SYNTHESIS OF COMPOUNDS OF MEDICINAL INTEREST POSSESSING VICINAL DIARYL HETEROCYCLIC SCAFFOLD

A THESIS SUBMITTED TO
THE MAHARAJA SAYAJIRAO UNIVERSITY OF BARODA
FOR THE AWARD OF THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

PHARMACY

BY

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UNDER THE GUIDANCE OF

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March - 2013

CERTIFICATE

This is to certify that the thesis entitled **"SYNTHESIS OF COMPOUNDS OF MEDICINAL INTEREST POSSESSING VICINAL DIARYL HETEROCYCLIC SCAFFOLD"** submitted for Ph. D. degree in pharmacy by Mr. Palash Pal incorporates the original research work carried out by him under my supervision.

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DECLARATION

I hereby declare that the thesis entitled **"SYNTHESIS OF COMPOUNDS OF MEDICINAL INTEREST POSSESSING VICINAL DIARYL HETEROCYCLIC SCAFFOLD"** submitted herewith to The Maharaja Sayajirao University of Baroda for the fulfillment for the degree of Doctor of Philosophy in Pharmacy is the result of the work carried out by me in Pharmacy Department, Faculty of Technology and Engineering, The M. S. University of Baroda, Vadodara.

The results of this work have not been previously submitted for any degree/ fellowship.

PALASH PAL

DEDICATED TO

MY

PARENTS

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Above All I Thank ALMIGHTY GOD For Giving Me Courage And Strength Through Out The Life.

At inception I am confessing to all my well wishers, whose name not mentioned in these pages and I express my sincere thanks to all those who were instrumental both directly and indirectly in completing my dissertation work successfully.

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1. Introduction

High serum cholesterol levels have been associated with cardiovascular diseases (CVD), a leading cause of death in the world.[1,2] Atherosclerosis is a disease of medium and large arteries, characterized by progressive thickening of arterial intima. Occlusion of these vessels may ultimately lead to myocardial infarction.[3] This is a leading cause of morbidity and mortality in the US and developed as well as developing countries.

Cholesterol levels are affected by various factors such as rate of endogenous cholesterol synthesis, biliary cholesterol excretion and dietary cholesterol absorption.[3] Several lipid lowering strategies, especially HMG-CoA reductase inhibitors ('Statins') or cholesterol synthesis inhibitors have been developed[1,5] and are currently in therapeutic use. Nevertheless, a substantial number of patients who receive a statin monotherapy, do not achieve the ultimate treatment goals.[1,6] Moreover, augmenting the dose of statins may also increase adverse side effects.[1,7] Given the limitations of the statins and other lipid lowering agents such as fibrates and bile acid sequestrants, the research for discovering novel lipid lowering agents continues and studies are currently targeting the process of inhibition of absorption of intestinal cholesterol. The plant sterols and stanols[1,8], ACAT inhibitors[1,9], microsomal triglyceride transfer protein (MTP) inhibitors[1,10], and Niemann-pick C1-L1 ligand inhibitors (NPC1-L1)[1,11] are candidate compounds that lower intestinal cholesterol absorption.

For absorption of cholesterol in the intestine, esterification of cholesterol was found to be a rate limiting step in intestine. The seminal work of Norum[12], Heiders[13], Field[14] and others[15] ultimately led to the conclusion that Acyl CoA: cholesterol O-acyltransferase (ACAT; EC 2.3.1.26)[16] was one of the primary enzymes responsible for the esterification of cholesterol in intestinal mucosal cells and it played vital role for the esterification and absorption of intestinal cholesterol.

1.1 Atherosclerosis

Atherosclerosis (also known as arteriosclerotic vascular disease or ASVD) is a condition in which an artery wall thickens due to the build-up of fatty materials, mainly cholesterol. Atherosclerosis affects mainly the walls of large arterial blood vessels as a result of accumulation of macrophage white blood cells and low-density lipoproteins (plasma proteins that carry cholesterol and triglycerides) without adequate removal of fats and cholesterol from the

macrophages by the functional high-density lipoproteins (HDL). It is commonly referred to as hardening of the arteries.

1.2 Pathophysiology of atherosclerosis

Atherogenesis is the developmental process of atheromatous plaques (Fig. 1). It is characterized by remodeling of arteries leading to subendothelial accumulation of fatty substances called plaques. The pathogenesis of atherosclerosis involves a complex series of events, similar to a chronic inflammatory process, with the formation of atherosclerotic plaque as the end result. Injury to the endothelial cell of the artery, resulting in endothelial cell dysfunction, is the first step in the process. Activated endothelial cells attract leukocytes and vascular smooth

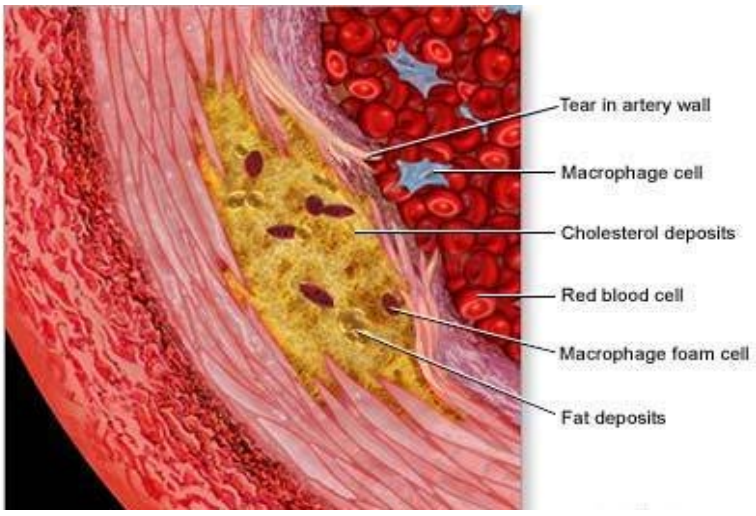


Figure 1: Cut section of atheromatous artery[17]

muscle cells (VSMC), which accumulate and proliferate in the arterial wall. These cellular components produce an excessive amount of connective tissue matrix. The ultimate end point is the formation of a mature fibrous plaque. The plaque rupture, hemorrhage of the rupture plaque, and formation of emboli or thrombosis make the lesions more complicated. 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.[4]

1.3 Acyl Coenzyme A: Cholesterol O-Acyl Transferase (ACAT)

The acyl-coenzyme A: cholesterol O-acyltransferase (ACAT) is a small enzyme family comprising three homologous members, namely acyl-coenzyme A: cholesterol O-acyltransferase 1 and 2 (ACAT-1 and ACAT-2), and acyl-coenzyme A: diacylglycerol acyltransferase 1 (DGAT-1). ACAT has generated interest as a potential means of exploring the atherosclerotic disease

process by both lipid and non-lipid mechanisms.[18] Earlier biochemical studies using cell fractionation assays revealed that ACAT activity is found only in microsomal fraction, but not in soluble fraction, suggesting that ACAT is an integral membrane enzyme.[19,20]

ACAT family enzymes perform important biological functions. ACAT-1 and ACAT-2 are critical for *in vivo* cholesterol homeostasis. At the single cell level, they prevent free excess cholesterol from building up in the cell membranes. At physiological level, they contribute toward formation of cholesteryl esters as part of neutral lipid cargo, to be packaged into the cores of very low-density lipoproteins and chylomicrons. Under pathophysiological conditions, these enzymes convert excess cholesterol into cholesteryl esters in cholesterol-loaded macrophages. The macrophages are gradually converted into foam cells, which is a hallmark of early lesions of atherosclerosis.[21]

1.3.1 Identification of ACAT isozymes

The ACAT activity was known as early as the 1970s[14], but purification of the enzyme failed due to its presence in minute quantities in various tissues. Using an ACAT-deficient Chinese hamster ovary (CHO) cell line[22], Chang's laboratory at Dartmouth College first cloned the full-length cDNA of human ACAT-1 in 1993. The cloning of human ACAT-1 is a milestone in research on ACAT family.[23]

ACAT-1 knockout in mice results in decreased cholesterol esterification in fibroblasts and adrenal membranes that markedly reduces cholesterol ester levels in adrenal glands and peritoneal macrophages, suggesting that ACAT-1 plays a major role in these tissues. However, the liver of ACAT-1 deficient mice contains substantial amounts of cholesterol esters and exhibits no reduction in cholesterol esterification activity, suggesting other unknown ACAT isozyme(s) is present in the liver. In 1998, these laboratories reported the cloning of ACAT-2 enzyme, an homologous isozyme of ACAT-1.[24, 25]

1.3.2 ACAT expression and regulation

The tissue distribution of ACAT-1 and ACAT-2 are quite different. ACAT-1 is more ubiquitous and has been found in macrophages, adrenal glands, hepatocytes, enterocytes, renal tubular cells and neurons,[26] whereas ACAT-2 has been found in the apical region of the intestinal villi[27] and in the hepatocytes.[28] ACAT-1 is expressed in macrophage-derived foam cells present in human atherosclerotic lesions. Adiponectin, an adipocytokine that has been shown to inhibit foam cell formation[29], can down-regulate ACAT-1 expression in macrophages derived from

human peripheral mononuclear cells[30]. Parini[28] et al. demonstrated that ACAT-2 is also expressed in human liver. ACAT-2 expression was shown to be up-regulated in a puromycin-induced rat nephritic syndrome model.[31] This study reported a correlation between the ACAT-2 protein expression and the plasma total cholesterol.

1.3.3 Membrane topology of ACAT enzymes

The ACAT family enzymes are integral endoplasmic reticulum (ER) membrane proteins with multiple transmembrane domains (TMDs) as predicted by TMD algorithms. Membrane topology is important for understanding substrate-binding and catalysis of membrane enzymes. Therefore, various experimental methods have also been designed to investigate membrane topology. The membrane topology of ACAT-1 has been experimentally studied using different approaches. In 1999, Lin et al. first proposed a 7-TMD model for ACAT-1 based on the results of HA-tag insertion and subsequent immunofluorescence observation after selective permeabilization of the cell membrane and the ER membrane.[32] In this model, they also propo-

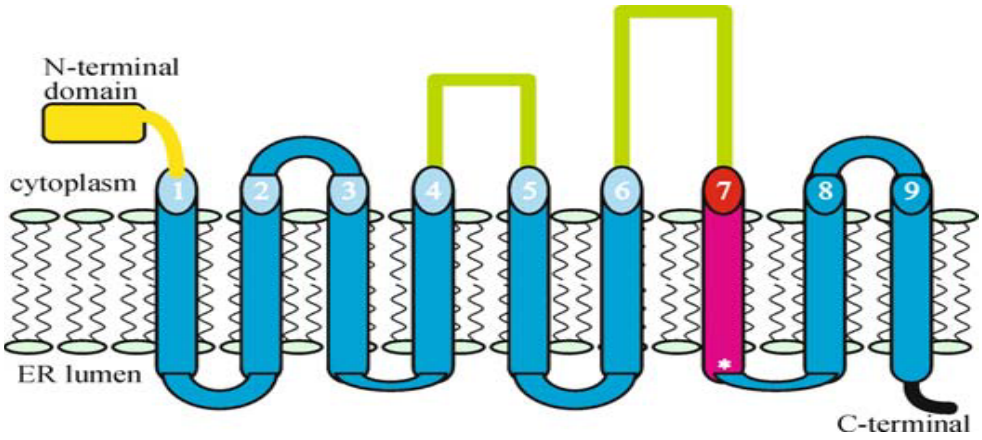


Figure 2: A general ER membrane topology model for ACAT family enzymes. The possible cholesterol/diacyglycerol- regions [binding region (TMD7) is shown in red, and other TMDs are shown in blue. The possible acyl-coenzyme A-binding the loop between TMD6 and TMD7 and the loop between TMD4 and TMD5] are shown in green. The position of the active site His in TMD7 is indicated by a white star.[18]

sed that the two long hydrophobic polypeptide stretches and a long hydrophilic polypeptide stretch, rich in conserved residues, were located in the ER lumen. One year later, Joyce et al. proposed a 5-TMD model for ACAT-1 based on their C-terminal truncation method.[33] In this model, they reported the three hydrophobic polypeptide stretches located in the cytosol. In 2005, Guo et al. reported a 9-TMD model for ACAT-1 based on their cysteine-scanning mutagenesis

and subsequent cysteine-specific modification approach.[34] In the 9-TMD topology model (Fig.2), all long hydrophobic polypeptide stretches are imbedded in the membrane bilayer. In this model, a long polypeptide stretch rich in conserved hydrophilic and hydrophobic residues between TMD6 and TMD7 is located in the cytosol. This peptide stretch may form the binding site of acyl-coenzyme A that is synthesized in the cytosol and is impermeable to the ER membrane. In the 9-TMD model, the so-called active site His-460 of ACAT-1 is located in a membrane sealed region at the luminal end of TMD7. This location seems to be responsible for catalysis.

The membrane topology of ACAT-2 has also been experimentally studied using two different approaches.[35] HA-tag insertion and subsequent immunofluorescence observation led to a 2-TMD model,[35] while the C-terminal truncation approach led to a 5-TMD model.[33] However, sequence analysis shows that ACAT-2 contains nine long hydrophobic peptide stretches corresponding to the nine TMDs of ACAT-1 (Fig. 2). So probably, ACAT-2 also contains nine TMDs. In the proposed 9-TMD model, all long hydrophobic peptide stretches of ACAT-2 are imbedded in the membrane bilayer; the probable acyl-coenzyme-A binding site between TMD6 and TMD7 is located in the cytosol; the so-called active site His-434 is located at the luminal end of TMD7 (Fig. 2).

For ACAT family enzymes, a general topology model with nine TMDs (Fig. 2) has been proposed. Among these, TMD7 is crucial because it is probably involved in substrate-binding and catalysis. TMD7 is rich in conserved residues. The absolutely conserved His-460 at the luminal end is proposed to be an active site. Probably other conserved residues are responsible for cholesterol/diacylglycerol-binding. Since cholesterol and diacylglycerol are insoluble in water, ACAT family enzymes may use the membrane-bound cholesterol and diacylglycerol as substrates. Two long cytosolic loops (between TMD6 and TMD7, and between TMD4 and TMD5) are rich in conserved hydrophobic and hydrophilic residues. They are probably involved in binding of acyl-coenzyme A that is synthesized in the cytosol and is impermeable to the ER membrane.[18]

1.4 Role of ACATs in cholesterol metabolism

During the past twenty years many types of therapeutic agents have been shown to limit the absorption of cholesterol into the mucosal cell of the intestinal lumen. The mechanism by which most of these agents act is still unknown. Such diverse structural types as neomycin, guar

gums, surfactants, sucrose polyesters and plant sterols have all been reported to act as cholesterol absorption inhibitors.[36,37]

1.4.1 Role of ACATs in intestinal wall

Even though cholesterol is absorbed exclusively in the unesterified form, most cholesterol appearing in the lymph is esterified by various long-chain unsaturated fatty acids. Moreover, the mass of cholesterol esters in lymph increases in proportion to the amount of cholesterol absorbed.[36,38] Thus, re-esterification of cholesterol occurs during the absorptive process. The bulk of available data suggests that the enzyme responsible for this action is ACAT an enzyme that utilizes long-chain fatty acyl coenzyme A and cholesterol as substrates.[31,34] Theoretically, this enzyme would allow the continued passive uptake of dietary cholesterol into the mucosal cells.[36] Indeed, it has been shown in cholesterol fed rats that inhibition of ACAT appears to have beneficial effects on plasma cholesterol via the prevention of the absorption of dietary cholesterol.[36,37] In recent years the implications of inhibiting this enzyme in other tissues (e.g. liver, artery wall) for the treatment of hypercholesterolemia and atherosclerosis, have become more clear. As illustrated in Fig.3, dietary cholesterol enters the small intestine from the stomach in the form of a crude emulsion. Endogenous cholesterol also enters from the bile. Together with pancreatic digestive enzymes, the bile converts this emulsion into mixed micelles which can incorporate the insoluble cholesterol into their hydrophobic cores. There is general agreement that cholesterol esters must be hydrolyzed to free cholesterol before absorption. This is achieved through the action of pancreatic cholesterol ester hydrolase. The micelles cross the unstirred water layer, a negatively charged hydrophilic region that is separate from the bulk aqueous phase of the lumen, and transfer free cholesterol to the brush border of the mucosal cells, where it is esterified by ACAT to cholesterol esters. These esters are then incorporated into chylomicrons, which are secreted into the lymph.[15,17,36] Earlier controversy over whether cholesterol ester hydrolase or ACAT was the rate-limiting enzyme for cholesterol absorptions[31,39] has been resolved by experiments with inhibitors that have shown that *in vitro* and *ex vivo* inhibition of ACAT activity can be correlated with the inhibition of cholesterol absorption, at least in rats[36,37] and rabbits.[31,40]

1.4.2 Role of ACATs in hepatocytes

The importance of ACAT in the liver, especially in humans, is less clear compared to its documented importance in the intestine and artery. The liver receives its cholesterol from a number of sources, including endogenous biosynthesis, removal of the lipolytic remnants

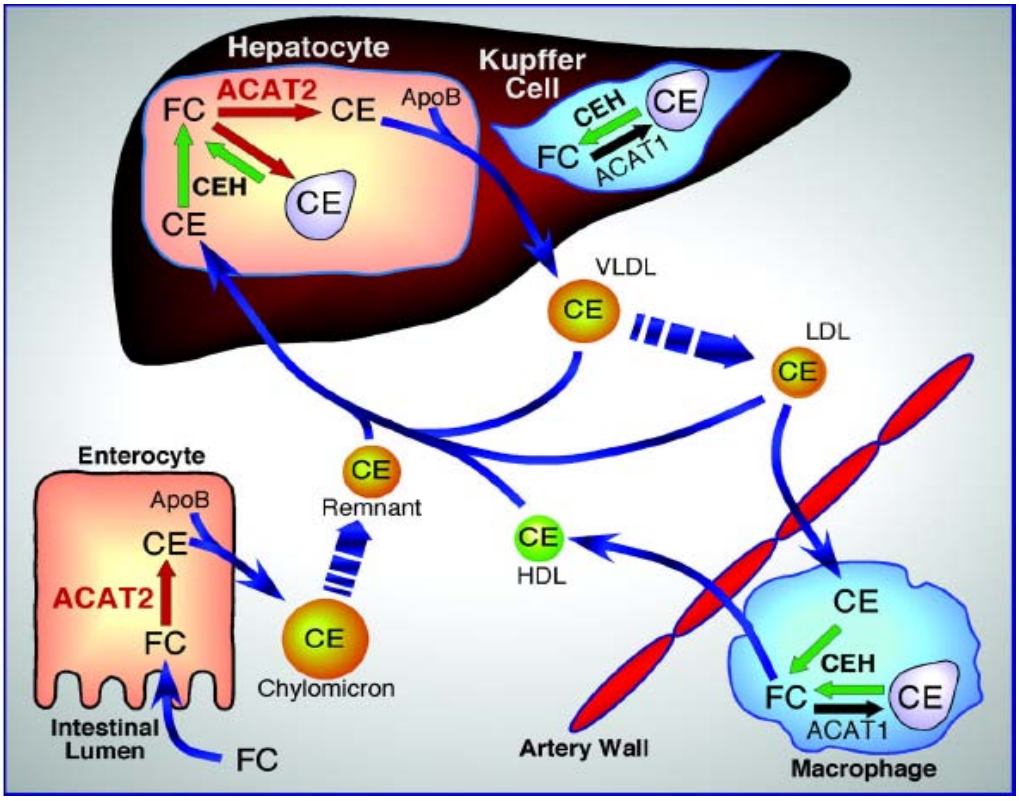


Figure 3: Schematic representation of the exogenous and endogenous sources of cholesterol within the body[36] (CEH- cholesterol ester hydrolase; LDL-R - LDL receptor; TG- trglecerides; FC- Free cholesterol).

of chylomicrons via the chylomicrons/remnant receptor and catabolism of LDL via the LDL receptor pathway.[36,] This cholesterol is then esterified and stored within the hepatocytes. At least a portion of the resulting ester is available for packaging into very low density lipoproteins (VLDL) and subsequent secretion back into the plasma compartment. A number of studies imply that ACAT inhibition in the liver may result in lowering of plasma lipids. For example, in perfused rat liver the concentration of cholesterol esters is correlated positively with VLDL secretion, suggesting that esterification is required for VLDL formation.[36,40] More recently it has been shown that ACAT may be required for the secretion of apoB-containing lipoproteins, both in cultured human liver (HepG2) cells[36,43] and perfused primate liver.[36,44] However, the possibility remains that the cholesterol substrate of the enzyme may accumulate and causes down regulation of the LDL receptor. This has been observed in HepG2 cells (but not in fibroblasts[45]) with the Sandoz

ACAT inhibitor SaH58035.[46] Also, an inverse relationship between biliary cholesterol output and ACAT activity has been described in rodents, and patients with gallstones have a reduced ability to esterify free cholesterol because of decreased hepatic ACAT activity.[47] It is therefore possible that liver ACAT inhibition may result in a lithogenic bile (high in free cholesterol) and subsequent gallstone formation.

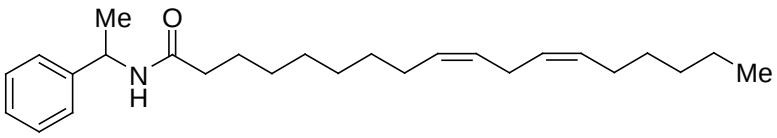
1.4.3 Role of ACATs in arterial walls

The accumulation of lipid-laden foam cells of monocyte origin in the aortic intima is an early event in the development of atherosclerosis.[48] Monocyte-macrophages take up and degrade native LDL at a slow rate via the LDL receptor. However, certain chemically modified forms of LDL are taken up very rapidly by a distinct receptor, designated as scavenger receptor. Recent *in vitro* and *in vivo* studies[49] support the hypothesis that there is an oxidative modification of LDL that targets it for uptake by the macrophages through the scavenger receptor. This uptake is not regulated; there is no feedback control comparable to the LDL receptor, and macrophages continue to take up these particles as long as they are available. Once inside the cell, the cholesterol esters are hydrolysed and immediately re-esterified by ACAT. This results in a massive accumulation of intracellular esters, resulting in the appearance of characteristic foam cells[50]. Administration of an ACAT inhibitor with systemic bioavailability would be expected to decrease the accumulation of cholesterol esters and prevent foam cell formation within the artery wall.[51] The free cholesterol thus generated may then be removed by HDL or other acceptors and targeted back to the liver. This mechanism provides direct anti-atherosclerotic activity for an ACAT inhibitor, and thus targets the site of the disease process.

2. Literature Review

At present ACAT has not been isolated in its pure form. This has prevented the use of crystallographic and computer assisted drug design techniques in the designing and synthesis of potent inhibitors. However Chang and co-workers have cloned an ACAT cDNA from human macrophage cDNA library. This clone, labeled K1, was expressed in an ACAT deficient line of Chinese hamster ovary cells and shown to encode an integral membrane protein of 550 amino acids[23]. Even in the absence of this information, a very large number of structurally diverse ACAT inhibitors have been discovered using more traditional techniques.

Compound (**1)**, a prototypical fatty acid amide was shown to be potent and specific ACAT enzyme inhibitor, which lowered plasma cholesterol in a variety of cholesterol fed rodent models. When humans were treated with 2.25 g/day of compound **(1)**, 19.6% decrease in total

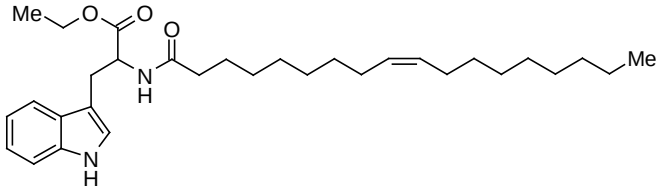


(1) Melinamide

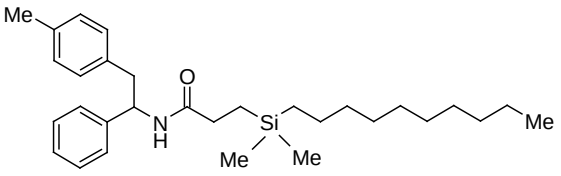
cholesterol was observed over 12 months. It was the only marketed ACAT inhibitor in Japan at one time.[52] However, it was shown that this compound was poorly bioavailable and lowered arterial ACAT directly but later it was discontinued in Japan.[51]

2.1 Amide containing ACAT inhibitors

The potential of ACAT inhibitors to block atherosclerosis was appreciated as early as 1986 and the early work on ACAT inhibitors were directed at finding agents that would lower plasma total cholesterol and/or LDL-C by blocking cholesterol absorption.[15,40] Thus, several fatty



(2) SaH 57-118

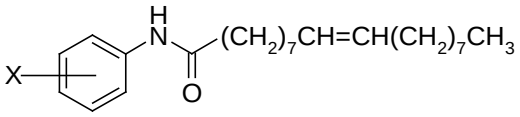


(3) SaH 58-035

acid amides such as **SaH 57-118** (**2**) and **SaH 58-035 (3)** were developed during the early work on ACAT inhibitors at Sandoz,[15, 46] that were found to potently and selectively inhibit ACAT *in*

vitro, block cholesterol absorption and lower plasma total cholesterol in cholesterol-fed animal models *in vivo*. Compound **(3)** was noted to down-regulate LDL uptake in HepG2 cells.

A systematic study to evaluate the potential fatty acid amides as ACAT inhibitors was carried out by scientists at Parke-Davis. A series of oleic acid anilides were synthesized and evaluated for their ability to inhibit ACAT *in vitro*. The 2,4,6-trimethoxy substituted phenyl ring

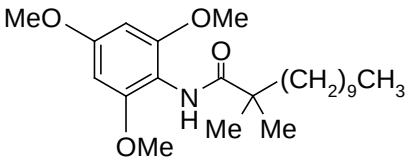


(4)

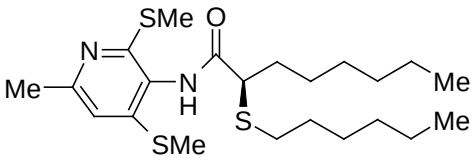
a: X = H
b: X = 2,4,6-$(OMe)_3$
c: X = 2,6-(*i*-Pr)$_2$

of anilides **(4b, IC_{50} 50 nM)** showed 500 fold improvement in potency compared to the unsubstituted anilide derivative **(4a)**. A bulky 2,6-diisopropyl substitution resulted in a highly potent compound **(4c, IC_{50} 7 nM)** in this series.[54]

The first bioavailable ACAT inhibitor that surfaced with the publication of studies in a unique atherosclerotic cholesterol-fed rabbit model was **CI-976 (5)**. The discovery of this agent had prompted a renewed interest in amide containing compounds as ACAT inhibitors.[54] The best profile of *in vivo* activity was found with **5 (IC_{50} 0.073 µM),** which produced significant reductions in non-HDL-C and elevations in HDL-C as compared to cholesterol-fed controls.



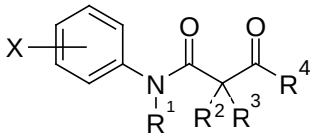
(5) CI-976



(6) CP-113,818

Compound **(5)** has also been found to produce marked reduction in atherosclerotic lesions in cholesterol-fed rabbits.[55] Based in part on this data, compound (**5)** has been proved to be a lipid regulating agent and selected for further detailed preclinical and clinical evaluation. Pfizer had identified **CP-113,818 (6, IC_{50} 30 nM)** an analog of **CI-976 (5)**, that showed extremely potent *in vitro* inhibition (both in microsomes and cellular preparations) and was found to be efficacious in variety of animal models[56]. It also decreased apoB secretion from perfused monkey livers.[57]

In continuing research at Parke-Davis, the fatty acid anilide moiety of **CI-976 (5)** was replaced with substituted β-ketoamide to incorporate extra carbonyl group and conformational constraint in the compound **(7)** expecting better inhibitions of ACAT enzymes.[58] Introduction of the β-keto group **(7a)**, while maintaining the same chain length as existing in CI-976 **(5)** resulted in similar *in vitro* potency. The C-13 alkyl chain in compound **(7a)** showed an exceptionally potent ACAT inhibition **(IC_{50} 0.006 μM)**. The plasma total cholesterol was lowered by 66% at

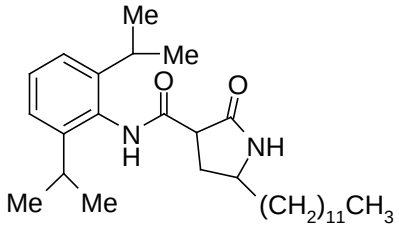


(7)

a: X = 2,6-(*i*-Pr)$_2$, $R^1 = R^2 = R^3 = H$, $R^4 = (CH_2)_{12}CH_3$
b: X = 2,4,6-(OMe)$_3$, $R^1 = H$, $R^2 = R^3 = CH_3$, $R^4 = (CH_2)_{10}CH_3$
c: X = 2,6-(*i*-Pr)$_2$, $R^1 = CH_3$, $R^2 = R^3 = H$, $R^4 = (CH_2)_{10}CH_3$
d: X = 2,6-(*i*-Pr)$_2$, $R^1 = H$, $R^2 = R^3 = H$, $R^4 = (CH_2)_{10}$OTHP

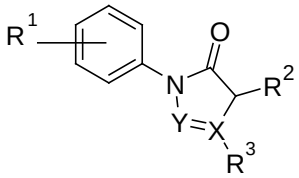
30 mg/kg and 38% at 3mg/kg with this compound. Thus, its potency appears to be greater than that observed for CI-976, which typically lowers plasma total cholesterol by 56% and 19% at 30 and 3 mg/kg doses, respectively. The introduction of α,α-dimethyl substitution in acyclic β-ketoamide **(7b)** did not cause any improvement in its *in vitro* potency unlike CI-976. However, *N*-methylation of the anilide nitrogen **(7c)** showed a marked reduction in its *in vitro* activity. This indicated that the amide NH was essential for ACAT inhibition, which was not addressed in the previously reported series of amides and ureas. Addition of free hydroxyl group in this series at the end of the alkyl chain decreased lipophilicity and *in vitro* activity but masking this hydroxyl unit with a tetrahydropyran (THP) ring restored both *in vitro* and *in vivo* activity **(7d, IC_{50} 0.057 μM)**. It was established previously that 2,6-disubstitution on the phenyl ring was necessary for potent ACAT inhibition.

Further, the cyclic β-ketoamide analogs **(**e.g. **8)** were synthesized in which the second carbonyl group was directly incorporated into a ring. Incorporation of this rigidity into the molecule did not affect activity significantly. The seven membered lactam ring, with C_{12} alkyl chain substituted on it yielded slightly better *in vitro* and *in vivo* activity **(IC_{50} 0.022 μM**, 47% reduction in plasma total cholesterol at 30 mg/kg while the compound **(8)** with five membered lactam ring having the same chain length had IC_{50} of 0.053 μM and 20% reduction at 30mg/kg.[58]



(8)

Further interest in ACAT inhibitors at Parke-Davis resulted into synthesis of two series of conformationally constrained analogs such as imidazolidinones **(9a, IC_{50} 1.3 µM)** and pyrazolones **(9b, IC_{50} > 5 µM)**. This type of modification caused a reduction in the ACAT inhi-



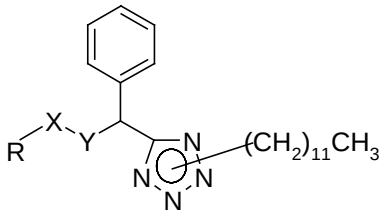
(9)

a: R^1 = 2,6- (*i*-Pr)$_2$, X = N, Y = CH, R^2 = H, R^3 = $CHPh_2$
b: R^1 = 2,6-$(Me)_2$, X = CH, Y = N, R^2 = H, R^3 = $(CH_2)_9Me$

bitory activity (in *vitro* and *in vivo)*. On the basis of this study it was concluded that either the enzyme active site could not tolerate the rigid molecules or the requirement of hydrogen bond donor in the molecule was essential for activity.[59]

To further explore structural requirements of amide containing ACAT inhibitors, the same group of researchers has investigated the effects of incorporation of the tetrazole moiety into the side chain of the α-substituted anilides. The parent compound **(10a)** showed significantly potent *in vitro* and *in vivo* activity (**IC_{50} 0.11µM** & 40% decrease in plasma total cholesterol). SAR studies revealed that the replacement of the 2,6-dimethylphenyl moiety of compound (**10a)** with 2,6-diisopropylphenyl **(10b, IC_{50} 0.81 µM)**, 2,6-dichlorophenyl **(10c, IC_{50} 0.38 µM)** or 2,4,6-trimethoxyphenyl **(10d, IC_{50} 1.70 µM)** failed to increase potency or efficacy. 3-Nitrobenzamide derivative **(10e, IC_{50} 0.08 µM)** showed the optimal potency. The benzamide ring was replaced with a basic nicotinamide moiety **(10f, IC_{50} 0.08µM)** to improve aqueous solubility and possibly absorption properties of the compound. The length of the alkyl chain attached to the tetrazole side chain was crucial for potent ACAT inhibition, whereas its position (in case of regioisomers) was less critical.[60,61] Since the fatty acid anilides had been shown to be significantly more potent

than the corresponding benzamide isosteres, it was sought to improve the *in vitro* activity by replacing the benzamide bond with anilide bioiosteres **(10g, IC_{50} 0.010 µM)**. Individual enantiomers of **10g** were resolved to assess the biological activity of individual enantiomeric forms. The *in vitro* evaluation of the isomers suggested that the **(+)-10g** was more potent than **(-)-10g**.[60,62] Next, it was planned by this group to systematically replace substituents appended to the amide and tetrazole moieties with structurally diverse functionalities and assess their effects on biological activity. The structure-activity relationship studies identified aryl and heteroaryl replacements **(10h, IC_{50} 0.013 µM** & **10i, IC_{50} 0.013 µM)**[60,63] for 2,6-diisopropyl phenyl to be



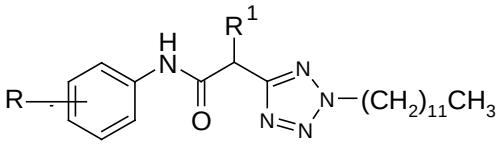
(10)

a: R = 2,6-$(Me)_2$Ph, X = CO, Y = NH
b: R = 2,6-(i-Pr)$_2$Ph, X = CO, Y = NH
c: R = 2,6-$(Cl)_2$Ph, X = CO, Y = NH
d: R = 2,4,6-$(OMe)_3$Ph, X = CO, Y = NH
e: R = 3- NO_2Ph, X = CO, Y = NH
f: R = 2-MeSPyr, X = CO, Y = NH
g: R = 2,6-(i-Pr)$_2$Ph, X = NH, Y = CO
h: R = 2,4-$(OMe)_2$Pyr, X = NH, Y = CO
i: R = 1,2,3-$(Me)_3$Pyrazole, X = NH, Y = CO
j: R = 2,4,6-$(OMe)_3$Ph, X = NH, Y = CO
k: R = Ph, X = NH, Y = CO

potent inhibitors of liver microsomal and macrophage ACAT *in vivo* and exhibited good cholesterol lowering activity (56-66 % decrease in plasma total cholesterol at 30 mg/kg) relative to the parent compound **(10g).** Surprisingly, the unsubstituted derivative **(10k)** was found to be essentially equipotent to the parent compound **(10a)** *in vitro*, although it was not efficacious *in vivo*.

Further, the α-phenyl moiety was replaced with 4-fluorophenyl analogs. Compound (**11b)** showed equipotency to the parent compound **(11a, IC_{50} 0.023 µM)**. Replacement of the α-phenyl moiety with smaller electron-withdrawing substituents (CN, tetrazoyl) showed reduction in potency in both microsomal and cellular assays whereas the 2-pyridyl analog **(11c, 0.026 µM)**

maintained the potency. Among all of the electron donating anilide substituents, the benzyl derivative **(11d, IC_{50} 0.049 µM)** potently inhibited macrophage ACAT *in vitro* and maintained excellent *in vivo* hypocholesterolemic activity **(IC_{50} 0.049 µM)**. In order to evaluate the role of the dodecyl side chain appended to the tetrazole ring, C_{12} functionality showed potent inhibitory

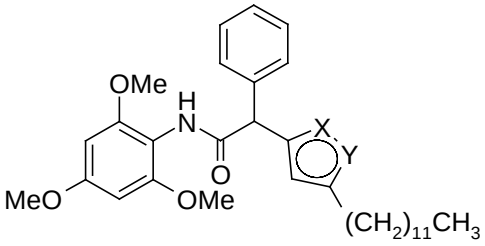


(11)

a: R = 2,4,6-$(OMe)_3$, R^1 = Ph.
b: R = 2,4,6-$(OMe)_3$, R^1 = 4-FPh.
c: R = 2,6-(*i*-Pr)$_2$, R^1 = 2-Pyridyl
d: R = 2,4,6-$(OMe)_3$, R^1 = CH_2Ph

activity. Few moieties in this series exhibited drug-related adrenal toxicity in guinea pigs following oral administration at a dose of 100 mg/kg whereas the corresponding α-phenyl derivatives did not exhibit any histopathologic alterations to the adrenal or liver of guinea pigs.[63]

The tetrazole moiety was replaced next by various heterocyclic rings. The two optimal isoxazole analogs **(12a, 12b)** showed good potency and were found to be nontoxic in a guinea pig model of adrenal toxicity.[60,64] These two compounds (**12a, 12b IC_{50} 0.015** & **0.022 µM** respectively) significantly lowered cholesterol in cholesterol-fed rabbit and cholesterol-fed dog models. Both of the compounds were selected for evaluation in a long-term model of atherosclerosis.

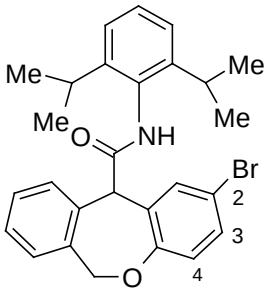


(12)

a: X = O, Y = N
b: X = N, Y = O

Kumaza *et al.* have reported the synthesis of N-phenyl-6,11-dihydrodibenz[*b*,*e*]oxepine-11-carboxamide and their derivatives.[65] SAR studies of these compounds suggested that the 2,6-diisopropyl substitution in the anilide ring in compound (**13**) resulted into maximum potency,

although the 2,4,6-trimethoxy derivative also provided a good ACAT inhibitory activity profile. 3-Bromo derivative was found to be less potent than 2-bromo derivative. 2-Methylthio derivative showed the highest *in vitro* potency (**IC_{50} 7 nM**) but showed negligible *in vivo* potency.

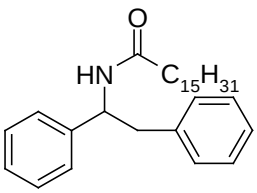


(13) KF 17828

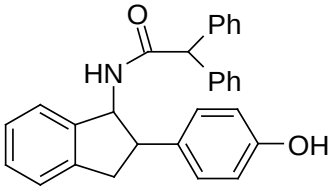
Replacement of the amide bond with thioamide resulted in complete loss of biological activity. Compound **KF 17828** (**13)** was found to be the most promising one (**IC_{50} 23 nM**) amongst the series.

