methylsulfinyl group retained some of the activity of parent compound 64. The 5-methyl substituted analogue of 64 was most potent positive inotropic agent and was more potent than milrinone. While 64 was more active than amrinone (12).

Various forms of PDE3 are present in cardiac muscle and their role in regulating the cardiac contractility has been thoroughly examined. Variation in inotropic response of imazodan like cardiotonic agents in various species such as dog, rhesus monkey and rat is attributed to the presence of subclass of low Km, cAMP specific PDE in cardiac muscle. Further, two functional subclasses of low Km cAMP specific PDE3 are: i) an imazodan sensitive form, which is membrane bound and ii) an imazodan insensitive form, which is soluble. The maximum inotropic response to imazodan was observed only in those species in which imazodan sensitive subclass of PDE3 was present and was membrane bound. Low Km cAMP specific form is believed to represent the site of action of several of new cardiotonic agents including imazodan, amrinone cilostamide and enoximone.

Ring-opened analogs of imazodan (64) were prepared and evaluated for inotropic activity in an anesthetized dog model. Although the overall cardiovascular profile of the acylhydrazone series was similar to the corresponding cyclic analogs, the inotropic potency was significantly reduced. The guanylhydrazone series demonstrated enhanced inotropic potency that was
comparable to 4,5-dihydropyridazinones. Although these acyclic analogs qualified to fit a 5-point model developed for several cyclic inotropes, at least partly, the inotropic mechanism of the guanylhydrazones seems to differ from that of the corresponding acylhydrazones and cyclic 4,5-dihydropyridazinones.\(^{226}\)

As a variation on the imazodan series, several analogs of (E)-4,5-dihydro-6-[2-[4-(1/-/imidazol-1-yl)phenyl]ethenyl]-3(2/-/)-pyridazinone were synthesized. The compounds were evaluated for hemodynamic activity, cAMP-phosphodiesterase inhibitory activity (human platelets and guinea pig heart tissue) and platelet aggregation inhibitory activity.\(^{227}\) The insertion of the ethenyl

\[
\text{HN—N} \quad (65)
\]

moiety between the phenyl and dihydropyridazinone rings produced novel compounds that retained the potent inotropic/vasodilator activity of the parent imazodan series and enhanced the platelet aggregation inhibitory potency. One such compound 65 displayed most potent platelet aggregation inhibitory activity along with antithrombotic activity \textit{in vivo}.\(^{227}\)

The structure-activity relationships of a series of 4,5-dihydro-6-[4-(1H-imidazol-1-yl)phenyl]-3(2H)-pyridazinones and related compounds were

\[
\text{(66)}
\]

investigated for the \textit{in vivo} inhibition of different forms of PDE isolated from guinea pig ventricular muscle. The most potent inhibitor of PDE3 was the 4,5,6,7-tetrahydrobenzimidazole derivative 66, with an ED\(_{50}\) of 0.15 µM. With in this

38
series, the studies revealed that i) the 4,5-dihydro-3(2H)-pyridazinone (ring-A) is responsible for inhibitory potency; ii) the B ring mainly acts as spacer and iii) the imidazole moiety (ring C) is primarily responsible for PDE enzyme specificity.\(^{228}\)

Out of a series of ring contracted analogs of imazodan, imidazolyl pyrazoles,

![Chemical structure](67)

synthesized and evaluated for positive inotropic activity, only 67 with small alkyl groups at C-4 showed significant activity.\(^{229}\)

In another study on imazodan type compounds, fused triazolo-pyridazines

![Chemical structure](68)

were prepared and activity was compared with imazodan. All the fused bicyclic ring compounds were found less active, however, the intermediate hydrazine derivatives such as 68 exhibited good positive inotropic activity, but inhibition of cardiac PDE was nonselective.\(^{230}\)

Two dihydropyridazinone derivatives, cyanoguanidine (SK&F 94836, 69) and pyridone (SK&F 95654, 70), were developed by Smith Kline and French research limited. Of these 70 emerged as potent PDE3 inhibitor with sustained inotropic effect.\(^{231}\)
Levosimendan, (R)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)-phenyl]hydrazono]propanedinitrile (71), has been marketed by the name Simadex® as a potential drug for treatment of CHF. This pyridazinone dinitrile derivative has Ca\textsuperscript{2+}-sensitizing activity in preparations isolated from guinea-pig and human hearts, and is a weak PDE3 inhibitor. Its cardiotonic action is attributed to increase in Ca\textsuperscript{2+}-sensitization of cardiac muscle. Levosimendan is also a vasodilator both \textit{in vitro} and \textit{in vivo}, but its mechanism is not well understood. The evidence points to a novel mechanism that might involve its direct effect on the smooth muscle contractile or regulatory proteins. OR-1896, R- isomer of 60 is the primary active metabolite of 71.

