INTRODUCTION
Thienopyrimidines are condensed bioesters of quinazolines and possess a variety of biological activities. Their notable biological activities are anti-malarial (Klemm et al., 1970); anti-bacterial (Kuwada et al., 1976a,b); appetite depressant (Sauter et al., 1978); anxiolytic and anti-depressant (Thompson and Thomson, 1985); analgesic and anti-inflammatory (Tahara and Toshio, 1976); Nakanishi et al., 1970a,b,c,d); tranquilizing; anti-convulsant; sedative; amphetamine antagonistic activity (Nakanishi et al., 1970 a,b,c,d). Recently, some of the thienopyrimidine derivatives have been shown to possess anti-hypertensive (Henning et al., 1983); anti-arrhythmic (Parcor, 1976; Troxler and Wiskoff, 1980); alpha- adrenoceptor antagonistic (Troxler and Wiskoff, 1980) and anti-thrombic or platelet aggregation inhibitory activity (Parcor, 1977a,b).

In the past few years thienopyrimidine-4-ones, suitably substituted at the 2-position have been looked upon with considerable interest. There are reports of promising antihyperlipaemic activity in such derivatives, namely, thieno [2,3-d]pyrimidin-2-propionic acids (Shiroki, 1976) and 2-mercaptothieno [2,3-d]pyrimidin-4-ones (Sauter, 1972). Kulshrestha et al. (1981) reported anihypertensive activity in certain 2-methyl-3-N-substitutedthienopyrimidin-4(3H)-ones derivatives. Our laboratory has been involved for more than a decade in synthesising various series of thienopyrimidines. A novel route of synthesis of condensed pyrimidines has been reported (Dave et al., 1980) from our laboratory by condensing o-aminocarbonyl compounds with nitriles in the presence of excess of HCl gas (Scheme-1). A number of thieno [2,3-d]pyrimidin-4-(3H)-ones were synthesised by the same approach. While screening these agents for central, autonomic and cardiovascular activities, two compounds, LM-2616 and LM-1554 were found to possess specific pharmacological activity.

The compound LM-1554 (Fig.-64a) [2-chloromethyl-5,6,7,8-tetrahydrobenzo(b)thieno[2,3-d]pyrimidin-4-(3H)-one]was found to possess antihyperlipaemic activity (Shishoo et al., 1990). The compound LM-2616 (Fig.-64b) [2,7,9-Trimethyl-4(N-methyl-piperazino)pyrido(3,'2':4,5)thieno(3,2-d)pyrimidine)] appears to be a specific β₁ -adrenoceptor antagonist with β₂- adrenoceptor agonistic activity.
In the present investigation we have made an attempt to elucidate the mechanism of action of these two prospective compounds using suitable pharmacological tools. In addition we have also synthesised and evaluated various analogues of both these compounds to find out the more potent compounds by use of QSAR and SAR.

**SCHEME-I**

![Scheme Diagram]

Fig.-64

![Chemical Structures]

**LM 1554**

![Chemical Structure]

**LM 2616**

![Chemical Structure]
Ventuallyall the lipids of human plasma are transported as complexes with proteins. Except for fatty acids, which are bound chiefly to albumin, the lipids are carried in special macromolecular complexes termed lipoproteins. A number of metabolic disorders that involve elevations in plasma lipoprotein concentrations are thus termed hyperlipoproteinemias. The term hyperlipemia is restricted to conditions that involve increased levels of triglyceride in plasma. Hypothyroidism, nephrotic syndrome (Malloy and Kane, 1987), diabetes-mellitus (New et al., 1963), obesity, anabolic steroids (Schaefer, 1991) cigarette-smoking (Eysenck and Eaves, 1980), alcohol intake (Belfrage et al., 1977), obstructive liver disease and renal insufficiency (Man et al., 1945) are also important as secondary causes for lipid disturbances.

Major clinical sequel of the hyperlipoproteinemias are acute pancreatitis and atherosclerosis. Acute pancreatitis occurs in patients with marked hyperlipaemia (Greenberg et al., 1977). In this type of patients, triglyceride is deposited in the pancreas and they may have paresthesias and emotional lability (Fredrickson et al., 1967). They often have delayed chylomicron and VLDL clearance and excess VLDL apoB production (Sigurdsson et al., 1970). In such persons, control of triglyceride levels can prevent recurrent attacks of this life-threatening disease (Malloy and Kane, 1987).

Atherosclerosis is one of the leading causes of death in the U.S.A. and other western countries (Campeau et al., 1984). It is the basic pathologic process responsible for most ischemic heart disease (IHD) and requires lipid deposition and smooth muscles cell proliferation is thought to be the key event. Any factor(s) that contributes to endothelial injury, thickening of the arterial intima, accumulation of connective tissue within the intima, and deposition of blood constituents may narrow the lumen, decrease blood flow, and predispose to atherosclerosis (Ross, 1990a).