Amides of some substituted 1,2-diaryl ethylamines (**14**) have been reported as very potent microsomal ACAT inhibitors *in vitro* but found to be poor inhibitors in the *in vivo* animal model.[66] Designing of conformationally restricted amides of 1,2-diaryl ethylamine led to the synthesis of *cis*-[2-(4-hydroxyphenyl)-1-indanyl]diphenylacetamide (**15**) which was found to be a potent ACAT inhibitor (**IC_{50} 0.04 µM** in an *in vitro* rat hepatic microsomal ACAT assay, ED_{50} 0.72 mg/kg/day in cholesterol-fed hamsters).[67]

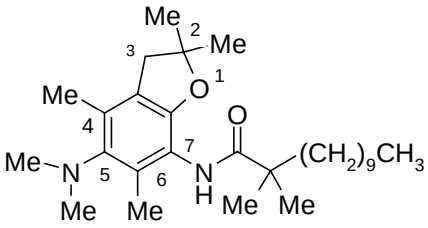
The SAR studies on novel *N*-(2,2-dimethyl-2,3-dihydrobenzofuran-7-yl)amide (**16**) derivatives revealed that a methyl group at 6th position of the 2,3-dihydrobenzofuran moiety was



(**14**)



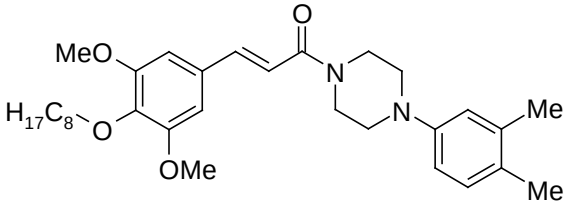
(**15**)



(**16**) **TEI-6620**

important for potent ACAT inhibitory activity.[68] Incorporation of highly lipophilic moieties exhibited improved potency and introduction of a dimethylamino group at position 5 of the 2,3-dihydrobenzofuran moiety also resulted in highly potent compound. The most potent compound **TEI-6620** (**16**) of the series exhibited highly potent ACAT inhibitory activity (rabbit small intestine **IC_{50} 0.020 µM**, rabbit liver **IC_{50} 0.009 µM**), foam cell formation inhibitory activity (rat peritoneal macrophage **IC_{50} 0.030 µM**) and extremely potent serum cholesterol lowering activity in cholesterol-fed rats (71% at a dose of 0.3 mg/kg/day) with good bioavailability in dogs (Cmax 2.68 µM/mL at 1 hr, 10 mg/kg *po*).

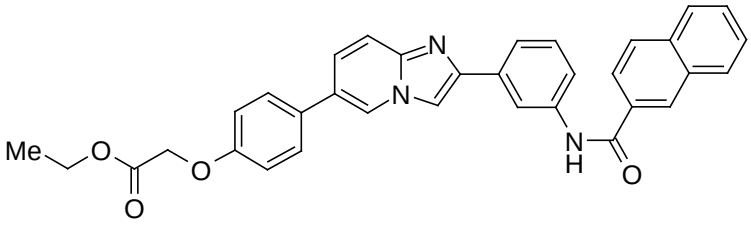
A novel series of ACAT inhibitors were synthesized. The synthesized compounds inhibited rat hepatic ACAT in a more striking manner than **CI-976** and inhibited both microsom-



(17)

al ACAT prepared from HepG2 (a cell line derived from human hepatocarcinoma) and Caco2 (a cell line derived from human colon adenocarcinoma). Compound **(17**, **IC_{50} 11 nM)** did not show any adrenal gland toxicity in rats. The compound **(17)** could fulfill expectations as a new therapeutic drug or at least as a lead compound in future for further development as a potent drug for hypercholesterolemia and atherosclerosis.[69]

A novel series of various 2,6-substituted imidazo[1,2-*a*]pyridines were designed, synthesized and evaluated for their ability to inhibit ACAT activity. The compound **(18)** was



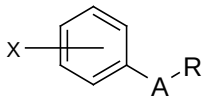
(18)

established to be a potent inhibitor of ACAT activity in HepG2 cell line and reduced cholesterol ester formation significantly in a dose-dependent manner.[70]

2.2 Urea based ACAT inhibitors

In addition to the work on the amide ACAT inhibitors, a series of analogs have been prepared in which bioisosteres of the amide group are incorporated. The bioisosteric replacement

Table 1: Bioisosteric analogs of oleic acid anilides and comparison of their *in vitro* activity[60]

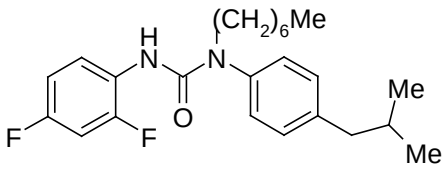


Comp	X	A	R	*In vitro* (IC_{50} µM)
I.	2,4,6-tri-OMe	-NHC(O)-	$(CH_2)_7CH{=}CH(CH_2)_7CH_3$	0.44
II.	2,4,6-tri-OMe	-NHC(S)-	$(CH_2)_7CH{=}CH(CH_2)_7CH_3$	0.9
III.	2,4,6-tri-OMe	-CONH-	$(CH_2)_8CH{=}CH(CH_2)_7CH_3$	9.4
IV.	2,4,6-tri-OMe	-NHCONH-	$(CH_2)_8CH{=}CH(CH_2)_7CH_3$	0.32
V.	2,4,6-tri-OMe	-O-C(O)-	$(CH_2)_8CH{=}CH(CH_2)_7CH_3$	>5.0
VI.	2,4,6-tri-OMe	-NHCOO-	$(CH_2)_8CH{=}CH(CH_2)_7CH_3$	0.86
VII.	2,6-di-Me	-NHCONH-	$(CH_2)_8CH{=}CH(CH_2)_7CH_3$	0.16
VIII.	2,6-di-Me	-NHCSNH-	$(CH_2)_8CH{=}CH(CH_2)_7CH_3$	5.4
IX.	2,6-di-Me	-NHC(O)-	$(CH_2)_7CH{=}CH(CH_2)_7CH_3$	0.043

rendered all of the analogs significantly less active than the parent compound but the urea analogs **(IV & VII; Table 1)** retained the *in vitro* activity. As the urea derivatives were shown to be more efficacious than the amide analogs in lowering total plasma cholesterol in the cholesterol-fed rat model, a series of urea analogs were synthesized to explore the urea containing moieties as potential ACAT inhibitors.

2.2.1 Trisubstituted ureas as ACAT inhibitors

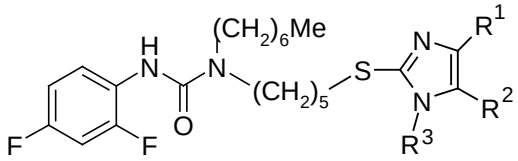
As a class the development of trisubstituted ureas as therapeutic agents have been plagued with difficulties. Initially, DeVries et al. reported the synthesis and biological properties



(19) CL-277082

of **CL-277082** (**19**). Compound (**19)** has shown significant *in vitro* ACAT inhibitory activity (**IC_{50} 0.14µM**) both in isolated microsomes and in intact cells.[71,72]

The DuPont Merck Research Laboratories synthesized and reported a series of diphenyl substituted heterocycle based trisubstituted ureas. **Dup-128** (**20a**) was a potent ACAT inhibitor



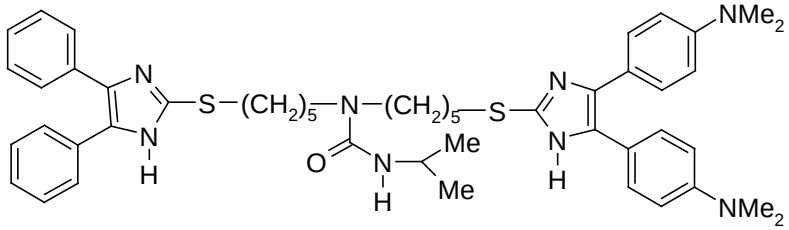
(20)

a: R^1= R^2= Ph, R^3= H **(Dup-128)**
b: R^1= Ph, R^2= H, R^3=H
c: R^1= R^2= R^3= H
d: R^1= R^2= Ph, R^3= CH_3
e: R^1= R^2= R^3= Ph

with the diaryl imidazole (**20a**) moiety that was 50 times more potent in the *in vitro* assay than the monoarylimidazole (**20b, IC_{50} 0.49µM**) and was approximately 300 times more potent than the corresponding 4,5-unsubstituted imidazole (**20c, IC_{50} 2.9µM**). *N*-Methylation on the imidazole nitrogen (**20d, IC_{50} 3.6 µM**) resulted in a 350-fold decrease in potency in comparison to the parent compound **(20a)**. The requirement of unsubstituted imidazole NH for potent ACAT inhibition was further borne out by the observation that the 1,4,5-triphenyl analog (**20e, IC_{50} >50 µM**) was shown to be poor inhibitor of ACAT. The sulfide, sulfoxide or sulfone groups at 2-position of the imidazole ring maintained the potency and were presumed to be involved in electronically modifying the *p*Ka of the imidazole. The length of five or more carbon atom chain between the sulfur and the tertiary nitrogen showed improved ACAT inhibitory activity due to the flexibility in the molecule. The isosteric replacement of urea moiety with other groups resulted in a 2-4 fold decrease in activity.[73]

Dup-128 (20a) was found to be a potent inhibitor of ACAT in rat hepatic microsomes but had shown modest activity in whole macrophage cells (the J774 murine cell line; **IC_{50} 1.0 µM**). In their efforts to discover a systemic inhibitor, a compound with good potency in the hepatic microsomal and macrophage cells, the models for inhibition of ACAT in human liver and arterial tissue, was sought. Such a compound exhibited both the serum lipid-lowering and anti-

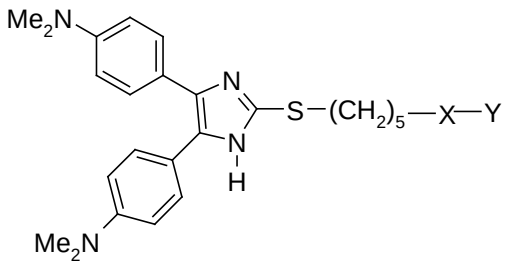
atherosclerotic properties. SAR studies revealed that the compounds bearing imidazole ring with two unsubstituted phenyl groups were potent in the avian influenza virus (AIV microsomal assay), but poor in the J774 (macrophage cell) assay. Activity against the AIV was observed to be better for difluorophenyl ureas while the isopropyl ureas showed better potencies against J774. Compounds bearing two diaryl imidazole rings exhibited better activity profile. For the



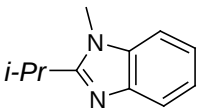
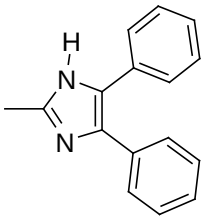
(**21**)

compound **(21)** with good dual activity it was concluded that the "diphenyl" end of the molecule was responsible for AIV potency (**IC_{50} 0.03 µM**), and the "substituted diphenyl" end was found to be responsible for good J774 macrophage potency (**IC_{50} 0.06 µM**).[74]

Further, the urea moiety of compound **(21)** was replaced by various bioisoteric aromatic heterocyclic groups.[75] It was proposed that at least one of the heterocycles would fulfill the criteria like spatial and electronic requirements for the inhibitor-enzyme interaction. One ring would mimic the urea by linking the heterocycle through a ring nitrogen atom in compound **(22a)**. In compound **(22b)** the 2-thiaimidazole would mimic the urea moiety as an exocyclic



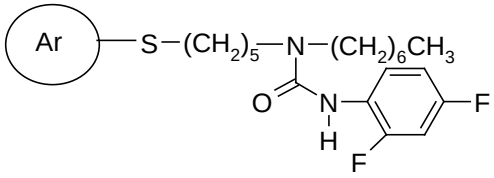
(22)

a: X- Y =  **b:** X = S, Y = 

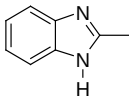
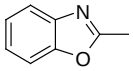
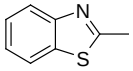
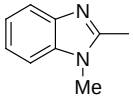
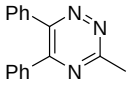
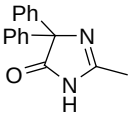
heteroatom. The compound **(22a)** showed very good potency towards the J774 macrophage cell cultures (**IC_{50} 0.08 µM**) and **22b** was found to be effective towards the AIV (**IC_{50} 0.03 µM**).

From the biological data (**Table 2**) it was recognized that the 4,5-diarylimidazole compounds were superior[73,74]. The role of heterocyclic groups in ACAT inhibitors was explored.

Table 2: Incorporation of different heterocycles and comparison of the inhibitory potency towards ACAT enzyme

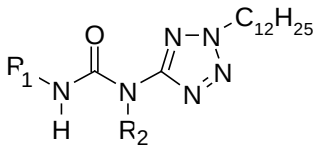


(23)

Cmpd	Ar	AIV IC_{50} (µM)
23a		0.50
23b		51.0
23c		4.00
23d		2.49
23e		0.44
23f		0.09

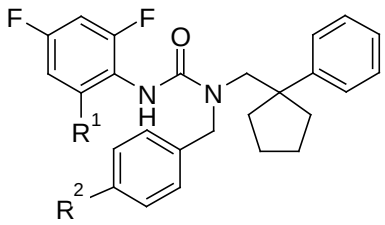
The 4,5-diaryl imidazole moiety was replaced by various nitrogen containing fused rings to reduce the molecular weight and to improve the bioavailability of the compounds.[76] Fused imidazoles (**23a**), oxazoles (**23b**), thiazoles (**23c**), *N*-substituted imidazoles (**23d**) and triazines (**23e**) were observed to be less potent but the imidazolinone derivative (**23f**) was having the same magnitude of activity as **DuP-128** (**20a**).

Researchers at Parke-Davis Pharmaceuticals have reported a novel series of tetrazole-substituted ureas.[77] The compound **(24a**, **IC_{50} 0.047 µM**) was found to be more active in the macrophage ACAT assay than **CI-976** but unfortunately it exhibited adrenotoxicity in the guinea pig. In this model, compound (**24b**, **IC_{50} 0.057 µM**) at a dose of 5 mg/kg was shown to be as efficacious at lowering total serum cholesterol as **CI-976** and it did not show any adrenal toxicity to the guinea pig.



(24)

a: R_1 = 2,6-(*i*-Pr)$_2$Ph, R_2 = Ph
b: R_1 = 2,4,6-(OMe)$_3$Ph, R_2 = C_6H_{11}

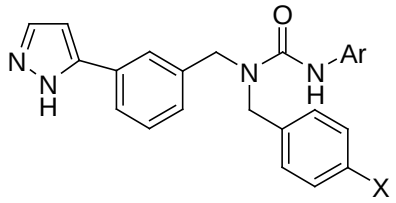


(25)

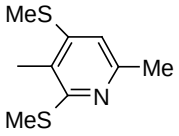
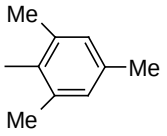
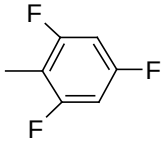
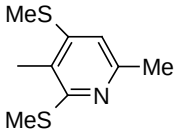
a: R^1= H, R^2= H
b: R^1= F, R^2= NMe_2

In their continuing interest in developing novel, potent ACAT inhibitors, they synthesized a series of trisubstituted ureas that were structurally hybrids of the disubstituted ureas. This series of compounds has shown more potent activity with 2,4-difluoro (**25a, IC_{50} 0.09 µM**) and 2,4,6-trifluoro (**25b, IC_{50} 0.022 µM**) substitutions on phenyl ring of the urea nitrogen than the compounds containing bulky substituents at 2,6-positions on the phenyl ring at the same nitrogen.[78]

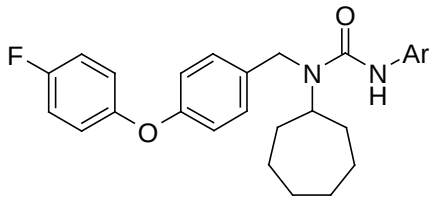
Tanaka *et al.* have designed and synthesized a new ACAT inhibitor, **FR186054** (**26a**), bearing a pyrazole ring that exhibited potent *in vitro* ACAT inhibitory activity and excellent hypocholesterolemic effects in cholesterol-fed rats.[79] SAR studies revealed that **26b** and **26c** showed more potent ACAT inhibitory activity *in vitro* than **CL 277082** and **26a**. However, the *in vivo* hypocholesterolemic effect of **26a** was clearly superior when dosed as a dietary admixture, being 100-fold more potent compared to the reference compound, presumably as a result of improved pharmacokinetics. The introduction of dimethylamino group on to the 4-position of *N*-benzyl moiety (**26d**) resulted in reduced *in vitro* activity but retained the *in vivo* efficacy.



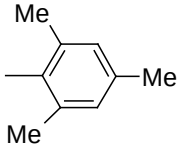
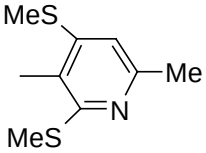
(26)

Comp	Ar	X
a		H
b		H
c		H
d		$N(Me)_2$

Further, the above group has prepared a series of *N*-alkyl-*N*-biphenylmethyl-N'-aryl urea and related derivatives and evaluated them for the ability to inhibit ACAT *in vitro* and to lower plasma cholesterol levels in cholesterol-fed rats *in vivo*. From the SAR studies, it was concluded

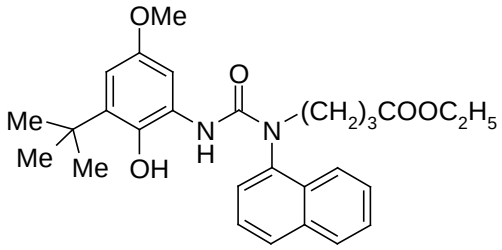


(27)

a: Ar =  **b:** Ar = 

that the linking of two phenyl groups via oxygen and introduction of fluorine at appropriate positions on the biphenyl moiety improved *in vitro* and *in vivo* activity. From this series of analogs, compound **FR179254** (**27a**) has shown potent *in vitro* potency (rabbit intestinal microsomes **IC_{50} 25 nM**) and excellent plasma cholesterol-lowering activity (**ED_{50} 0.045 mg/kg**). Modification of the N'-aryl moiety led to the identification of compound **FR182980** (**27b**) which was efficacious in both of the dosing models (**ED_{50} 0.034 mg/kg** and **0.11 mg/kg** respectively).[80]

Novel hydroxyphenyl urea derivatives **(**e.g. **28)** were synthesized and their inhibitory potency evaluated against both ACAT and LDL oxidation.[81] QSAR analysis revealed that their

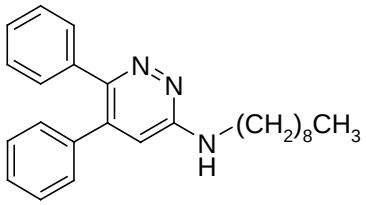


(28)

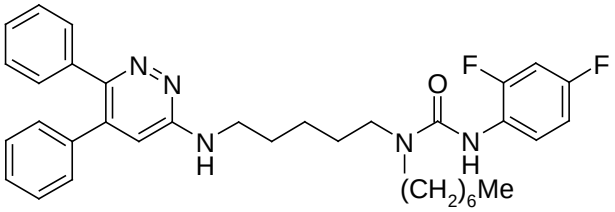
ACAT inhibitory activities were controlled by the hydrophobicity of the whole molecule, the substitution pattern of urea moiety, and the existence of carboxylic acid group. These derivatives inhibited foam cell formations. Moreover, these compounds showed antioxidative effects against low density lipoprotein (LDL), owing to their characteristic 3-*t*-butyl-2-hydroxy-5-methoxyphenyl substructure. Based on the mechanism of atherosclerosis generation, they hypothesized that this hydroxyphenylurea-type (**28**) dual inhibitors (against both ACAT and LDL oxidation) were expected to be promising drugs for atherosclerosis in the time to come.

N-Alkyl5,6-diphenylpyridazine derivatives (**29a)** possessing several main features of ACAT inhibitors, such as a long alkyl side chain linked to a heterocycle and the *o*-diphenyl system, were synthesized and tested by Gelain et al. Modeling studies were also performed on the compounds. Some of the compounds displayed ACAT inhibition in the micromolar range (**29a, IC_{50} 18 µM**), both on the enzyme isolated from rat liver microsomes and in cell-free homogenate of murine macrophages.[82] Keeping the above features in mind, they reported the mono- and diphenylpyridazineureido derivatives **(29b)**, structurally related to **DuP 128 (20a)** and

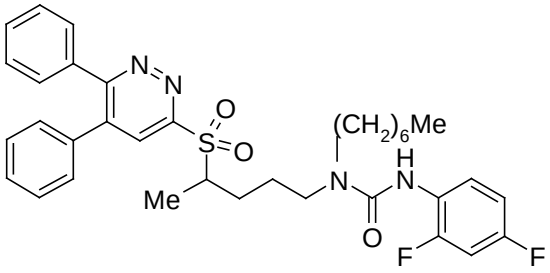
tested them for their inhibitory activity against ACAT, isolated from rat liver microsomes. Compound (**29b)** showed the most interesting activity against hACAT-1 (**IC_{50} 0.94 μM**) and hACAT-2 (**IC_{50} 1.74 μM**) isoforms.[83] This group has described a series of *N*-(2,4-difluorophenyl)-*N'*-heptyl-*N'*-{4-[(substituted pyridazin-3-yl)sulfonyl]pentyl}urea derivative **(30)** having phenyl rings at 5 and 6 positions of the heterocycle. The compound showed



(**29a**)



(**29b**)



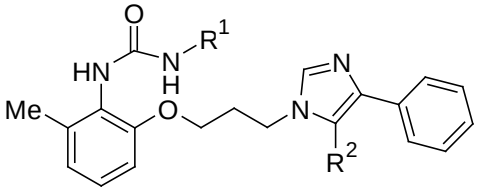
(30)

inhibitory activity against the ACAT enzyme prepared from rat liver microsomes (78% inhibition at a conc. of 50 μg/mL). Theoretical studies were also performed to correlate the activity with the structural features.[84]

2.2.2 Disubstituted ureas as ACAT inhibitors

A series of disubstituted phenylureas linked to 4-phenylimidazole were synthesized and evaluated for *in vitro* inhibitory activity for both aortic and intestinal ACAT and *in vivo* hypocholesterolemic activity.[85] The SARs were studied involving strategic modification of five regions in the compound (**31**) i.e., by introducing functional groups or exchanging carbon atoms for heteroatoms. Methyl group in the ortho position of the phenyl urea showed better pharmacokinetic property. Butyl, pentyl, isopentyl, and neopentyl groups were better substituents in the urea moiety. Propoxy was the optimal moiety in the bridging portion. Hydrogen, methyl, ethyl, isopropyl, hydroxymethyl and chloro were observed to be better substituents at the 5-position of the imidazole moiety. Unsubstituted phenyl ring on the imidazole ring was observed to provide better compounds. Subsequent comparative study of compounds containing various

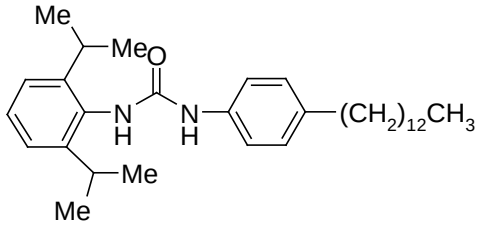
combinations of the substituents in each region resulted in the selection of two compounds for further pharmacological and toxicological testing. These compounds were orally bioavailable and possessed potent *in vitro* aortic ACAT inhibitory activity (**31a, 31b IC_{50} 0.16** and **0.012 µM,** respectively) and *in vivo* cholesterol lowering effect (46% and 52 % at 1 mg/kg PO, respectively).



(31)

a: $R^1 = C_4H_9$, $R^2 = C_2H_5$ **(E 5324)**
b: $R^1 = C_4H_9$, $R^2 = CH(Me)_2$

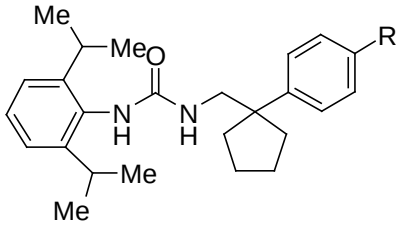
Trivedi *et al.* synthesized and reported a series of *N, N'*-diphenylureas with a *para* alkyl substituent larger than *n*-pentyl. The group was found to be essential for potent ACAT inhibition *in vitro*.[86] In this series, compound **(32, IC_{50} 0.011 µM**) represented a simple urea derivative with



(32)

an excellent profile for development as a hypocholesterolemic agent. In their continuing research programme, a series of *N*-phenyl-*N'*-aralkyl- and *N*-phenyl-*N'*-(1-phenylcycloalkyl)ureas have been reported as inhibitors of ACAT.[87] From this series compound **(33a, PD 129337)** was identified as a potent inhibitor of ACAT with an IC_{50} value of 17 nM. Due to lack of efficacy of compound **(33a)** in aqueous vehicle, the *N'*-phenyl moiety was modified by incorporating polar functional groups which were amenable to forming salt to reduce lipophilicity. Introduction of any bulky group in the *para* position and polar groups such as carboxyl lowered the *in vitro* activity. In chronic cholesterol fed rat model of hypercholesterolemia, compound **(33b, PD 132301-2)** dose-dependently reduced non-HDL cholesterol and significantly elevated the HDL cholesterol. It showed significantly greater aqueous solubility than the parent compound **(33a)**.

Later on compound **(33b)** was reported to exhibit organ toxicity. Administration of compound (**33b)** to beagle dogs for two weeks at doses ranging from 6-800 mg/kg/day resulted in significant decreases (60-80%) in adrenal, total and esterified cholesterol.[88] However, it was shown to cause the adrenal toxicity in guinea pigs[89] and monkeys.[90] This led to design of a series

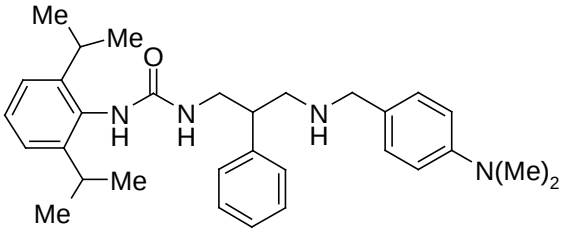


(33)

a: R= H **(PD 129337)**
b: R= *p*-$N(CH_3)_2$.HCl **(PD 132301-2)**
c: R= *m*-$CH_2N(CH_3)_2$.HCl

of homologs with increased basicity and lower lipophilicity. Finally, compound **(33c)** was reported not to produce adrenal toxicity in guinea pigs unlike compound **(33b)** and it demonstrated excellent lipid-modulating activity in the chronic model of hyperlipidemic rats.

Further, a series of di-substituted ureas containing amide or amine groups were prepared and evaluated for their ability to inhibit ACAT *in vitro* and lower total plasma cholesterol in a

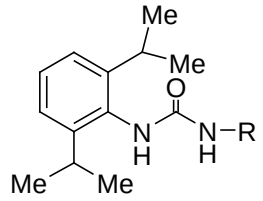


(34)

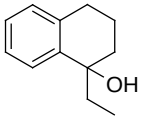
variety of cholesterol-fed rat models *in vivo*.[91] Presence of polar or ionizable functionalities within this class of compounds imparted greater aqueous solubility and showed its improved transportation to the enzyme location within the intestinal enterocyte. In general, the amine containing compounds showed more potency and efficacy than the amides in the acute rat model of hypercholesterolemia. SAR studies showed that the preferred position of the amide/amine

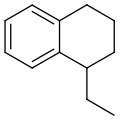
group was β to the urea moiety and the presence of a secondary amine hydrogen is required for good *in vitro* potency. One (**34**) of these compounds lowered plasma total cholesterol (47 %) and elevated high density lipoprotein (HDL) cholesterol when dosed in an aqueous vehicle to rats with pre-established hypercholesterolemia.

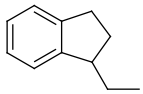
Later, Trivedi *et al.* have reported a series of conformationally and sterically constrained analogs of *N*-phenyl-*N*'-aralkylureas (**35**).[92] SAR studies revealed that a polar group like hydro-



(35)

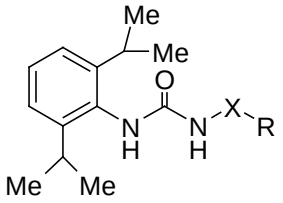
a: R = 

b: R = 

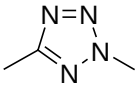
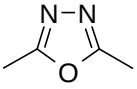
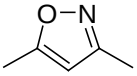
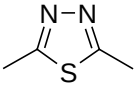
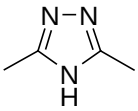
c: R = 

xyl at the β-carbon was found to be detrimental to activity (**35a, IC_{50} 0.35 µM**). Two of the homologs (**35b, 35c**) showed significant increase in potency with the IC_{50} values of 27 and 36 nM.

Researchers at Parke-Davis research Lab developed diaryl-substituted heterocyclic urea and examined their ACAT inhibitory activities.[93] In order to determine the supremacy of aryl moiety in the heterocyclic ureas, they identified that the 2,6-diisopropylphenyl analog (**36**) was more active when compared to the 2,4,6-trimethoxyphenyl analog. The potency of the tetrazole urea (**36a, IC_{50} 0.009 µM**) was found to be a modest one. The 1,3,4-oxadiazole (**36b, IC_{50} 0.018 µM**) and isoxazole (**36c, IC_{50} 0.013 µM**) moieties proved excellent bioisosteric replacements for tetrazole *in vitro* and in the APCC rat at a dose of 30 mg/kg but the 1,3,4-thiadiazole (**36d, IC_{50} 0.036 µM**) and the triazole (**36e, IC_{50} 4.2 µM**) were considerably less active *in vitro* than the tetrazoles. Alkylation of the tetrazole NH was found to be essential for activity. Activity was maximal with C-13 side chain analog and declined with a further increase in chain length, probably being extremely lipophilic and consequently not getting absorbed.

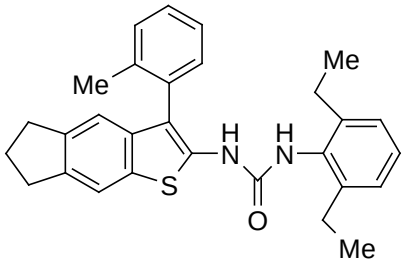


(36)

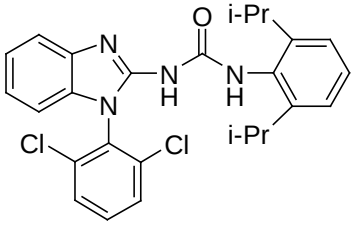
Comp	X	R
a		$-(CH_2)_{12}CH_3$
b		$-(CH_2)_{12}CH_3$
c		$-(CH_2)_{12}CH_3$
d		$-(CH_2)_{12}CH_3$
e		$-(CH_2)_{11}CH_3$

A novel ACAT inhibitor **R-755 (37)** has been characterized *in vitro*, *ex vivo* and *in vivo*. **R-755** potently inhibited ACAT activities with IC_{50} values from 2.5 to 64 nM in rabbit intestinal microsomes and several cell lines (Caco-2, THP-1 and J-774A.1 cells). It has been proved that **37** was more potent than **CI-976 (5)**. These results suggested that **R-755** can be expected to be a therapeutically useful drug that not only has lowering effects on plasma cholesterol and triglycerides but also has an antiatherosclerotic effect by causing direct inhibition of ACAT activity in the arterial wall.[94]

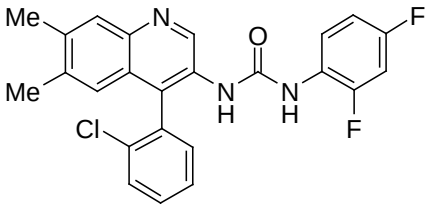
Kumazawa *et al.* at Kyowa Hakko kogyo Co Ltd in Japan described the synthesis of a novel series of *N*-(1-phenyl-2-benzimidazolyl)-*N'*-phenylurea derivative as ACAT inhibitors. Few compounds showed very good ACAT inhibitory activity. Out of them compound **(38, IC_{50} 11nM**) was found to be very potent.[95] **TMP-153 (39)** is another potent urea ACAT inhibitor



(37) R-755



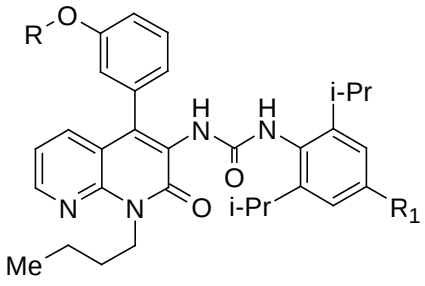
(38)



(39)

that has been reported.[96] **TMP-153** is very potent against liver and intestinal ACAT from a variety of animal species. It has an IC_{50} value of 9 nM in rat liver microsomes and 6.4 nM in rat intestinal microsomes. This compound (**39)** also displays potent lowering of plasma cholesterol *in vivo* with an ED_{50} of 0.25 mg/kg when dosed for one week to cholesterol-fed rats.

A group of researchers at Sumitomo Pharmaceuticals Co Ltd in Japan developed urea derivatives of 3-amino-4-aryl-1,8-naphthyridin-2(1*H*)-one. In particular, compound **(40a, SM-32504)** exhibited potent ACAT inhibitory activity.[97] However, this compound was poorly absorbed by oral absorption due to its low aqueous solubility. Extensive studies led to the development of compound **(40b, SMP-797, IC_{50} 31 nM**), which possessed 4-amino group on the

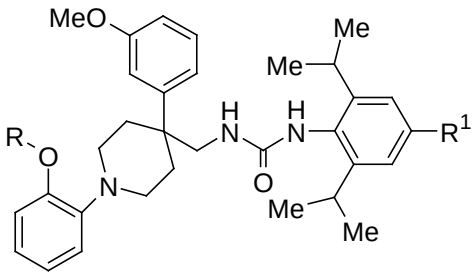


(40)

a: R = Me, R_1 = H **(SM-32504)**
b: R = $(CH_2)_3OH$, R_1 = $NH_2.2HCl$ **(SMP-797)**

aniline and 3-hydroxypropoxy group on the 4-phenyl group of the naphthyridinone moiety of compound (**40a)**. Compound (**40b)** decreased the serum cholesterol level by 53% compared to control at a dosage of 1.0 mg/kg/day orally for 3 weeks in a rabbit model fed on a casein-rich diet. This effect can be compared with atrovastatin (potent HMG-CoA reductase inhibitor), which decreased cholesterol level by 54% at a dose of 10 mg/kg/day orally for 6-weeks.[98]

Although compound **(40b)** was a promising one, its preparation required very long steps. Therefore to find back-up compounds with different mother templates and easy synthetic routes,



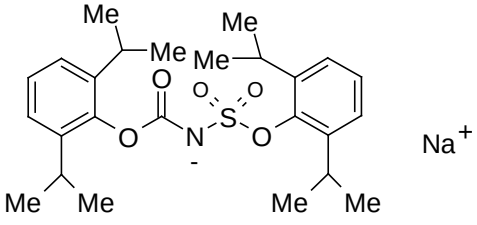
(41)

a: R = *n*-Bu, R^1= NH_2
b: R = $(CH_2)_3OH$, R^1= NH_2.HCl

the research group examined replacement of the 1,8-naphthyridine moiety with other hydrophilic groups and succeeded in finding compound **(41a**, **IC_{50} 32 nM**) as a potent ACAT inhibitor.[99] Later it was described that compound **(41b)**, inhibited ACAT activity with an IC_{50} value of **18nM**,[100] which was superior to that of a known ACAT inhibitor and also revealed an LDL-R up-regulatory activity comparable to that of compound **(40b)**.

2.3 Aminosulphonyl based ACAT inhibitors

The same group of researchers as previously mentioned at Parke-Davis Pharmaceutical Research Lab, New Jersy designed ACAT inhibitors with improved bioavailability. They hoped to design an ACAT inhibitor with a relatively low lipophilicity (calculated LogP value between

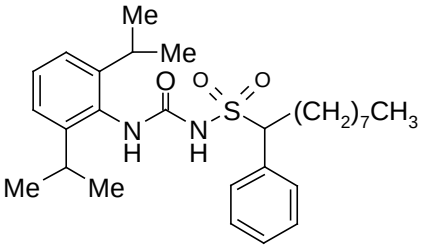


(**42**) **CI-999 (PD 138142-15)**

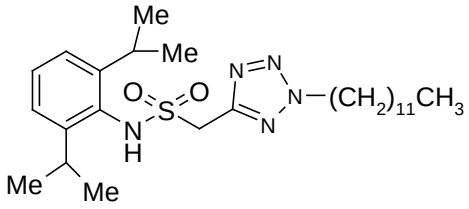
1.79 - 2.44 was considerably less than the one commonly encountered in the ACAT inhibitor field *i.e.* 6 - 12), which could be completely absorbed.

They synthesized a novel, water soluble ACAT inhibitor. The IC_{50} value of the compound (**42)** was found to be 5.3 μM [101] whereas the **IC_{50}** values for potent established compounds **(19** and **20a)** were 0.47 and 0.018 μM respectively. Similar ACAT inhibitory activities were found for **42** and **20a** using microsomes isolated from the intestinal mucosa of cholesterol-fed rabbits but compound **(19)** was reported to be more potent in this system. This compound caused a decrease in adrenal cholesterol esters and a nonreversible zonal atrophy and degeneration of the adrenal gland.[102] Compound **(42)** showed instability in acidic aqueous media and degraded into two products identified as 2, 6-diisopropyl phenol and sulphamate.

Further, a series of sulfonylureas (**43**) were described and identified as a series of moderately potent and highly efficacious ACAT inhibitors,[103] which lowered TC and elevated HDL-C as effectively as **42** in a chronic rat model of hypercholesterolemia. A series of novel sulfonamide tetrazole **(44)**[104] derivatives as ACAT inhibitors have been described. The use of



(43)

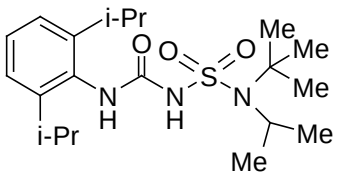


(44)

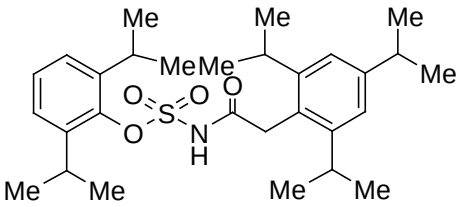
sulfonamide as isosteric replacement of the amide group in the series of tetrazole amide resulted in comparable *in vivo* efficacy but lower *in vitro* potencies. It was reported that the position and the length of the alkyl substituents on the tetrazole ring had a marked effect on ACAT inhibitory activity. Compound (**44**) exhibited lower *in vitro* potency (**IC_{50} 0.022 μM**) and good *in vivo* efficacy.

Further, several ACAT inhibitors have been described by stepwise addition of nitrogen, oxygen and sulphur nucleophiles to N-chlorosulfonyl isocyanate.[105] The aminosulphonylureas were the most potent inhibitors *in vitro* with several compounds having **IC_{50}** values less than **1**

µM. Compound **(45)**, in which the *N,N*-dialkylamino group contains 6 to15 carbon atoms, exhibited good ACAT inhibitory *in vitro* potency and *in vivo* efficacy. In an effort to overcome the inherent chemical instability of compound **(42)**, compound **(46, CI-1011**, **Avasimibe**) has been identified with equivalent or better *in vitro* and *in vivo* activities but higher solution stability



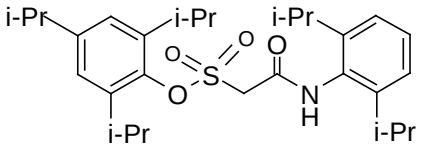
(45)



(46) CI-1011, Avasimibe

especially at pH <7. Compound **(46)** was highly stable in acidic or basic solutions and displayed excellent *in vivo* efficacy in standard cholesterol-fed rat models. The calculated **ED_{50}** value was 0.4 mg/kg,[106] which was much less than the dose reported for potent compounds like **CL 277082** (**19, ED_{50} 16 mg/kg**), **Dup128** (**20a, ED_{50} 15 mg/kg**), and **41a** (**ED_{50} 2 mg/kg**).

Finally, the best compound **(47)** was identified showing similar *in vivo* efficacy as the previously reported potent compounds like **19** and **20a**. The reason for the greater *in vitro*

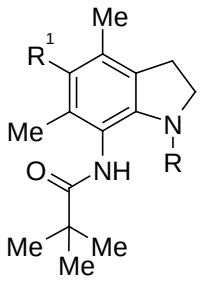


(**47**)

potency of compound **(47)** was unclear (**IC_{50} 0.007 µM**).[107]These findings had prompted further pharmacological investigations in this series of compounds.