NSP-513, chemically, (R)-4,5-dihydro-5-methyl-6-[4-(2-propyl-3-oxo-1-cyclohexenyl)amino]phenyl-3(2H)-pyridazinone (72), a structural analogue of SK&F 95654 (70) is a selective PDE3 inhibitor with cardiotonic activity. It has the potential to prevent not only \textit{in vitro} platelet aggregation but also \textit{in vivo} thrombus
formation. The highly selective PDE3 inhibitory effect of 72 may make this compound useful for assessing the physiological role of PDE3.\textsuperscript{239} The benzyl vinylogous amide substituted aryldihydropyridazinone derivatives 73 and 74 displayed potent PDE3 inhibition with selectivity towards PDE3B enzyme and are the most potent agents known till date. These compounds displayed lipolysis induction and increased metabolic rate and have potential for the treatment of obesity.\textsuperscript{240}

Gouault \textit{et al.} carried out the solid-phase parallel preparation of a library of amino-substituted 4, 5-dihydropyridazin-3(2H)-ones. In this series 75 and 76 proved to be efficacious and potent relaxants of the isolated rat aorta with low inhibitory effect against PDE3 isoenzyme. The significant vasorelaxation produced by these compounds could be of therapeutic interest even if their mechanism of action remains to be established.\textsuperscript{241}

A novel pyridazinone derivative 6-[4-(4'-pyridylaminophenyl)-4,5-dihydropyridazinone hydrochloride (MCI-154, 77) exerted a unique effect in the chemically skinned papillary muscles of the guinea pig ventricle. Its cardiotonic effect...
activity was about 5.4 and 2.5 times more potent than those of amrinone and milrinone, respectively. In terms of cardiovascular profile, 77 resembles milrinone the most, among new cardiotonic agents, although unlike milrinone, its main mechanism is believed to be the sensitization of the contractile proteins to calcium. Recent studies have further proved its worth in the treatment of CHF.

Hybrid molecules

Further research efforts directed towards the development of PDE3 inhibitory cardiotonic agents resulted in development of various hybrid molecules. These were synthesized by combining pyridazinone moiety with pharmacologically essential structural features of compounds belonging to other chemical classes of PDE3 inhibitory cardiotonic agents. Indolylpyridazinones,

![Indolylpyridazinones](78)

indolidan (78) and its N-methyl analogue, have been developed as a positive inotropic agent with selective PDE3 inhibition.

Several more indolyldihydropyridazinones and related compounds were

![Indolyldihydropyridazinones](79)

synthesized and evaluated for positive inotropic activity. In rats, most of these indole derivatives produced a dose-related increase in myocardial contractility with little effect on heart rate and blood pressure. The compound 79 was found
most active of the series and was further investigated in cats, there it exhibited potency more than pimobendan. The structural requirements for optimal cardiotonic activity within this class of indole derivatives are; a heterocyclic aromatic ring in position 2, hydrogen or a methyl group in position 3 and a dihydropyridazinone ring system in position 5 of the indole.\(^{255}\)

A benzimidazole-pyridazinone hybrid, pimobendan (80), which is chemically, 4,5-dihydro-6-(2-(4-methoxyphenyl)-1H-benzimidazol-5-yl)-5-methyl-3(2H)-pyridazinone was discovered with both vasodilating and inotropic properties and is marketed in the name of Acardi.\(^{®}\) It is a new inotropic drug that augments Ca\(^{2+}\) sensitivity and inhibits phosphodiesterase in cardiomyocytes.\(^{256,257}\) Pimobendan (80) is well absorbed after oral administration and is metabolized in the liver to its primary O-demethyl metabolite UD-CG 212 Cl, which is also active. The calcium-sensitizing effects may assume greater importance in patients with heart failure. Studies in naturally occurring canine heart failure suggest that effects of pimobendan are at least comparable to those of ACE inhibitors, if not superior and is likely to play an important role in future in the treatment of canine heart disease.\(^{258-261}\)

