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One of the quantitative traits in human physiology is blood pressure. The control of blood pressure is governed by multifactorial conduits. Well-coordinated regulatory systems mainly involving the brain, heart, conduction vessels and kidney govern the control of blood pressure. During the course of evolution and consequent natural selection, humans gradually became susceptible to genetically and environmentally induced hypertension. This in turn led to the evolution of regulatory systems to compensate the hypertensive phenotype. Blood vessel cross-sectional diameter, pressure natriuresis and resultant volume adjustments are frequently affected as a means for regulation of blood pressure and maintaining a normotensive phenotype. The available data suggests that faults in these regulatory systems can occasionally lead to the development of hypertension, a condition that stands as a root-cause for the development of several cardiovascular abnormalities in individuals (Kunes *et al*, 2012). Definitions of hypertension have metamorphosed over time owing to clinical studies in diverse populations and research elaborating the etiopathology of hypertension (Hajjar *et al*, 2006). It may be generalized on the basis of available guidelines (JNC, CHEP, ESH, ISH, ASH, etc.) that an individual is hypertensive if his/her blood pressure is above 140/90 mm Hg.

Recently, the problem of uncontrolled or resistant hypertension has gained enormous proportions (Daugherty *et al*, 2012). Further, diet modifications and exercise seldom cause any benefit in controlling this condition and the patient is usually recommended for pharmacological therapy. It is very well accepted that mono-drug therapy is no longer effective due to the multifactorial etiology and lack of proper lifestyle modifications by the patients. Clinical practice has adopted the use of two or more classes of antihypertensive agents (Elliott, 2002; Paulis and Unger, 2010) for effective control of blood pressure in hypertensive patients. The basis behind such a decision is that since the etiology of hypertension is complex, it is prudent to employ a parallel control of more than one systems affecting increase in blood pressure.

The homeostasis of blood pressure is maintained by two major systems: a) The Renin-Angiotensin-Aldosterone-System (RAAS) and b) The Sympathetic Nervous System (SNS) (Shepherd and Mancia, 1986; Hall *et al*, 1999; Lohmeier, 2001). Release of catecholamines upon SNS stimulation leads to vasoconstriction in the peripheral

beds, alongwith an increase in the chronotropic and inotropic action of the heart. On the other hand, RAAS stimulation modulates blood pressure directly and indirectly. Directly, through the vasoconstrictive action of the octapeptide angiotensin II (ang II) released upon ACE-mediated hydrolysis of angiotensin I and indirectly, through stimulating aldosterone release leading to sodium-water retention contributing to increase in total blood volume. A few clinical and experimental studies have demonstrated that the SNS and RAAS are in fact, intertwined in the homoestatic control of blood pressure (Shepherd and Mancia, 1986; Hall *et al*, 1999; Lohmeier, 2001). These demonstrations have generated the relevance of the concept of renin-angiontensin-sympathetic crosstalks in hypertension (Li *et al*, 1997; Grassi, 2001). The information regarding the mutual interaction of these systems may be derived from the literature which suggests that renin secretion and angII formation are amplified upon stimulation of the SNS (DiBona, 1989a; DiBona, 1989b). Norepinephrine modulates angII receptors via interaction with α_1 adrenergic receptors (Du *et al*, 1997; Li *et al*, 1997) while intracerebral injection of angII may trigger a sympathetically mediated rise in blood pressure(Wolff *et al*, 1984; Zimmerman *et al*, 1984; Hall *et al*, 1999). Stimulation of presynaptic angII receptors can stimulate norepinephrine release from nerve terminals (Starke, 1977; Zimmerman *et al*, 1984; Reid, 1992) and angII may amplify vasoconstrictor responses affected by the α_1-receptors. AT_1 and α_1 receptors are important targets in this regard and hence a simultaneous blockade of these targets might prove favorable towards the effective management of hypertension.

The past decade has witnessed the development of a concept termed as "Designed Multiple Ligands" (DMLs). DMLs are novel synthetic compounds possessing the pharmacological ability to bind to more than one target. This effect is supposed to be deliberate rather than by chance as observed in serendipitous discoveries. A superior therapeutic efficiency can be achieved through evenhanded modulation of multiple targets (Morphy *et al*, 2004). This may also be achieved through polypharmacy, administration of fixed dose combinations or an agent directed to all the required targets, i.e. a designed multiple ligand. When compared to the other alternatives, the administration of a DML may offer certain advantages like predictable pharmacokinetics, simple pharmacodynamic relationships, improved patient compliance and ease of therapeutic drug monitoring, if at all required (Morphy *et al*, 2004).

The present work describes the screening of a series of new chemical entities for potential dual-antagonist activity on the AT_1 and α_1 receptors. The compounds belong to a series of 6,7-dimethoxyquinazolines with different substitutions at 2^{nd} position based on structural modifications involving prazosin and losartan. These compounds were assumed to show a balanced modulation of both the receptors in question. One of the compounds, **MCR-1329** (a 6,7-dimethoxyquinazoline derivative), has been evaluated pharmacologically for its potential as an antihypertensive agent.