Takahashi *et al.* described a series of novel indoline derivatives with an ionizable moiety to find a bioavailable ACAT inhibitor with antiperoxidative activity. [7-(2,2-Dimethylpropanamido)-4,6-dimethyl-1-octylindolin-5-yl]acetic acid hemisulfate (**Pactimibe**, **48a)**[108] with low lipophilicity and high water solubility showed good oral absorption and inhibitory activity against foam cell formation in THP-1 cells exposed to acetyl-LDL after differentiation (**IC_{50} 0.3 μM**) and an antiperoxidative effect in LDL of hypercholesterolemic

rabbits (**IC_{50} 1.0 μM**). Compound **(48a)** inhibited macrophage, hepatic and intestinal ACAT activity (**IC_{50} 1.9, 0.7** and **0.7 μM** respectively).The same group of researchers described a novel series of indoline-based ACAT inhibitors with methanesulfonamide group and evaluated their lipophilicity and biological activities.[109] From the series, compound **(48b)** showed greater inhibitory effects on hepatic cholesterol secretion in mice. It was concluded that the introduction

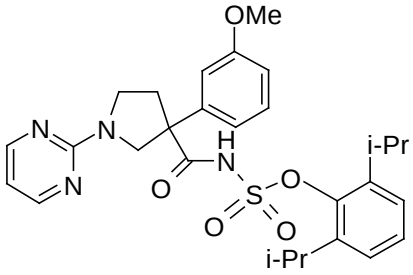


(48)

a: R = $-(CH_2)_7CH_3$, R^1 = $-CH_2COOH$ (**Pactimibe**)
b: R = $-C_2H_5$, R^1 = $-NHSO_2Me$

of a methanesulfonamide group was effective to provide less lipophilic, more efficacious and bioavailable compound than **48a**.

Asano *et al*. have synthesized compounds that possessed LDL-R up-regulating activity without ACAT inhibition. They started this approach by modification of 1,4-diarylpiperidine-4-methylurea (**41)**. Replacement of the methyleneurea linker **(41)** with the acylsulfonamide **(49)** was effective in keeping the up-regulatory activity for LDL-R expression and reducing ACAT inhibitory activity.[110] Introduction of 2-pyrimidyl group in compound **(49)** enhanced LDL-R up-regulatory activity and abolished ACAT inhibitory activity. Additionally, the sodium salt of the

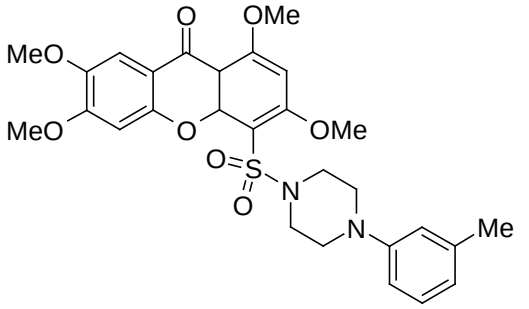


(49)

selected compound **(49)** showed good oral pharmacokinetics properties in hamsters, and it reduced plasma TC and LDL-C levels in a dose-dependent manner in an experimental animal

model of hyperlipidemia. These results indicated that LDL-R up-regulation is important for plasma lipids reduction. Finally, they clarified the mechanism of action of **50** toward LDL-R up-regulation using ARH specific RNA interference, and revealed that ARH, an adaptor protein of LDL-R, was a potential target for LDL-R up-regulation. The results of this study indicated that this compound **(49)** with its unique mechanism of action could be a lead for future novel antihyperlipidemic agents.

Honggang Hu *et al.* have described a series of xanthone sulfonamides that resulted in the identification of several potent ACAT inhibitors. Out of them compound **(50**, 32.4% inhibition at

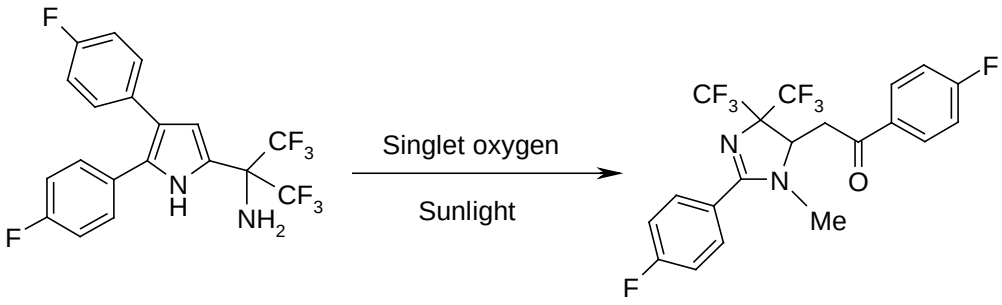


(50)

10 μg/mL) [111] proved to be equipotent to the positive control **Sandoz58-35** (an ACAT inhibitor, from Sigma, 55% inhibition at 10 μg/ mL).

2.4 Imidazoline based ACAT inhibitors

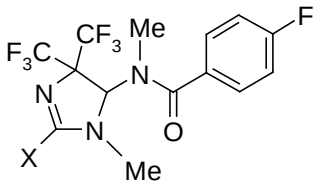
Li Hui-Yin *et al.*, a group of researcher from DuPont Merck Pharmaceutical Company designed and synthesized new series of 4,4-bis(trifluoromethyl)imidazolines with a *p*-fluorophenacyl side chain using a facile photooxidative cleavage of pyrrole **(51)** with singlet



(51) **(52)**

oxygen. Finally, compound **(52)** showed good activity as ACAT inhibitor (**IC_{50} 11 μM**) and cholesterol biosynthesis inhibitor (**IC_{50} 4 μM**).[112]

Further, they synthesized molecule **(53a),** a very potent ACAT inhibitor (**IC_{50} 1.4 μM**) with remarkable oral activity in lowering the serum cholesterol level in several animal models and it was also reported that the *R*-enantiomer of **53a** was about 25 times more potent than the *S*-enantiomer in the ACAT *in vitro* assay.[113] Finally, they synthesized 4,4-bis(trifluoromethyl)imidazolines with a *p*-cyano group on 2-phenyl and 4-alkylcyclohexylamide, as the side chain possessed the most potent inhibitory activity **(53b, IC_{50} 0.09 μM**).

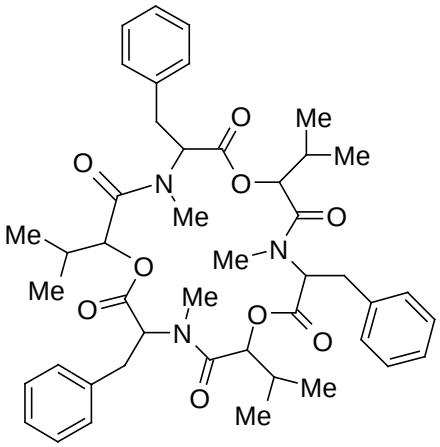


(53)

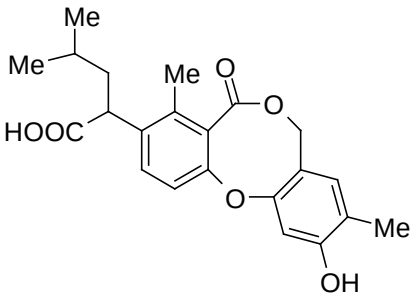
a: X = 4-Cyanophenyl
b: X = 3-Propylcyclohexyl

2.5 Natural products as ACAT inhibitors

Some products of microbial origin were shown to inhibit ACAT enzyme to varying degrees. These compounds provided additional insights into the pharmacophore necessary for



(54)



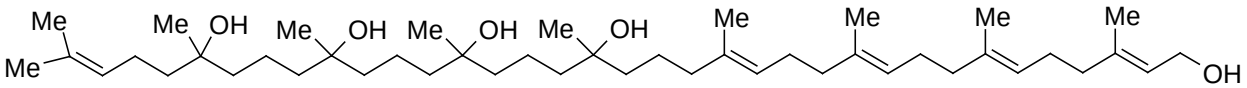
(55)

ACAT inhibition. Fungal strains of *Fusarium sp*. FO-740 and FO-1305 were shown to produce a number of cyclodepsipeptide antibiotics like a number of derivatives of beauvericin (**54**) which

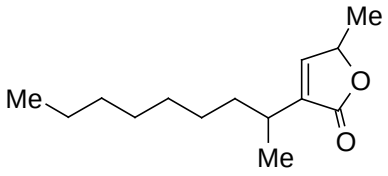
were subsequently shown to inhibit ACAT. All of these compounds inhibited ACAT using rat liver microsomes with IC_{50} values less than 3 μM.[114,115]

Purpactins A, B and C, isolated from the fermentation broth of *Penicillium purpurogenom* were shown to be modestly potent inhibitors of ACAT using rat liver microsomes. Purpactin A (**55**) has the IC_{50} value of 126 μM.[116]

Glisoprenin (**56**) isolated from the fermentation broth of *Gliocladium sp FO-1513*, was shown to be inhibitor of ACAT using rat liver microsomes. In a cellular assay using J774 macrophages, the compound was much more potent with IC_{50} value of less than 1 μM.[117,118]



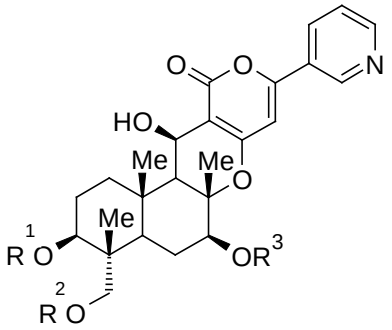
(56)



(57)

Acaterin (**57**) was isolated from a culture broth of *Pseudomas sp*. A92. In the presence of oxidized LDL, acaterin inhibited cholesteryl ester synthesis in J774 macrophages with an IC_{50} value of 45 μM.[119]

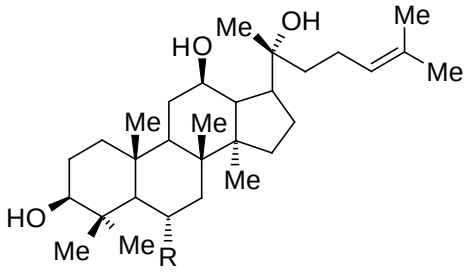
Further, in their continuing research, pyripyropene **A (58a)**, **B (58b)**, **C(58c)** & **D (58d)** were isolated from the fermentation broth of *Aspergillus fumigatus FO-1289* and were showed to be potent inhibitors of ACAT **(IC_{50} = 89, 270, 67 and 140 nM** respectively).[120] The activity of **PR-45** (**58e, IC_{50} 13 nM**) and **PR-109** (**58g, IC_{50} 6nM**) were almost the same as that of pyripyropene A. Remarkably, **PR-86** (**58f**) showed 10 times improved *in vivo* activity (**IC_{50} 19 nM**) with an ED_{50} value of 10 mg/kg via single oral administration over the other compounds in this series.



(58)

Comp	R^1	R^2	R^3
a: Pyripyropene A	Ac	Ac	Ac
b: Pyripyropene B	Ac	Pr	Ac
c: Pyripyropene C	Ac	Ac	Pr
d: Pyripyropene D	Pr	Ac	Ac
e: PR-45	Ac	Ac	*n*-Val
f: PR-86	Ac	SO_2Me	Ac
g: PR-109	>CHPh		*n*-Val

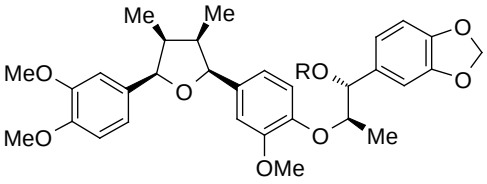
Kwon *et al.* at Korea Research Institute of Bioscience and Biotechnology have isolated the Ginseng sapogenin from ginseng saponins.[121] Ginseng saponins very mildly inhibited ACAT enzyme *in vitro*, however the sapogenins showed strong inhibitory activity on microsomal ACAT. Compounds **(59a** & **59b)** inhibited rat liver ACAT enzyme with IC_{50} values of **10 & 6 μM** respectively.



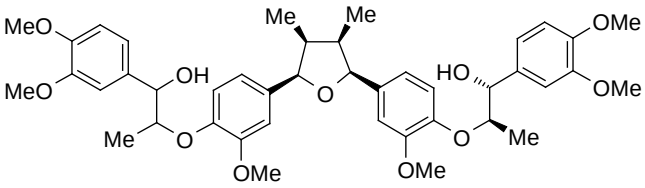
(59)

a: R= H (20*R*-Protopanaxadiol)
b: R= OH (20*R*-Protopanaxatriol)

Lee *et al.* have isolated the sesquineolignan, saucerneol B (**60a**) and manassantin A (**60b**) from the methanol extracts of *Saururus Chinensis* root.[122] Both compounds inhibited hACAT-1 and hACAT-2 with IC_{50} values of 43.0 and 124 μM for compound **(60a)** and 39 and 8 μM for



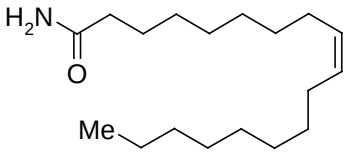
(60a) R= H
(60c) R= *n*-Pr



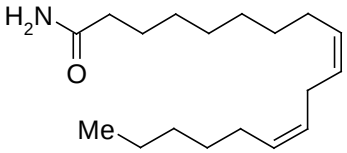
(**60b**)

compound **(60b)**. Saucerneol B preferentially inhibited hACAT-1 than hACAT-2, however manassantin A strongly inhibited hACAT-2 compared to hACAT-1. Further, they discovered a novel class of hACAT-1 specific enzyme inhibitors. An *n*-propoxy derivative **(60c)** showed IC_{50} value of **14 μM**.[123]

The same group of researchers isolated the unsaturated fatty acid amides, 9Z-octadecenamide **(61a)** and 9Z,12*Z*-octadecadienamide **(61b)** as potent inhibitors of ACAT from



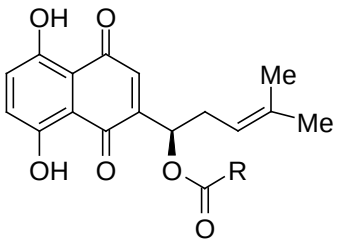
(61a)



(61b)

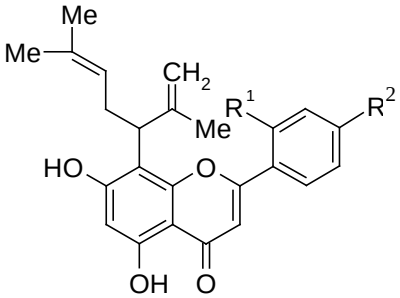
the ethyl acetate extract of the insect, *Mylabris phalerate pallas*.[124] Both of the compounds were shown to inhibit rat microsomal ACAT, hACAT-1 and hACAT-2 with IC_{50} values of 170, 85 and 63 μM for compound (**61a)** and of 151, 53 and 45 μM for compound **(61b)** respectively.

In their continuing research, Lee *et al.* indentified three nahpthoquinones namely, acetylshikonin **(62a)**, isobutyrylshikonin **(62b)** and β-hydroxyisovalerylshikonin **(62c)**, which were isolated by bioassay-guided fractionation from the chloroform extracts of roots of *Lithospermum erythrorhizon.* These compounds were tested for their inhibitory activities against hACAT-1 and hACAT-2.[125] Compound **(62b)** preferentially inhibited the hACAT-2 **(IC_{50} 57.5 μM)** than hACAT-1 (**32% at 120 μM**), whereas compounds **(62a** and **62c)** showed weak inhibitory activities in both hACAT-1 and hACAT-2. Jeong et al. have discovered a new class of hACAT inhibitors. Nine flavonoids and one chalcone were isolated from the methanolic extracts of root of *S. flavescens* and among them two flavonoids **(63a, 63b)** showed potent activity.



(62)

a: R = Me
b: R = $CH(CH_3)_2$
c: R = $CH_2C(CH_3)_2OH$

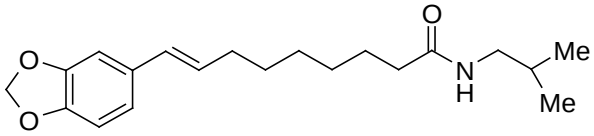


(63)

a: R^1 = OMe, R^2 = OH.
b: R^1 = OH, R^2 = H.

Compound **(63a)** inhibited significantly the enzymatic activities of both hACAT-1 and -2 in cell-based assay system with IC_{50} of **16.4 µM** for hACAT-1 and IC_{50} of **13.6 µM** for hACAT-2. Compound **(63b)** exhibited a slight decrease in potency for both hACAT-1 and -2 with IC_{50} values of **19.7** and **20.4 µM** respectively.[126]

Rho *et al.* have isolated a series of active compounds from the methanolic extract of *Piper nigrum*. Out of the compounds, a new compound, designated dehydroretrofractamide C



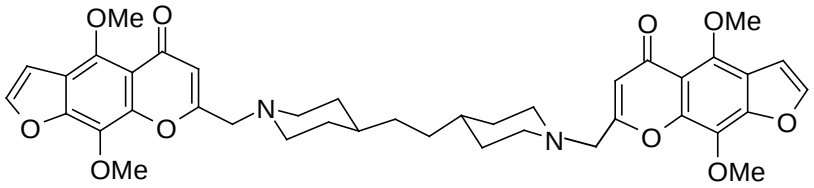
(64)

(64, IC_{50} 60 µM) inhibited ACAT activity in both rat liver microsomes and HepG2 cells.[127]

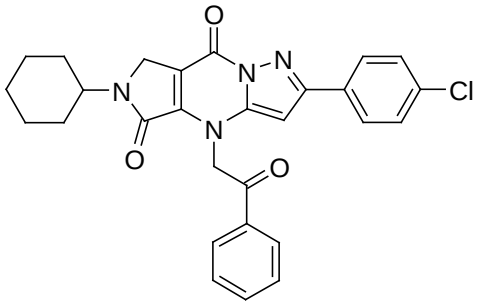
2.6 Miscellaneous ACAT inhibitors

The scientists at The Upjohn Lab in Michigan have synthesized a novel series of bisaminofurochromone derivatives **(65, IC_{50} 0.08 μM)** as ACAT inhibitors.[128] They also reported that the 2-3 aliphatic carbon chain between the two piperidine rings in compound **(65)** showed moderate potency.

In their continuing research, they reported a novel series of 6,7-dihydro-*4H*-pyrazolo[1,5-*a*]pyrrolo[3,4-*d*]pyrimidine-5,8-dione **(66, IC_{50} 1.5 μM)** inhibitors of the enzyme ACAT. A



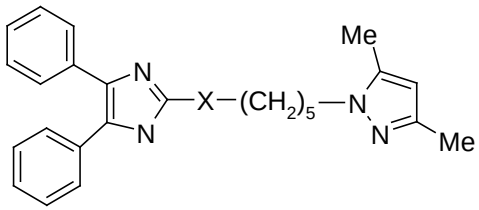
(65)



(66)

number of these derivatives were found to be potent modulators of serum lipoprotein levels in cholesterol-fed rats. Further, they evaluated one of the most effective analogs, which was significantly blocking the absorption of cholesterol from the gut.[129]

Ashton *et al.* identified (**67a, RP 70676)**, a potent systemically available inhibitor of ACAT (**IC_{50} 40 nM**).[130] It was an effective hypocholesterolaemic agent in the cholesterol-fed rabbit, that reduced the accumulation of both cholesterol and cholesterol esters in rabbit aorta and thoracic artery. The compound was readily bioavailable in rabbits with significant levels of parent compound present in plasma up to 6 hours after an oral dose. **RP 70676** had been shown to be an effective inhibitor of ACAT derived from a number of tissues and species including man. Further, they identified that **67b (RP 73163)**, [131] a major metabolite of compound **(67a)** retained

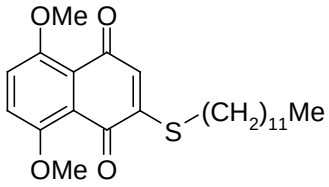


(67)

a: X = S (**RP 70676**)
b: X = SO (**RP 73163**)

ACAT inhibitory activity. Compound **(67b)** had higher systemic bioavailability than the parent compound **(67a)**.

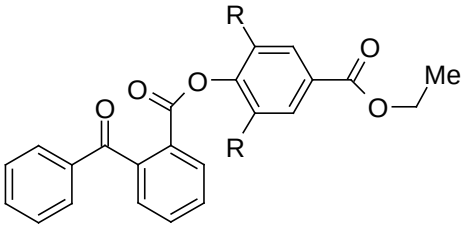
On the basis of ACAT inhibitory activity of the 1,4-naphthoquinone derivatives,[125] researchers were interested to synthesize similar derivatives with different side chains to understand the structural requirement for ACAT enzyme inhibitory effect. A novel series of 2-



(68)

thia/amino-5,8-dimethoxy-1,4-naphthoquinone **(DMNQ, 68)** analogs were synthesized and compound (**68)** showed potent ACAT inhibitory activity with IC_{50} value of **22.8 μM**. In SAR study, it was observed that 2-thia-DMNQs with side chains of carbon number 11 to 15 exhibited significant ACAT inhibitory activity.[132]

Recently, Chhabaria *et al.* have described ligand-based pharmacophore modeling of a series of structurally diverse ACAT inhibitors. It has been reported that two most potent compounds of the retrieved hits from pharmacophore modeling study were synthesized and biologically evaluated. These compounds (**69a, 69b**) showed 86% and 88% inhibition of ACAT (at 10 μg/mL) with IC_{50} values of 3.6 and 2.5 nM respectively.[133]



(69)

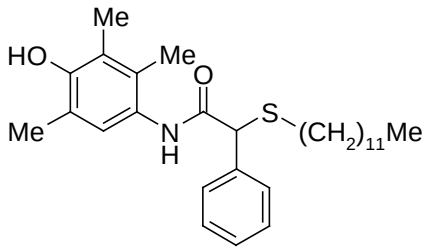
a: R = Cl , b: R = Br

2.7 Clinical trails of some ACAT inhibitors

Despite showing promising efficacy in various animal studies, only a few ACAT inhibitors have been evaluated in clinical trials. **Melinamide** (**1)** successfully made its way

through clinical development and was approved for use as a cholesterol absorption inhibitor in Japan.[134] However the drug was withdrawn later on.

Development of **Avasimibe** (**46**), another ACAT inhibitor that reached phase 3, was halted in October 2003 by Pfizer (New York) after the drug was shown to have potentially unfavorable effects. It lowered both VLDL and triglycerides by approximately 30% in doses ranging from 50-500 mg/day in an eight-week study in 130 patients.[135] Daiichi Sankyo, the com-



(70) Eflucimibe

pany that was developing **Pactimibe** (**48a**) that had reached phase 3 clinical trials, announced on October 26, 2005 that it had decided to discontinue all ongoing clinical studies with this drug due to some discouraging results. ACAT inhibitors have so far failed to progress inclinical development. **Eflucimibe (70)** is another same category of inhibitor, developed by Pierre Fabre SA and Eli Lilly & Co for the potential treatment of hypercholesterolemia and atherosclerosis. Phase II clinical trials were commenced during 2002 but discontinued later due to discouraging lipid effects of the drug.

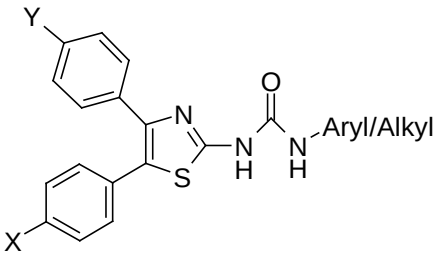
3. Aims and Objectives

Vicinal diaryl heterocycles have shown wide range of biological activities. It has been shown that vicinal diaryl heterocyclic scaffold is a prerequisite for COX-II enzyme inhibition, antiplatelet activity, TNF-α inhibitor, p^{53} Map Kinase inhibitory and cytotoxic activity.

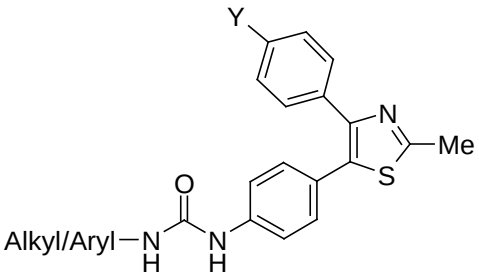
A review of literature has revealed the existence of a plethora of compounds possessing ACAT inhibitory activity in the *in vitro* and *in vivo* models. All of these have some common characteristic features in their structures. They possessed either an amide or a urea moiety, one of the most essential functionality for ACAT inhibitory activity. Between these two functionalities, the urea derivatives have shown better activity than amide derivatives.

Other characteristic features found to be essential for ACAT inhibitory activity included a polar head linked to lipophilic tail and various heterocyclic or carbocyclic rings. The heterocyclic ring systems found more prevalent in the molecules were imidazole, oxazole, isoxazole, tetrazole and pyrazole. A disubstituted urea derivative with a thiazole or 1,2,5-oxadiazole rings possessing ACAT inhibitory activity could not be traced in the literature.

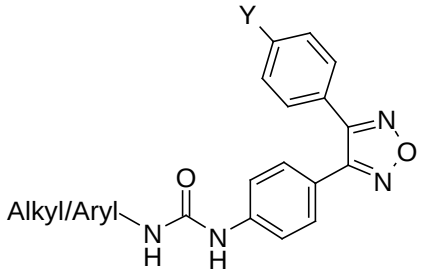
Keeping the above points in mind it was planned to design disubstituted ureas **(I-III)** incorporating all necessary functionalities required for ACAT inhibitory activity. It was envisaged to synthesise the designed three series of compounds and characterize them using spectral and elemental analyses. Since the aim of the project was to develop ACAT inhibitors it was also planned to evaluate the synthesized compounds for their ACAT inhibitory activity.



(I)



(II)



(III)

X = Cl, F, Me, OMe, COMe, SO_2Me, $CH(Me)_2$

Y = Cl, F, Me, OMe etc.

Aryl = Phenyl, 2,4-difluorophenyl, 2,6-diethylphenyl etc.

Alkyl = Butyl, heptyl, dodecyl etc.

The research work leading to the fulfillment of the above laid down aims and objectives has been discussed in the following sections.

4. Results and Discussion

The work carried out towards achieving the proposed plan has been discussed under the following two main headings:

1. Chemical Studies
2. Biological Studies

4.1 Chemical Studies

To synthesize the envisaged compounds research schemes were planned and discussed under the following headings:

4.1.1. Synthesis of 1,2-diaryl-2-bromoethanone derivatives

4.1.1.1. Synthesis of substituted phenylacetic acids **(3,6)**

4.1.1.2. Synthesis of substituted diaryl ethanones by Friedel-Craft acylation reaction **(8a-8g)**

4.1.1.3. Bromination of substituted diaryl ethanones or desoxybenzoins **(9a-9g)**

4.1.2. Synthesis of 2-thiazolylurea derivatives

4.1.2.1. Synthesis of derivatives of 2-aminothiazole **(10a-10g)**

4.1.2.2. Synthesis of urea derivatives **(11a-11t)**

4.1.2.3. Reduction of nitro derivatives to corresponding amino derivatives **(12a-12h)**

4.1.2.4. Synthesis of amino derivatives of 2-thiazolylurea **(13a-13t)**

4.1.3. Synthesis of 4-thiazolylphenylurea derivatives

4.1.3.1. Synthesis of 4-nitrophenylthiazole derivatives **(14i-14iv)**

4.1.3.2. Synthesis of 4-thiazolylaniline derivatives **(15i-15iv)**

4.1.3.3. Synthesis of diaryl thiazoleurea derivatives **(16a-16x)**

4.1.4. Synthesis of 4-furazanylphenylurea derivatives

4.1.4.1. Synthesis of diarylethane-1,2-dione derivatives **(17i-17iv)**

4.1.4.2. Synthesis of diaryl oxadiazole derivatives **(19i-19iv)**

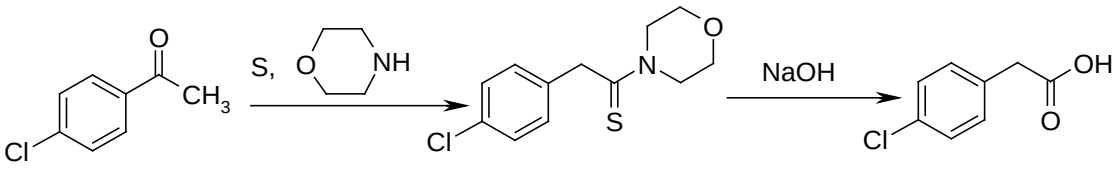
4.1.4.3. Synthesis of 4-furazanylaniline derivatives **(20i-20iv)**

4.1.4.4. Synthesis of substituted vicinal diaryl oxadiazoleurea derivatives **(21a-21t)**

4.1.1. Synthesis of 1,2-diaryl-2-bromoethanone derivatives

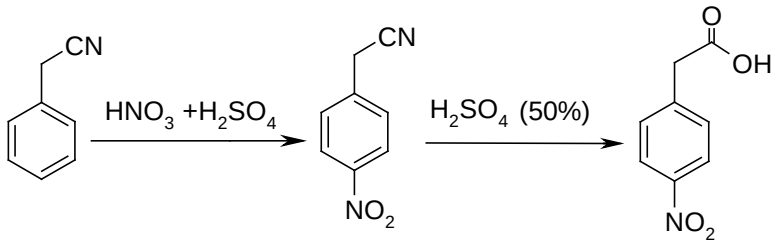
4.1.1.1. Synthesis of substituted phenylacetic acids (3, 6)

Commercially available 4-chloroacetophenone **(1)** was used for the preparation of 4-chlorophenylacetic acid by the reported procedures through Kindler-modified Willgerodt reaction. 4-Chloroacetophenone **(1)** was refluxed with sulphur in morpholine to afford thiomorpholide **(2)**. The thiomorpholide without further purification and characterization was hydrolysed in alkaline media to afford the desired 4-chlorophenylacetic acid **(3) (Scheme I)**. It showed a broad peak of -OH at 3325 cm^{-1} and C=O str at 1705 cm^{-1}.



(1) **(2)** **(3)**

Scheme I



(4) **(5)** **(6)**

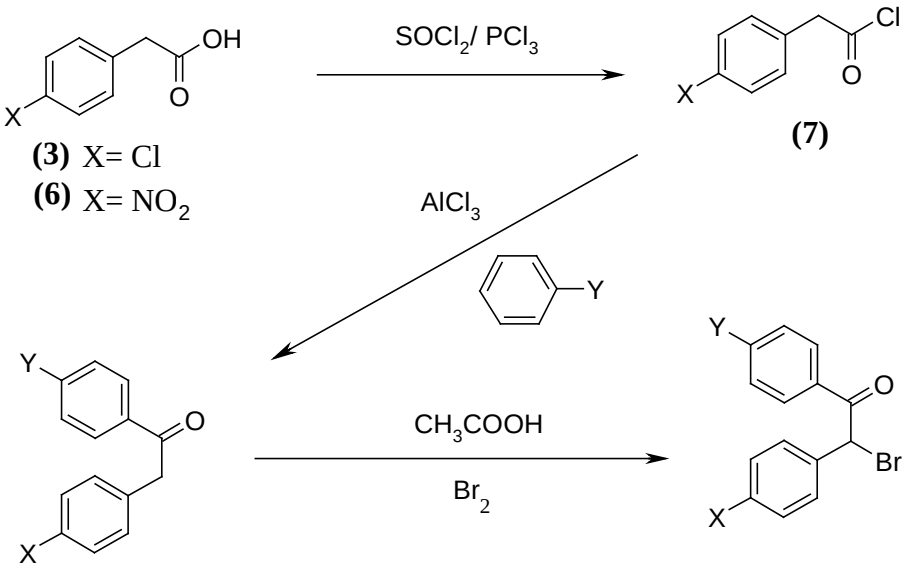
Scheme II

4-Nitrophenyl acetic acid **(6)** was synthesized by nitration of benzyl cyanide **(4)** in presence of fuming nitric acid followed by hydrolysis of the *p*-nitro product **(5)** under acidic conditions (**Scheme II**). Its IR spectrum showed strong peaks at 1523 (N=O asym. str), 1336 (N=O sym. str) and 1705 cm^{-1} (C=O str).

4.1.1.2. Synthesis of substituted diarylethanones by Friedel-Craft acylation reaction (8a-8g)

Various substituted diaryl ethanones or desoxybenzoins **(8a-8g)** were important intermediates required for this work. 4-Chloro/nitrophenylacetyl chloride was prepared by

treating 4-chloro/nitrophenylacetic acid with thionyl chloride. Friedel-Craft acylation reaction was carried out between the 4-chloro/nitrophenylacetyl chloride **(7)** and substituted benzenes to obtain the substituted diaryl ethanones or deoxybenzoins, as common intermediates **(8a-8g)**. The synthesis was carried out following **Scheme III**. The derivatives were characterized on the basis of their IR spectra which showed shifting of characteristic peak of C=O from 1705 to 1670 cm^{-1} and the disappearance of peak of carboxylic -OH at 3300 cm^{-1}.



(3) X= Cl
(6) X= NO_2

(7)

(8a-8g) **(9a-9g)**

(8a, 9a)	X = Cl	Y = F
(8b, 9b)	X = Cl	Y = Me
(8c, 9c)	X = Cl	Y = OMe
(8d, 9d)	X = NO_2	Y = Cl
(8e, 9e)	X = NO_2	Y = F
(8f, 9f)	X = NO_2	Y = Me
(8g, 9g)	X = NO_2	Y= OMe

Scheme- III

4.1.1.3. Bromination of substituted diaryl ethanones or desoxybenzoins (9a-9g)

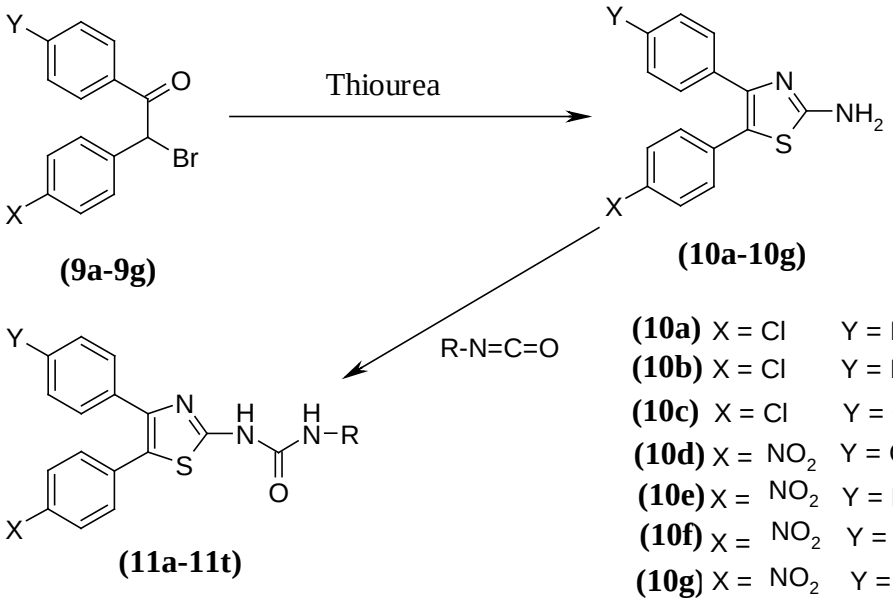
The common intermediates **(8a-8g)** were brominated by reacting them with bromine in glacial acetic acid medium to obtain the bromo derivatives **(9a-9g), (Scheme III)**. The

corresponding 2-bromo-1-(4-substituted phenyl)-2-(substituted phenyl)ethanones **(9a-9g)** were synthesized by controlled addition of aectic acid solution of bromine drop by drop in acetic acid solution of diaryl ethanones or desoxybenzoins **(8a-8g)**. Glacial acetic acid is used to protonate the oxygen and facilitates the bromination of the intermediates (**8a-8g)**. The pure compounds were obtained by recrystallisation of the crude products in methanol. All of the synthesized derivatives **(9a-9g)** were characterized on the basis of their IR spectra. The purity of the derivatives was checked by TLC in different solvent systems.

4.1.2. Synthesis of 2-thiazolylurea derivatives

4.1.2.1. Synthesis of derivatives of 2-aminothiazoles (10a-10g)

Synthesis of 4,5-diaryl-2-aminothiazoles (**10a-10g**) was accomplished by the general **Scheme IV**. As per the reports that amino thiazoles are obtained by reacting bromoketone with



(10a) X = Cl Y = F
(10b) X = Cl Y = Me
(10c) X = Cl Y = OMe
(10d) X = NO_2 Y = Cl
(10e) X = NO_2 Y = F
(10f) X = NO_2 Y = Me
(10g) X = NO_2 Y = OMe

(a)	X = Cl	Y = F	R = 2,4-Difluorophenyl	**(k)**	X = Cl	Y = OMe	R = *n*-Butyl
(b)	X = Cl	Y = F	R = *n*-Butyl	**(l)**	X = Cl	Y = OMe	R = *n*-Dodecyl
(c)	X = Cl	Y = F	R = 2,6-Diethylphenyl	**(m)**	X = NO_2	Y = Cl	R = 2,4-Diflurophenyl
(d)	X = Cl	Y = F	R = *n*-Dodecyl	**(n)**	X = NO_2	Y = F	R = 2,4-Diflurophenyl
(e)	X = Cl	Y = Me	R = Phenyl	**(o)**	X = NO_2	Y = Me	R = 2,4-Diflurophenyl
(f)	X = Cl	Y = Me	R = 2,4-Difluorophenyl	**(p)**	X = NO_2	Y = OMe	R = 2,4-Diflurophenyl
(g)	X = Cl	Y = Me	R = *n*-Butyl	**(q)**	X = NO_2	Y = Cl	R = *n*-Butyl
(h)	X = Cl	Y = Me	R = 2,6-Diethylphenyl	**(r)**	X = NO_2	Y = F	R = *n*-Butyl
(i)	X = Cl	Y = OMe	R = Phenyl	**(s)**	X = NO_2	Y = Me	R = *n*-Butyl
(j)	X = Cl	Y = OMe	R = 2,4-Difluorophenyl	**(t)**	X = NO_2	Y = OMe	R = *n*-Butyl

Scheme IV

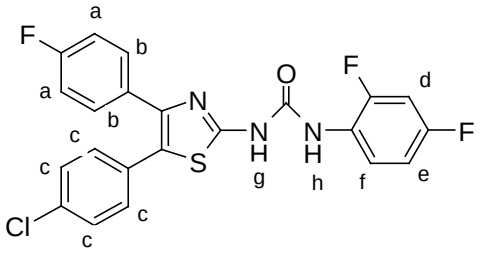
thiourea, the intermediates (**9a-9g**) and thiourea were refluxed for 3-4 hr in ethanol to obtain the corresponding substituted 4,5-diphenylthiazoles (**10a-10g**). Purity of all of the synthesized compounds was checked by TLC in different solvent systems. All of the synthesized derivatives were characterized by their IR and mass spectra.

2-Bromo-2-(4-chlorophenyl)-1-(4-fluorophenyl)ethanone **(9a)** was reacted with thiourea to yield 5-(4-chlorophenyl)-4-(4-fluorophenyl)thiazol-2-ylamine **(10a)**. IR spectrum of compound (**10a)** displayed the characteristic peaks at 3481(N-H str) and 1330 cm^{-1}(C-N str). Its mass spectrum displayed M+H peak at m/z 303.98. Similarly, 2-bromo-2-(4-chlorophenyl)-1-(4-methylphenyl)ethanone **(9b)** was reacted with thiourea to yield 5-(4-chlorophenyl)-4-(4-methylphenyl)thiazol-2-ylamine **(10b)**. Its IR spectrum showed characteristic peaks at 3472 (N-H str) and 1334 cm^{-1} (C-N str.). Its mass spectrum displayed M+H peak at m/z 316.02. 5-(4-Chlorophenyl)-4-(4-methoxyphenyl)thiazol-2-ylamine **(10c)** was prepared by the reaction between the 2-bromo-2-(4-chlorophenyl)-1-(4-methoxyphenyl)ethanone **(9c)** and thiourea. Its mass spectrum showed the M+H peak at m/z 299.98. All of the 4-(4-substituted phenyl)-5-(4-nitrophenyl)thiazol-2-ylamines **(10d-10g)** were prepared in a similar way from the intermediates **(9d-9g)**. All of the synthesized derivatives **(10d-10g)** showed characteristic peaks at 3432 & 3454 (N-H str.) for primary amine, 1633-1640 (C=N str.), 1589-1592 (N-H bend.), 1528-1535 (N=O str) and 1335 cm^{-1}(N=O str.) in their IR spectra.