UD-CG 212 Cl is also a potent inodilator with mechanism of action same as that of 80. Several studies in experimental animals as well as in humans have shown the importance of this compound in the treatment of CHF.\(^{262-267}\)

The success with hybrid pyridazinones prompted the researchers to combine quinazoline moiety with pyridazinone ring. In the process, optically active 6-(4-(benzylamino)-7-quinazolinyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone (81) was synthesized and it was found that racemic 81 and its levorotatory isomer were more potent than those of dextroisomer and generated much
interest for the treatment of CHF. Although, (+)-(81) showed weak cardiotonic effects, it displayed maximum Ca\(^{2+}\)-sensitizing activity. This result corresponds to the findings that the structural requirements for inodilating activity were different from those for myofibrillar Ca\(^{2+}\)-sensitizing activity.

Lee et al. using two approaches performed a facile synthesis of substituted 1,2,3,4-tetrahydro-1-oxocarbolines as potential antihypertensive agents. The rationale of drug design was based on the Bristol's hypothesis of 5-point model for PDE3 inhibition activity. The target hybrid molecule comprises a nucleus of 1,2,3,4-tetrahydro-1-oxocarboline and a pyridazinone moiety. In vitro studies revealed that 82 exhibited particularly potent and long-lasting hypotensive activity. Molecular modeling showed that 82 met all the stipulations of 5-point model required for PDE3 inhibition.

Cyano-substituted pyridazinone derivative, SCH00013 (83) exhibited inotropic effects in a concentration dependent manner on isolated dog and rabbit
ventricular muscle and rabbit ventricular cardiomyocytes. It is a novel Ca\textsuperscript{2+} sensitizer that elicits a moderate positive inotropic effect without significant alteration of Ca\textsuperscript{2+} transients.\textsuperscript{271} SCH00013 (83) does not show a positive chronotropic effect and has a weak PDE3 inhibitory action along with class III antiarrhythmic action. The unique pharmacological profile of 83 implies that this agent may be potentially beneficial for pharmacotherapy of contractile dysfunction in congestive heart failure.\textsuperscript{272,274}

The cardiovascular properties of two novel cardiotonic agents; NSP-804, chemically, 4,5-dihydro-6-[4-(2-methyl)-3-oxo-1-cyclopentenyl)-amino]phenyl-3(2H)-pyridazinone (84) and NSP-805, chemically, 4,5-dihydro-5-methyl-6-[4-(2-methyl-3-oxo-1-cyclopentenyl)-amino]phenyl]-3(2H)-pyridazinone (85) were investigated \textit{in vitro} and \textit{in vivo} in comparison with those of other cardiotonic agents like indolidan, milrinone, imazodan and amrinone.\textsuperscript{275} In the propranolol-induced heart failure model in isolated guinea pig left atria, both compounds completely improved the hemodynamic state of heart failure to normal levels. NSP-805 (85) was the most potent and selective inhibitor of guinea pig cardiac PDE3 among the agents examined with potency similar to indolidan.

6-Benzoxazinylpyridazin-3-ones exemplified by bemoradan (86) were
review of literature

prepared and evaluated for inhibition of PDE3 \textit{in vitro} and for positive inotropic activity \textit{in vivo}. Bemoradan (86) was an extremely potent and selective inhibitor of canine PDE3 and a long acting, potent, orally active inotropic vasodilator agent in various canine models.\textsuperscript{276} Altering the pyridazinone substitution from the 6-position to the 7-position produced a 14-fold increase in the cardiotonic potency while substitution at the 8-position reduced potency. The positive inotropic activity was maintained for 8-24 h after a single oral dose (100 mg/kg) in dogs, thus making it one of the most potent and long-acting orally effective inotrope.\textsuperscript{277}

Pyridazinone moiety was also combined with other structural moieties, which exhibit potent cardiovascular effects to reduce certain complications associated with congestive heart failure. A recently patented invention details compounds that possess inhibitory activity against PDE3 and L-type calcium channels. Compound 87 blocked rat cerebral L-type calcium channels and inhibited human platelet cAMP PDE3 \textit{in vitro}. In a paced dog model of congestive heart failure, it gave a dose-dependent response for contractility and ejection fraction with a maximal increase of 53-61\% of that produced by milrinone. However, in contrast to milrinone, which gave ventricular tachycardia at all tested dosages, 87 showed no apparent QT prolongation. The study concluded
that simultaneous antagonism of the L-type calcium channel activity by 87 antagonized the increase in calcium influx into the cardiac myocyte via the hyperphosphorylated L-type calcium channel and thus prevented the toxicities associated with higher levels of PDE3 inhibition.278