It is generally agreed that diet and weight control are the first line treatment of all patients with high cholesterol or triglyceride blood levels (Committee on Diet and
Health, 1989). Such measures are continued for several months, and in many patients, this is sufficient to adequately reduce the concentrations of cholesterol or triglyceride (Hegsted et al., 1965 and Keys et al., 1965). However, there are patients who do not respond adequately to non-drug management, and in such cases, the use of a lipid-lowering agent is considered necessary (Thomas, 1991). The choice of lipid-reducing agent is usually related to the dominant abnormality (elevated plasma concentrations of cholesterol or triglyceride, or both). On occasions, combination treatment with reduced doses of two drugs is more effective than a single agent with fewer adverse effects (Malloy et al., 1987).

In spite of the availability of various antihyperlipaemic agents, there is an increase in coronary heart disease and risk of congestive heart failure. Thus there is still considerable interest in synthesis and evaluation of new antihyperlipaemic agents.

The compound LM-1554 was found to be an antihyperlipaemic agent. It is reported that it reduces lipid levels in hyperlipaemic rabbits and that results are comparable to that produced by clofibrate at the same dose level. The compound LM-1554 was also found to reduce free cholesterol and triglyceride levels in rats and guinea pigs and those results were also comparable to that produced by clofibrate. The LD50 was found to be high. Further chronic toxicity studies of the compound LM-1554 revealed the compound to be safe in animals. Acute toxicity studies in rats and mice also revealed the compound to have high therapeutic-index (Shishoo et al., 1990). Thus the compound LM-1554 seems to have the potential to be developed as an antihyperlipaemic drug.

However, before this drug can enter into Phase I of the clinical trials, it is essential to have pharmacokinetic and pharmacodynamic data on the animals as well as its likely mechanism of action. The objective of the present investigation was to obtain pharmacokinetic and pharmacodynamic data for various animal models. We have also synthesised and evaluated analogues of LM-1554 for antihyperlipaemic effect to obtain more potent compounds among the series. An attempt was made to study Quantitative Structure Activity Relationship (QSAR) among the series of synthesised condensed thienopyrimidines. We have also tried to throw some light on likely mechanism and site of action of the compound LM-1554.
LM-2616: \( \beta_1 \)-ADRENOCEPTOR ANTAGONIST WITH \( \beta_2 \)-ADRENOCEPTOR AGONIST EFFECT

Ahlquist (1948), on the basis of the different relative potencies of a series of agonists, suggested a division of adrenoceptors into two: \( \alpha \)-adrenoceptors and \( \beta \) adrenoceptors. It eventually became apparent that this classification was not sufficient to explain the multifold effects of catecholamine observed in physiological and pharmacological studies. Thus two subtypes of \( \alpha \)-adrenoceptors were subsequently defined and termed \( \alpha_1 \) and \( \alpha_2 \) (Langer 1974; Berthelsen and Pettinger, 1977; Starke and Langer, 1979). However, it seemed to be necessary to further subdivide these subtypes; thus at present three \( \alpha \), adrenoceptor subtypes (\( \alpha_A, \alpha_B \), and \( \alpha_C \)), three \( \alpha_2 \)-adrenoceptor subtypes (\( \alpha_2A=\alpha_2-C_1 \), \( \alpha_2B=\alpha_2-C_2 \), and \( \alpha_2-C_3 \)) have been cloned (Watson and Abbott, 1991). Whether all of these subtypes have a functional importance, however, remains to be elucidated.

Till the year 1958, no compound was available to block specifically the adrenergic beta receptors. It was Powell and Slater (1958) who first demonstrated the efficacy of dichloroisoproterenol to block these receptors. Therapeutic use of a beta-blockers in medicine was initially shown by using pronethalol in patients with angina pectoris (Alleyne et al., 1963). Unfortunately, this drug could not be used further, since it was shown to produce tumors of the thymus gland in mice (Alcock and Bond, 1964). Nevertheless, this loss was compensated by the introduction of propranolol, which was found to be effective in angina pectoris without any major adverse effects (Black and Stephenson, 1962). But soon it became conspicuous that propranolol caused hypotension, heart failure, bronchial spasm, cold extremities, easy fatiguability etc.

The sub-classification of \( \beta \)-adrenoceptors into \( \beta_1 \)- and \( \beta_2 \)-adrenoceptors by Lands et al. (1967a,b) was another milestone in the history of \( \beta \)-adrenoceptor. The specific \( \beta_1 \)-adrenoceptor antagonists, such as metoprolol, atenolol etc., unlike propranolol, do not interfere with insulin-induced hypoglycemia or bronchodilatation. Hence specific \( \beta_1 \)-adrenoceptor antagonists can be used in asthmatic and diabetic patients whose hypertension is not controlled by other anti-hypertensive medication. Further, patients treated with specific \( \beta_1 \)-adrenoceptor antagonists experience a much
smaller elevation in stress induced systolic and diastolic blood pressure, as compared to subjects who have received a non-selective β-blocker (Houben et al., 1982; McGibney et al., 1983).