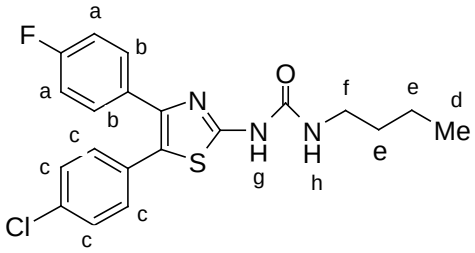
4.1.2.2. Synthesis of urea derivatives (11a-11t)

The disubstituted urea derivatives were synthesized from the above discussed intermediate amines **(10a-10g)**. Various commercially available isocyanates like phenyl isocyanate, 2,4-difluorophenyl isocyanate, 2,6-diethylphenyl isocyanate, *n*-butyl isocyanate, *n*-heptyl isocyanate, and *n*-dodecyl isocyanate were procured. The selection of these isocyanates was based on literature reports that suggested optimal ACAT enzyme inhibitory activity associated with these groups. The respective 4,5-diaryl-thiazol-2-ylamines **(10a-10g)** were dissolved in dry toluene and were reacted with different substituted isocyanates to yield the desired disubstituted urea derivatives **(11a-11t)**. These disubstituted ureas were purified by column chromatography using different solvent systems.

1-[5-(4-Chlorophenyl)-4-(4-fluorophenyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea **(11a)** was prepared by reaction of the amine **(10a)** with 2,4-difluorophenyl isocyanate. Compound **(11a)** showed characteristic IR peaks at 3416 (N-H str), 3118 (C-H str), 1720 (C=O str), 1610 and 1430 cm^{-1}(C=N str). It offered signals at δ 7.37-7.42 (m, 2H, ArH_a), 7.18-7.28 (*d*, 4H, ArH_c), 6.87- 6.98 (*m*, 3H, ArH_b & ArH_f), 6.82- 6.88 (*m*, 1H, ArH_e), 8.08-8.15 (*m*, 1H, ArH_d), 8.92 (*bs*, 1H, NH_g) and 10.43 (*bs*, 1H, NH_h) in its ^{1}H-NMR spectrum. Mass spectrum showed a characteristic peak at m/z 303.98 for molecular weight of amine (**10a**) and molecular ion peak at m/z 458.0 (M^++1).



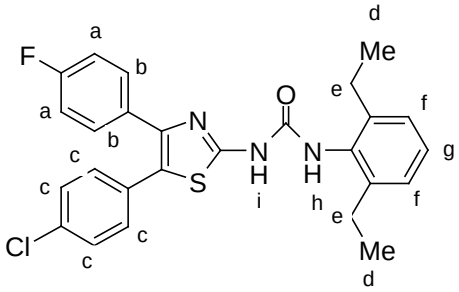
(11a)



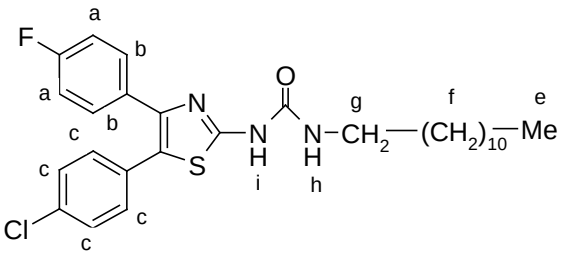
(11b)

1-[5-(4-Chlorophenyl)-4-(4-fluorophenyl)thiazol-2-yl]-3-butylurea (**11b**) was prepared by reaction of the amine **(10a)** with *n*-butyl isocyanate. It showed characteristic IR peaks at 3490 (N-H str), 1691 (C=O str), 1561, 1402 and 826 cm^{-1} representing vibrational bands for heterocyclic ring and aromaticity while its ^{1}H-NMR spectrum displayed peaks at δ 7.18- 7.28 (*d*, 4H, ArH_c), 7.37-7.42 (*m*, 2H, ArH_a), 6.87- 6.98 (*m*, 2H, ArH_b), 0.91-0.95 (*t*, 3H, CH_{3d}), 1.11-1.23 (*m*, 4H, CH_{2e}), 3.21-3.4 (*m*, 2H, CH_{2f}), 8.95 (bs, 1H, NH_g) and 10.45 (bs, 1H, NH_h). Mass spectrum showed peak at m/z 303.97, characteristic for molecular weight of amine **(10a)** and molecular ion peak at m/z 403.15 (M^+).

1-[5-(4-Chlorophenyl)-4-(4-fluorophenyl)thiazol-2-yl]-3-(2,6-diethylphenyl)urea **(11c)** was prepared by reaction of the amine **(10a)** with 2,6-diethylphenyl isocyanate. IR spectrum of the compound **(11c)** offered peaks at 3403 (N-H str), 1688 (C=O str), 1510 (C=N str.) and 826 cm^{-1}(aromatic). Signals at δ 7.11-7.5 (*m*, 6H, ArH_b & ArH_c), 7.3-7.5 (m, 2H, ArH_a), 7.0-7.1 (*d*, 2H, ArH_f), 7.4-7.5 (*m*, 1H, ArH_g), 1.21-1.31 (*t*, 6H, CH_{3d}) and 2.32-2.51 (*q*, 4H, CH_{2e}) were observed in its ^{1}H-NMR spectrum.

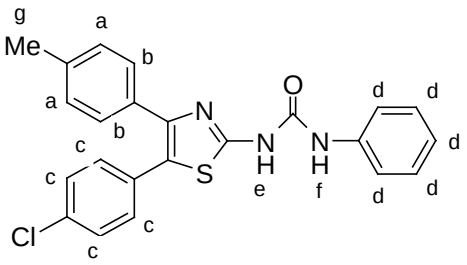


(11c)

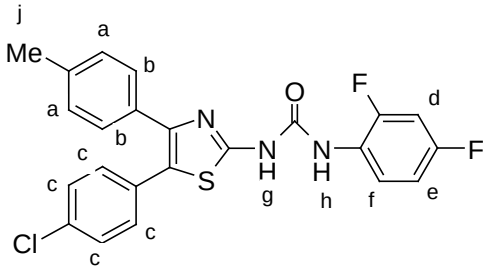


(11d)

1-[5-(4-Chlorophenyl)-4-(4-fluorophenyl)thiazol-2-yl]-3-dodecylurea **(11d)** was also prepared in similar way by reacting the amine **(10a)** with *n*-dodecyl isocyanate. Compound **(11d)** showed characteristic peaks at 3344 (N-H str), 1688 (C=O str), 1504 (C=N str.) and 821 cm^{-1} (aromatic) in its IR spectrum. Characteristic signals at δ 7.11-7.21 (*m*, 6H, ArH_b & ArH_c), 7.2-7.3 (*m*, 2H, ArH_a), 0.91-0.93 (*t*, 3H, CH_{3e}), 1.32-1.51 (*m*, 20H, CH_{2f}), 2.9-3.2 (*m*, 2H, CH_{2g}), 4.5 (*s*, 1H, NH_h) and 10.45 (*s*, 1H, NH_i) were observed in its ^{1}H-NMR spectrum. Mass spectrum of the compound showed peaks at m/z 303.9, characteristic for molecular weight of amine **(10a)** and molecular ion peak at m/z 516.15 (M^+).



(11e)

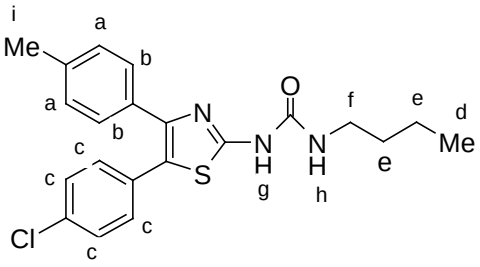


(11f)

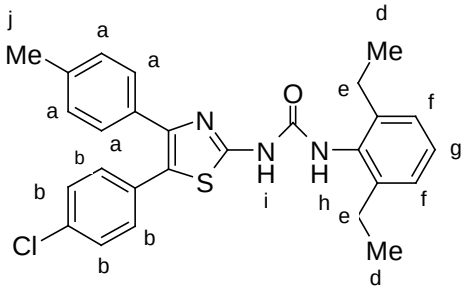
1-[5-(4-Chlorophenyl)-4-(4-methylphenyl)thiazol-2-yl]-3-phenylurea (**11e**) was prepared by reaction of the amine **(10b)** with phenyl isocyanate. IR spectrum of compound **(11e)** displayed the characteristic peaks at 3403 (N-H str), 3118 (C-H str), 1688 (C=O str) and 1430 cm^{-1}(C=N str). It offered signals at δ 7.18- 7.28 (*m*, 11H, ArH_b, ArH_c & ArH_d), 7.37-7.42 (*d*, 2H, ArH_a), 2.02 (*s*, 3H, CH_{3g}), 8.92 (*bs*, 1H, NH_e) and 10.43 (*bs*, 1H, NH_h) in its ^{1}H-NMR spectrum.

1-[5-(4-Chlorophenyl)-4-(4-methylphenyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea (**11f**) showed IR characteristic peaks at 3209 (N-H str), 3098 (Ar C-H str), 1689 (C=O str) and 1506 cm^{-1}(C=N str). Its ^{1}H-NMR spectrum displayed signals at δ 6.81-6.92 (*d*, 2H, ArH_a), 7.0-7.21 (*d*,

2H, ArH_b), 7.2-7.41 (*m*, 4H, ArH_c), 7.42-7.61 (*m*, 2H, ArH_e & ArH_f), 8.2- 8.3 (*m*, 1H, ArH_d), 2.31 (*s*, 3H, Ar-CH_{3j}) and 8.7 (*bs*, 1H, NH_g). Its mass spectrum showed M+H peak at m/z 455.



(11g)

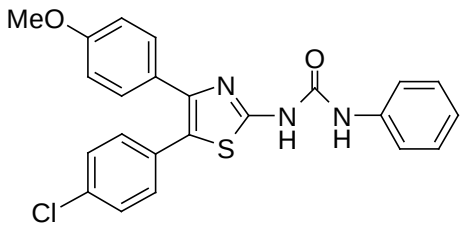


(11h)

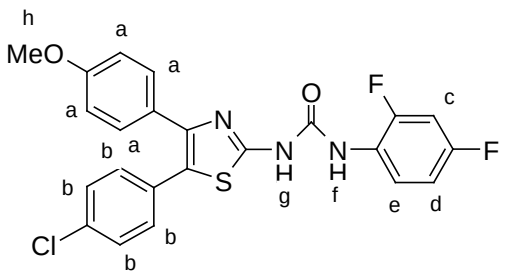
IR spectrum for the compound **(11g)** showed characteristic peaks at 3410 (N-H str), 1698 (C=O str) and 1534 cm^{-1}(C=N str). Its ^{1}H-NMR spectrum showed singlet for CH_{3i} proton (δ 2.52), triplet for CH_{3d} proton (δ 0.92) and multiplet for CH_{2e} (δ 1.42-1.62) and a multiplet for CH_{2f} (δ 2.92). The aromatic eight protons (ArH_a, ArH_b & ArH_c) appeared in the region between δ 7.11-7.41 and an N*H* proton appeared as broad peak at δ 11.01.

1-[5-(4-Chlorophenyl)-4-(4-methylphenyl)thiazol-2-yl]-3-(2,6-diethylphenyl)urea (**11h**) showed characteristic peaks at 3409 (N-H str), 1690 (C=O str), and 1430 cm^{-1}(C=N str) in its IR spectrum. Signals at δ 7.11-7.21 (*m*, 8H, ArH_a & ArH_b), 7.0-7.1 (*m*, 3H, ArH_f & ArH_g), 0.91-0.93 (*t*, 6H, ArH_d), 2.32-2.51 (*q*, 4H, ArH_e) and 2.12 (*s*, 3H, CH_{3j}) were observed in its ^{1}H-NMR spectrum.

1-[5-(4-Chlorophenyl)-4-(4-methoxyphenyl)thiazol-2-yl]-3-phenylurea (**11i**) was prepared by reacting the amine **(10c)** with phenyl isocyanate. It showed the peaks at 3377 (N-H str), 3108 (C-H str), 1692 (C=O str) and 1248 cm^{-1}(Ar-O str) in its IR spectrum. ^{1}H-NMR spectrum for the compound **(11i)** displayed multiplets at δ 6.82-7.63 (for thirteen aromatic protons) and a singlet for protons of one methoxy group was observed at δ 3.81. Its mass spectrum showed M+H peak at 436.3 and base peak at 316.8 (fragment for **10c**).



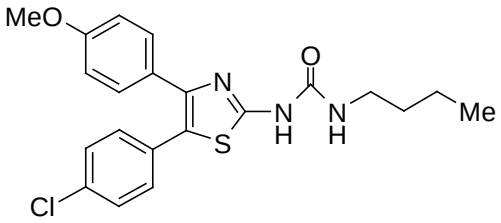
(11i)



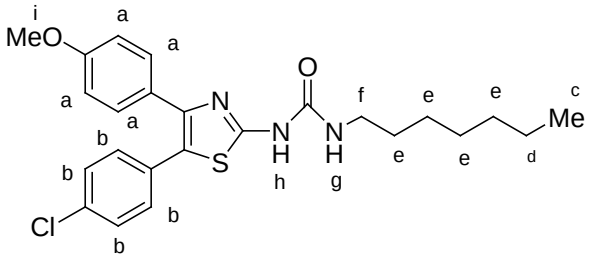
(11j)

1-[5-(4-Chlorophenyl)-4-(4-methoxyphenyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea (**11j**) displayed peaks at about 3403 (N-H str), 1695 (C=O str) and 1251 cm^{-1}(Ar-O str) in its IR spectrum. Its ^{1}H-NMR spectrum displayed signals at δ 6.81-7.32 (*m*, 8H, ArH_a & ArH_b), 8.12-8.15 (*m*, 1H, ArH_c), 6.86-7.12 (*m*, 2H, ArH_d & ArH_e), 3.62 (*s*, 3H, OCH_{3h}), 9.14-10.12 (*bs*, 1H, NH_g) and 11.03 (*bs*, 1H, NH_f).

Compound **(11k)** displayed the characteristic IR peaks at 3404 (N-H str), 1692 (C=O str), 1249 (Ar-O str) and 1021 cm^{-1}(O-CH_3) in its IR spectrum. Its mass spectrum showed M+H peak at 414.97 and base peak at 316.02 (fragment for **10c**).



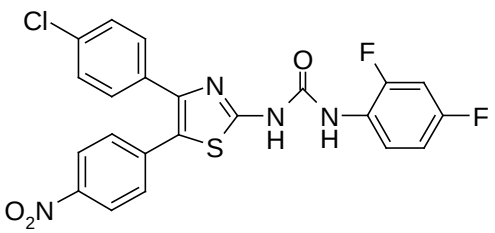
(11k)



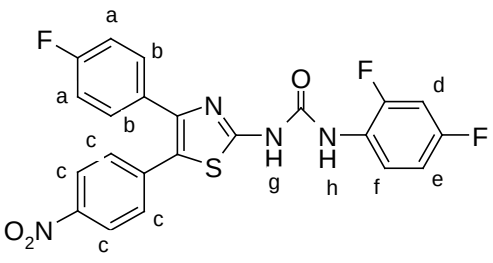
(11l)

1-[5-(4-Chlorophenyl)-4-(4-methoxyphenyl)thiazol-2-yl]-3-heptylurea (**11l**) showed the IR peaks at 3420 (N-H str), 1693 (C=O str), 1250 (Ar-O str) and 1027 cm^{-1}(O-CH_3str.). ^{1}H-NMR spectrum of the compound **(11l)** displayed signals at δ 6.81-7.42 (*m*, 8H, ArH_a & ArH_b), 0.91-0.95 (*t*, 3H, CH_{3c}), 1.41-2.61(*m*, 12H, C$H_{2d,e,f}$), 3.81(*s*, 3H, OCH_{3i}) and 11.0-11.5 (*bs*, 2H, N$H_{g,h}$).

1-[4-(4-Chlorophenyl)-5-(4-nitrophenyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea **(11m)** was prepared by reaction of the amine **(10d)** with 2,4-difluorophenylisocyanate. The IR spectrum of the compound **(11m)** showed the presence of characteristic peaks at 3403 (N-H str), 1699 (C=O str), 1430 (C=N str), 1540 (N=O asym str) and 1352 cm^{-1}(N=O sym str). The mass spectrum showed the molecular ion peak at m/z 487 (M^++1).



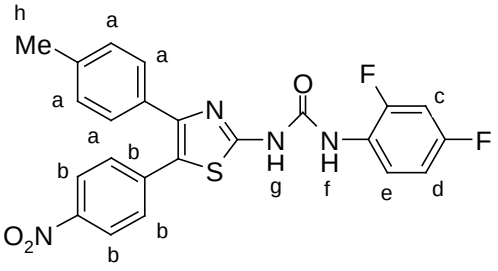
(11m)



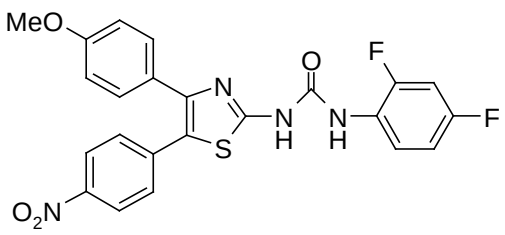
(11n)

1-[4-(4-Fluorophenyl)-5-(4-nitrophenyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea **(11n)** displayed the peaks at 3408 (N-H str), 3118 (C-H str), 1691 (C=O str), 1430 (C=N str), 1505 (N=O asym str) and 1333 cm^{-1}(N=O sym str) in its IR spectrum. It offered signals at δ 7.20-7.28 (*d*, 4H, ArH_c), 7.32-7.42 (*m*, 2H, ArH_a), 6.87- 6.98 (*m*, 2H, ArH_b), 6.82- 6.88 (*m*, 2H, ArH_e & ArH_f), 8.08-8.15 (*m*, 1H, ArH_d), 8.92 (*bs*, 1H, NH_g) and 10.43 (*bs*, 1H, NH_h) in its ^{1}H-NMR spectrum.

IR spectrum of the compound **(11o)** displayed peaks at 3411 (N-H str), 1691 (C=O str), 1275 (C=N str), 1504 (N=O asym str) and 1333 cm^{-1}(N=O sym str). Its ^{1}H-NMR spectrum displayed signals at δ 7.0-7.21 (*m*, 4H, ArH_a), 7.2-7.41 (*m*, 4H, ArH_b), 7.42-7.61 (*m*, 2H, ArH_e & ArH_d), 8.2- 8.3 (*m*, 1H, ArH_c), 2.31 (*s*, 3H, Ar-CH_{3h}) and 8.7- 8.8 (*bs*, 1H, NH_g).



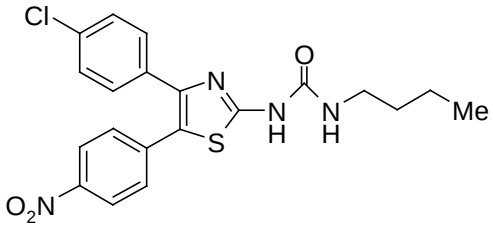
(11o)



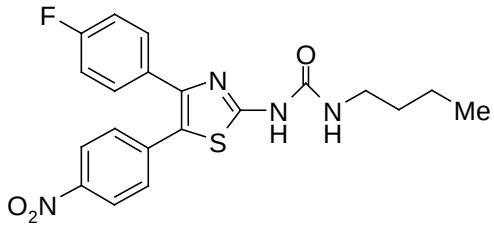
(11p)

1-[4-(4-Methoxyphenyl)-5-(4-nitrophenyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea **(11p)** displayed peaks at 3409 (N-H str), 3118 (C-H str), 1702 (C=O str), 1275 (C=N str), 1507 (N=O asym str) and 1339 cm^{-1}(N=O sym str) in its IR spectrum. Mass spectrum showed peaks at m/z 328.02, characteristic for molecular weight of amine **(10g)** and molecular ion peak at m/z 482.46 (M^+).

1-Butyl-3-(4-(4-chlorophenyl)-5-(4-nitrophenyl)thiazol-2-yl)urea **(11q)** was also synthesized in similar way as mentioned above, by reacting the amine **(10d)** with *n*-butyl isocyanate in dry toluene. Its IR spectrum displayed the peaks at 3394 (N-H str), 1692 (C=O str), 1591 (C=N str), 1515 and 1352 cm^{-1} (N=O str).



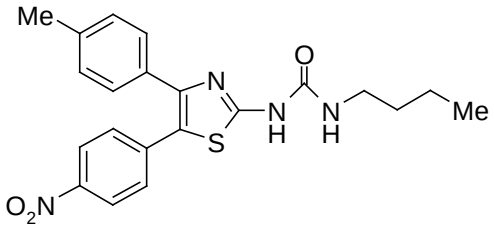
(11q)



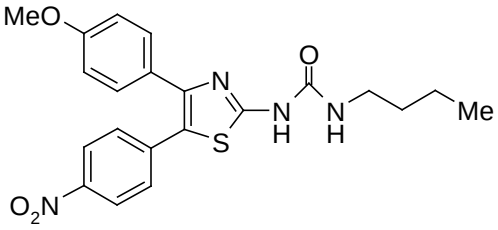
(11r)

Compound **(11r)** displayed the peaks at 3410 (N-H str), 3179 (N-H str), 1670 (C=O str), 1592 (C=N str), 1546 (N-H bend), 1515 and 1340 cm^{-1} (N=O str). Mass spectrum showed peaks at m/z 315.02, characteristic for molecular weight of amine **(10e)** and molecular ion peak at m/z 414.46 (M^+).

1-[4-(4-Methylphenyl)-5-(4-nitrophenyl)thiazol-2-yl]-3-butylurea **(11s)** displayed the peaks at about 3399 (N-H str), 3156 (N-H str), 1693(C=O str), 1591(C=N str), 1553(N-H bend), 1515 and 1340 cm^{-1} (N=O str) in its IR spectrum.



(11s)



(11t)

Compound **(11t)** showed the characteristic IR peaks at 3421 (N-H str), 3144 (N-H str), 1700 (C=O str), 1639 (C=N str), 1537 (N-H bend), 1514 and 1341 cm^{-1} (N=O str). It showed the M+H peak at m/z 427.01 in its mass spectrum.

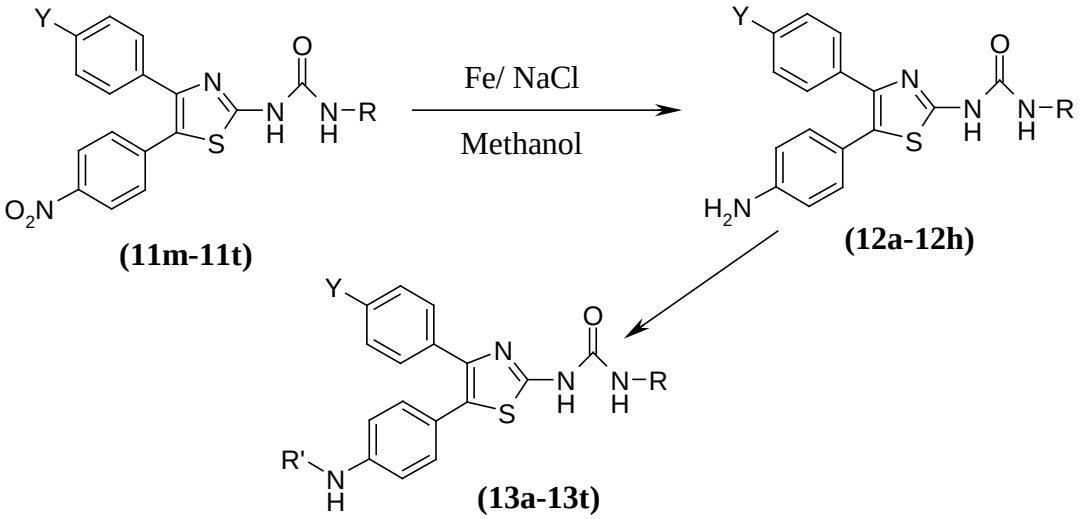
4.1.2.3. Reduction of nitro derivatives (11m-11t) to amino derivatives (12a-12h)

The nitro group containing derivatives **(11m-11t)** were reduced in presence of iron powder (Fe) and NaCl solution in methanol to produce the amino derivatives **(12a-12h)(Scheme V)**.

1-[5-(4-Aminophenyl)-4-(4-chlorophenyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea (**12a**) was synthesized by reducing the compound **(11m).** The compound **(12a)** displayed the characteristic IR peaks at 3413 & 3338 (N-H str. aromatic primary NH_2), 3403 (amide N-H str), 1699 (C=O str) and 1430 cm^{-1}(C=N str). Its mass spectrum showed the molecular ion peak at m/z 457.02.

1-[5-(4-Aminophenyl)-4-(4-fluorophenyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea (**12b**) showed the characteristic IR peaks at 3416 (N-H str), 3312 (N-H str), 3220 (N-H str), 3144 (N-H str), 1685 (C=O str), and 1611 cm^{-1} (C=N str). It offered signals at δ 7.20-7.28 (*d*, 4H, ArH_c),

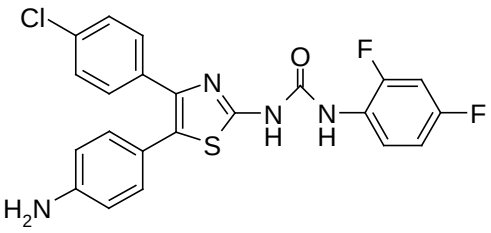
7.32-7.42 (*m*, 2H, ArH_a), 6.87- 6.98 (*m*, 3H, ArH_b & ArH_f), 6.82-6.88 (*m*, 1H, ArH_e), 8.08-8.15 (*m*, 1H, ArH_d), 4.21 (*s*, 2H, NH_{2i}), 8.92 (*bs*, 1H, NH_g), and 10.43 (*bs*, 1H, NH_h) in its ^{1}H-NMR spectrum.



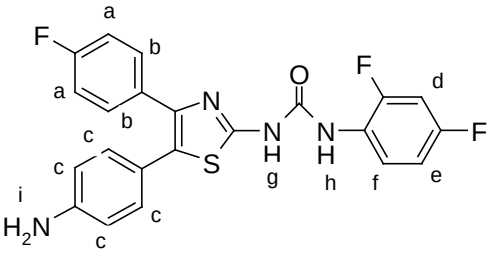
(11m-11t) **(12a-12h)** **(13a-13t)**

(a)	Y = Cl	R = 2,4-Difluorophenyl	R’ = COMe
(b)	Y = Cl	R = 2,4-Difluorophenyl	R’ = SO_2Me
(c)	Y = Cl	R = *n*-Butyl	R’ = COMe
(d)	Y = Cl	R = *n*-Butyl	R’ = SO_2Me
(e)	Y = F	R = 2,4-Difluorophenyl	R’= COMe
(f)	Y = F	R = 2,4-Difluorophenyl	R’ = SO_2Me
(g)	Y = F	R = *n*-Butyl	R’ = COMe
(h)	Y = F	R = *n*-Butyl	R’ = SO_2Me
(i)	Y = Me	R = 2,4-Difluorophenyl	R’ = COMe
(j)	Y = Me	R = 2,4-Difluorophenyl	R’ = SO_2Me
(k)	Y = Me	R = *n*-Butyl	R’ = COMe
(l)	Y = Me	R = *n*-Butyl	R’ = SO_2Me
(m)	Y = OMe	R = 2,4-Difluorophenyl	R’ = *i*-Propyl
(n)	Y = OMe	R = 2,4-Difluorophenyl	R’ = *n*-Dodecyl
(o)	Y = OMe	R = 2,4-Difluorophenyl	R’ = COMe
(p)	Y = OMe	R = 2,4-Difluorophenyl	R’ = SO_2Me
(q)	Y = OMe	R = *n*-Butyl	R’ = *i*-Propyl
(r)	Y = OMe	R = *n*-Butyl	R’ = *n*-Dodecyl
(s)	Y = OMe	R = *n*-Butyl	R’ = COMe
(t)	Y = OMe	R = *n*-Butyl	R’ = SO_2Me

Scheme V

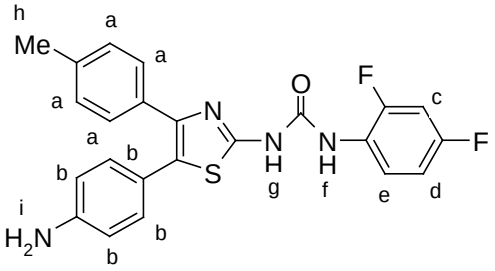


(12a)

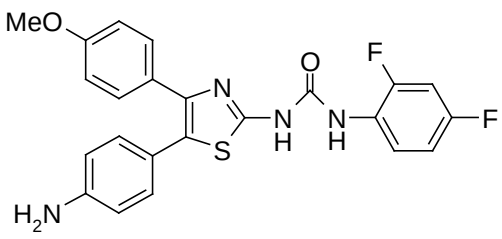


(12b)

Compound **(12c)** displayed IR peaks at 3415 (N-H str), 3141 (N-H str), 1687 (C=O str), 1615 (C=N str) and 1561 cm^{-1}(N-H bend). Its ^{1}H-NMR spectrum displayed signals at δ 7.0-7.21 (*m*, 4H, ArH_a), 7.2-7.41 (*d*, 4H, ArH_b), 7.42-7.61 (*m*, 2H, ArH_e & ArH_d), 8.2- 8.3 (*m*, 1H, ArH_c), 2.31 (*s*, 3H, Ar-CH_{3h}), 3.92 (*s*, 2H, NH_{2i}) and 8.7- 8.8 (bs, 1H, NH_g). Its mass spectrum showed the molecular ion peak at m/z 436.48.



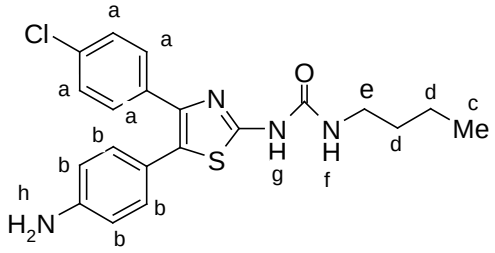
(12c)



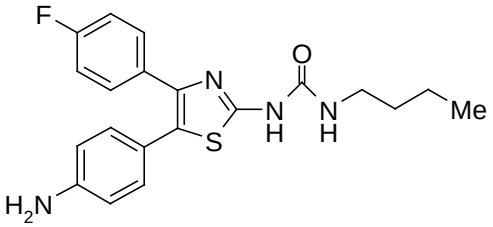
(12d)

1-[5-(4-Aminophenyl)-4-(4-methoxyphenyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea **(12d)** showed the IR peaks at 3143 (N-H str), 1703 (C=O str), 1611 (C=N str), 1549 (N-H bending) and 1230 cm^{-1}(Ar-OCH_3 str). Its mass spectrum showed the molecular ion peak at m/z 452.15.

1-[5-(4-Aminophenyl)-4-(4-chlorophenyl)thiazol-2-yl]-3-butylurea **(12e)** was synthesized by reducing the compound **(11q)**. Compound **(12e)** displayed the IR peaks at 3413 & 3338 (N-H str. aromatic primary NH_2), 3403 (N-H str), 1700 (C=O str) and 1430 cm^{-1}(C=N str).



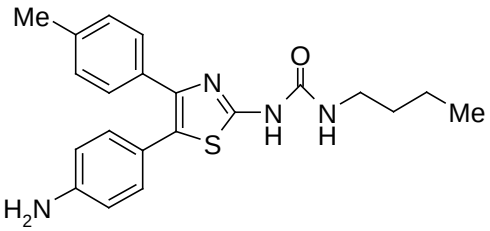
(12e)



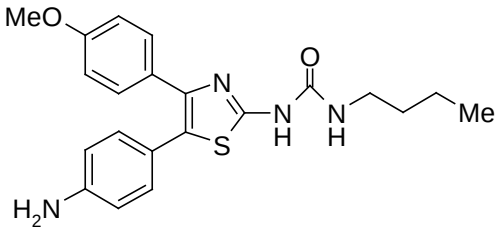
(12f)

1-[5-(4-Aminophenyl)-4-(4-fluorophenyl)thiazol-2-yl]-3-butylurea **(12f)** showed IR peaks at 3456, 3318 (N-H str. aromatic primary NH_2), 3403 (N-H str), 1665 (C=O str), 1607 (C=N str) and 1567 cm^{-1} (C-N bend).

1-[5-(4-Aminophenyl)-(4-methylphenyl)thiazol-2-yl]-3-butylurea **(12g)** displayed the IR peaks at 3415, 3141 (N-H str), 1687 (C=O str), 1615 (C=N str) and 1561 cm^{-1}(N-H bend).



(12g)

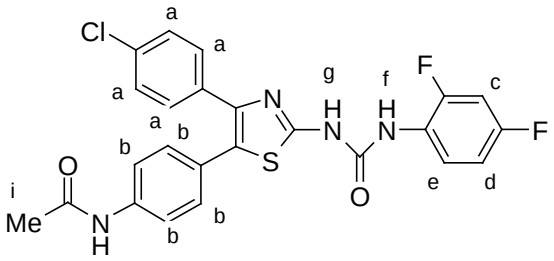


(12h)

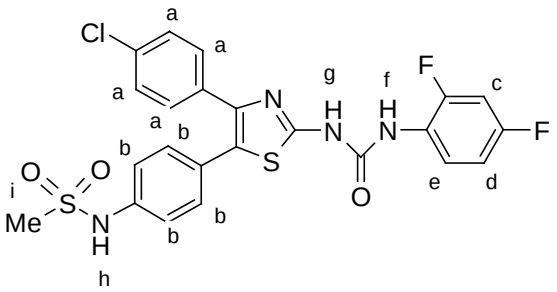
1-[5-(4-Aminophenyl)-4-(4-methoxyphenyl)thiazol-2-yl]-3-butylurea **(12h)** showed the peaks at 3410 (N-H str), 3145 (N-H str), 1678 (C=O str), 1615 (C=N str) and 1561 cm^{-1}(N-H bend) in its IR spectrum. Its mass spectrum showed the molecular ion peak at m/z 397.

4.1.2.4. Synthesis of amino derivatives of 2-thiazolylurea (13a-13t)

N-{4-[4-(4-Chlorophenyl)-2-(3-(2,4-difluorophenyl)ureido)thiazol-5-yl]phenyl}acetamide **(13a)** was prepared by reacting the amine **(12a)** with acetic anhydride in THF. Its IR spectrum showed bands at 3351 (N-H str), 3151 (N-H str), 1663 (C=O str), 1608 (C=N str) and 1562 cm^{-1} (N-H bending). PMR signals for the compound **(13a)** appeared at δ 7.62-7.70 (*m*, 4H, ArH_a), 6.83-7.03 (*m*, 4H, ArH_b), 8.00-8.10 (*m*, 1H, ArH_c), 7.19-7.21 (*m*, 2H, Ar$H_{e,d}$), 3.12 (*s*, 3H, aliphatic CH_{3i}), 9.92 (bs, 1H, NH_f) and 9.33 (s, 1H, NH_g).



(13a)

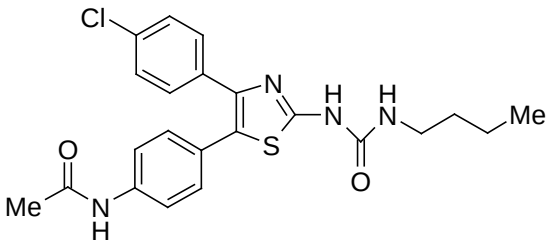


(13b)

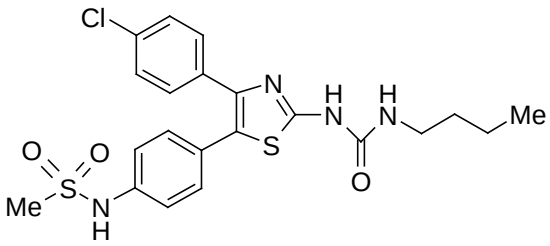
In IR spectrum of the compound **(13b),** bands were obtained at 3251 (N-H str), 3118 (N-H str), 1697 (C=O str), 1612 (C=N str), 1547 (N-H bending), and 1398 cm^{-1}(C-N str) while,

PMR spectrum showed signals at δ 7.58-7.68 (*m*, 4H, ArH_a), 8.00-8.10 (*m*, 1H, Ar-H_c), 7.19-7.21 (*m*, 2H, Ar$H_{e,d}$), 6.83-7.03 (*m*, 4H, ArH_b), 3.02 (*s*, 3H, aliphatic CH_{3i}), 9.94 (*s*, 1H, NH_f) and 10.3 (*s*, 1H, NH_g).

IR spectrum of the compound **(13c)** showed bands at 3252 (N-H str), 3182 (N-H str), 3115 (N-H str), 1685 (C=O str), 1599 (C=N str) and 1524 cm^{-1} (N-H bending). PMR spectrum showed three singlets at δ 10.30, 9.84 and 6.40 for amide (-NH). The compound showed doublets at δ 7.56-7.58, 7.40-7.43 and multiplets at 7.17-7.22 for aromatic protons (Ar-H), it also showed quartet at δ 3.19-3.24, multiplet at 1.47-1.59, 1.32-1.41 and triplet at 0.92-0.95 for aliphatic protons and singlet at 3.02 for acyl CH_3 group in its PMR spectum.



(13c)



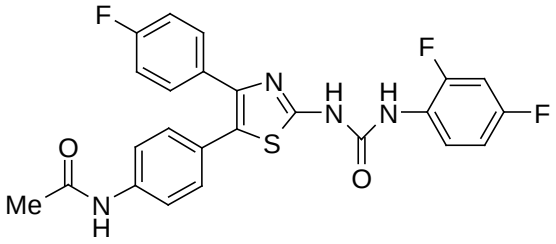
(13d)

The IR spectrum of **13d** showed bands at 3348 (N-H str), 3142 (N-H str), 1665 (C=O str), 1608 (C=N str) and 1564 cm^{-1}(N-H bending). PMR spectrum showed three singlets at δ 10.30, 9.77 and 6.39 for amide (-NH), two doublets at δ 7.40-7.42 and 7.19-7.24 for aromatic protons (Ar-*H*), one singlet at 2.24 for acyl CH_3 and one triplet at 0.92-0.95, two multiplets at δ 1.47-1.54 and 1.32-1.41 and one quartet at δ 3.19-3.2 for aliphatic protons (Al-H).

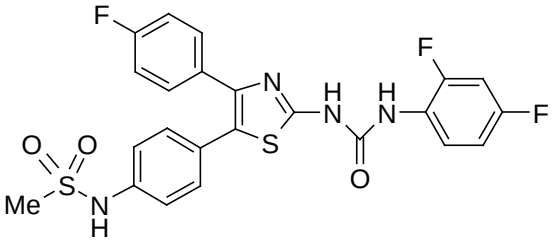
N-{4-[2-[3-(2,4-Difluorophenyl)ureido}-4-(4-fluorophenyl)thiazol-5-yl]phenyl}acetamide **(13e)** gave peaks at 3474 (N-H str), 3414 (N-H str), 3127 (N-H str), 1723 (C=O str), 1671 (C=O str), 1617 (C=N str) and 1560 cm^{-1} (N-H bending) in its IR spectrum. PMR spectrum showed two singlets peak at δ 9.92 and at 9.33 for amide (-NH), two doublets, two triplets and a multiplet at δ 7.60-7.62, 7.46-7.50 and 6.83-7.03 respectively for aromatic proton (Ar-H). It also showed singlet for aliphatic proton (-CH_3) at δ 2.12. Its mass spectrum gave a peak at m/z 482.7 (M^+).

The IR spectrum of *N*-{4-[2-(3-(2,4-difluorophenyl)ureido)-4-(4-fluorophenyl)thiazol-5-yl]phenyl}methanesulfonamide **(13f)** showed the peaks at 3255 (N-H str), 3115 (N-H str), 1693

(C=O str), 1609 (C=N str), 1545 (N-H bending) and 1397 cm^{-1} (C-N str). In PMR spectrum signals were observed at δ 7.58-7.68 (*d*, 4H, Ar-*H*), 8.00-8.10 (*m*, 1H, Ar-*H*), 7.19-7.21 (*m*, 2H, Ar-*H*), 6.83-7.21 (*m*, 4H, Ar-*H*), 3.02 (*s*, 3H, aliphatic CH_3), 9.94 (*bs*, 1H, N*H*) and 10.3 (*bs*, 1H, N*H*).