The hemodynamic and β-adrenergic blocking effects of GI-104313 (88), a chimeric molecule containing a phosphodiesterase-inhibiting pyridazinone and a β-blocking phenoxypropanolamine, were examined in barbiturate anesthetized, vagotomized dogs. The results of these studies were compared to those of indolidan, a known phosphodiesterase inhibitor and xamoterol, a partial β-adrenoceptor agonist. This unique chimeric molecule 88 exhibited β-adrenoceptor blockade and cardiac inotropy via a nonadrenergic mechanism, most likely due to PDE inhibition.279

The PDE3 inhibitory, inotropic and vasodilator potencies of methylindeno-

![Chemical structure](image)

pyridazinones (89) (n=1) and benzocinnolinones (n=2) were compared with those of their normethyl and bicyclic 4,5-dihydro-6-phenylpyridazinone analogs.280 The structure-activity relationships of the tricyclic pyridazinones differ
from those of bicyclic pyridazinones mainly in respect of the effect of introducing the methyl group into the pyridazinone ring. Although in 4,5-dihydro-6-phenylpyridazin-3(2H)-ones, introduction of a 5-methyl group has been widely reported to lead to compounds of significantly greater potency, as in case of 60 and 61, the novel tricyclic 4a-methylpyridazinones (89) showed inotropic, vasodilator and PDE3 inhibitory potency similar to their normethyl analogs.

Structure-activity relationships

The various substitutions in pyridazinone ring system have led to some promising compounds with optimum cardiotonic activity. QSAR studies suggest that 5-methyl group, free 2-NH and 3-oxo of pyridazinone ring is essential for cardiotonic activity. Various substitutions at 6-phenyl ring particularly at 4-position with an electronegative group is also essential for optimum activity.109,223,228

Inhibitors of cAMP PDE3 were studied by using solid-state, solution and theoretical methods in order to refine a 5-point model for positive inotropic activity. The cAMP PDE3 inhibitors bear a striking resemblance to cAMP itself. This investigation supports the importance of an overall planar topology for selective and potent cAMP PDE3 inhibition. Possible reasons for the potency of certain nonplanar compounds have been investigated and it was found that cardiotonics like imazodan and CI-930 can readily achieve essentially planar geometries, as emerged from various spectral studies such as x-ray crystallography, IR, UV, NMR and theoretical data. Small alkyl substituents that occupy space corresponding to certain portions of the cAMP sugar region increase potency. Selective inhibition of cAMP PDE3 can be achieved by mimicking the attractive electrostatic potential associated with the phosphate group (e.g., with an amide) and by providing an additional attractive potential spatially opposite to the oxo group, in the vicinity of the adenine N1 and extending to N3 (e.g., with an imidazole), together with a partial dipole moment comparable to the adenine dipole moment.270

For nonglycoside cardiotonics a five-point model has been established for
their activity as shown in figure 5, the salient features are: (1) the presence of a strong dipole, (2) an adjacent acidic proton, (3) a methyl-sized lipophilic space, (4) a relatively flat overall topography and (5) a basic or hydrogen-bond acceptor site opposite to the dipole. Most PDE3 inhibitory compounds fit into this model and this model has helped in design of potent PDE3 inhibitors.109

6-Arylpuridinazinones were also subjected to conformational analysis in order to better define the relationship between the cardiovascular properties of some derivatives and their preferred conformations. The highly active compounds were found to exist in a conformation showing a near-planar arrangement of the phenyl and the pyridazinone ring.281

**PHTHALAZINONES**

Success with puridinazinones as novel cardiotonic agents led to design and study of several fused ring derivatives for the treatment of congestive heart failure. Phthalazinol (EG-626, 6,8-dimethyl-7-ethoxycarbonyl-4-hydroxymethyl-1(2H)-phthalazinone, 90) was found to be a considerably potent cardiotonic agent.282,283 It produced both positive chronotropic and inotropic actions in
the guinea pig heart muscle as well as in the isolated right atria and was more selective for increasing contractility than for increasing the sinus rate. The increase in the intracellular cyclic AMP due to the phosphodiesterase inhibition is tentatively the most likely mechanism of action of this molecule.