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Development of chronic hypercholesterolemia predisposes an individual to the development of a metabolic condition termed as atherosclerosis. Atherosclerosis is a condition characterized by formation of lipid-rich plaques in the inner walls of arteries. Technically, the entire process is a remodeling event in the inner walls of the arteries that leads to subendothelial deposition of fatty substances (Vassiliadis *et al*, 2013). This event is initiated by acute or chronic injury to the arterial endothelium which leads to endothelial dysfunction. Dysfunction of a few endothelial cells leads to activation of the surrounding cells which begin attracting leukocytes and vascular smooth muscle cells (VSMCs) at the site of injury. VSMCs activated in presence of the leukocytes activate, proliferate further and secrete unwarranted amounts of connective tissue matrix that forms the mass of the plaque. The convoluted sequence of events occurring during atherosclerosis progression resemble to that of a chronic inflammatory process (Falk, 2006). The end result of such a process is formation of thick, mature and obstructive plaque which is fibrous in nature. Though this situation is detrimental, compensatory flow adjustments are sufficient to handle the narrowing of the luminal diameter in the arteries as long as the plaque remains stable. Complications arise when the plaque ruptures leading to hemorrhage of the ruptured plaque and formation of emboli or thrombosis at the lesion (Falk, 2006). A thorough understanding of the pathogenesis of atherosclerosis is essential for the development of strategies for the prevention of the disease, and for the development of new and effective treatments. Cholesteryl esters contribute significantly to the metamorphosis of an atherosclerotic plaque. It has been suggested that cholesteryl esters present in LDL can be considered not only as a risk factor but rather a diagnostic marker for atherosclerosis progression (Spector and Haynes, 2007).

It was routinely believed that esterification of cholesterol in the body is catalyzed solely by LCAT (Glomset, 1973). This perspective was changed with the discovery of ACAT (Chang *et al*, 1993) which catalyses the linkage between fatty acyl CoA and polar cholesterol, resulting in the formation of non-polar cholesteryl esters (Buhman *et al*, 2001). Two isoforms of ACAT are known: ACAT1 and ACAT2. Apart from the physiological aspect, production of cholesteryl esters by ACAT isoforms makes a noteworthy contribution to the pathogenesis of atherosclerosis. ACAT1 aids

the progression of atherosclerosis via accumulation of cholesteryl esters in macrophages and leading to conversion of smooth muscle cells to foam cells, ultimately leading to plaque initiation and subsequent events (Fazio *et al*, 2001; Linton and Fazio, 2003). In macrophages, which form an important part of the pathophysiology of atherosclerosis, ACAT1 regulates the allocation of intracellular cholesterol to esterified- and free-cholesterol pools (Akopian and Medh, 2006). This is a very important event for any cell, as esterification of cholesterol sequesters free cholesterol in the form of esterified lipid droplets by making it unavailable for ABCA1-mediated efflux (Akopian and Medh, 2006; Voloshyna and Reiss, 2011; Sorci-Thomas and Thomas, 2012). This massive accumulation of cholesteryl esters in the form of lipid droplets leads to the formation of lipid-laden foam cells. Cholesterol ester accumulation in vascular smooth muscle cells is also controlled by ACAT1 (Yagyu *et al*, 2000; Rong *et al*, 2005; Rong *et al*, 2013). Both of these events contribute significantly to the development of the lipid-rich core of the plaque and are the hallmarks of atherosclerosis (Chang *et al*, 2006a; Chang *et al*, 2006b). ACAT2 significantly contributes to the absorption of dietary cholesterol to deliver it to the lymph and plasma by esterifying it in the enterocytes. This absorbed cholesterol, alongwith cholesterol synthesized *de novo* by the HMG-CoA reductase pathway, contribute to the total pool of cholesterol in the body. In this manner, both the isoforms of ACAT are responsible for the development of atherosclerosis. Owing to the direct as well as indirect role played by ACAT in development of the atherosclerotic plaque, inhibition of ACAT has been a potential pharmacological target for researchers for preventing atherosclerosis progression (Chang *et al*, 2006a). Pan-specific or non-specific ACAT inhibition has been tried by different researchers with varying levels of success. Several studies identifying potential ACAT inhibitors for the management of hyperlipidemia and atherosclerosis have been reviewed (Pal *et al*, 2012). The past 2 decades have seen a generous number of publications on the subject of ACAT inhibitors. Filing of more than 150 patents (and still counting...) suggests a keen interest amongst researchers and in the commercial arena about ACAT inhibition as a potential therapeutic strategy for atherosclerosis. The development of several synthetic, herbal or microbial origin ACAT inhibitors has allowed the researchers to understand the role of ACAT in cholesterol turnover. The field of ACAT studies saw great impetus after the discovery of ACAT cDNA by Chang and colleagues (1993). Since then, abundance of research in this area has resulted in thorough understanding of the structure, function, localization and inhibition of ACAT

isoforms. In fact, a few studies have also found ACAT inhibition to be a detrimental strategy since it prevents esterification of toxic polar cholesterol leading to its accumulation in cells. Though variety exists in the observations made from studies that have evaluated different aspects of ACATs, their physiological role has been well-studied and understood.

The present work is aimed at identifying ACAT inhibitors as potential drug molecules to be used in atherosclerosis. For this purpose, an HPTLC-based analytical method was developed for the estimation of cholesteryl esters.

This method could be utilized for quantifying cholesteryl esters and screening of potential ACAT inhibitors by observing their ability to prevent formation of cholesteryl esters. Consequently, screening of a series of NCEs for potential ACAT inhibitory activity (present in liver microsomes) is reported. Chemically, these NCEs belong to a class of urea derivatives. Based on the preliminary screening results, a few potent compounds were selected for evaluation of their effect on triglyceride turnover and the potential compound(s) were further studied in an animal model of diet-induced atherosclerosis.