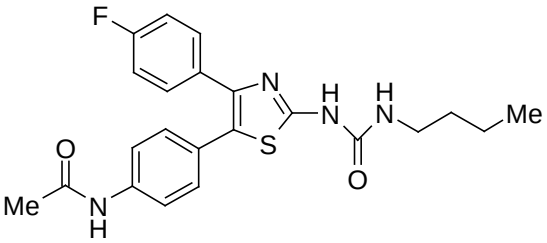


(13e)

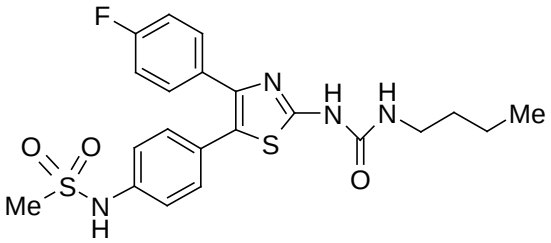


(13f)

Compounds **(13g & 13h)** were prepared from the amine **(12f)**. The IR spectrum of compound **(13g)** showed peaks at 3475 (N-H str), 3312 (N-H str), 3177 (N-H str), 1679 (C=O str), 1592 (C=N str) and 1549 cm^{-1} (N-H bending). PMR spectrum showed three singlets at δ 10.25, 9.80 and 6.44 for amide (-N*H*), multiplet at δ 6.79-7.85 for aromatic protons (Ar*H*), three multiplets at δ 3.23-3.32, 1.26-1.5 and 2.01-2.11 and one triplet at δ 0.94-1.09 for the aliphatic protons (Al*H*).



(13g)

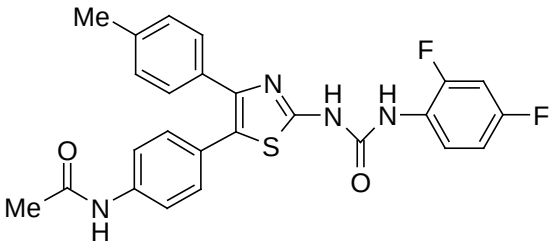


(13h)

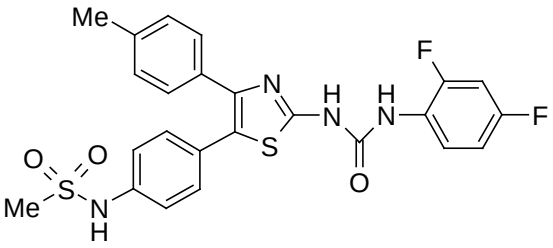
Compound **(13h)** showed bands at 3351 (N-H str), 3151 (N-H str), 1663 (C=O str), 1608 (C=N str) and 1562 cm^{-1} (N-H bending) in its IR spectrum. It displayed the signals at δ 7.56-7.58 and 7.40-7.43 as doublets and multiplet at δ 7.17-7.22 for aromatic protons (Ar-*H*) in its PMR spectrum. It also displayed quartet at δ 3.19-3.24, multiplets at 1.47-1.59 and 1.32-1.41 and triplet at δ 0.92-0.95 for aliphatic protons and singlet at δ 3.02 for acyl CH_3 group.

N-{4-[2-(3-(2,4-Difluorophenyl)ureido)-4-*p*-tolylthiazol-5-yl]phenyl}acetamide **(13i)** was synthesized by reacting the amine **(12c)** with acetic anhydride. The IR spectrum of the

compound **(13i)** showed peaks at 3415 (N-H str), 3310 (N-H str), 3126 (N-H str), 1702 (C=O str), 1666 (C=O str), 1615 (C=N str) and 1554 cm^{-1} (N-H bend). Its ^{1}H-NMR spectrum displayed signals at δ 7.0-8.31 (*m*, 11H, Ar*H*), 2.41 (*s*, 3H, Ar-CH_3), 10.12 (*s*, 1H, N*H*), 8.8 (*bs*, 1H, N*H*) and 2.25 (*s*, 3H, CH_3). Its mass spectrum showed molecular ion peak at m/z 478.7(M^+).



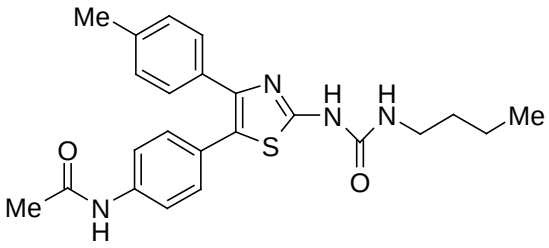
(13i)



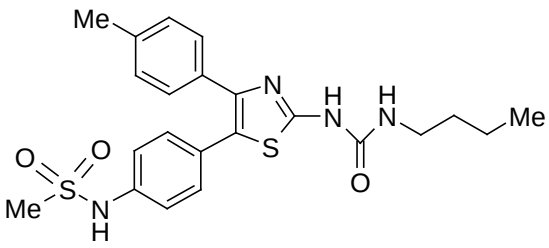
(13j)

The IR spectrum of compound **(13j)** showed bands at 3423 (N-H str), 3183 (N-H str), 1713 (C=O str), 1615 (C=N str), 1299 (S=O str) and 1550 cm^{-1} (N-H bending). Its ^{1}H-NMR spectrum displayed signals at δ 7.0-7.21 (*m*, 4H, Ar*H*), 7.2-7.41 (*d*, 4H, Ar*H*), 7.42-7.61 (*d*, 2H, Ar*H*), 8.2- 8.3 (*m*, 1H, Ar*H*), 2.31 (*s*, 3H, Ar-CH_3), 9.92 (*bs*, 1H, N*H*) , 8.7 (*bs*, 1H, N*H*) and 2.64 (*s*, 3H, CH_3). Mass spectrum offered molecular ion peak at m/z 514.7 (M^+).

The IR spectrum of compound **(13k)** showed characteristic IR peaks at 3425 (N-H str), 3134 (N-H str), 1688 (C=O str), 1609 (C=N str), 1573 (N-H bending) and 1400 cm^{-1} (C-N str).



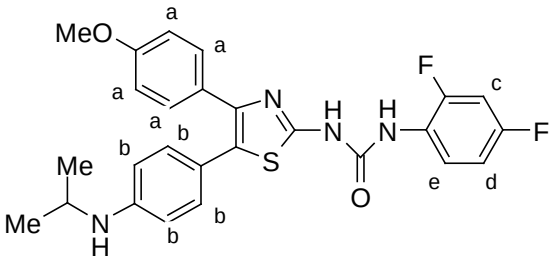
(13k)



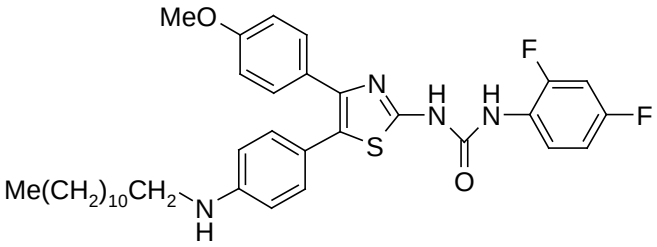
(13l)

The IR spectrum of compound **(13l)** displayed bands at 3342 (N-H str), 3133 (N-H str), 1664 (C=O str), 1615 (C=N str), 1560 (N-H bend) and 1399 cm^{-1}(C-N str). PMR spectrum showed three singlets at δ 10.15, 9.32 and 8.63 for amide (-N*H*), two doublets at δ 7.43-7.34 and 7.15-7.30 for aromatic proton and singlet at δ 3.13 for aromatic –CH_3 , one quartet at δ 3.23-3.65, two multiplets at δ 1.45-1.65 and one triplet at δ 0.93 for *n*-butyl protons.

The IR spectrum of compound **(13m)** showed the characteristic peaks at 3353 (N-H str), 3126 (N-H str), 1688 (C=O str), 1509 (N-H bend) and 1402 cm^{-1} (C-N str). PMR spectrum showed singlets at δ 10.63 and 8.22 for amide (-N*H*). It showed doublet at δ 0.91-0.93, multiplet at δ 3.81-3.93 and singlet at δ 4.0 for two –isopropyl CH_3, one tertiary C*H* and one OCH_3 respectively in its proton NMR spectrum. It also gave the PMR signals at δ 7.0-7.21 (*m*, 4H, ArH_a), 7.2-7.41 (*d*, 4H, ArH_b), 7.42-7.61 (*d*, 2H, Ar$H_{d,e}$) and 8.2-8.3 (*m*, 1H, ArH_c). Mass spectrum showed molecular ion peak at m/z 494.7(M^+).



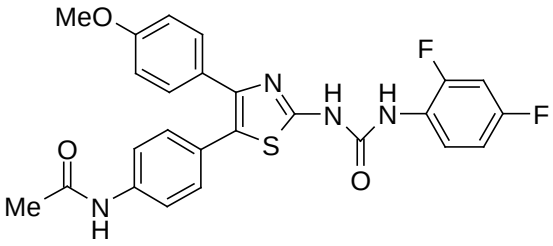
(13m)



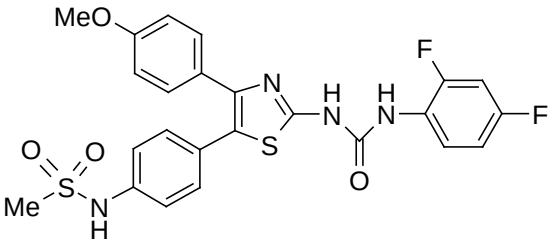
(13n)

PMR spectrum of compound **(13n)** showed two singlets for proton (-N*H*) at δ 10.63 and 8.13. It showed multiplets for aromatic protons at δ 7.38-7.36, 7.04-7.02 and 8.2-8.3. It also showed singlet at δ 4.1 for methoxy and multiplets in the region of 0.9 to 3.02 for the aliphatic protons. Mass spectrum showed molecular ion peak at m/z 536.9 (M^+).

The IR spectrum of compound **(13o)** showed peaks at 3353 (N-H str), 3406 (N-H str), 1675 (C=O str), 1610 (C=N str), 1548 (N-H bend) and 1402 cm^{-1} (C-N str). PMR spectrum showed three singlets at δ 9.87, 8.09 and 7.91 for amides (N-*H*) and another singlet at δ 4.12 for -OCH_3. It also showed multiplets at δ 7.51-7.56, 7.31-7.36, 8.12-8.27 and 7.46-7.56 for aromatic protons.



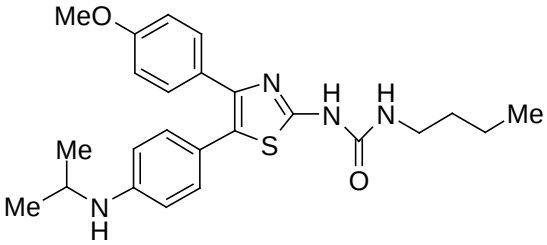
(13o)



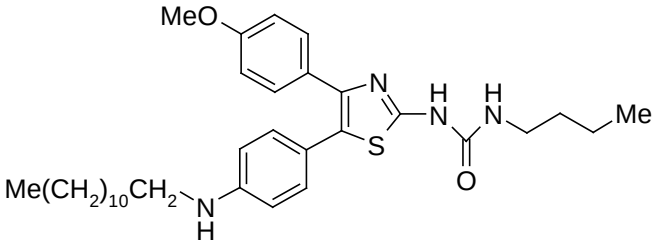
(13p)

The IR spectrum of the compound **(13p)** showed bands at 3409 (N-H str), 3235 (N-H str), 1715 (C=O str), 1613 (C=N str) and 1555 cm^{-1} (N-H bend). Molecular ion peak was observed at m/z 530 (M^+) in its mass spectrum.

The IR spectrum of compound **(13q)** showed bands at 3425 (N-H str), 3134 (N-H str), 1688 (C=O str), 1609 (C=N str), 1573 (N-H bend) and 1400 cm^{-1} (C-N str). Its PMR spectrum showed two singlets at δ 10.63 and 8.22 for amide (-N*H*). It showed doublet at δ 0.91-0.93, multiplet at 3.81-3.93 and singlet at 4.0 for two –isopropyl CH_3, one tertiary C*H* and one OCH_3 respectively, in its proton NMR spectrum. It also displayed the multiplets at δ 7.0-7.41 for aromatic protons. The signals for aliphatic butyl group were observed at δ 0.9-1.03 (*t*, 3H, CH_3), 1.5-1.6 (*m*, 4H, 2CH_2) and 3.23-3.45 (*q*, 2H, CH_2). Mass spectrum showed molecular ion peak at m/z 439.1 (M^+).



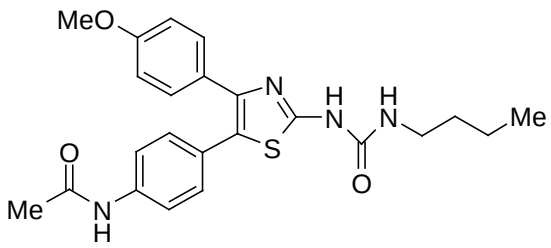
(13q)



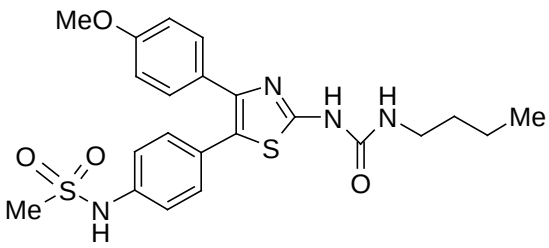
(13r)

The IR spectrum of the compound **(13r)** showed bands at 3437 (N-H str), 3138 (N-H str), 1689 (C=O str), 1616 (C=N str), 1575 (N-H bend) and 1400 cm^{-1} (C-N str). Molecular ion peak was observed at m/z 564.9 (M^+) in its mass spectrum.

N-{4-[2-(3-Butylureido)-4-(4-methoxyphenyl)thiazol-5-yl]phenyl}acetamide **(13s)** gave the characteristic IR bands at 3405 (N-H str), 3247 (N-H str), 2953 (C-H str), 1668 (C=O str)



(13s)



(13t)

and 1529 cm^{-1} (C-N str). Its PMR spectrum showed singlet for amide at δ 7.5 (-N*H*), it showed multiplets in the region δ 6.73-7.40 for aromatic protons (Ar-*H*). It also showed singlet at δ 3.90 for OCH_3. It also displayed a quartet at δ 2.98-2.97, multiplet at δ 1.26-1.14 and triplet at δ 0.81-0.91for aliphatic protons. Mass spectrum showed the molecular ion peak at m/z 438.8 (M^+).

The IR spectrum of compound **(13t)** showed bands at 3431 (N-H str), 3254 (N-H str), 3173 (N-H str), 1710 (C=O str), 1674 (C=O str), 1563 (C=N str) and 1299 cm^{-1} (S=O str). Its PMR spectrum showed three singlets for amide (-N*H*) at δ 8.8, 8.5 and 8.2. It showed multiplets for the aromatic protons between δ 7.14-7.23 (Ar-*H*). It also showed singlet at δ 4.00 for –OCH_3 proton and signals at δ 3.23-3.45, 1.28-1.48 and 0.93-0.94 for *n*-butyl protons with their characteristic splitting pattern in proton NMR spectrum.

4.1.3. Synthesis of 4-thiazolylphenylurea derivatives (16a-16x)

The common intermediates **(9d-9g)** were reacted with thioacetamide in methanol to form intermediate diaryl thiazoles **(14i-14iv)**. Upon reduction, the diaryl thiazoles **(14i-14iv)** were converted to the 4-thiazolylaniline derivatives **(15i-15iv)**. The 4-thiazolylphenylurea derivatives **(16a-16x)** were synthesized by reacting 4-thiazolylaniline derivatives **(15i-15iv)** with various isocyanates. The selection of these isocyanates was based on literature reports that suggested optimal ACAT enzyme inhibitory activity associated with these groups. Purity of all of the synthesized compounds was checked by TLC in different solvent systems. All synthesized derivatives were characterized by their spectral data.

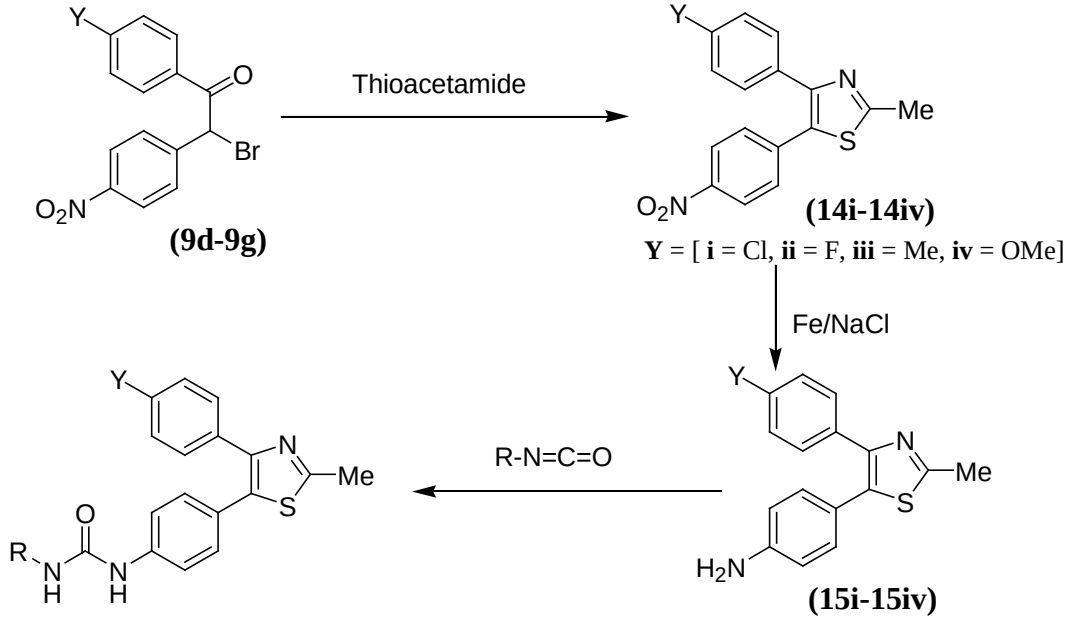
4.1.3.1. Synthesis of 4-nitrophenylthiazole derivatives (14i-14iv)

Synthesis of 4-nitrophenylthiazole derivatives **(14i-14iv)** was accomplished by the general **scheme VI**. The intermediates **(9d-9g)** and thioacetamide were refluxed in ethanol for 5-6 hr to obtain the corresponding compounds **(14i-14iv)**. All synthesized derivatives **(14i-14iv)** showed the characteristic peaks at 1633-1640 (C=N str), 1528 (N=O str) and 1335 cm^{-1}(N=O str) in their IR spectra.

4.1.3.2. Synthesis of 4-thiazolylaniline derivatives (15i-15iv)

4-[4-(4-Chlorophenyl)-2-methylthiazol-5-yl]aniline **(15i)** was synthesized by reducing the compound **(14i)** in presence of iron and sodium chloride in methanol. IR spectrum of the compound **(15i)** showed characteristic peaks at 3413 & 3338 (N-H str. aromatic primary NH_2) 1497 (thiazole C=N Str.) and 1292 cm^{-1} (Ar C-N str.). It displayed signals at δ 6.51 -7.53 (*m*, 8H,

Ar C$H_{a,b}$), 2.75 (*s*, 3H, CH_{3c}) and 4.1 (*s*, 2H, NH_{2d}) in its ^{1}H-NMR spectrum. Its mass spectrum showed the M+H ion peak at m/z 300.5.



(9d-9g)

(14i-14iv)

Y = [**i** = Cl, **ii** = F, **iii** = Me, **iv** = OMe]

(15i-15iv)

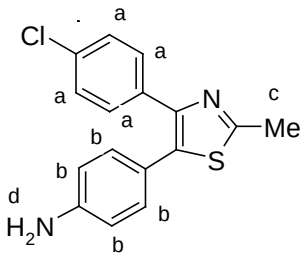
Y = [**i** = Cl, **ii** = F, **iii** = Me, **iv** = OMe]

(16a-16x)

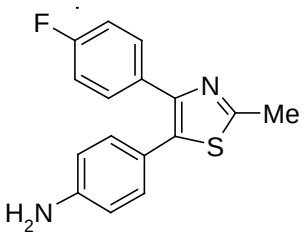
(a)	R = Phenyl	Y = Cl	**(m)**	R = Phenyl	Y = Me
(b)	R = 2,4-Difluorophenyl	Y = Cl	**(n)**	R = 2,4-Difluorophenyl	Y = Me
(c)	R = 2,6-Diethylphenyl	Y = Cl	**(o)**	R = 2,6-Diethylphenyl	Y = Me
(d)	R = *n*-Butyl	Y = Cl	**(p)**	R = *n*-Butyl	Y = Me
(e)	R = *n*-Heptyl	Y = Cl	**(q)**	R = *n*-Heptyl	Y = Me
(f)	R = *n*-Dodecyl	Y = Cl	**(r)**	R = *n*-Dodecyl	Y = Me
(g)	R = Phenyl	Y = F	**(s)**	R = Phenyl	Y = OMe
(h)	R = 2,4-Difluorophenyl	Y = F	**(t)**	R = 2,4-Difluorophenyl	Y = OMe
(i)	R = 2,6-Diethylphenyl	Y = F	**(u)**	R = 2,6-Diethylphenyl	Y = OMe
(j)	R = *n*-Butyl	Y = F	**(v)**	R = *n*-Butyl	Y = OMe
(k)	R = *n*-Butyl	Y = F	**(w)**	R = *n*-Heptyl	Y = OMe
(l)	R = *n*-Dodecyl	Y = F	**(x)**	R = *n*-Dodecyl	Y = OMe

Scheme VI

4-[4-(4-Fluorophenyl)-2-methylthiazol-5-yl]aniline **(15ii)** showed the peaks at 3414 & 3340 (N-H str), 1493 (thiazole C=N Str.) and 1294 cm^{-1}(Ar C-N str.) in its IR spectrum. The appearance of the peak in the region of 3400-3340 (N-H str.) and disappearance of the peak at 1504 (N=O str.) indicated the formation of amino derivatives. It showed the molecular ion peak at m/z 284.01 in its mass spectrum.

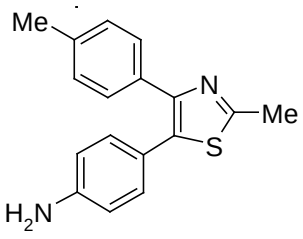


(15i)

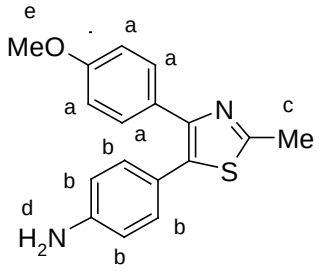


(15ii)

4-[4-(4-Methylphenyl)-2-methylthiazol-5-yl]aniline **(15iii)** showed the characteristic peaks at 1509 (thiazole C=N Str.), 3408 & 3352 (N-H str. aromatic primary NH_2) and 1285 cm^{-1} (Ar C-N str.) in its IR spectrum. Its ^{1}H-NMR spectrum showed multiplets for aromatic protons (δ



(15iii)



(15iv)

6.51-7.52), two sharp singlets for two methyl groups attached to thiazole (δ 2.75) and phenyl ring (δ 2.46) and one singlet for the amino group (δ 3.87).

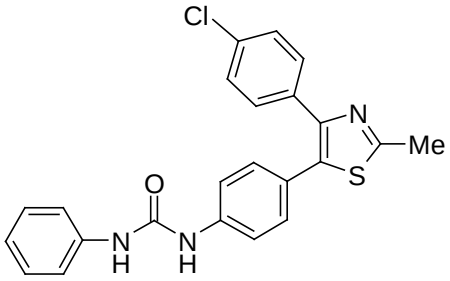
4-[4-(4-Methoxyphenyl)-2-methylthiazol-5-yl]aniline **(15iv)** displayed peaks at 3362 & 3309 (N-H str. aromatic primary NH_2), 1510 (thiazole C=N Str.),1288 (Ar C-N str.) and 1245 cm^{-1}(Ar-OCH_3) in its IR spectrum. It offered signals at δ 6.5 -7.5 (*m*, 8H, Ar C-$H_{a,b}$), 2.81 (*s*, 3H, thiazole CH_{3c}), 3.92 (*s*, 3H, Ar-OCH_{3e}) and 3.75 (*s*, 2H, NH_{2d}) in its ^{1}H-NMR spectrum.

4.1.3.3. Synthesis of diaryl thiazole urea derivatives (16a-16x)

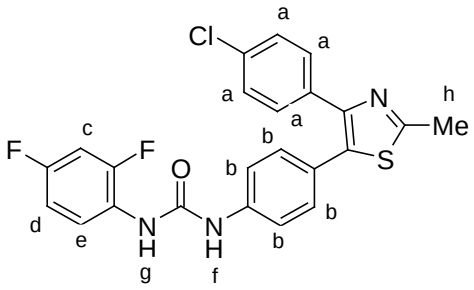
1-{4-[4-(4-Chlorophenyl)-2-methylthiazol-5-yl]phenyl}-3-phenylurea **(16a)** was prepared by reaction of the amine **(15i)** with phenyl isocyanate in dry toluene. The compound **(16a)** showed the peaks at 1649 (sec C=O str.), 3318 (N-H str. amide) and 1552 cm^{-1} (thiazole C=N str) in its IR spectrum. It offered the signals at δ 7.0-7.9 (*m*, 13H, Ar C-H), 6.51 (*s*, 2H, NH), 2.61 (*s*, 3H, $CH_{3)}$ in its proton NMR spectrum.

1-{4-[4-(4-Chlorophenyl)-2-methylthiazol-5-yl]phenyl}-3-(2,4-difluorophenyl)urea **(16b)** was prepared by reaction of the amine **(15i)** with 2,4-difluorophenyl isocyanate. Compound **(16b)** showed the characteristic IR peaks at 1636 (sec C=O str), 3326 (N-H str.

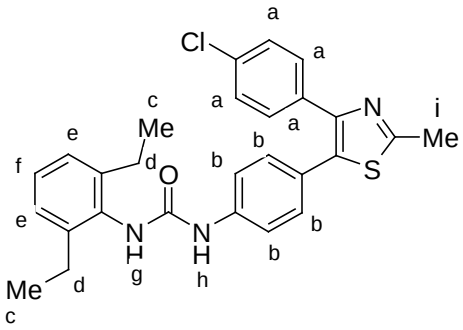
amide) and 3100 cm^{-1} (Ar. C-H str). It showed the ^{1}H-NMR spectrum at δ 7.21-7.42 (*m*, 4H, Ar CH_a), 7.42-7.62 (*m*, 4H, Ar CH_b), 8.21-8.41 (*m*, 1H, Ar CH_c), 6.71-7.05 (*m*, 2H, Ar C$H_{e,d}$), 8.41 (b*s*, 1H, NH_f), 8.91 (b*s*, 1H, NH_g) and 2.81(*s*, 3H, CH_{3h}). It showed the molecular ion peak at m/z 454.76 in its mass spectrum.



(16a)



(16b)

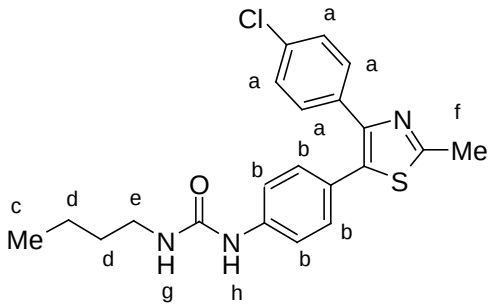


(16c)

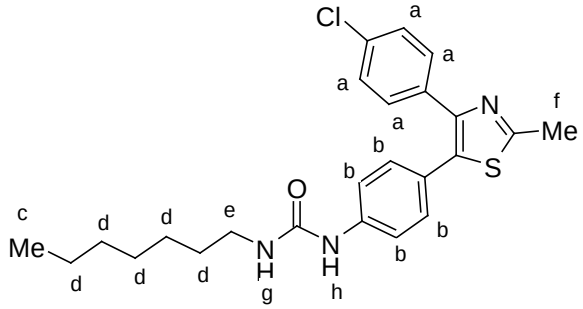
Characteristic peaks at 1637 (sec C=O str) and 3285 cm^{-1} (N-H str amide) were observed in IR spectrum for 1-{4-[4-(4-chlorophenyl)-2-methylthiazol-5-yl]phenyl}-3-(2,6-diethylphenyl) urea **(16c).** The appearance of strong C=O str. at 1637 cm^{-1} in its IR spectrum indicated the conversion of amine **(15i)** to urea **(16c)**. It was further confirmed by signals at δ 7.01-7.51 (*m*, 8H, ArC$H_{a,b}$), 7.62-7.81 (*d*, 2H, ArCH_e), 7.82-7.91 (*m*, 1H, Ar CH_f), 2.72 (*s*, 3H, CH_{3i}), 2.61-2.67 (*q*, 4H, 2CH_{2d}) and 1.2-1.4 (*t*, 6H, 2CH_{3c}) in its ^{1}H-NMR spectrum. Molecular ion peak was observed in its mass spectrum at m/z 474.87.

1-Butyl-3-{4-[4-(4-chlorophenyl)-2-methylthiazol-5-yl]phenyl}urea **(16d)** was prepared by reacting amine **(15i)** with *n*-butyl isocyanate. Its IR spectrum showed peaks at 1636 (C=O str.), and 3326 (amide N-H str.). The ^{1}H-NMR spectrum displayed signals at δ 7.2-7.7 (*d*, 8H, Ar-C$H_{a,b}$), 2.71 (*s*, 3H, CH_{3f}), 0.9-1.01 (*t*, 3H, CH_{3c}), 1.2-1.4 (*m*, 4H, CH_{2d}), 3.27-3.41 (*q*, 2H, CH_{2e}), 5.91 (*bs*, 1H, NH_g) and 8.41 (*bs*, 1H, NH_h).

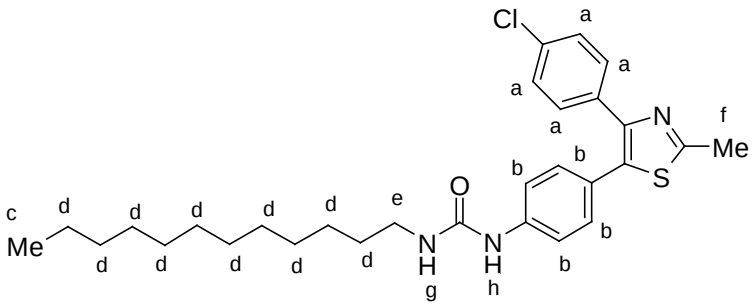
1-Heptyl-3-{4-[4-(4-chlorophenyl)-2-methylthiazol-5-yl]phenyl}urea **(16e)** was also prepared in the same way by reacting the amine **(15i)** with *n*-heptyl isocyanate. Compound **(16e)** showed the peaks at 1633 (C=O str.) and 3321 (N-H str. amide) in its IR spectrum. The ^{1}H-NMR spectrum displayed signals at δ 7.21-7.72 (*m*, 8H, Ar-C$H_{a,b}$), 2.72 (*s*, 3H, CH_{3f}), 0.9-1.01 (*t*, 3H,



(16d)



(16e)



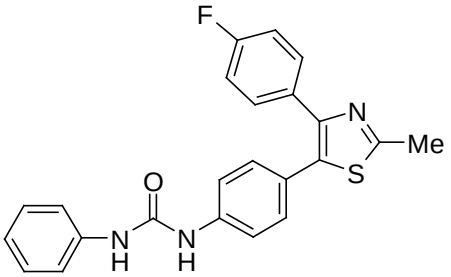
(16f)

CH_{3c}), 1.2-1.4 (*m*, 10H, CH_{2d}), 3.2-3.4 (*q*, 2H, CH_{2e}), 5.91 (*s*, 1H, NH_g) and 8.41 (*s*, 1H, NH_h). Molecular ion peak was observed in its mass spectrum at m/z 440.98.

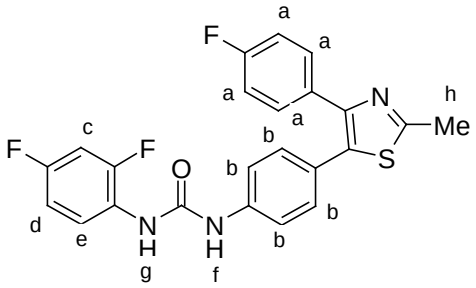
The characteristic IR peaks at 1634 (C=O str.), 3320 (N-H str. amide) and 1556 cm^{-1} (thiazole C=N str.) were observed in the spectrum for 1-dodecyl-3-{4-[4-(4-chlorophenyl)-2-methylthiazol-5-yl]phenyl}urea **(16f).** Its proton NMR spectrum showed signals at δ 7.21-7.61 (*m*, 8H, ArC-$H_{a,b}$), 6.41 (*s*, 1H, NH_g), 4.51 (*s*, 1H, NH_h), 2.82 (*s*, 3H, CH_{3f}), 0.9- 1.2 (*t*, 3H, CH_{3c}), 1.22-1.42 (*m*, 20H, CH_{2d}) and 3.21-3.41(*q*, 2H, CH_{2e}). The molecular ion peak was observed at m/z 511.02 in its mass spectrum.

1-{4-[4-(4-Fluorophenyl)-2-methylthiazol-5-yl]phenyl}-3-phenylurea **(16g)** was prepared by reacting the amine **(15ii)** with phenyl isocyanate. Its IR spectrum showed the characteristic peaks at 1641 (C=O str.), 3299 (N-H str. amide) and 1552 cm^{-1} (thiazole C=N Str). ^{1}H-NMR

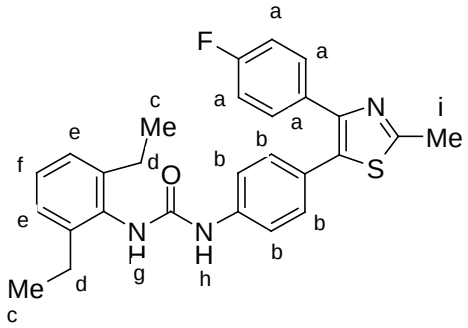
spectrum displayed signals at δ 7.0-7.9 (*m*, 13H, Ar C-*H*), 6.51 (*bs*, 2H, N*H*) and 2.61 (*s*, 3H, CH_3).



(16g)



(16h)



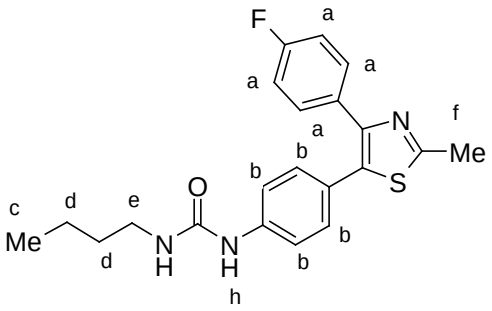
(16i)

The compound **(16h)** displayed the characteristic peaks at 1640 (sec C=O str.), 3291 (N-H str. amide) and 1556 cm^{-1} (thiazole C=N str.) in its IR spectrum. The ^{1}H-NMR spectrum gave signals at δ 7.25-7.38 (*m*, 4H, Ar CH_a), 7.48-7.62 (*m*, 4H, Ar CH_b), 8.21-8.41 (*m*, 1H, Ar CH_c), 6.71-7.05 (*m*, 2H, Ar C$H_{e,d}$), 8.41 (*bs*, 1H, NH_f), 8.81 (*bs*, 1H, NH_g) and 2.81 (*s*, 3H, CH_{3h}). It showed the molecular ion peak at m/z 439.

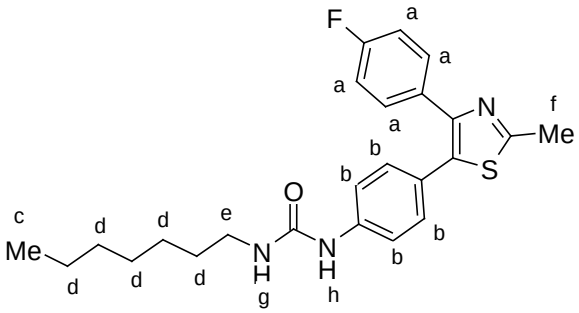
1-{4-[4-(4-Fluorophenyl)-2-methylthiazol-5-yl]phenyl}-(2,6-diethylphenyl)urea **(16i)** was prepared by reacting amine **(15ii)** with 2,6-diethylphenyl isocyanate. Its IR spectrum showed the peaks at 1641 (sec C=O str.), 3294 (N-H str. amide), 1549 (thiazole C=N str.) and 3134 cm^{-1} (Ar C-H str.). Protons Ar-H_a and Ar-H_b appeared as multiplets at δ 7.21-7.42 and 7.42-7.62 respectively in the PMR spectrum. One singlet, one multiplet, one triplet and one quartet appeared at δ 2.61, 7.62-7.81, 2.61-2.67 and 1.2-1.4 respectively. Its mass spectrum showed the molecular ion peak at m/z 459.0.

1-Butyl-3-{4-[4-(4-fluorophenyl)-2-methylthiazol-5-yl]phenyl}urea **(16j)** showed the peaks at 1634 (C=O str.) and 3314 cm^{-1}(N-H str. amide) in its IR spectrum. Its proton NMR

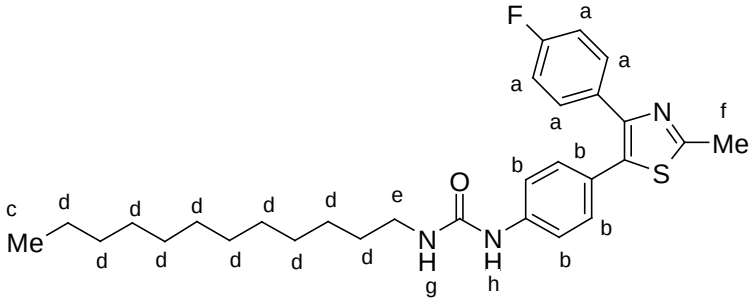
showed the signals at δ 7.2-7.7 (*d*, 8H, Ar-C$H_{a,b}$), 5.9 (*s*, 1H, NH_g), 8.4 (*s*, 1H, NH_h), 2.7 (*s*, 3H, CH_{3f}), 0.9-1.01 (*t*, 3H, CH_{3c}), 1.2-1.4 (*m*, 4H, CH_{2d}), 3.32-3.40 (*q*, 2H, CH_{2e}).



(16j)



(16k)



(16l)

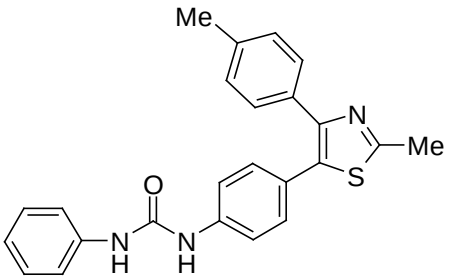
Compound **(16k)** showed the IR peaks at 1633 (C=O str.) and 3321 (amide N-H str.). It gave signals at δ 7.2-7.7 (*m*, 8H, Ar-C$H_{a,b}$), 5.9 (b*s*, 1H, NH_g), 8.4 (b*s*, 1H, NH_h), 2.7 (*s*, 3H, CH_{3f}), 0.9-1.10 (*t*, 3H, CH_{3c}), 1.2-1.4 (*m*, 10H, CH_{2d}), 3.4 (*m*, 2H, CH_{2e}) in its proton NMR spectrum.

1-Dodecyl-3-{4-[4-(4-fluorophenyl)-2-methylthiazol-5-yl]phenyl}urea **(16l)** was prepared by the reaction between the amine **(15ii)** with *n*-dodecyl isocyanate. It showed the peaks in its IR spectrum at 1634 (C=O str.), 3320 (amide N-H str.) and 1556 cm^{-1} (thiazole C=N Str.) and signals at δ 7.2-7.7 (m, 8H, Ar-C$H_{a,b}$), 5.5 (*b*s, 1H, NH_g), 8.0 (*s*, 1H, NH_h), 2.7 (*s*, 3H, CH_{3f}), 0.9-1.01 (t, 3H, CH_{3c}), 1.2-1.4 (*s*, 20H, CH_{2d}) and 3.2-3.4 (*q*, 2H, CH_{2e}) in its NMR spectrum.