Phthalazinone 91 and pyridazinone 92 bearing similar structural features at para position of 6-phenyl moiety were synthesized by Demirayak et al. and their vasorelaxant effects were studied on isolated rat aorta and antihypertensive activity was also studied in rats by tail cuff method. Both emerged as potent antihypertensive agents when compared with standard drugs hydralazine and dihydralazine.

**CALCIUM SENSITIZERS**

Catecholamines, selective PDE3 inhibitors and digitalis exert their inotropic effects by increasing intracellular Ca$^{2+}$ concentration. Mobilization of Ca$^{2+}$ may produce several serious adverse effects such as arrhythmias, Ca$^{2+}$ overload and cardiac myopathies. Some of the cardiotonic agents like sulmazole, isomazole and APP 201-533 produce inotropic effects at distinctly lower concentration as compared to that required for PDE3 inhibition. This suggests that PDE3 inhibition
only may not account for their cardiotonic activity and another novel mechanism, which contributes to the inotropic profile of these agents was described by Solaro and Ruegg. It led to the development of a new class of cardiotonic agents called calcium sensitizers, which enhance the sensitivity of myofilaments to already available calcium and exert a positive inotropic effect without increasing the intracellular calcium concentration and therefore may be able to overcome the disadvantages of calcium mobilizers.

EMD 53998 (93), a novel thiadiazinone derivative, increases the contractile force of cardiac tissue in vitro through both selective inhibition of PDE3 and sensitization of cardiac contractile proteins to Ca\(^{2+}\). Interestingly, 93 elevated the maximum of the Ca\(^{2+}\)-response curve for both parameters. It increases force development of guinea pig papillary muscle in a concentration dependent manner and is 10 times more potent than pimobendan. The compound 93 appeared to be a promising inotropic agent with high Ca\(^{2+}\)-sensitizing potency. However, the Ca\(^{2+}\)-sensitizing effects of the compound 93 are highly stereospecific and resides in the dextrorotatory isomer, while the other isomer is a PDE inhibitor devoid of any Ca\(^{2+}\)-sensitizing activity.

BA 41899, chemically, 5-methyl-6-phenyl-1,3,5,6-tetrahydro-3,6-methano-1,5-benzodiazocine-2,4-dione, (94) is a structurally novel 1,5-benzodiazocine derivative and represents the prototype of a hitherto unknown class of positive inotropic Ca\(^{2+}\)-sensitizing agents. It is completely devoid of PDE3 inhibitory activity or any other known inotropic mechanism and is a pure calcium sensitizer. The dextro isomer again carries Ca\(^{2+}\)-sensitization properties and a corresponding positive inotropic effect. Conversely, the negative chronotropic action resides in the levo isomer. All the effects are exerted in the low micromolar range.
positive inotropic action of CGP 48506 [(+)-94] is associated with an accelerating
effect on contraction, and more prominently, relaxation dynamics in isolated
guinea pig atria. In contrast to Ca\(^{2+}\)-sensitizing PDE inhibitors, it does not
increase maximum Ca\(^{2+}\) activated force in myocardial skinned fibers.\(^{289}\) The
cardiotonic activity of several clinically available drugs such as pimobendan and
levosimendan is also mainly due to calcium sensitization effects.

**Ca\(^{2+}\) CHANNEL PARTIAL AGONISTS**

These agents produce positive inotropic activity because of their ability to
promote an influx of Ca\(^{2+}\) through direct interaction with Ca\(^{2+}\) channels.
Bay K 8644 (95), a dihydropyridine, is a representative from this category that

acts primarily as a Ca\(^{2+}\) agonist.\(^{290}\) However, this compound through the same
mechanism also causes vasoconstriction.

**ANALOGUES OF cAMP**

While major attention has focused on PDE inhibition, which leads to
increase in cAMP levels, a small effort has also been directed towards preparing
cAMP analogues with the thought that they might penetrate the sarcolemma of cardiac cells and stimulates the messenger role played by cAMP. Since cAMP is destroyed rapidly, therefore, initially much success was not achieved in this area.

Only one compound, the dibutyryl derivative known as bucladesine (96) has shown promise as a potential inodilator among analogues of cAMP.

In a series of N^6-alkyl 3',5'cyclic adenosine phosphates, two compounds 97 and 98 were shown to be highly potent positive inotropic agents with moderately negative chronotropic effects.