The original subclassification of β-adrenoceptors into β₁-adrenoceptors in the heart (where noradrenaline and adrenalin are equally potent) and β₂-adrenoceptors in vascular and bronchial smooth muscles (where adrenalin is about 10-30 fold more potent than noradrenaline) presumes a high degree of organ specificity of the β-adrenoceptor subtypes (Land et al., 1967a,b). This hypothesis has now evolved (mainly used on data derived from radioligand-binding studies) into the concept that in a variety of organs, including the heart, both β₁- and β₂-adrenoceptors coexist, although often one subtype predominates. This was first suggested in 1972 by Carlsson et al. (1972), who showed that equal submaximal chronotropic responses of the cat heart to β-adrenoceptor agonists were antagonised to different extents by the β₁-adrenoceptor selective antagonists, practolol, and by the β₂-adrenoceptor selective antagonist, H35/25. Similar effects have been reported in numerous in vivo as well as in vitro experiments in cat, dog and guinea pig heart, as well as in guinea pig and rabbit trachea, thus supporting the concept of the coexistence of β₁- and β₂-adrenoceptors in a single organ (Daly and Levy, 1979; Minneman et al., 1981; Stiles et al., 1984; Brodde, 1989).

It is now possible to determine the relative proportion of β₁- and β₂-adrenoceptors in a tissue using radioligand-binding studies. The coexistence of β₁- and β₂-adrenoceptors has been demonstrated by this technique in the hearts of rats, cats, guinea pigs, dogs and rabbits (Minneman et al., 1981; Stiles et al., 1984; Brodde, 1987, 1989). As a general rule, β₂-adrenoceptors are present in larger amounts in atria than in ventricles. However, the physiological role of these cardiac β₂-adrenoceptors is still not completely understood. Although β₂-adrenoceptors are involved in the positive chronotropic effects of β-adrenoceptor agonists in the right atria of rats, guinea pigs, cats and dogs (Carlsson et al., 1972, 1977; Dreyer and Offermeier, 1975; Yabuuchi, 1977; Yabuuchi et al., 1977; Johansson and Persson, 1983; Kaumann and Lemoine, 1985; Liang et al., 1985; O'Donnell and Wanstall, 1985; Kaumann, 1986; Molennar and Summers, 1987) but not rabbits (Costin et al., 1983; Wilson and Lincoln, 1984; Tenner et al., 1989), it is still a matter of controversy whether β₂-adrenoceptors can contribute to the positive inotropic effects of β-adrenoceptor agonists in atrial and ventricular preparations from these species (Yabuuchi, 1977; O'Donnell and Wanstall, 1979; Bryan et al., 1981;
The first evidence that a heterogeneous population of $\beta_1$- and $\beta_2$-adrenoceptors also might exist in human myocardium was presented by Ablad et al. (1974). Similar results were reported by Bonelli (1978) who observed that in humans $\beta$-adrenoceptor antagonist, mepindolol, inhibited the positive chronotropic effect of isoprenaline much more effectively than it did isoprenaline's positive inotropic effect. During the last one decade, $\beta_1$- and $\beta_2$-adrenoceptors have been directly identified in human atrial and ventricular tissues by radioligand binding studies.

The demonstration of $\beta_2$-adrenoceptors also has an implication for the pathophysiology and treatment of heart failure, where selective down regulation of $\beta_1$-adrenoceptors associated with high sympathetic drive (Bristow et al., 1982, 1986; Cohn et al., 1989) may increase the contribution of $\beta_2$-adrenoceptors to the positive inotropic and chronotropic response. A pool of cardiac $\beta_2$-adrenoceptors which mediate inotropic responses and the resistant to down regulation (Bristow et al., 1986), highlights the therapeutic potential of $\beta_2$-adrenoceptors in the treatment of heart failure. In other words, a compound with $\beta_1$-antagonistic and $\beta_2$-agonistic activity seems the drug of choice in the treatment of heart failure. Third-generation $\beta$-adrenoceptor blockers like celiprolol were also found to possess $\beta$-adrenoceptor blocking activity with $\beta_2$-adrenoceptor agonistic activity. Milne and Buckley (1991) reported that this third generation $\beta$-blocker appears to be safe and effective alternative to $\beta$-blockers for antihypertensive effect. The compound LM2616 found to possess a specific $\beta_1$-adrenoceptor antagonistic activity with $\beta_2$-agonistic activity. LM-2616 may have potential to be developed as antiarrhythmic and/or antihypertensive agent.

In the present investigation, we have studied the autonomic effects as well as local anaesthetic effect of the compound LM-2616. We have also made an attempt to find out the structure activity relationship for the various analogues of the compound LM-2616.