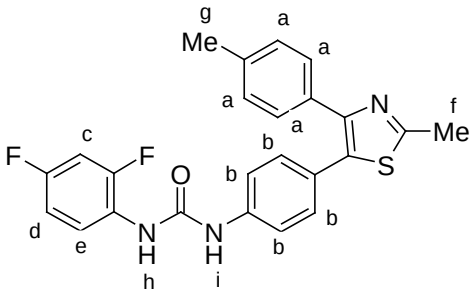
1-{4-[4-(4-Methylphenyl)-2-methylthiazol-5-yl]phenyl}-3-phenylurea **(16m)** was prepared by reacting the amine **(15iii)** with phenyl isocyanate. The compound **(16m)** showed the characteristic IR peaks at 1647 (sec C=O str.), 3310 (amide N-H str.) and 1548 cm^{-1} (thiazole C=N str). It displayed the signals at δ 6.9-7.4 (*m*, 13H, Ar C-*H*), 8.2 (*s*, 2H, N*H*), 2.72 (*s*, 3H,

thiazole CH_3) and 2.30 (*s*, 3H, phenyl CH_3) in its NMR spectrum and gave the molecular ion peak at m/z 400.0 in its mass spectrum.

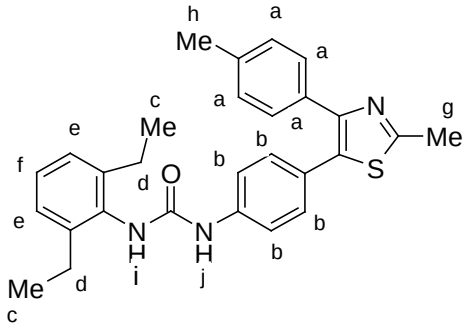
Compound **(16n)** displayed the characteristic IR peaks at 1634 (sec C=O str.), 3322 (N-H str. amide) and 1554 cm^{-1} (thiazole C-N str.). Its ^{1}H-NMR spectrum showed the signals at δ 7.25-7.38 (*m*, 4H, Ar CH_a), 7.48-7.62 (*m*, 4H, Ar CH_b), 8.21-8.41 (*m*, 1H, Ar CH_c), 6.71-7.05 (*m*, 2H, Ar C$H_{e,d}$), 8.41 (*s*, 1H, NH_h), 8.81 (*s*, 1H, NH_i), 2.92 (*s*, 3H, CH_{3f}) and 2.52 (*s*, 3H, CH_{3g}). It showed the molecular ion peak at m/z 436.0 in its mass spectrum.



(16m)



(16n)

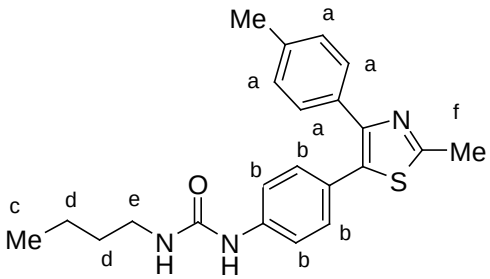


(16o)

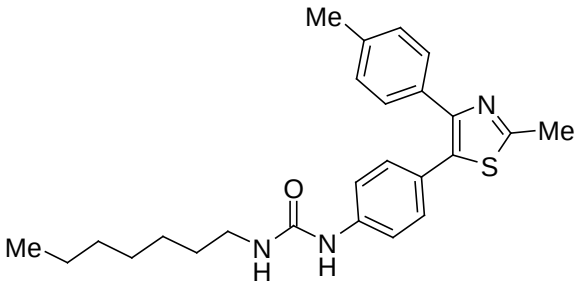
1-{4-[4-(4-Methylphenyl)-2-methylthiazol-5-yl]phenyl}-3-(2,6-diethylphenyl)urea **(16o)** was synthesized by reacting the amine **(15iii)** with 2,6-diethylphenyl isocyanate. Characteristic IR peaks at 1647 (sec C=O str.), 3309 (N-H str. amide) and 1550 cm^{-1} (thiazole C=N str) appeared in its IR spectrum and it displayed the proton NMR peaks at δ 7.01-7.51 (*m*, 8H, ArC$H_{a,b}$), 7.62-7.81 (*m*, 2H, Ar CH_e), 7.82-7.91 (m, 1H, Ar CH_f), 2.62 (*s*, 3H, CH_{3g}), 2.61-2.67 (*q*, 4H, 2CH_{2d}), 1.2-1.4 (*t*, 6H, 2CH_{3c}) and 2.30 (*s*, 3H, CH_{3h}). Its mass spectrum showed the molecular ion peak at m/z 455.06.

1-Butyl-3-{4-[4-(4-mehtylphenyl)-2-methylthiazol-5-yl]phenyl}urea **(16p)** was synthesized by reacting the amine **(15iii)** with *n*-butyl isocyanate. Compound **(16p)** showed the

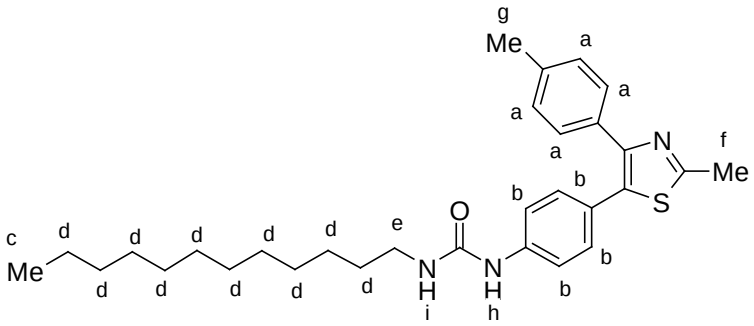
IR peaks at 1639 (C=O str.) and 3318 (N-H str. amide) . Protons Ar-H_a and Ar-H_b appeared as multiplets at δ 7.21-7.42 and δ 7.42-7.62 respectively. Two singlets appeared in the region δ 2.61



(16p)



(16q)



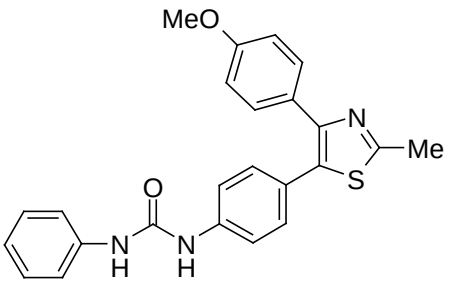
(16r)

and δ 2.31respectively. One multiplet, one quartet and one triplet appeared at δ 1.2-1.4, 3.21-3.42 and 0.9-1.02 respectively. The molecular ion peak appeared at m/z 380.1.

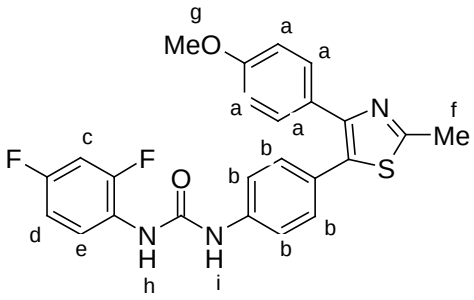
Compound **(16q)** showed the peaks at 1633 (C=O str.) and 3321 cm^{-1} (N-H str. amide) in its IR spectrum. 1-Dodecyl-3-{4-[4-(4-methylphenyl)-2-methylthiazol-5-yl]phenyl}urea **(16r)** showed the characteristic IR peaks at 1639 (C=O str.) and 3318 cm^{-1} (N-H str. amide). It displayed peaks in the NMR spectrum at δ 7.2-7.7 (*m*, 8H, Ar-C$H_{a,b}$), 5.5 (*s*, 1H, NH_i), 8.25 (*s*, 1H, NH_h), 2.9 (*s*, 3H, CH_{3f}), 0.9-1.01 (*t*, 3H, CH_{3c}), 1.2-1.4 (*m*, 20H, CH_{2d}), 3.2-3.5 (*m*, 2H, CH_{2e}) and 2.4 (*s*, 3H, CH_{3g}).

1-{4-[4-(4-Methoxyphenyl)-2-methylthiazol-5-yl]phenyl}-3-phenylurea **(16s)** was synthesized by treating the amine **(15iv)** with phenyl isocyanate. It showed the characteristic IR peaks at 1633 (C=O str.), 3321 (N-H str. amide) and 1222 cm^{-1} (Ar-O str.) and displayed the signals at δ 6.95-7.41(m, 13H, Ar C*H*), 8.62 (*s*, 2H, N*H*), 2.82 (*s*, 3H, thiazole C$H_{3)}$ and 3.82 (*s*, 3H, phenyl OCH_3) in its NMR spectrum.

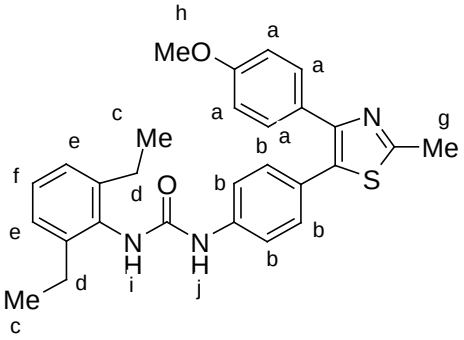
Compound **(16t)** showed the characteristic peaks at 1647 (sec C=O str), 3309 (N-H str amide) and 1550 cm^{-1} (thiazole C=N str) in its IR spectrum and displayed the signals at δ 6.8-7.4 (*m*, 8H, Ar C$H_{a,b}$), 7.8-8.2 (*m*, 3H, Ar C$H_{c,d,e}$), 2.92 (*s*, 3H, CH_{3f}), 8.4 (*s*, 1H, NH_h), 8.8 (*s*,1H, NH_i) and 3.75 (*s*, 3H, Ar OCH_{3g}).



(16s)



(16t)

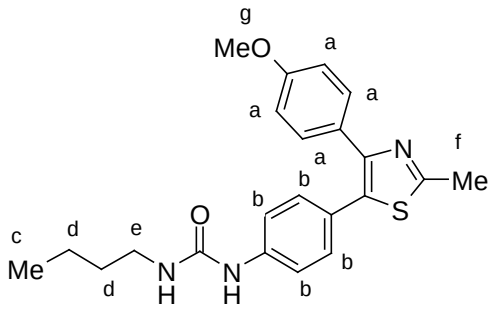


(16u)

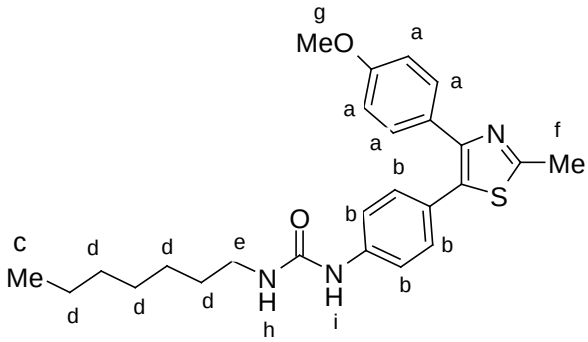
1-[4-(4-(4-Methoxyphenyl)-2-methylthiazol-5-yl)phenyl]-3-(2,6-diethylphenyl)urea **(16u)** showed the peaks at 1634 (sec C=O str.), 3322 (N-H str. amide) and 1554 cm^{-1} (Ar.thiazole C-N str.) in its IR spectrum. Compound **(16u)** displayed the signals at δ 7.01-7.51 (*m*, 8H, ArC$H_{a,b}$), 7.62-7.81 (*d*, 2H, ArCH_e), 7.82-7.91 (*m*, 1H, Ar CH_f), 2.72 (*s*, 3H, CH_{3i}), 2.67 (*q*, 4H, 2CH_{2d}), 1.2-1.4 (*t*, 6H, 2CH_{3c}) and 3.75 (*s*, 3H, Ar OCH_{3h}) in its ^{1}H-NMR spectrum.

1-Butyl-3-{4-[4-(4-methoxyphenyl)-2-methylthiazol-5-yl]phenyl}urea **(16v)** was synthesized by treating the amine **(15iv)** with *n*-butyl isocyanate. Compound **(16v)** showed the characteristic IR peaks at 1633 (C=O str.), 3321 (N-H str. amide) and 1222 cm^{-1} (ArO str.) and displayed the signals for Ar-H_a and Ar-H_b as multiplets at δ 7.21-7.42 and 7.42-7.62 respectively. Two singlets appeared in the region at δ 2.72 and 4.00 for thiazole methyl and methoxy group respectively. One multiplet, one quartet and one triplet appeared at δ 1.2-1.4, 3.2-3.4 and 0.9-1.02 respectively.

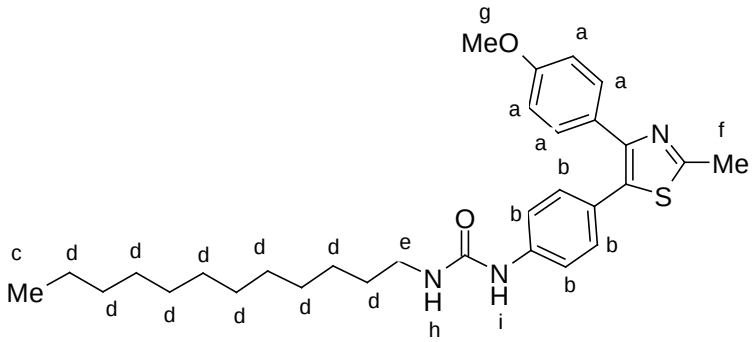
Compound **(16w)** showed the peaks at 1647 (sec C=O str.), 3309 (N-H str. amide) 1550 (thiazole C=N str) and 1220 cm^{-1} (Ar-O str) in its IR spectrum. It displayed peaks in the ^{1}H-NMR spectrum at δ 6.8-7.5 (*m*, 8H, ArC$H_{a,b}$), 8.52 (*s*, 1H, NH_h), 5.62 (*s*, 1H, NH_i), 2.81 (*s*, 3H, thiazole-CH_{3f}), 0.9-1.01 (*t*, 3H, aliphatic-CH_{3c}), 1.2-1.4 (*m*, 10H, CH_{2d}), 3.41-3.51 (*m*, 2H, CH_{2e}) and 3.90 (*s*, 3H, Ar-OCH_{3g}).



(16v)



(16w)



(16x)

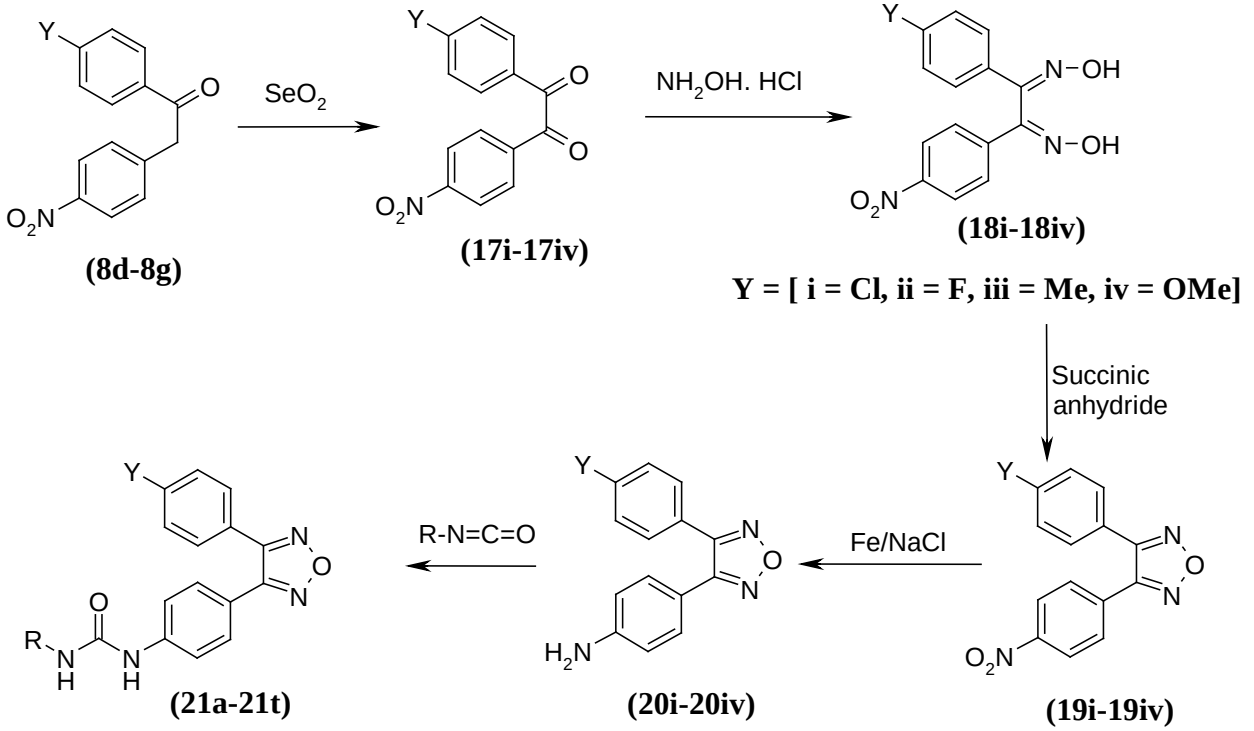
1-Dodecyl-3-{4-[4-(4-methoxyphenyl)-2-methylthiazol-5-yl]phenyl}urea **(16x)** was synthesized by reacting the amine **(15iv)** with *n*-dodecyl isocyanate. It displayed the characteristic IR peaks at 1647 (sec C=O str.), 3309 (N-H str. amide), 1550 (thiazole C=N str) and 1220 cm^{-1}(Ar OCH_3) and displayed the PMR signals at δ 6.81-7.43 (*m*, 8H, Ar C$H_{a,b}$), 6.8 (*s*, 1H, NH_h), 5.1 (*s*, 1H, NH_i), 2.81 (*s*, 3H, thiazole-CH_{3f}), 0.9-1.01 (*t*, 3H, CH_{3c}), 1.2-1.4 (*m*, 20H, CH_{2d}), 3.2-3.6 (*t*, 2H, CH_{2e}), and 4.0 (*s*, 3H, Ar- OCH_{3g}).

4.1.4. Synthesis of 4-furazanylphenylurea derivatives

4.1.4.1. Synthesis of diaryl ethan-1,2-dione derivatives (17i-17iv)

The common intermediates **(8d-8g)** were oxidized in presence of selenium dioxide in different solvents to obtain the title intermediates (**17i-17iv**). The oxidation was tried in different

solvents like glacial acetic acid, acetic anhydride and DMSO under conventional heating and/or microwave irradiation to reduce reaction time and to improve the yield. The most preferred



(8d-8g) **(17i-17iv)** **(18i-18iv)**

Y = [i = Cl, ii = F, iii = Me, iv = OMe]

(21a-21t) **(20i-20iv)** **(19i-19iv)**

Y = [i = Cl, ii = F, iii = Me, iv = OMe]

(a)	R = 2,4-Difluorophenyl	Y = Cl	**(k)**	R = 2,4-Difluorophenyl	Y = Me
(b)	R = 2,6-Diethylphenyl	Y = Cl	**(l)**	R = 2,6-Diethylphenyl	Y = Me
(c)	R = *n*-Butyl	Y = Cl	**(m)**	R = *n*-Butyl	Y = Me
(d)	R = *n*-Heptyl	Y = Cl	**(n)**	R = *n*-Heptyl	Y = Me
(e)	R = *n*-Dodecyl	Y = Cl	**(o)**	R = *n*-Dodecyl	Y = Me
(f)	R = 2,4-Difluorophenyl	Y = F	**(p)**	R = 2,4-Difluorophenyl	Y = OMe
(g)	R = 2,6-Diethylphenyl	Y = F	**(q)**	R = 2,6-Diethylphenyl	Y = OMe
(h)	R = *n*-Butyl	Y = F	**(r)**	R = *n*-Butyl	Y = OMe
(i)	R = *n*-Butyl	Y = F	**(s)**	R = *n*-Heptyl	Y = OMe
(j)	R = *n*-Dodecyl	Y = F	**(t)**	R = *n*-Dodecyl	Y = OMe

Scheme VII

solvent was found to be DMSO in presence of sufficient quantity of selenium dioxide under the microwave irradiation.

4.1.4.2. Synthesis of diaryl oxadiazole derivatives (19i-19iv)

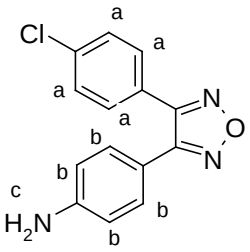
The oximation of intermediates **(17i-17iv)** yielded the substituted diaryl dioximes **(18i-18iv)** which upon dehydration form the substituted diaryl oxadiazole derivatives **(19i-19iv)**. All of the synthesized derivatives were recrystallised in methanol to afford the pure compound. The

IR spectra of all the synthesized derivatives **(18i-18iv)** displayed characteristic IR peaks at 3253 (N-OH str), 1520 (N=O str) and 1346 cm^{-1} (N=O str) and disappearance of C=O str at 1666-1668 cm^{-1}. All derivatives (**18i-18iv**) were dehydrated in presence of succinic anhydride to obtain the desired diaryl furazans (**19i-19iv**). All synthesized diaryl furazans or oxadiazoles (**19i-19iv)** displayed characteristic IR peaks at 1230 (C-N str) and disappearance of peak at 3253 cm^{-1} (N-OH str).

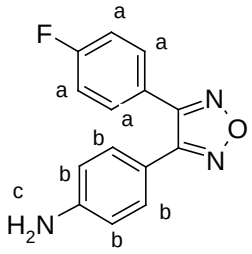
4.1.4.3. Synthesis of 4-furazanylaniline derivatives (20i-20iv)

The nitro derivatives **(19i-19iv)** were reduced in presence of iron powder in acidic medium to obtain the 4-furazanylaniline derivavatives **(20i-20iv)**. All of the derivatives **(20i-20iv)** were purified by column chromatography and characterized on the basis of their IR, NMR and mass spectrum.

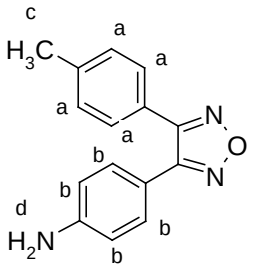
4-[(4-Aminophenyl)-3-(4-chlorophenyl)]-1,2,5-oxadiazole **(20i)** displayed the characteristic IR peaks at 3482 (NH str) and 1624 cm^{-1} (N-H bending). It showed the signals at δ



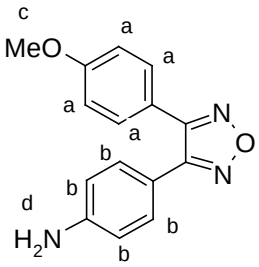
(20i)



(20ii)



(20iii)



(20iv)

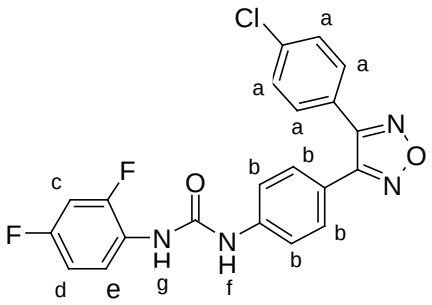
6.95-7.42 (*m*,8H, Ar$H_{a,b}$) and 3.75 (*s*, 2H, NH_{2c}). Its mass spectrum showed the M+H peak at m/z 272. 4-[(4-Aminophenyl)-3-(4-fluorophenyl)]-1,2,5-oxadiazole **(20ii)** showed the IR peaks at 3378 (NH str), 3221 (Ar C-H str) and 1624 cm^{-1}(N-H bending). It displayed the NMR spectrum at δ 6.51-7.91(*m*, 8H, Ar$H_{a,b}$) and 4.21(*s*, 2H, NH_{2c}). It showed the molecular ion peak at m/z 255.24 in its mass spectrum.

4-[(4-Aminophenyl)-3-(4-methylphenyl)]-1,2,5-oxadiazole **(20iii)** showed peaks at 3469 (N-H str), 3134 (Ar C-H str) and 1620 cm^{-1} (N-H bending) in its IR spectrum. It displayed peaks in the NMR spectrum at δ 6.51-7.91(*m*, 8H, Ar$H_{a,b}$), 2.40 (*s*, 3H, ArCH_{3c}), and 4.21(s, 2H, NH_{2d}). 4-[(4-Aminophenyl)-3-(4-methoxyphenyl)]-1,2,5-oxadiazole **(20iv)** displayed the IR peaks at 3469 (N-H str.), 1620 (N-H bending) and 1244 cm^{-1}(Ar-OCH_3 str). It displayed the proton peaks at δ 6.72-7.85 (*m*, 8H, Ar$H_{a,b}$), 4.52 (*s*, 2H, NH_{2d}) and 4.0 (*s*, 3H, Ar-OCH_{3c}) in its NMR spectrum.

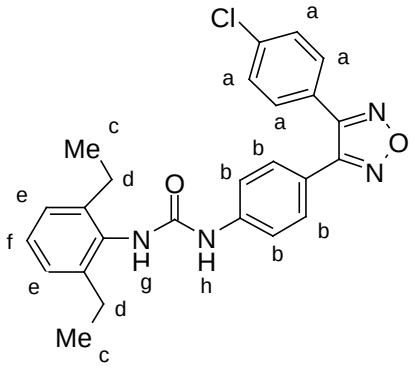
4.1.4.4. Synthesis of substituted vicinal diaryl oxadiazole urea derivatives (21a-21t)

The synthesized anilines **(20i-20iv)** were reacted further with isocyanates in toluene at room temperature to obtain the diaryl oxadiazole ureas **(21a-21t)**. All of the synthesized compounds were characterized on the basis of their IR, NMR and Mass spectra.

1-{4-[4-(4-Chlorophenyl)furazan-3-yl]phenyl}-3-(2,4-difluorophenyl)urea **(21a)** was prepared by reaction of the amine **(20i)** with 2,4-difluorophenyl isocyanate in dry toluene. It showed the IR peaks at 3292 (N-H str), 1656 (C=O str) and 3124 cm^{-1} (Ar C-H str.). It showed sitgnals in the ^{1}H-NMR spectrum at δ 7.21-7.42 (*m*, 4H, Ar CH_a), 7.42-7.62 (*m*, 4H, Ar CH_b), 8.21-8.41(*m*, 1H, Ar CH_c), 6.71-7.05 (*m*, 2H, Ar C$H_{d,e}$), 8.41 (bs, 1H, NH_f) and 8.81 (bs, 1H, NH_g).



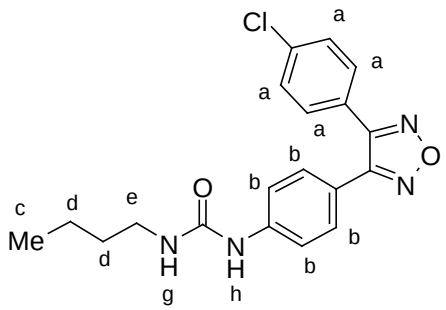
(21a)



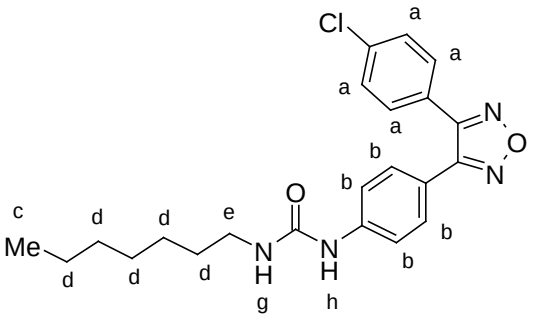
(21b)

Compound **(21b)** displayed the IR peaks at 3321 (amide NH str), 1650 (C=O str) and 3124 cm^{-1} (Ar C-H str.) and showed the signals at δ 7.01-7.51 (*m*, 8H, ArC$H_{a,b}$), 7.62-7.81 (*m*, 2H, ArCH_e), 7.82-7.91 (*t*, 1H, Ar CH_f), 2.61-2.67 (*q*, 4H, 2CH_{2d}) and 1.2-1.4 (*t*, 6H, 2CH_{3c}) in its proton NMR spectrum.

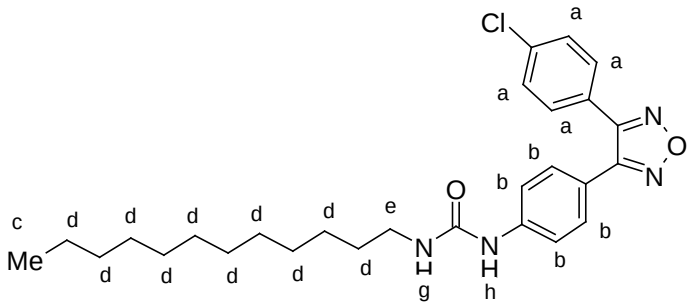
1-Butyl-3-{4-[4-(4-chlorophenyl)furazan-3-yl]phenyl}urea **(21c)** showed the IR peaks at 3299 (amide NH str.), 1638 (C=O str) and 3124 cm^{-1} (Ar C-H str) and displayed the signals at δ 7.2-7.7 (*m*, 8H, Ar-C$H_{a,b}$), 0.9-1.01 (*t*, 3H, CH_{3c}), 1.2-1.4 (*m*, 4H, CH_{2d}), 3.2-3.45 (*m*, 2H, CH_{2e}), 5.91 (*s*, 1H, NH_g) and 8.41 (*s*, 1H, NH_h) in its NMR spectrum.



(21c)



(21d)



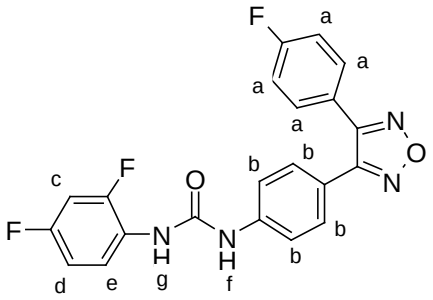
(21e)

1-Heptyl-3-{4-[4-(4-chlorophenyl)furazan-3-yl]phenyl}urea **(21d)** was synthesized by the reaction of the amine **(20i)** with *n*-heptyl isocyanate. It showed the characteristic peaks at 3321 (amide NH str), 1650 (C=O str) and 3100 cm^{-1}(Ar CH str.) in its IR spectrum. Protons Ar-H_a and Ar-H_b appeared as typical mutiplets at δ 7.51-8.1 (*m*, 8H, ArC$H_{a,b}$) and proton Ar-H_c appeared as triplet at δ 0.9-1.01(*t*, 3H, CH_{3c}). The protons for the five methylene group appeared at δ 1.51-1.61(*m*, 10H, CH_{2d}) and other protons appeared at δ 3.35-3.52 (*m*, 2H_e), 5.21 (*s*, 1H_g) and 6.91 (*s*, 1H_h) for one methylene and two amide protons respectively in its PMR spectrum.

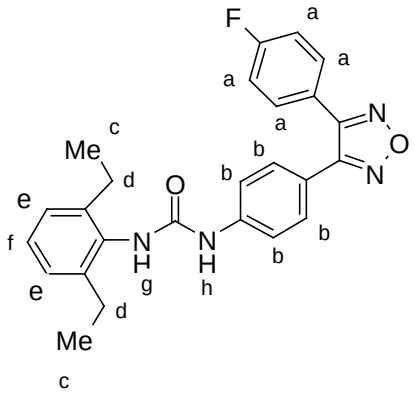
Compound **(21e)** showed the peaks at 3336 (NH str) and 1636 cm^{-1} (C=O str) in its IR spectra and displayed the PMR signals at δ 7.2-7.4 (*m*, 8H, Ar C$H_{a,b}$), 3.1-3.3 (*q*, 2H, N-CH_{2e}), 0.9-1.01 (*t*, 3H, CH_{3c}), 1.3-1.5 (*m*, 20H, CH_{2d}), 8.2 (*s*, 1H, NH_g) and 6.1 (*s*, 1H, NH_h).

1-{4-[4-(4-Fluorophenyl)furazan-3-yl]phenyl}-3-(2,4-difluorophenyl)urea **(21f)** gave the peaks at 3301 (NH str) and 1654 cm^{-1} (C=O str) in its IR spectrum and displayed the signals at δ

7.21-7.42 (*m*, 4H, Ar CH_a), 7.42-7.62 (*m*, 4H, Ar CH_b), 8.21-8.41 (*m*, 1H, Ar CH_c), 6.71-7.05 (*m*, 2H, Ar C$H_{d,e}$), 8.41 (*s*, 1H, NH_f) and 8.81 (*s*, 1H, NH_g) in its ^{1}H-NMR spectrum.



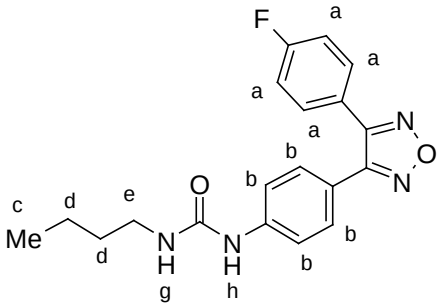
(21f)



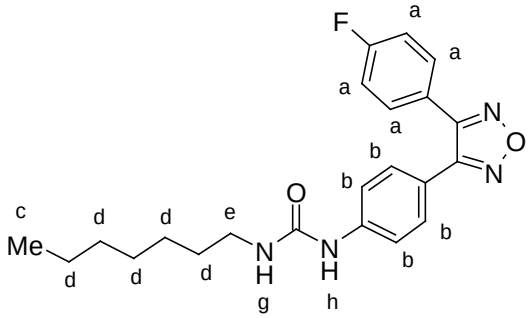
(21g)

Compound **(21g)** showed the IR peaks at 3286 (NH str.) and 1639 cm^{-1} (C=O). The ^{1}H-NMR signals appeared at δ 7.01-7.51 (*m*, 8H, ArC$H_{a,b}$), 7.62- 7.81 (*m*, 2H, ArCH_e), 7.82-7.91 (*m*, 1H, Ar CH_f), 2.61-2.67 (*q*, 4H, 2CH_{2d}) and 1.2-1.4 (*t*, 6H, 2CH_{3c}).

1-Butyl-3-{4-[4-(4-fluorophenyl)furazan-3-yl]phenyl}urea **(21h)** showed the peaks at 1637 (C=O) and 3300 cm^{-1} (N*H* str) in its IR spectrum. Compound **(21h)** displayed the signals for protons Ar-H_a and Ar-H_b as multiplets at δ 7.21-7.42 and 7.42-7.62 respectively. One quartet, one multiplet and one triplet appeared at δ 3.62-3.81, 2.61-2.67 and 1.2-1.4 respectively.



(21h)

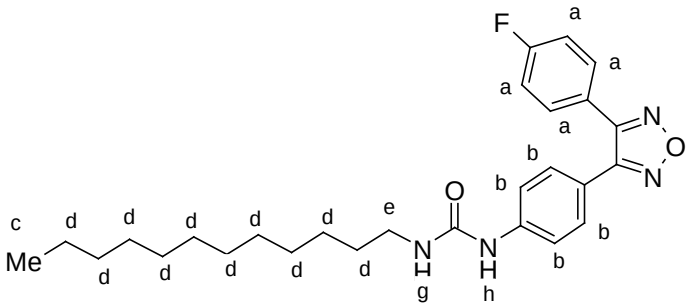


(21i)

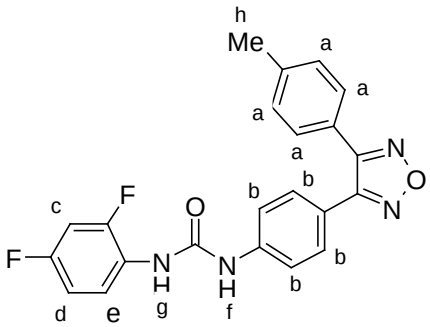
Compound **(21i)** showed the IR peaks at 3298 (NH str.) and 1637 cm^{-1} (C=O str.) and displayed the signals at δ 7.2-7.7 (*m*, 8H, Ar-C$H_{a,b}$), 0.9-1.01 (*t*, 3H, CH_{3c}), 1.37-1.45 (*m*, 10H, CH_{2d}), 3.37-3.45 (*m*, 2H, CH_{2e}), 5.91 (*s*, 1H, NH_g) and 8.41 (*s*, 1H, NH_h) in its NMR spectrum.

Compound **(21j)** displayed the peaks at 3336 (NH str) and 1636 cm^{-1} (C=O str) in its IR spectrum. The ^{1}H-NMR signals appeared at δ 7.2-7.4 (*m*, 8H, Ar C$H_{a,b}$), 0.9-1.02 (*t*, 3H, CH_{3c}), 1.3-3.5 (*m*, 20H, CH_{2d}), 8.5 (*s*, 1H, NH_g) and 7.8 (*s*, 1H, NH_h).

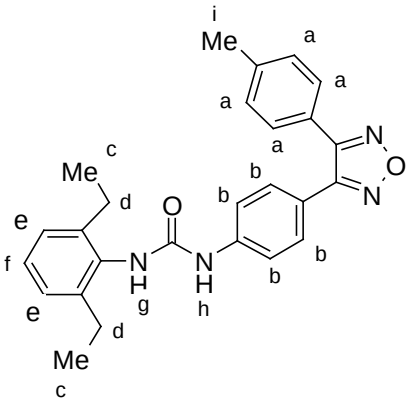
1-[(2,4-Difluorophenyl)-3-(*p*-tolyl-1,2,5-oxadiazol-3-yl)phenyl]urea **(21k)** was synthesized by reacting the amine **(20iii)** with 2,4-difluorophenyl isocyanate. It showed the



(21j)



(21k)



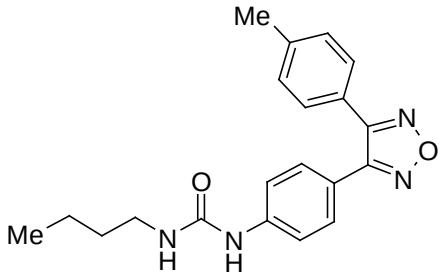
(21l)

characteristic IR peaks at 3446 (NH str) and 1650 cm^{-1} (C=O str) and displayed PMR signals at δ 6.8-8.2 (*m*, 10H, Ar C$H_{a,b,c,d,e}$), 8.4 (bs, 1H, NH_f), 9.3 (*s*, 1H, NH_g) and 2.3 (*s*, 3H, Ar-CH_{3h}).

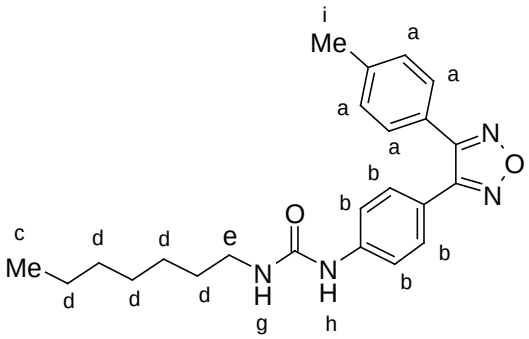
1-(2,6-Diethylphenyl)-3-[4-(*p*-tolyl-1,2,5-oxadiazol-3-yl)phenyl]urea **(21l)** showed the peaks at 3286 (NH str.) and 1639 cm^{-1} (C=O str) in its IR spectrum and displayed PMR signals at δ 7.01-7.51 (*m*, 8H, ArC$H_{a,b}$), 7.62-7.81 (*m*, 2H, ArCH_e), 7.82-7.91 (*m*, 1H, Ar CH_f), 2.61-2.67 (*q*, 4H, 2CH_{2d}), 1.2-1.4 (*t*, 6H, 2CH_{3c}) and 2.37 (*s*, 3H, Ar CH_{3i}).

Compound **(21m)** showed the peaks at 3298 (amide NH str.), 1637 (C=O str.) and 3121 cm^{-1} (Ar C-H str.) in its IR spectrum. Its ^{1}H-NMR spectrum displayed the signals at δ 7.2-7.7(*m*, 8H, Ar-C*H*), 5.91 (*s*, 1H, N*H*), 8.42 (*s*, 1H, N*H*), 0.9-1.06 (*t*, 3H, CH_3), 1.2-1.4 (*m*, 4H, CH_2),

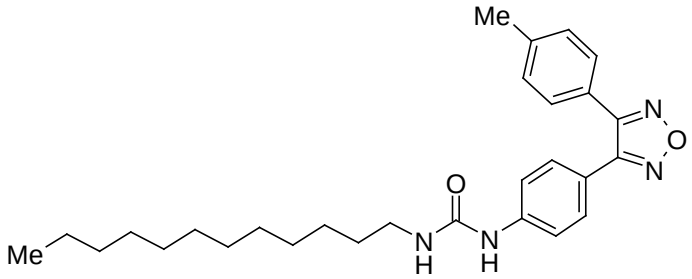
3.37-3.40 (*m*, 2H, CH_2) and 2.37 (*s*, 3H, Ar-CH_3). Its mass spectrum showed the molecular ion peak at m/z 350.4.