HISTAMINERGIC RECEPTOR AGONISTS

These agents do not downregulate as congestive heart failure progresses. Impromidine (99) is a potent and selective H_2-agonist which has been studied for its cardiovascular effects in man. Despite a lot of research in the H_2-mediated
gastric acid system, very few studies have been carried out to separate H$_2$-mediated cardiac and gastric effects.\textsuperscript{292} Such information would be very important for the design of histamine receptor agonists with desired selectivity.

**MISCELLANEOUS CARDIOTONIC AGENTS**

Veratrum alkaloids, the gyratoxins, the sea-anemone polypeptides, batrachotoxins and scorpion poison have been reported to prolong the cardiac action potential. It has been observed that these toxins increased the sodium influx by increasing the resting sodium permeability. The various alkaloids of veratrum, which have shown positive inotropism include veratridine, germitrine, cevadin and cevine.\textsuperscript{293, 294}

The natural product forskolin (100), isolated from Indian herb *Coleus forskohlii*, is thought to interact directly with the regulatory or catalytic subunit of

![Chemical structure of forskolin](https://example.com/forskolin_structure)

(100) $R = H$

(101) $R = CO(CH_2)_2N(CH_3)_2$

the adenylate cyclase system. This compound exhibits both inotropic and pronounced vasodilator properties. Forskolin (100) does not inhibit either phosphodiesterase or the Na$^+$, K$^+$-ATPase but it depletes K$^+$ from the heart. Forskolin (100) increased the cardiac content of cAMP by an action on the catalytic unit of the adenylate-cyclase system.\textsuperscript{295, 296} NKH477 (101), a novel water soluble forskolin derivative, also produced similar activity as that of 100 and can
be characterized as a potent, orally active, water-soluble inodilator for treatment of heart failure, especially in the severe stage with β-adrenoceptor downregulation.\(^{297}\)

A synthetic compound, DPI 201-106 (102), increases the intracellular Na\(^+\) resulting in prolongation of open time for the Na\(^+\) channel gates rather than an inhibition of Na\(^+\), K\(^+\)-ATPase. This 2-cyanoindole compound has also shown significant vasodilator effects\(^{298}\) in addition to increase in sensitivity of myofibrils to calcium. The effect of 102 on the sodium channel is stereospecific.\(^{299}\)

Coenzyme Q\(_{10}\) (ubiquinone) was isolated in 1959 and is mainly concentrated in mitochondria of various organs, including cardiac muscle. Depletion of cardiac CoQ\(_{10}\) (103) to 75% leads to serious impairments of cardiac function and it was found that the concentration of CoQ\(_{10}\) was markedly reduced in hearts obtained from heart failure cases. Administration of CoQ\(_{10}\) causes improvement in patients suffering from CHF.\(^{300}\)

A new series of unsaturated γ and δ lactones with pyridyl, quinolyl and
nitrophenyl substituents have been synthesized by the condensation of unsaturated methyl lactones with heteroyl aldehyde or nitrobenzaldehyde in the base-catalyzed aldol reaction. The antiarrhythmic, vasodilating and cardiotonic activities of the synthesized compounds were studied in vivo and in vitro. Five-membered lactones, particularly 3-cyano-4-(4-pyridylvinyl)-5,5-dimethyl-2(5H)-furanone (104), exhibited a remarkable cardiotonic activity. The replacement of a pyridyl substituent by a nitrophenyl group in the pyranone derivative did not change the cardiovascular activity and toxicity.$^{301}$

**RECENT APPROACHES FOR THE TREATMENT OF CHF**

**NEUROHORMONAL AGENTS**

As the neurohormonal model of heart failure has become more accepted, several new neurohormonal agents have emerged as potential therapies in heart failure. These agents antagonize the neurohormonal reflexes that have detrimental effects on the heart or augment the reflexes that may be beneficial in maintaining organ perfusion.

Atrial and brain (B-type) natriuretic peptides (ANP and BNP) as well as adrenomedulin and bradykinin are metabolized by neutral endopeptidase (NEP). NEP inhibitors increase plasma concentrations of these counter-regulatory neurohormones. Omapatrilat, an orally active, long-acting dual inhibitor of NEP and ACE, is the most prominent for the treatment of CHF. Omapatrilat improved
heart failure cases among those patients with more severe symptoms when compared with lisinopril.  
Nesiritide is a recombinant human BNP, an important counter-regulatory neurohormone in the pathogenesis of heart failure and has also been recently approved for the treatment of patients hospitalized with decompensated heart failure.