(21m)



(21n)



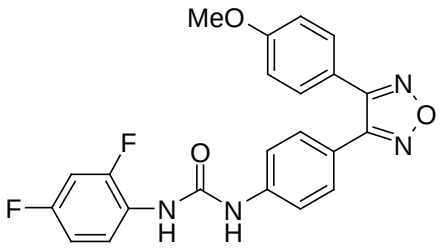
(21o)

1-Heptyl-3-[4-(*p*-tolyl-1,2,5-oxadiazol-3-yl)phenyl]urea **(21n)** showed the characteristic IR spectral peaks at 3321 (amide NH str) and 1650 cm^{-1} (C=O str). Its NMR spectral data showed the signals at δ 7.51-8.12 (*m*, 8H, ArC$H_{a,b}$), 3.31-3.51 (*m*, 2H, NCH_{2e}), 1.52-1.81 (*m*, 10H, CH_{2d}), 0.91-1.02 (*t*, 3H, CH_{3c}), 6.92 (*s*, 1H, NH_g), 5.25 (*s*, 1H, NH_h) and 2.37 (*s*, 3H, Ar-CH_{3i}).

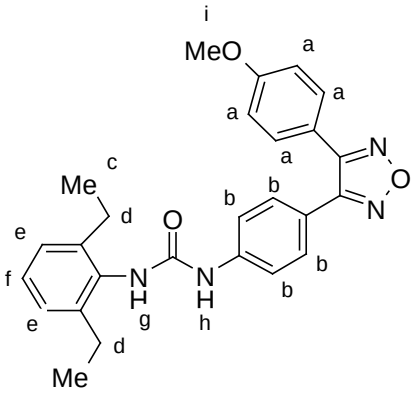
1-Dodecyl-3-[4-(*p*-tolyl-1,2,5-oxadiazol-3-yl)phenyl]urea **(21o)** showed the peaks at 3336 (NH str) and 1636 cm^{-1} (C=O str) in its IR spectrum. It displayed the signals at δ 7.2-7.4 (*m*, 8H, Ar C*H*), 0.9-1.05 (*t*, 3H, CH_3), 1.3-3.5 (*m*, 22H, CH_2), 8.51 (*s*, 1H, N*H*), 7.82 (*s*, 1H, N*H*) and 2.33 (*s*, 3H, Ar-CH_3).

1-(2,4-Difluorophenyl)-3-[4-(4-methoxyphenyl)-1,2,5-oxadiazol-3-yl]phenylurea **(21p)** was synthesized by reacting the amine **(20d)** with 2,4-difluorophenyl isocyanate. It showed the IR spectrum at 3401 (amide NH str), 1654 (C=O str), 3124 (Ar C-H) and 1220 cm^{-1} (Ar OCH_3) and gave the PMR signals at δ 6.8-8.2 (m, 11H, Ar C*H*), 8.4 (s, 1H, N*H*), 9.3 (s, 1H, N*H*) and 4.0 (s, 3H, Ar-OCH_3).

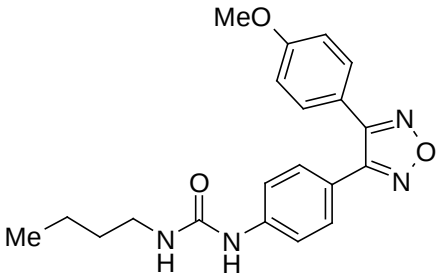
Compound **(21q)** showed the peaks at 3298 (NH str.), 1637 (C=O) and 1220 cm^{-1} (Ar-OCH_3 str) in its IR spectrum. It displayed the ^{1}H-NMR signals at δ 7.01-7.51 (*m*, 8H, Ar C$H_{a,b}$), 7.62-7.81 (*d*, 2H, Ar CH_e), 7.82-7.91 (*m*, 1H, Ar CH_f), 2.61 (*q*, 4H, 2CH_{2d}), 1.2-1.4 (*t*, 6H, 2CH_{3c}) and 4.0 (*s*, 3H, OCH_{3h}).



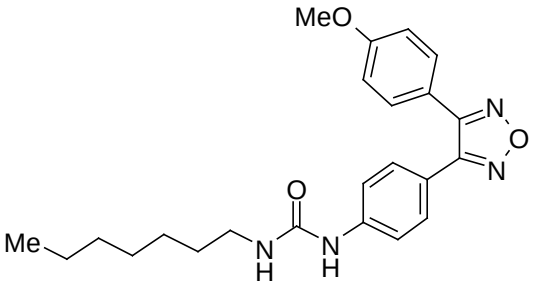
(21p)



(21q)



(21r)



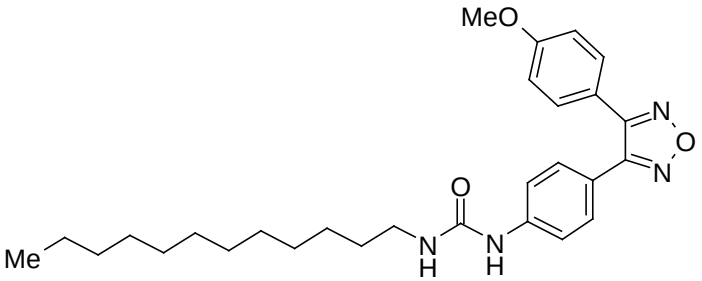
(21s)

1-Butyl-3-[4-(4-(4-methoxyphenyl)-1,2,5-oxadiazol-3-yl)phenyl]urea **(21r)** gave the IR peaks at 3321 (NH str), 1650 (C=O str) and 1222 cm^{-1}(Ar-OCH_3 str). It displayed the ^{1}H-NMR signals at δ 7.2-7.7(*m*, 8H, Ar C-*H*), 5.91 (*s*, 1H, N*H*), 8.45 (*s*, 1H, N*H*), 0.9-1.05 (*t*, 3H, CH_3), 1.2-1.4 (*m*, 4H, CH_2), 3.37-3.40 (*m*, 2H, CH_2) and 4.05 (*s*, 3H, Ar-OCH_3).

Compound **(21s)** showed the IR peaks at 3446 (NH str), 1650 (C=O str) and 1225 cm^{-1} (Ar-OCH_3 str.) and signals at δ 7.5-8.1 (*m*, 8H, Ar C*H*), 3.3 (*m*, 2H, N- CH_2), 1.5-1.8 (*m*, 10H, CH_2), 0.9-1.02 (*t*, 3H, CH_3), 6.9 (*s*, 1H, N*H*), 5.2 (*s*, 1H, N*H*) and 4.2 (*s*, 3H, Ar-OCH_3) in its ^{1}H-NMR spectrum.

Compound **(21t)** displayed the characteristic IR peaks at 3336 (amide NH str), 1636 (C=O str) and 1220 cm^{-1} (Ar OCH_3 str.). It gave signals at δ 7.2-7.4 (*m*, 8H, aromatic C*H*), 0.9-

1.08 (*t*, 3H, C*H*$_3$), 1.3-3.5 (*m*, 20H, C*H*$_2$), 8.5 (*s*, 1H, N*H*), 7.8 (*s*, 1H, N*H*) and 4.0 (*s*, 3H, Ar-OC*H*$_3$).



(21t)

4.2 Biological studies

The biological studies were carried out in the pharmacology division of this department. All the compounds were evaluated for their inhibitoty potency towards the ACAT enzymes. Screening of test compounds was performed as per the method of Largis et al[141,142] with some modifications. Data of the compounds screened for these activities is given in table 3:

Table 3: *In vitro* ACAT enzyme inhibitory activity of selected compounds

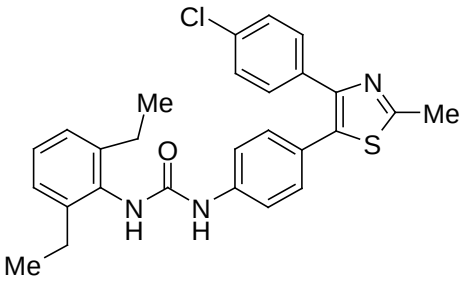
Compound Code	Percentage inhibition (at 10 µM conc)	Compound Code	Percentage inhibition (at 10 µM conc)
11a	42.39*	**13n**	1.77
11b	20.43	**13o**	38.98
11c	12.46	**13p**	48.98*
11d	31.86	**13q**	27.95
11e	1.25	**13r**	9.28
11f	16.58	**13s**	39.45
11g	36.37	**13t**	5.45
11h	13.72	**16a**	6.88
11i	56.86*	**16b**	1.30
11j	1.67	**16c**	63.32*
11k	27.58	**16d**	60.71*
11l	35.66	**16e**	52.18*
13a	2.03	**16f**	5.75

13b	6.39	**16g**	16.81
13c	3.75	**16h**	4.97
13d	5.63	**16i**	46.68*
13e	23.32	**16j**	59.91*
13f	18.90	**16k**	62.96*
13g	15.40	**16l**	34.47
13h	0.43	**16m**	0.00
13i	3.06	**16n**	0.00
13j	2.17	**16o**	30.94
13k	5.23	**16p**	64.91*
13l	32.67	**16q**	33.41
13m	51.73*	**16r**	46.19*
16s	11.37	**21i**	30.93
16t	22.27	**21j**	50.7*
16u	31.62	**21k**	13.52
16v	0.00	**21l**	0.34
16w	22.21	**21m**	2.83
16x	0.00	**21n**	18.65
21a	21.23	**21o**	9.15
21b	8.25	**21p**	10.3
21c	23.03	**21q**	2.51
21d	4.3	**21r**	10.04
21e	18.51	**21s**	8.53
21f	47.06*	**21t**	5.42
21g	44.85*	**Avasimibe (std)**	73.63*
21h	54.5*		

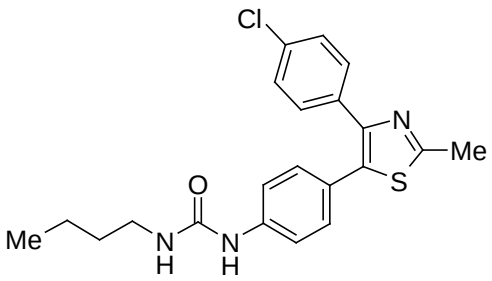
* Indicates the compounds showing more than 40% inhibition in the *in vitro* study.

4-Thiazolylphenylurea derivatives with 2,6-diethylphenyl (**16c**, **16i**), *n*-butyl (**16d**, **16j**, **16p**) and *n*-heptyl (**16e**, **16k**) side chain exhibited good ACAT inhibitory activity (more than 60%

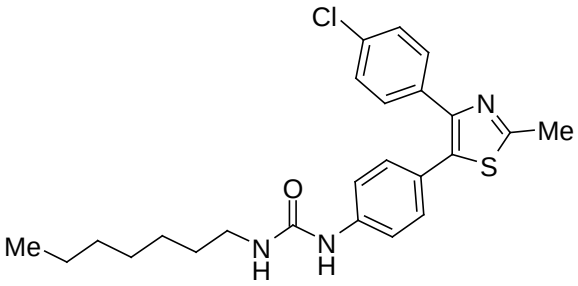
inhibition at 10 µM conc) in comparison to standard drug Avasimibe (73.63% at 10 µM conc). This was expected of them due to their moderate non-polar nature.



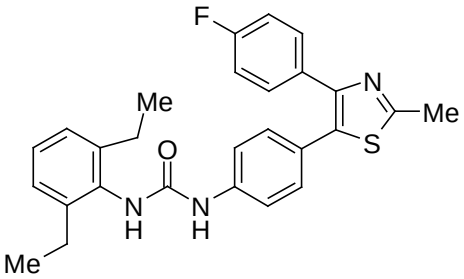
(16c, 63.32 %**)**



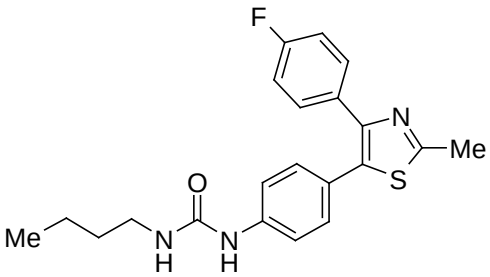
(16d, 60.71%**)**



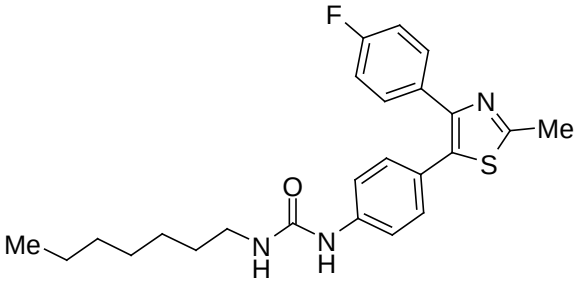
(16e, 52.18 %**)**



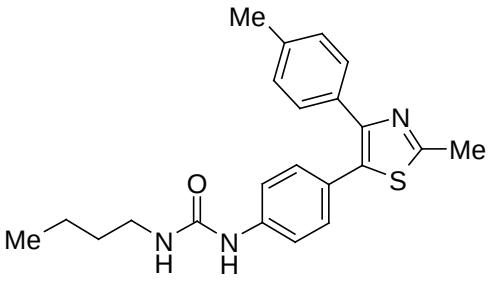
(16i, 46.68 %**)**



(16j, 59.91%**)**



(16k, 62.96 %**)**



(16p, 64.91%**)**

2-Thiazolylurea derivatives (**11a**, **11i** and **13m**) and 4-furazanylphenylurea derivatives (**21f**, **21g** and **21h**) showed moderate inhibition (more than 45% inhibition at 10 µM conc) in comparison to the standard drug Avasimibe.

From the *in vitro* biological data of all synthesized compounds it can be concluded that the 4-thiazolylphenylurea **(16a-16x)** moiety showed better degree of ACAT inhibition rather than the 2-thiazolylurea **(13a-13t)** and 4-furazanylphenylurea **(21a-21t)** derivatives. The compounds (**16c, 16i)** having bulky group (diethyl) at both the ortho position of the phenyl ring on urea nitrogen showed excellent inhibition. Compounds having moderate length of the alkyl chain (*n*-butyl, *n*-heptyl) on urea nitrogen **(16d, 16e, 16j, 16k and 16p)** showed better activity rather than very long chain (*n*-dodecyl). *p*-Chloro and *p*-fluoro substituted aryl ring of the diaryl heterocyclic scaffold showed better activity than the *p*-methyl and *p*-methoxy substituted aryl ring. 2-Thiazolylurea derivatives **(11a, 11i)** having 2,4-difluoro substituted aryl ring on urea nitrogen exhibited good inhibition than the other synthesized derivatives. Incorporation of any acetamido, sulphonamido, isopropryl or n-dodecyl group in one of the aryl ring of 2-thiazolylurea derivatives **(13a-13t)** did not improve any extent of activity.

5. Experimental

All the reagents and solvents required for syntheses were purified by general laboratory techniques before use. Compounds were purified by passing them through silica gel H purifying column using mixture of ethyl acetate and *n*-hexane as eluent. Melting points were determined using a Veego make silicon oil bath-type melting point apparatus and are uncorrected. Purity of the compounds and completion of reactions were monitored by thin layer chromatography (TLC) on silica gel GF plates, visualizing with ultraviolet light or iodine vapors. The yields reported here are un-optimized. The IR spectra were recorded using KBr disc method on a Bruker FT-IR spectrophotometer. The H-NMR spectra were recorded in either $CDCl_3$ or DMSO-d_6. Microwave reactions were performed in CEM-Discovery, USA microwave reactor. Anhydrous sodium sulphate was used for drying of solutions. All proton magnetic resonance (PMR) values were considered on the basis of chemical shift (δ) values.

5.1. Synthesis of 4-chlorophenylacetic acid (3)

To a solution of 4-chloroacetophenone **(1)** (20 mL, 0.15 mol) in morpholine (18 mL, 0.2 mol) was added precipitated sulphur (8.0 g, 0.25 mol) and the reaction mixture was refluxed for 18 hr. To this hot solution, warm methanol (10 mL) was added and the mixture was refrigerated for 3 hr to obtain a yellow crystalline thiomorpholide **(2)**. It was filtered and washed with cold methanol. The thiomorpholide (22 g) was taken in a 250 mL round-bottomed flask and aqueous sodium hydroxide (150 mL, 20%) was added to it. The reaction mixture was refluxed for 18 hr and poured onto crushed ice (1 kg). The resulting suspension was extracted thrice with small portions of chloroform (3 x 15 mL) and the organic layer was rejected. The aqueous layer was acidified with conc. HCl to get off-white colored precipitate of 4-chlorophenylacetic acid. Recrystallisation from methanol afforded the pure acid **(3)**, (17.0 g, 76.5%), **m.p.** 90-92°C. Lit[136] 90-91°C.

Anal:

TLC : R_f 0.5 ($CHCl_3$: MeOH) (9.5 : 0.5)

IR (KBr, cm^{-1}) : 3325, 1705, 1517, 1409, 1240 and 1170

5.2. Synthesis of 4-nitrophenylacetic acid (6)

Concentrated nitric acid (20 mL) and an equal volume of concentrated sulphuric acid were placed in a two-necked flask fitted with a thermometer and a dropping funnel. The mixture was

cooled to 10^0C with stirring in ice-bath and benzyl cyanide **(4)** (15 mL, 0.126 mol) was run into it at such a rate (about 30 min) that the temperature remained at about 10^0C and did not rise above 20^0C. The solution was further stirred for 1 hr at room temperature and then poured onto crushed ice. A pasty mass that slowly separated contained 4-nitrobenzyl cyanide **(5)** and the oily 2-nitrobenzyl cyanide. Recrystallisation from methanol afforded white needles of compound **(5)**, (10.15 g, 50%), **m.p.** 105-106°C (Lit[137]105-106°C)

A dilute solution of sulphuric acid was prepared by adding concentrated sulphuric acid (25 mL) cautiously to water (25 mL). Two thirds of the sulphuric acid was added into an RBF containing 4-nitrobenzyl cyanide **(5)** (7.45 g, 0.046 mol) and the nitrile adhering to the walls of the flask was washed down with the remaining quantity of sulphuric acid. The mixture was boiled under reflux for 15 min and then diluted with an equal volume of ice-cold water (50 mL). The resulting yellow solid mass was filtered, washed, decolorized and recrystallised from water to yield the acid **(6)**, (8.0 g, 96%), **m.p.** 154-155°C (Lit[137]151-152°C)

Anal:

TLC : R_f 0.5 (Benzene : Chloroform (1 : 1) + 2 drops of AcOH)

IR (KBr, cm^{-1}): 1705, 1523, 1336, 1252 and 709.

5.3. 2-(4-Chlorophenyl)-1-(4-fluorophenyl)ethanone (8a)

A mixture of 4-chlorophenylacetic acid **(3)** (10 g, 48.54 mmol) and thionyl chloride (4 mL, 33.61 mmol) was refluxed in a RBF for 1.5 hrs under anhydrous conditions. Excess of thionyl chloride was removed under vaccum. The resulting solution so obtained was added dropwise into a stirred solution of anhydrous aluminum chloride (7.5 g, 56.39 mmol) and fluorobenzene (5.2 mL, 54.104 mmol) in dry dichloromethane (DCM) (100 mL) at a temperature below 20^0C over a period of 30 min under anhydrous conditions and the reaction mixture was stirred continuously for further 4 hr at room temperature. The reaction was monitored by TLC. The resulting reaction mixture was quenched in a mixture of ice-cold water (500 g) containing concentrated hydrochloric acid (75 mL). The resulting solution was extracted with chloroform (3x50 mL), the combined chloroform layer was washed with sodium bicarbonate solution (5%, 3x50 mL) followed by water (2x50 mL). The chloroform layer was dried and recovered. The crude product so obtained was crystallized from methanol to yield the title compound **(8a)**, (5.4 g, 37%), **m.p.** 115-118°C.(Lit[138]116-118°C)

Anal:

TLC : R_f 0.73 (*n*-Hexane: Ethyl acetate) (8:2)

IR (KBr, cm^{-1}) : 3111, 1681, 1594, 1498, 1218 and 849

5.4. 2-(4-Chlorophenyl)-1-(4-methylphenyl)ethanone (8b)

The title compound **(8b)** was synthesized as per the method described for compound **(8a)** by replacing fluorobenzene with toluene (5.5 mL, 59.78 mmol). The crude product so obtained was crystallized from methanol to afford the desired compound **(8b)**, (8.1 g, 88.18%), **m.p.** 108-110°C. (Lit[138]106-108°C)

Anal:

TLC : R_f 0.75 (*n*-Hexane: Ethyl acetate) (8:2)

IR (KBr, cm^{-1}) : 3119, 1681, 1598, 1408, 1219 and 851

5.5. 2-(4-Chlorophenyl)-1-(4-methoxyphenyl)ethanone (8c)

The title compound **(8c)** was synthesized as per the method described for compound **(8a)** by replacing fluorobenzene with anisole (5.4 mL, 50.08 mmol). The crude product so obtained was crystallized from methanol to afford the desired compound **(8c)**, (10.1 g, 83.82%), **m.p.** 128-130°C. (Lit[138]126-128°C)

Anal:

TLC : R_f 0.73 (*n*-Hexane: Ethyl acetate) (8:2)

IR (KBr, cm^{-1}) : 3112, 1676, 1601, 1414, 1220 and 845

5.6. 1-(4-Chlorophenyl)-2-(4-nitrophenyl)ethanone (8d)

A mixture of *p*-nitrophenylacetic acid (10 g, 64.50 mmol) and phosphorous trichloride (10 mL, 55.30 mmol) was refluxed in a round bottom flask (100 mL) for 1.5 hrs under anhydrous conditions. Excess of phosphorous trichloride was removed under vaccum. The resulting liquid so obtained was added drop-wise into a stirred solution of anhydrous aluminium chloride (7.55 g, 56.65 mmol) and chlorobenzene (6.1 mL, 55.45 mmol) in dry dichloromethane (DCM) (100 mL) at a temperature below 20°C over a period of 30 min under anhydrous conditions and stirred continuously for further 4 hr at room temperature. The reaction mixture was processed as described for compound **(8a)**. The crude product so obtained was crystallized from methanol to afford the desired compound **(8d)**, (12.2 g, 55 %), **m.p.** 105-107°C.

Anal:

TLC : R_f 0.80 (*n*-Hexane: Ethyl acetate) (8:2)

IR (KBr, cm^{-1}) :1687, 1590, 1508, 1339, 1093 and 843.

5.7. 1-(4-Fluorophenyl)-2-(4-nitrophenyl)ethanone (8e)

The title compound **(8e)** was synthesized as per the method described for compound **(8d)** by replacing chlorobenzene with fluorobenzene (5.4 mL, 57.708 mmol). The crude product so obtained was recrystallised from methanol to yield crystalline compound **(8e)**, (5.7 g, 68.94%), **m.p.** 107-109°C.

Anal:

TLC : R_f 0.80 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}) : 1686, 1597, 1505, 1342, 1250, 997 and 826.

5.8. 2-(4-Nitrophenyl)-1-(*p*-tolyl)ethanone (8f)

The title compound **(8f)** was synthesized as per the method described for compound **(8d)** by replacing chlorobenzene with toluene (5.2 mL, 56.52 mmol). The crude product thus obtained was crystallised from methanol to yield crystalline compound **(8f)**, (5.8 g, 74.04%), **m.p.** 125-127°C.

Anal:

TLC : R_f 0.78 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}) : 1679, 1603, 1514, 1346, 1107 and 857.

5.9. 1-(4-Methoxyphenyl)-2-(4-nitrophenyl)ethanone (8g)

The title compound **(8g)** was synthesized as per the method described for compound **(8d)** by replacing chlorobenzene with anisole (5.5 mL, 50.92 mmol). The crude product was crystallised from methanol to yield crystalline compound **(8g)**, (10.5 g, 84.94 %), **m.p.** 123-125 °C.

Anal:

TLC : R_f 0.78 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}) : 1665, 1598, 1516, 1350, 1277, 1169, 1027 and 835.

5.10. 2-Bromo-2-(4-chlorophenyl)-1-(4-fluorophenyl)ethanone (9a)

2-(4-Chlorophenyl)-1-(4-fluorophenyl)ethanone **(8a) (**2.5 g, 10.08 mmol) was taken in a 100mL RBF and dissolved in sufficient quantity of glacial acetic acid (10 mL) by warming.

Bromine (5 mL) was added drop-wise into the stirred solution and the reaction was monitored by TLC until completion. The reaction mixture was poured into the ice cold water (200 mL) containing sodium metabisulphite to neutralize the excess bromine. The white precipitate so obtained was extracted with chloroform (3x20 mL) and the separated chloroform layer was dried, the solvent was distilled off and the resulting residue was crystallised in methanol to yield pure compound **(9a)**, (2.5 g, 70%), **m.p.** 40-42°C.

Anal:

TLC : R_f 0.71 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}) : 3002, 1676, 1599, 1450, 1277, 1008 and 835.

5.11. 2-Bromo-2-(4-chlorophenyl)-1-(4-methylphenyl)ethanone (9b)

The title compound **(9b)** was synthesized as per the method described for compound **(9a)** taking compound 2-(4-chlorophenyl)-1-(4-methylphenyl)ethanone **(8b)** (2.5 g, 10.24 mmol) as the starting material. The product so obtained was crystallized from methanol to afford the desired compound **(9b)**, (2.5 g, 71.72 %), **m.p.** 71-73°C.

Anal:

TLC : R_f 0.70 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}) : 3010, 1679, 1601, 1457, 1285, 1017 and 853.

5.12. 2-Bromo-2-(4-chlorophenyl)-1-(4-methoxyphenyl)ethanone (9c)

The title compound **(9c)** was synthesized as per the method described for compound **(9a)** taking compound 2-(4-chlorophenyl)-1-(4-methoxyphenyl)ethanone **(8c) (**2.5 g, 9.619 mmol) as the starting material. The product so obtained was crystallized from methanol to afford the desired compound **(9c)**, (2.6 g, 95.38 %), **m.p.** 97-100°C.

Anal:

TLC : R_f 0.77 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}) : 3015, 1679, 1604, 1457, 1290, 1021 and 845.

5.13. 2-Bromo-1-(4-chlorophenyl)-2-(4-nitrophenyl)ethanone (9d)

The title compound **(9d)** was synthesized as per the method described for compound **(9a)** taking compound 1-(4-chlorophenyl)-2-(4-nitrophenyl)ethanone **(8d)** (2.5 g, 9.09 mmol) as the starting material. The product was crystallized from methanol to obtain the desired compound **(9d)**, (2.6 g, 93.75%), **m.p.** 95-97°C.

Anal:

TLC : R_f 0.82 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}) : 3112, 1675, 1597, 1456, 1279, 1021 and 840.

5.14. 2-Bromo-1-(4-fluorophenyl)-2-(4-nitrophenyl)ethanone (9e)

The title compound **(9e)** was synthesized as per the method described for compound **(9a)** starting with 1-(4-fluorophenyl)-2-(4-nitrophenyl)ethanone **(8e)** (2.5 g, 9.65 mmol) as the starting material. The crude product so obtained was crystallised from methanol to obtain the desired compound **(9e)**, (2.4 g, 70%), **m.p.** 40-42°C.

Anal:

TLC : R_f 0.71 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}) : 3121, 1679, 1587, 1456, 1280, 1043 and 840.

5.15. 2-Bromo-2-(4-nitrophenyl)-1-(*p*-tolyl)ethanone (9f)

The title compound **(9f)** was synthesized as per the method described for compound **(9a)** starting with compound 2-(4-nitrophenyl)-1-(*p*-tolyl)ethanone **(8f) (**2.5 g, 9.09 mmol). The crude product so obtained was crystallized from methanol to obtain the desired compound **(9f)**, (2.6 g, 91 %), **m.p.** 110-112°C.

Anal:

TLC : R_f 0.82 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}) : 3111, 1678, 1598, 1452, 1278, 1021 and 835.

5.16. 2-Bromo-1-(4-methoxyphenyl)-2-(4-nitrophenyl)ethanone (9g)

The title compound **(9g)** was synthesized as per the method described for compound **(9a)** starting with compound 1-(4-methoxyphenyl)-2-(4-nitrophenyl)ethanone **(8g) (**2.5 g, 8.71 mmol). The crude product so obtained was crystallised from methanol to obtain the desired compound **(9g)**, (2.6 g, 91 %), **m.p.** 93-94°C.

Anal:

TLC : R_f 0.81 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}) : 3112, 1675, 1597, 1456, 1279, 1021 and 840

5.17. 5-(4-Chlorophenyl)-4-(4-fluorophenyl)thiazol-2-ylamine (10a)

2-Bromo-2-(4-chlorophenyl)-1-(4-fluorophenyl)ethanone **(9a)** (2.0 g, 6.104 mmol) was dissolved in sufficient quantity of methanol in a 100 mL round bottom flask. Thiourea (0.6 g, 7.32 mmol) and 3-4 drops of water were added into the reaction mixture and refluxed for 4-6 hrs. The reaction was monitored by TLC. After completion of the reaction, it was poured onto ice-cold water and the resulting solution was basified with ammonia. The product so precipitated was filtered, dried and crystallized in methanol to obtain the title compound **(10a)**, (1.3 g, 54 %), **m.p.** 71-72°C.

Anal:

TLC : R_f 0.31 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}) : 3481, 3103, 1634, 1527, 1330, 1217, 1086 and 832

MS : m/z 303.98 (M^+)

5.18. 5-(4-Chlorophenyl)-4-(4-methylphenyl)thiazol-2-ylamine (10b)

The title compound **(10b)** was synthesized as per the method described for compound **(10a)** taking 2-bromo-2-(4-chlorophenyl)-1-(4-methylphenyl)ethanone **(9b) (**2.0 g, 6.18 mmol) as the starting material. The crude product was crystallized from methanol to afford the desired compound **(10b)**, (1.4 g, 69.56 %), **m.p.** 71-72°C.

Anal:

TLC : R_f 0.41 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}): 3450, 1633, 1531, 1331, 1084 and 822

MS : m/z 299.98 (M^+)

5.19. 5-(4-Chlorophenyl)-4-(4-methoxyphenyl)thiazol-2-ylamine (10c)

The title compound **(10c)** was synthesized as per the method described for compound **(10a)** taking 2-bromo-2-(4-chlorophenyl)-1-(4-methoxyphenyl)ethanone **(9c)** (2.0 g, 5.88 mmol) as the starting material. The crude product was crystallized from methanol to afford the desired compound **(10c)**, (1.94 g, 86.95 %), **m.p.** 193-195°C.

Anal:

TLC : R_f 0.32 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}) : 3479, 3105, 1639, 1530, 1337, 1219, 1086 and 835

MS : m/z 316.02 (M^+)

5.20. 4-(4-Chlorophenyl)-5-(4-nitrophenyl)thiazol-2-ylamine (10d)

The title compound **(10d)** was synthesized as per the method described for compound **(10a)** taking 2-bromo-1-(4-chlorophenyl)-2-(4-nitrophenyl)ethanone **(9d)** (2.0 g, 5.64 mmol) as the starting material. The crude product was crystallized from methanol to afford the desired compound **(10d)**, (1.7 g, 89.93 %), **m.p.** 225-227°C.

Anal:

TLC : R_f 0.14 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}) : 3437, 3129, 1633, 1402 and 845

5.21. 4-(4-Fluorophenyl)-5-(4-nitrophenyl)thiazol-2-ylamine (10e)

The title compound **(10e)** was synthesized as per the method described for compound **(10a)** taking 2-bromo-1-(4-fluorophenyl)-2-(4-nitrophenyl)ethanone **(9e)** (2.0 g, 5.46 mmol) as the starting material. The crude product was crystallized from methanol to afford the desired compound **(10e)**, (3.5 g, 90 %), **m.p.** 242-243°C.

Anal:

TLC : R_f 0.42 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}) : 3481, 3275, 1635, 1589, 1521 and 1339

5.22. 5-(4-Nitrophenyl)-4-(*p*-tolyl)thiazol-2-ylamine (10f)

The title compound **(10f)** was synthesized as per the method described for compound **(10a)** taking 2-bromo-2-(4-nitrophenyl)-1-(*p*-tolyl)ethanone **(9f)** (2.0 g, 5.98 mmol) as the starting material. The product was crystallized from methanol to afford the desired compound **(10f)**, (1.33 g, 70.96%), **m.p.** 215-216°C.

Anal:

TLC : R_f 0.31 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}) : 3420, 3120, 1635, 1402 and 847

5.23. 4-(4-Methoxyphenyl)-5-(4-nitrophenyl)thiazol-2-ylamine (10g)

The title compound **(10g)** was synthesized as per the method described for compound **(10a)** taking 2-bromo-1-(4-methoxyphenyl)-2-(4-nitrophenyl)ethanone **(9g) (**2.0 g, 5.71 mmol) as

the starting material. The product was crystallized from methanol to afford the desired compound **(10g)**, (1 g, 53.53%), **m.p.** 232-234°C.

Anal:

TLC : R_f 0.07 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}) : 3452, 3103, 1633, 1403 and 843

5.24. 1-(5-(4-Chlorophenyl)-4-(4-fluorophenylthiazol-2-yl)-3-(2,4-difluorophenyl)urea (11a)

5-(4-Chlorophenyl)-4-(4-fluorophenyl)thiazol-2-ylamine **(10a)** (0.25 g, 0.82 mmol) was dissolved in sufficient quantity of dry toluene (30 mL) in a 100 mL RBF. 2,4-Difluorophenyl isocyanate (0.25 mL, 1.60 mmol) was added to the reaction mixture and the reaction mixture was further stirred at room temperature and monitored by TLC. The solid precipitate so obtained was filtered, dried and collected as the product **(11a),** (0.13 g, 36%), **m.p.** 207-209°C.

Anal:

TLC : R_f 0.51 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}) : 3416, 3118, 1720, 1610, 1430 and 829

PMR : 10.43 (bs, 1H), 8.92 (bs, 1H), 8.08-8.15 (m, 1H), 7.37-7.42 (m, 2H), 7.18-7.28 (d, 4H), 6.87-6.98 (m, 3H) and 6.82-6.88 (m, 1H).

MS : m/z 303.98, 458.9 (M^+)

5.25. 1-Butyl-3-(5-(4-chlorophenyl)-4-(4-fluorophenylthiazol-2-yl)urea (11b)

The title compound **(11b)** was synthesized as per the method described for compound **(11a)** taking 5-(4-chlorophenyl)-4-(4-fluorophenyl)thiazol-2ylamine **(10a)** (0.25 g, 0.82 mmol) and *n*-butyl isocyanate (0.25 mL, 2.17 mmol) as the starting materials. The crude product so obtained was purified through column chromatography to afford the desired product **(11b)**, (0.61 g, 45.86 %), **m.p.** 92-95°C.

Anal:

TLC : R_f 0.35 (*n*-Hexane: Ethyl acetate) (8: 2)

UV_{max} (MeOH) : 237 nm

IR (KBr, cm^{-1}) : 3490, 1691, 1561, 1402 and 826

PMR : 10.45 (bs, 1H), 8.95 (bs, 1H), 7.18- 7.28 (d, 4H), 7.37-7.42 (m, 2H), 6.87- 6.98 (m, 2H), 1.64-1.7 (m, 2H), 1.11-1.23 (m, 4H) and 0.91-0.95 (t, 3H).

MS : m/z 303.97, 403.15 (M^+)

5.26. 1-(5-(4-Chlorophenyl)-4-(4-fluorophenylthiazol-2-yl)-3-(2,6-diethylphenyl)urea (11c)

The title compound **(11c)** was synthesized as per the method described for compound **(11a)** taking 5-(4-chlorophenyl)-4-(4-fluorophenyl)thiazol-2-ylamine **(10a) (**0.25 g, 0.82 mmol) and 2,6-diethylphenyl isocyanate (0.38 mL, 1.785 mmol) as the starting materials. The crude product so obtained was purified through column chromatograpy to afford the pure compound **(11c)**, (0.125 g, 36.25%), **m.p.** 210-212°C.

Anal:

TLC : R_f 0.38 (*n*-Hexane: Ethyl acetate) (8: 2)

UV $_{max}$(MeOH) : 237.4 nm

IR (KBr, cm $^{-1}$) : 3403, 1688, 1510, 1402 and 826

PMR : 7.11-7.5 (m, 11H), 5.5 (bs, 1H), 2.32-2.51 (q, 4H) and 1.21-1.31 (t, 6H)

MS : m/z 303.97 (M^+)

5.27. 1-[5-(4-Chlorophenyl)-4-(4-fluorophenyl)thiazol-2-yl]-3-dodecylurea (11d)

The title compound **(11d)** was synthesized as per the method described for compound **(11a)** taking 5-(4-chlorophenyl)-4-(4-fluorophenyl)thiazol-2-ylamine **(10a) (**0.25 g, 0.82 mmol) and *n*-dodecyl isocyanate (0.3 mL, 1.77 mmol) as the starting materials. The crude product so obtained was crystallized from methanol to afford the desired compound **(11d)**, (0.15 g, 36.25%), **m.p.** 136-138°C.

Anal:

TLC : R_f 0.64 (*n*-Hexane: Ethyl acetate) (8: 2)

UV_{max}(MeOH) : 239 nm

IR (KBr, cm^{-1}) : 3344, 1688, 1637, 1504, 1327, 1156 and 821

PMR : 10.45 (bs, 1H), 7.2-7.3 (m, 2H), 7.11-7.21 (m, 6H), 4.5 (bs, 1H), 2.9-3.2 (q, 2H), 1.32-1.51(m, 20H), and 0.91-0.93 (t, 3H)

MS : m/z 303.97, 515.27 (M^+)

5.28. 1-[5-(4-Chlorophenyl)-4-(*p*-tolyl)thiazol-2-yl]-3-phenylurea (11e)

The title compound **(11e)** was synthesized as per the method described for compound **(11a)** taking 5-(4-chlorophenyl)-4-(*p*-tolyl)thiazol-2-ylamine **(10b)** (0.25 g, 0.831 mmol) and phenyl isocyanate (0.25 mL, 2.1 mmol) as the starting materials. The product was crystallized from methanol to obtain pure compound **(11e)**, (0.14 g, 41.72%), **m.p.** 228-229°C.

Anal:

TLC : R_f 0.6 (*n*-Hexane: Ethyl acetate) (8: 2)

UV_{max} (MeOH) : 267 nm

IR (KBr, cm^{-1}) : 3403, 1688, 1609, 1449, 1275 and 820

PMR : 10.43 (bs, 1H), 8.92 (bs, 1H), 7.37-7.42 (d, 2H), 7.18- 7.28 (m, 11H) and 2.02(s, 3H)

5.29. 1-[5-(4-Chlorophenyl)-4-(*p*-tolyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea (11f)

The title compound **(11f)** was synthesized as per the method described for compound **(11a)** taking 5-(4-chlorophenyl)-4-(*p*-tolyl)thiazol-2-ylamine **(10b)** (0.25 g, 0.831 mmol) and 2,4-difluorophenyl isocyanate (0.25 mL, 1.603 mmol) as the starting materials. The product was crystallized from methanol to obtain pure compound **(11f)**, (0.13 g, 33.5%), **m.p.** 223-226°C.

Anal:

TLC : R_f 0.8 (*n*-Hexane: Ethyl acetate) (8: 2)

UV_{max} (MeOH) : 244 nm

IR (KBr, cm^{-1}) : 3209, 1689, 1610, 1506 and 733

PMR : 8.7 (bs, 1H), 8.2- 8.3 (m, 1H), 7.0-7.21 (m, 8H), 6.81-6.92 (d, 2H) and 2.31 (s, 3H).

5.30. 1-Butyl-3-[5-(4-chlorophenyl)-4-(*p*-tolyl)thiazol-2-yl]urea (11g)

The title compound **(11g)** was synthesized as per the method described for compound **(11a)** taking 5-(4-chlorophenyl)-4-(*p*-tolyl)thiazol-2-ylamine **(10b)** (0.25 g, 0.831 mmol) and *n*-butyl isocyanate (0.13 mL, 0.099 mmol) as the starting materials. The crude product was crystallized from methanol to obtain the pure compound **(11g),** (0.1 g, 30.07 %), **m.p.** 181-183°C.