VASOPRESSIN RECEPTOR ANTAGONISTS

Vasopressin is usually elevated in patients with CHF. Vasopressin antagonists have been shown to reverse the impaired urinary diluting capacity seen in CHF, increase sodium free water excretion, promote peripheral vasodilation and improve cardiac output. Two orally active V2 receptor antagonists, SR 49059 and a combined V1a/V2 receptor antagonist YM087 are undergoing clinical trials in patients with class III and IV heart failure, who are currently on standard treatment such as continuous inotropic drug infusion.

THROMBOXANE INHIBITORS

The decline in renal plasma flow in heart failure leads to the renal production of such vasoconstrictor neurohormones as prostaglandin F2 (PGF2) and thromboxane A2 (TxA2) to preserve glomerular filtration. Persistently increased TxA2 levels, which exist in heart failure, can worsen renal function. Picotamide, an oral renal TxA2 / PGH2 receptor inhibitor was administered in a study of 14 patients with NYHA Class IV heart failure in an 8-day, randomized, double-blind cross-over study. Compared with placebo, effective renal plasma flow and glomerular filtration rate increased. After 8 days of treatment, picotamide was associated with an increase in diuresis, an improvement in serum creatinine, a decrease in pulmonary artery and right atrial pressure, a decrease in body weight and a corresponding reduction in dyspnea.

ENDOTHELIN ANTAGONISTS

Endothelin is a potent vasoconstrictor with remodeling effects similar to those of angiotensin II. Plasma endothelin levels are elevated in patients with
heart failure and increase with worsened hemodynamics and symptoms.\textsuperscript{307} Several selective and non-selective endothelin receptor antagonists are under investigation, although for the most part results have been discouraging. Bosentan is an oral, non-selective endothelin receptor antagonist, currently approved for use in patients with pulmonary hypertension, although it has not yet shown efficacy in heart failure. Several clinical trials have demonstrated its better effects.\textsuperscript{308,309}

**MATRIX METALLOPROTEINASES**

The cardiac extracellular matrix is composed of an extensive network of collagens. Collagen cross-linking is an important factor in the systolic and diastolic function of the heart. In response to myocyte damage, hemodynamic load or neurohormonal factors, the extracellular matrix of the heart undergoes remodeling. This remodeling is controlled by the interplay of matrix metalloproteinases (MMPs) that degrade collagens and inhibitors of metalloproteinases (TIMPs). Various cytokines (such as TNF-alpha and IL-6) and neurohormones (such as norepinephrine, angiotensin II and endothelin) upregulate MMP expression. Several animal studies have suggested that modulation of MMPs and TIMPs may be an exciting new direction in the prevention and treatment of heart failure, although there remain many concerns of potential adverse consequences of therapy.\textsuperscript{310,311}

**β-BLOCKERS**

There are also reports of beneficial effects of β-blockers like carvedilol in congestive heart failure. The goals of heart failure therapy have shifted from purely hemodynamic manipulation to a combination of hemodynamic and neurohumoral modulation. Vasodilators with neurohumoral modulatory properties such as ACE inhibitors and third generation β-blockers have become the cornerstone of chronic heart failure therapy. These newer agents have proven to improve morbidity and mortality in adults with chronic heart failure. The drugs like bisoprolol (Zebeta\textsuperscript{®}), metoprolol tartrate (Lopressor\textsuperscript{®}), metoprolol succinate
(Toprol®), carvedilol (Coreg®) and bucindolol (Bextra®) are beneficial in CHF. Compelling evidence now exists to support the safety and efficacy of β-blocker therapy in patients with heart failure.\textsuperscript{312-315}

The above survey of literature highlights the various approaches used to treat congestive heart failure. A variety of structurally and pharmacologically different molecules have been designed and developed as potent cardiotonic agents. To obtain dual inotropic and vasodilatory properties, different positions of pyridazinone nucleus have also been successfully exploited. Therefore it was endeavored to design and synthesize some newer therapeutically useful pyridazinone derivatives, which may address not only CHF but also underlying disease such as hypertension.

The research work carried out has been described in \textsc{Resumé and Discussion} section followed by \textsc{Experimental} details of synthetic and pharmacological work.