Anal:

TLC : R_f 0.69 (*n*-Hexane: Ethyl acetate) (8: 2)

UV_{max} (MeOH) : 242 nm

IR (KBr, cm^{-1}) : 3410, 1698, 1534 and 822

PMR : 11.01 (bs, 1H), 7.11-7.41 (m, 8H), 2.92-2.98 (m, 2H), 2.52 (s, 3H), 1.62-1.64 (m, 2H) and 0.92-0.96 (t, 3H)

5.31. 1-[5-(4-Chlorophenyl)-4-(*p*-tolyl)thiazol-2-yl]-3-(2,6-diethylphenyl)urea (11h)

The title compound **(11h)** was synthesized as per the method described for compound **(11a)** taking 5-(4-chlorophenyl)-4-(*p*-tolyl)thiazol-2-ylamine **(10b)** (0.25 g, 0.832 mmol) and 2,6-diethylphenyl isocyanate (0.25 mL, 1.428 mmol) as the starting materials. The product so obtained was purified through column chromatography to obtain the pure compound **(11h)**, (0.17 g, 42.76 %), **m.p**. 252-255°C.

Anal:

TLC : R_f 0.72 (*n*-Hexane: Ethyl acetate) (8: 2)

UV_{max} (MeOH) : 241 nm

IR (KBr, cm^{-1}) : 3409, 1690, 1592, 1430 and 852

PMR : 7.11-7.21 (m, 8H), 7.0-7.1 (m, 3H), 2.32- 2.51 (q, 4H), 2.12 (s, 3H) and 0.91-0.93 (t, 6H).

5.32. 1-(5-(4-Chlorophenyl)-4-(4-methoxyphenyl)thiazol-2-yl)-3-phenylurea (11i)

The title compound **(11i)** was synthesized as per the method described for compound **(11a)** taking 5-(4-chlorophenyl)-4-(4-methoxyphenyl)thiazol-2-ylamine **(10c) (**0.25 g, 0.78 mmol) and phenyl isocyanate (0.25 mL, 2.52 mmol) as the starting materials. The work up of reaction mixture afforded the desired compound **(11i)**, (0.18 g, 53.28%), **m.p.** 216-219°C.

Anal:

TLC : R_f 0.5 (*n*-Hexane: Ethyl acetate) (8: 2)

UV_{max} (MeOH) : 256 nm

IR (KBr, cm^{-1}) : 3377, 1692, 1510, 1301, 1248 and 825

PMR : 6.82-7.63 (m, 13H) and 3.62 (s, 3H)

MS : m/z 316.08, 436.34 (M^+)

5.33. 1-[5-(4-Chlorophenyl)-4-(4-methoxyphenyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea (11j)

The title compound **(11j)** was synthesized as per the method described for compound **(11a)** taking 5-(4-chlorophenyl)-4-(4-methoxyphenyl)thiazol-2-ylamine **(10c) (**0.25 g, 0.789 mmol) and 2,4-difluorophenyl isocyanate (0.2 mL, 0.757 mmol) as the starting materials. The work up of reaction mixture afforded the desired compound **(11j)**, (0.2 g, 55.4%), **m.p.** 222-225°C.

Anal:

TLC : R_f 0.58 (*n*-Hexane: Ethyl acetate) (8: 2)

UV_{max} (MeOH) : 253 nm

IR (KBr, cm^{-1}) : 3403, 1695, 1530, 1293, 1251 and 818

PMR : 11.03 (bs, 1H), 9.14 (bs, 1H), 8.12-8.15 (m, 1H), 6.81-7.32 (m, 8H), 6.86 -7.12 (m, 1H) and 3.62(s, 3H)

MS : m/z 315.88, 470.68 (M^+)

5.34. 1-Butyl-3-[5-(4-chlorophenyl)-4-(4-methoxyphenyl)thiazol-2-yl]urea (11k)

The title compound **(11k)** was synthesized as per the method described for compound **(11a)** taking 5-(4-chlorophenyl)-4-(4-methoxyphenyl)thiazol-2-ylamine **(10c) (**0.25 g, 0.789 mmol) and *n*-butyl isocyanate (0.2 mL, 0.757 mmol) as the starting materials. The work up of the reaction mixture afforded the desired compound **(11k)**, (0.15 g, 54.96%), **m.p.** 203-206°C.

Anal:

TLC : R_f 0.58 (*n*-Hexane: Ethyl acetate) (8: 2)

UV_{max} (MeOH) : 250.2 nm

IR (KBr, cm^{-1}) : 3404, 1532, 1293, 1249, 1692 and 831

MS : m/z 316.02, 414.97 (M^+)

5.35. 1-[5-(4-Chlorophenyl)-4-(4-methoxyphenyl)thiazol-2-yl]-3-heptylurea (11l)

The title compound **(11l)** was synthesized as per the method described for compound **(11a)** taking 5-(4-chlorophenyl)-4-(4-methoxyphenyl)thiazol-2-ylamine **(10c)** (0.25 g, 0.789 mmol) and *n*-heptyl isocyanate (0.2 mL, 1.44 mmol) as the starting materials. The crude product

so obtained was purified through column chromatography to afford compound **(11l)**, (0.14 g, 47.58%), **m.p.**133-135 °C.

Anal:

TLC : R_f 0.73 (*n*-Hexane: Ethyl acetate) (8: 2)

UV_{max} (MeOH) : 250 nm

IR (KBr, cm^{-1}) : 3420, 1693, 1514, 1294, 1250, 1027 and 828

PMR : 11.0-11.5 (bs, 2H), 6.81-7.42 (m, 8H), 3.81(s, 3H), 1.41-2.61(m, 12H) and 0.91-0.95 (t, 3H).

5.36. 1-[4-(4-Chlorophenyl)-5-(4-nitrophenyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea (11m)

The title compound **(11m)** was synthesized as per the method described for compound **(11a)** taking 4-(4-chlorophenyl)-5-(4-nitrophenyl)thiazol-2-ylamine **(10d)** (1 g, 3.02 mmol) and 2,4-difluorophenyl isocyanate (0.32 mL, 2.064 mmol) as the starting materials. The solid product **(11m)** so obtained was filtered and dried and collected, (0.91 g, 89.94 %), **m.p.** 210-212°C.

Anal:

TLC : R_f 0.41 (*n*-Hexane: Ethyl acetate) (7: 3)

IR (KBr, cm^{-1}) : 3403, 1699, 1540, 1515, 1430 and 1339.

5.37. 1-[4-(4-Fluorophenyl)-5-(4-nitrophenyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea (11n)

The title compound **(11n)** was synthesized as per the method described for compound **(11a)** taking 4-(4-fluorophenyl)-5-(4-nitrophenyl)thiazol-2-ylamine **(10e)** (1 g, 3.174 mmol) and 2,4-difluorophenyl isocyanate (0.32 mL, 2.064 mmol) as the starting materials. The crude solid so obtained was filtered, dried and collected as the desired product **(11n)**, (0.93 g, 87%), **m.p.** 275-278°C.

Anal:

TLC : R_f 0.57 (*n*-Hexane: Ethyl acetate) (5: 5)

IR (KBr, cm^{-1}) : 3408, 3118, 1691, 1430, 1547, 1515 and 1340

PMR : 10.43 (bs, 1H), 8.92 (bs, 1H), 8.08-8.15 (m, 1H), 7.20- 7.28 (d, 4H), 7.32-7.42 (m, 2H), 6.87- 6.98 (m, 3H) and 6.82-6.88 (m, 1H)

5.38. 1-[4-(4-Methylphenyl)-5-(4-nitrophenyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea (11o)

The title compound **(11o)** was synthesized as per the method described for compound **(11a)** taking 5-(4-nitrophenyl)-4-(*p*-tolyl)thiazol-2-ylamine **(10f)** (1 g, 2.241 mmol) and 2,4-difluorophenyl isocyanate (0.32 mL, 2.161 mmol) as the starting materials **(11o).** The solid product was filtered, dried and collected **(11o)**, (0.89 g, 89%), **m.p.** 222-225°C.

Anal:

TLC : R_f 0.6 (*n*-Hexane: Ethyl acetate) (5: 5)

IR (KBr, cm^{-1}) : 3411, 3109, 1691, 1574, 1504 and 1333

PMR : 8.7 (bs, 1H), 8.2- 8.3 (m, 1H), 7.42-7.61 (m, 2H), 7.0-7.21 (m, 4H), 7.2-7.41 (m, 4H) and 2.31 (s, 3H).

5.39. 1-[4-(4-Methoxyphenyl)-5-(4-nitrophenyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea(11p)

The title compound **(11p)** was synthesized as per the method described for compound **(11a)** taking 4-(4-methoxyphenyl)-5-(4-nitrophenyl)thiazol-2-ylamine **(10g)** (1 g, 3.05 mmol) and 2,4-difluorophenyl isocyanate (0.5 mL, 3.05 mmol) as the starting materials. The solid product was filtered, dried and collected **(38)**, (1.4 g, 89.16%), **m.p.** 221-224°C.

Anal:

TLC : R_f 0.32 (*n*-Hexane: Ethyl acetate) (5: 5)

IR (KBr, cm^{-1}) : 3409, 3115, 1702, 1613, 1575, 1507 and 1339

5.40. 1-Butyl-3-[4-(4-chlorophenyl)-5-(4-nitrophenyl)thiazol-2-yl]urea (11q)

The title compound **(11q)** was synthesized as per the method described for compound **(11a)** taking 4-(4-chlorophenyl)-5-(4-nitrophenyl)thiazol-2-ylamine **(10d)** (1 g, 3.05 mmol) and *n*-butyl isocyanate (0.3 mL, 3.05 mmol) as the starting materials **(11q)**. The solid product was filtered and collected **(11q)**, (1.2 g, 97.56%), **m.p.** 158-161°C.

Anal:

TLC : R_f 0.78 (*n*-Hexane: Ethyl acetate) (5: 5)

IR (KBr, cm^{-1}) : 3403, 1699, 1591, 1430, 1540 and 1352

5.41. 1-Butyl-3-[4-(4-fluorophenyl)-5-(4-nitrophenyl)thiazol-2-yl]urea (11r)

The title compound **(11r)** was synthesized as per the method described for compound **(11a)** taking 4-(4-fluorophenyl)-5-(4-nitrophenyl)thiazol-2-ylamine **(10e)** (1 g, 0.317 mmol) and

n-butyl isocyanate (0.35 mL, 0.317 mmol) as the starting materials. The solid product **(11r)** so obtained was filtered and collected, (0.93 g, 89.9%), **m.p.** 156-159°C.

Anal:

TLC : R_f 0.69 (*n*-Hexane: Ethyl acetate) (5: 5)

IR (KBr, cm^{-1}): 3410, 3179, 1670, 1592, 1546, 1515 and 1340

5.42. 1-[4-(4-Methylphenyl)-5-(4-nitrophenyl)thiazol-2-yl]-3-butylurea (11s)

The title compound **(11s)** was synthesized as per the method described for compound **(11a)** taking 5-(4-nitrophenyl)-4-(*p*-tolyl)thiazol-2-ylamine **(10f)** (1g, 3.21mmol) and *n*-butyl isocyanate (0.35 mL, 3.21 mmol) as the starting materials **(11a).** The solid product **(11s)** was filtered and dried to yield compound, (0.82 g, 87.9 %), **m.p.** 198-201°C.

Anal:

TLC : R_f 0.62 (*n*-Hexane: Ethyl acetate) (5: 5)

IR (KBr, cm^{-1}): 3411, 3156, 1693, 1591, 1553 and 1340.

5.43. 1-Butyl-3-[4-(4-methoxyphenyl)-5-(4-nitrophenyl)thiazol-2-yl]urea (11t)

The title compound **(11t)** was synthesized as per method described for compound **(11a)** taking 4-(4-methoxyphenyl)-5-(4-nitrophenyl)thiazol-2-ylamine **(10g)** (1 g, 3.054 mmol) and *n*-butyl isocyanate (0.3 mL, 3.054 mmol) as the starting materials. The solid product **(11t)** was filtered and dried to yield desired compound, (0.87 g, 85.87%**)**, **m.p.** 207-210°C.

Anal:

TLC : R_f 0.62 (*n*-Hexane: Ethyl acetate) (5: 5)

IR (KBr, cm^{-1}): 3421, 3144, 1700, 1639, 1430, 1514 and 1341.

5.44. 1-[5-(4-Aminophenyl)-4-(4-chlorophenyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea (12a)

1-[4-(4-Chlorophenyl)-5-(4-nitrophenyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea **(11m)** (0.5 g, 1.02 mmol) was dissolved in sufficient quantity of methanol (25 mL) and refluxed. Iron powder (2 g) and sodium chloride solution (50 %, 5 mL) were added into the refluxing solution portion wise. Completion of the reaction was confirmed by TLC. The reaction mixture was filtered out to collect the filtrate. The filtrate was concentrated *in vaccuo* and poured into the water (50 mL). The precipitate so formed was filtered, dried and collected as the desired compound **(12a)**, (0.4 g, 97.35%), **m.p.** 222-224°C.

Anal:

TLC : R_f 0.55 (*n*-Hexane: Ethyl acetate) (5: 5)

IR (KBr, cm^{-1}) : 3413, 3403, 1699, 1611, 1569 and 1430

5.45. 1-[5-(4-Aminophenyl)-4-(4-fluorophenyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea (12b)

The title compound **(12b)** was synthesized as per the method described for compound **(12a)** taking 1-[4-(4-fluorophenyl)-5-(4-nitrophenyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea **(11n)** (0.5 g, 1.063 mmol) as the starting material. The precipitate so formed was filtered, dried and collected to obtain the desired compound **(12b)**, (0.38 g, 90 %), **m.p.** 209-211°C.

Anal:

TLC : R_f 0.54 (*n*-Hexane: Ethyl acetate) (5: 5)

IR (KBr, cm^{-1}) : 3416, 3312, 1685, 1611 and 1563.

5.46. 1-[5-(4-Aminophenyl)-4-(*p*-tolyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea (12c)

The title compound **(12c)** was synthesized as per the method described for compound **(12a)** taking 1-[4-(4-methylphenyl)-5-(4-nitrophenyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea **(11o)** (0.5 g, 1.07 mmol) as the starting material. The precipitate so formed was filtered, dried and collected to afford the desired compound **(12c)**, (0.43 g, 91.34%), **m.p.** 223-226°C.

Anal:

TLC : R_f 0.49 (*n*-Hexane: Ethyl acetate) (5: 5)

IR (KBr, cm^{-1}) : 3415, 3314, 1687, 1615 and 1561

5.47. 1-[5-(4-Aminophenyl)-4-(4-methoxyphenyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea (12d)

The title compound **(12d)** was synthesized as per the method described for compound **(12a)** taking 1-[4-(4-methoxyphenyl)-5-(4-nitrophenyl)thiazol-2-yl]-3-(2,4-difluorophenyl)urea **(11p)** (500 mg, 1.036 mmol) as the starting material. The precipitate so formed was filtered, dried and collected to obtain the desired compound **(12d)**, (0.44 g, 89.24%), **m.p.** 186-188°C.

Anal:

TLC : R_f 0.5 (*n*-Hexane: Ethyl acetate) (5: 5)

IR (KBr, cm^{-1}) : 3143, 1703, 1685, 1611, 1549 and 1230

5.48. 1-[5-(4-Aminophenyl)-4-(4-chlorophenyl)thiazol-2-yl]-3-butylurea (12e)

The title compound **(12e)** was synthesized as per the method described for compound **(12a)** taking 1-butyl-3-[4-(4-chlorophenyl)-5-(4-nitrophenyl)thiazol-2-yl]urea **(11q)** (0.5 g, 1.2 mmol) as the starting material. The precipitate so formed was filtered, dried and collected to afford the desired compound **(12e)**, (0.48 g, 98.87%), **m.p.** 192-194°C.

Anal:

TLC : R_f 0.42 (*n*-Hexane: Ethyl acetate) (5: 5)

IR (KBr, cm^{-1}) : 3413, 3338, 1700, 1623, 1551 and 1430.

5.49. 1-[5-(4-Aminophenyl)-4-(4-fluorophenyl)thiazol-2-yl]-3-butylurea (12f)

The title compound **(12f)** was synthesized as per the method described for compound **(12a)** taking 1-butyl-3-[4-(4-fluorophenyl)-5-(4-nitrophenyl)thiazol-2-yl]urea **(11r)** (0.5 g, 1.20 mmol) as the starting material. The precipitate so formed was filtered, dried and collected **(12f)**, (0.43 g, 87.8%), **m.p.** 160-162°C.

Anal:

TLC : R_f 0.28 (*n*-Hexane: Ethyl acetate) (5: 5)

IR (KBr, cm^{-1}) : 3415, 3318, 3217, 1687, 1615 and 1561

5.50. 1-[5-(4-Aminophenyl)-4-(*p*-tolyl)thiazol-2-yl]-3-butylurea (12g)

The title compound **(12g)** was synthesized as per the method described for compound **(12a)** taking 1-butyl-3-[5-(4-nitrophenyl)-4-(*p*-tolyl)thiazol-2-yl]urea **(11s)** (0.5 g, 1.22 mmol) as the starting material. The precipitate so formed was filtered, dried and collected to obtain the desired compound **(12g)**, (0.36 g, 89%), **m.p.** 197-200°C.

Anal:

TLC : R_f 0.33 (*n*-Hexane: Ethyl acetate) (5: 5)

IR (KBr, cm^{-1}) : 3415, 3141, 1687, 1615 and 1561

5.51. 1-[5-(4-Aminophenyl)-4-(4-methoxyphenyl)thiazol-2-yl]-3-butylurea (12h)

The title compound **(12h)** was synthesized as per the method described for compound **(12a)** taking 1-butyl-3-[4-(4-methoxyphenyl)-5-(4-nitrophenyl)thiazol-2-yl]urea **(11t)** (0.5 g, 1.17 mmol) as the starting material. The precipitate so formed was filtered, dried and collected to obtain the desired compound **(12h)**, (0.46 g, 89%), **m.p.** 174-176°C.

Anal:

TLC : R_f 0.31 (*n*-Hexane: Ethyl acetate) (7: 3)

IR (KBr, cm^{-1}): 3410, 3145, 1678, 1615, 1561, 1259 and 1024.

5.52. *N*-{4-[2-[[(2,4-Difluorophenyl)carbamoyl]amino]-4-(4-chlorophenyl)-1,3-thiazol-5-yl]phenyl}acetamide (13a)

3-[5-(4-Aminophenyl)-4-(4-chlorophenyl)-1,3-thiazol-2-yl]-1-(2,4-difluorophenyl)urea **(12a)** (0.25 g, 1.02 mmol) was dissolved in THF (10 mL). Pyridine (2-3 drops) and acetic anhydride (0.12 mL, 1.02 mmol) were added drop wise into the stirred solution at 0-5^oC. The reaction was monitored by TLC. The reaction mixture was poured into ice water (50 g) and the excess amount of pyridine was neutralized with HCl. The precipitate so obtained was filtered, dried and collected. The crude product so obtained was purified through column chromatography to afford the pure compound (**13a)**, (0.2 g, 69.78 %), **m.p.** 240 -242$^{\circ}C$.

Anal:

TLC : R_f 0.32 (*n*-Hexane: Ethyl acetate) (5: 5)

IR (KBr, cm^{-1}): 3351, 3151, 1663, 1608, 1542 and 1562

PMR : 9.92 (bs, 1H), 9.33 (bs, 1H), 8.0-8.10 (m, 1H), 7.62-7.70 (d, 4H), 7.19-7.21 (d, 2H), 6.83-7.03 (m, 4H) and 3.12 (s, 3H)

5.53. 1-(2,4-Difluorophenyl)-3-[5-(4-methansulfonamidophenyl)-4-(4-chlorophenyl)-1,3-thiazol-2-yl]urea (13b)

3-[5-(4-Aminophenyl)-4-(4-chlorophenyl)-1,3-thiazol-2-yl]-1-(2,4-difluorophenyl)urea **(12a)** (0.25 g, 1.02 mmol) was dissolved in dry pyridine (2 mL). Methanesulfonyl chloride (0.09 mL, 1.02 mmol) was added drop-wise into the stirred solution at 0-5^oC. The reaction was further carried out as described for compound **(13a)** to obtain the desired compound **(13b)**. (0.24 g, 59.98 %), **m.p.** 250-252$^{\circ}C$.

Anal:

TLC : R_f 0.57 (*n*-Hexane: Ethyl acetate) (5: 5)

IR (KBr, cm^{-1}): 3251, 3118, 1697, 1612, 1547 and 1398

PMR : 10.3 (bs, 1H), 9.94 (bs, 1H), 8.00-8.10 (m, 1H), 7.58-7.68 (d, 4H), 7.19-7.21 (m, 2H), 6.83-7.03 (m, 4H) and 3.02 (s, 3H).

5.54. *N*-{4-[2-(Butylcarbamoyl)amidophenyl]-4-(4-chlorophenyl)-1,3-thiazol-5-yl}acetamide (13c)

1-[5-(4-Aminophenyl)-4-(4-chlorophenyl)thiazol-2-yl]-3-butylurea **(12e)** (0.25 g, 1.02 mmol) was dissolved in dry THF (10 mL). Pyridine (2-3 drops) and acetic anhydride (0.09 mL, 0.635 mmol) were added drop-wise into the stirred solution at 0-5^{o}C. The reaction was further carried out as described for compound **(13a)**, (0.19 g, 73.98 %), **m.p.** 208-210°C.

Anal:

TLC : R_f 0.14 (*n*-Hexane: Ethyl acetate) (5: 5)

IR (KBr, cm^{-1}) : 3252, 3182, 3115, 1685, 1599 and 1524

PMR : 10.30 (bs, 1H), 9.84 (bs, 1H), 6.40 (bs, 1H), 7.56-7.58 (d, 2H), 7.40-7.43 (d, 2H), 7.17-7.22 (m, 4H), 3.19-3.22 (q, 2H), 1.47-1.59 (m, 2H), 1.32-1.41 (m, 2H) and 0.92-0.95 (t, 3H).

5.55. 3-Butyl-1-[5-(4-mehtanesulfonamidophenyl)-4-(4-chlorophenyl)-1,3-thiazol-2-yl]urea (13d)

1-[5-(4-Aminophenyl)-4-(4-chlorophenyl)thiazol-2-yl]-3-butylurea **(12e)** (0.25 g, 1.02 mmol) was dissolved in dry pyridine (2 mL). Methanesulfonyl chloride (0.09 mL, 1.02 mmol) was added drop-wise into the stirred solution at 0-5^{o}C. The reaction was further carried out as described for compound **(13a)**, (0.21 g, 79.43%), **m.p** 188-191°C.

Anal:

TLC : R_f 0.29 (*n*-Hexane: Ethyl acetate) (5: 5)

IR (KBr, cm^{-1}) : 3348, 3142, 1665, 1608, 1564 and 1294

PMR : 10.30 (s, 1H), 9.77 (s, 1H), 6.39 (s, 1H), 7.4-7.42 (d, 2H), 7.24-7.42 (m, 6H), 3.19- 3.29 (m, 2H), 2.99 (s, 3H), 1.47-1.54 (q, 2H), 1.34-1.41 (m, 2H), and 0.92-0.95 (t, 3H).

5.56. *N*-{4-[2-(((2,4-Difluorophenyl)carbamoyl)amino)-4-(4-fluorophenyl)-1,3-thiazol-5-yl]phenyl}acetamide (13e)

3-[5-(4-Aminophenyl)-4-(4-fluorophenyl)1,3-thiazol-2-yl]-1-(2,4-difluorophenyl)urea **(12b)** (0.25 g, 0.568 mmol) was dissolved in THF (10 mL). Pyridine (2-3 drops) and acetic anhydride (0.12 mL, 1.02 mmol) were added drop-wise in to the stirred solution at 0-5^{o}C. The reaction was further carried out as described for compound **(13a).** The crude product so obtained was purified through column chromatography to obtain the pure product **(13e)**, (0.16 g, 60 %), **m.p** 221-223°C.

Anal:

TLC : R_f 0.38 (*n*-Hexane: Ethyl acetate) (6: 4)

IR (KBr, cm^{-1}) : 3474, 3414, 3127, 1723, 1671, 1617 and 1560

PMR : 9.92 (s, 1H), 9.33 (s, 1H), 7.6-7.62 (d, 2H), 7.46-7.5 (m, 2H), 7.19-7.21 (d, 2H), 6.83-7.03 (m, 4H) and 2.1 (s, 3H)

MS : m/z 482.7(M^+)

5.57. *N*-{4-[2-(3-(2,4-Difluorophenyl)ureido)-4-(4-fluorophenyl)thiazol-5-yl]phenyl}methane -sulfonamide (13f)

3-(5-(4-Aminophenyl)-4-(4-fluorophenyl)-1,3-thiazol-2-yl)-1-(2,4-difluorophenyl)urea **(12b)** (0.25 g, 0.568 mmol) was dissolved in dry pyridine (2 mL). Methanesulfonyl chloride (0.09 mL, 1.02 mmol) was added drop-wise into the stirred solution at 0-5^oC. The reaction was further carried out as described for compound **(13a)** to obtain the desired compound **(13f)**, (0.19 g, 68%), **m.p** 150-152°C.

Anal:

TLC : R_f 0.38 (*n*-Hexane: Ethyl acetate) (6: 4)

IR (KBr, cm^{-1}) : 3255, 3115, 3127, 1693, 1671, 1609 and 1545

PMR : 10.3(s, 1H), 9.94 (s, 1H), 8.00-8.10 (m, 1H), 7.58-7.68 (m, 4H), 7.19-7.21(m, 2H), 6.83-7.21(m, 4H) and 3.02(s, 3H).

MS : m/z 482.7(M^+)

5.58. *N*-{4-[2-(Butylcarbamoylamino)-4-(4-fluorophenyl)-1,3-thiazol-5-yl}phenyl}acetamide (13g)

1-[5-(4-Aminophenyl)-4-(4-fluorophenyl)-1,3-thiazol-2-yl]-3-butylurea **(12f)** (0.25 g, 0.65 mmol) was dissolved in THF (10 mL). Pyridine (2-3 drops) and acetic anhydride (0.09 mL, 0.65 mmol) was added drop-wise in to the stirred solution at 0-5^oC. The reaction was further carried out as described for compound **(13a).** The crude product so obtained was purified through column chromatography to obtain the pure compound **(13g)**, (0.16 g, 75.89 %), **m.p** 127-130°C.

Anal:

TLC : R_f 0.22 (*n*-Hexane: Ethyl acetate) (5: 5)

IR (KBr, cm^{-1}) : 3475, 3312, 3177, 1679, 1592, 1549 and 1403

PMR : 10.25 (s, 1H), 9.80(s, 1H), 6.44(s, 1H), 6.95-7.72 (m, 8H), 3.23-3.32 (m, 4H), 2.11 (s, 3H), 1.82-1.93 (m, 2H), 1.26-1.30 (m, 4H) and 0.94-1.02 (t, 3H).

5.59. 3-Butyl-1-[5-(4-methanesulfonamidophenyl)-4-(4-fluorophenyl)-1,3-thiazol-2-yl]urea (13h)

1-(5-(4-Aminophenyl)-4-(4-fluorophenyl)-1,3-thiazol-2-yl)-3-butylurea **(12f)** (0.25 g, 0.65 mmol) was dissolved in dry pyridine (2 mL). Methanesulfonyl chloride (0.09 mL, 1.02 mmol) was added drop-wise in to the stirred solution at 0-5^{o}C. The reaction was further carried out as described for compound **(13a)** to afford the pure compound **(13h)**, (0.16 g, 67.47 %), **m.p.** 175-178°C.

Anal:

TLC : R_f 0.30 (*n*-Hexane: Ethyl acetate) (5: 5)

IR (KBr, cm^{-1}) : 3351, 3151, 1663, 1608, 1562 and 1298

PMR : 7.58-7.68 (m, 2H), 7.26-7.36 (m, 4H), 6.92-6.98 (m, 2H), 3.24-3.30 (m, 2H), 3.00 (s, 3H), 1.48-1.58 (m, 2H), 1.34- 1.41(m, 2H) and 0.94-0.97 (t, 3H).

5.60. *N*-4-{2-[[(2,4-Difluorophenyl)carbamoyl]amino]-4-(4-methylphenyl)-1,3-thiazol-5-yl}phenylacetamide (13i)

3-[5-(4-Aminophenyl)-4-(4-methylphenyl)-1,3-thiazol-2-yl]-1-(2,4-difluorophenyl)urea **(12c)** (0.25 g, 0.57 mmol) was dissolved in THF (10 mL). Pyridine (2-3 drops) and acetic anhydride (0.09 mL, 0.6510 mmol) were added drop-wise into the stirred solution at 0-5^{o}C. The reaction was further carried out as described for compound **(13a)**. The crude product so obtained was purified through column chromatography to afford the pure compound **(13i)**, (0.16 g, 65%), **m.p.** 255-258°C.

Anal:

TLC : R_f 0.29 (*n*-Hexane: Ethyl acetate) (3: 7)

IR (KBr, cm^{-1}) : 3415, 3310, 3126, 1702, 1666, 1615 and 1554

PMR : 9.92 (bs, 1H), 8.7 (bs, 1H), 8.2- 8.3 (m, 1H), 7.0-7.21 (m, 4H), 7.2-7.41 (d, 4H), 7.42-7.61 (d, 2H), 2.31 (s, 3H), and 2.25 (s, 3H).

5.61. 1-(2,4-Difluorophenyl)-3-[5-(4-methanesulfonamidophenyl)-4-(4-methylphenyl)-1,3-thiazol-2-yl]urea (13j)

3-[5-(4-Aminophenyl)-4-(4-methylphenyl)-1,3-thiazol-2-yl]-1-(2,4-difluorophenyl)urea **(12c)** (0.25 g, 0.57 mmol) was dissolved in dry pyridine (2 mL). Methanesulfonyl chloride (0.09 mL, 1.02 mmol) was added drop-wise into the stirred solution at 0-5^{o}C. The reaction was further

carried out as described for compound **(13a)**. The crude product was purified through column chromatography to obtain the pure compound **(13j)**, (0.16 g, 70 %), **m.p** 190-192°C.

Anal:

TLC : R_f 0.51 (*n*-Hexane: Ethyl acetate) (3: 7)

IR (KBr, cm^{-1}): 3423, 3183, 1713, 1615, 1550 and 1299

PMR : 9.92 (s, 1H), 8.7 (bs, 1H), 8.2- 8.3 (m, 1H), 7.0-7.21 (m, 4H), 7.2-7.41 (d, 4H), 7.42-7.61 (d, 2H), 2.31 (s, 3H) and 2.64 (s, 3H).

MS : m/z 514.7 (M^+)

5.62. 1-[5-(4-Acetamidophenyl)-4-(*p*-tolyl)thiazol-2-yl]-3-butylurea (13k)

1-[5-(4-Aminophenyl)-4-(*p*-tolyl)thiazol-2-yl]-3-butylurea **(12g)** (0.25 g, 0.65 mmol) was dissolved in THF (10 mL). Pyridine (2-3 drops) and acetic anhydride (0.09 mL, 0.657 mmol) were added drop-wise into the stirred solution at 0-5°C. The reaction was further carried out as described for compound **(13a)**. The crude product so obtained was purified through column chromatography to afford the desired compound **(13k)**, (0.23 g, 83.79%), **m.p.** 184-186°C.

Anal:

TLC : R_f 0.18 (*n*-Hexane: Ethyl acetate) (6: 4)

IR (KBr, cm^{-1}) : 3425, 3134, 1688, 1609, 1573 and 1209.

5.63. 3-Butyl-1-[5-(4-methanesulfonamidophenyl)-4-(4-tolyl)-1,3-thiazol-2-yl]urea (13l)

1-[5-(4-Aminophenyl)-4-(*p*-tolyl)thiazol-2-yl]-3-butylurea **(12g)** (0.25 g, 0.65 mmol) was dissolved in dry pyridine (2 mL). Methanesulfonyl chloride (0.09 mL, 1.02 mmol) was added drop wise in to the stirred solution at 0-5°C. The reaction was further carried out as described for compound **(13a)**. The crude product so obtained was purified through column chromatography to afford the desired compound **(13l)**, (0.18 g, 65.13%), **m.p** 210-212°C.

Anal:

TLC : R_f 0.35 (*n*-Hexane: Ethyl acetate) (5: 5)

IR (KBr, cm^{-1}) : 3342, 3133, 1664, 1560, 1436 and 1296

PMR : 10.15 (bs, 1H), 9.32 (bs, 1H), 8.63 (bs, 1H), 7.34-7.43 (m, 2H), 7.15-7.30 (m, 4H), 7.01-7.13 (m, 2H), 3.23 (q, 2H), 2.97 (s, 3H), 2.35 (s, 3H), 1.52-1.65 (m, 2H), 1.37-1.43 (m, 2H) and 0.87-0.93 (t, 3H).

5.64. 1-(2,4-Difluorophenyl)-3-[4-(4-methoxyphenyl)-5-(4-((propan-2-yl)amino)phenyl)1,3-thiazol-2-yl]urea (13m)

3-[5-(4-Aminophenyl)-4-(4-methoxyphenyl)-1,3-thiazol-2-yl]-1-(2,4-difluorophenyl)urea **(12d)** (0.5 g, 0.55 mmol) was taken in the RBF and dissolved in DMF (2 mL) under nitrogen. Anhydrous K_2CO_3 (1 g) and isopropyl bromide (0.67 mL, 0.55 mmol) were added into the stirred solution. The reaction mixture was stirred for another 24 h and completion of the reaction was monitored by TLC. The reaction mixture was quenched in ice water (200 mL) and extracted with chloroform (3x15 ml). The chloroform layer was separated and dried over sodium sulphate. The organic layer so obtained was distilled off and the mixture so obtained was purified through column chromatography (methanol: dichloromethane 1: 9) to obtain the pure desired compound **(13m),** (0.24 g, 75.65%), **m.p.** 150-152°C.

Anal:

TLC : R_f 0.41 (*n*-Hexane: Ethyl acetate) (7: 3)

IR (KBr, cm^{-1}) : 3353, 3126, 1688, 1509, 1402 and 1322

PMR : 10.63 (bs, 1H), 8.22 (bs, 1H), 8.2-8.3 (m, 1H), 7.0-7.21 (m, 4H), 7.2-7.41 (d, 4H), 7.42- 7.61 (m, 2H), 3.9 (s, 3H), 3.81- 3.93 (m, 1H) and 0.91-0.93 (d, 6H).

MS : m/z 494.7 (M^+)

5.65. 1-(2,4-Difluorophenyl)-3-[5-(4-dodecylaminophenyl)-4-(4-methoxyphenyl)-1,3-thiazol-2-yl]urea (13n)

3-(5-(4-Aminophenyl)-4-(4-methoxyphenyl)-1,3-thiazol-2-yl)-1-(2,4-difluorophenyl)urea **(12d)** (0.25 g, 0.55 mmol) was taken in the RBF and dissolved in DMF (2 mL) under nitrogen. Anhydrous K_2CO_3 (1 g) and *n*-dodecyl bromide (1.37 mL, 0.55 mmol) were added into the stirred solution. The reaction was further carried out as described for compound **(13a).** The crude compound was purified through column chromatography to obtain the pure compound **(13n)**, (0.24 g, 70.47%), **m.p** 121-123°C.

Anal:

TLC : R_f 0.53 (*n*-Hexane: Ethyl acetate) (7: 3)

IR (KBr, cm^{-1}) : 3415, 3310, 3126, 1702, 1666, 1615 and 1554

PMR : 9.87 (bs, 1H), 8.13 (bs, 1H), 7.36-7.38 (d, 2H), 7.02-7.04 (d, 2H), 6.91-6.95(m, 1H), 6.82-6.90 (t, 1H), 6.72-6.74 (d, 2H), 6.59 (d, 2H), 3.74(s, 3H), 2.95-3.02 (m, 3H), 2.07(s, 3H), 1.52-1.57 (m, 3H), 1.24-1.19 (m, 22H) and 0.79-0.81(t, 3H).

MS : m/z 536.9 (M^+)

5.66. *N*-{4-[2-[((2,4-Difluorophenyl)carbamoyl)amino]-4-(4-methoxyphenyl)-1,3-thiazol-5-yl]phenyl}acetamide (13o)

3-[5-(4-Aminophenyl)-4-(4-methoxyphenyl)-1,3-thiazol-2-yl]-1-(2,4-difluorophenyl)urea **(12d)** (0.25 g, 0.55 mmol) was dissolved in THF (10 mL). Pyridine (2-3 drops) was added into the solution and acetic anhydride (0.09 mL, 0.657 mmol) was added drop wise into the stirred solution at 0-5°C. The reaction was further carried out as described for compound **(13a)**. The crude product so obtained was purified through column chromatography to obtain the pure compound **(13o)**, (0.18 g, 62.31%), **m.p.** 160-162°C.

Anal:

TLC : R_f 0.17 (*n*-Hexane: Ethyl acetate) (7: 3)

IR (KBr, cm^{-1}): 3406, 1675, 1610, 1615, 1548 and 1208

PMR : 9.87 (bs, 1H), 8.09 (bs, 1H), 7.9 (s, 1H), 7.51- 7.56 (m, 2H), 7.31- 7.36 (m, 2H), 7.15- 7.46 (d, 2H), 4.12 (s, 3H), 6.74-6.83 (d, 2H), 3.73 (m, 2H), 2.02 (m, 2H) and 1.20- 1.27 (t, 3H).

5.67. 1-(2,4-Difluorophenyl)-3-[5-(4-methansulfonamidophenyl)-4-(4-methoxyphenyl)-1,3-thiazol-2-yl]urea (13p)

3-(5-(4-Aminophenyl)-4-(4-methoxyphenyl)-1,3-thiazol-2-yl)-1-(2,4-difluorophenyl)urea **(12d)** (0.25 g, 0.553 mmol) was dissolved in dry pyridine (2 mL). Methanesulfonyl chloride (0.09 mL, 1.02 mmol) was added drop wise into the stirred solution at 0-5°C. The reaction was further carried out as described for compound **(13a)**. The crude compound was purified through column chromatography to obtain the pure compound **(13p)**, (0.22 g, 69.78 %), **m.p.** 176-178°C.

Anal:

TLC : R_f 0.33 (*n*-Hexane: Ethyl acetate) (7: 3)

IR (KBr, cm^{-1}) : 3409, 3235, 1715, 1613, 1555 and 1290

MS : m/z 530 (M^+)

5.68. 3-Butyl-1-{4-(4-methoxyphenyl)-5-[4-(propan-2-yl-amino)phenyl)]-1,3-thiazol-2-yl}urea (13q)

1-(5-(4-Aminophenyl)-4-(4-methoxyphenyl)-1,3-thiazol-2-yl)-3-butylurea **(12h)** (0.25 g, 0.63 mmol) was dissolved in the DMF (2 mL). Anhydrous K_2CO_3 (1 g) and isopropyl bromide (0.67 mL, 0.552 mmol) were added into the stirred solution. The crude product so obtained was

purified through column chromatography to obtain the pure compound **(13q)**, (0.18 g, 60%), **m.p.** 45-48°C.

Anal:

TLC : R_f 0.48 (*n*-Hexane: Ethyl acetate) (7: 3)

IR (KBr, cm^{-1}) : 3406, 2970, 1675, 1610, 1548 and 1230

MS : m/z 439.1(M^+)

5.69. 3-Butyl-1-{5-[4-(dodecylamino)phenyl]-4-(4-methoxyphenyl)-1,3-thiazol-2-yl}urea (13r)

1-(5-(4-Aminophenyl)-4-(4-methoxyphenyl)-1,3-thiazol-2-yl)-3-butylurea **(12h)** (0.25 g, 0.63 mmol) was taken in the RBF and dissolved in the DMF (2 mL). Anhydrous K_2CO_3 (1 g) and dodecyl bromide (0.14 mL, 0.631 mmol) were added into the stirred solution. The reaction was further carried out as described for compound **(13m)**. The pure compound **(13r)** was purified through column chromatography, (0.18 g, 63%), **m.p.** 120-123°C.

Anal:

TLC : R_f 0.21 (*n*-Hexane: Ethyl acetate) (7: 3)

IR (KBr, cm^{-1}) : 3437, 3138, 1689, 1616, 1400 and 1294

MS : m/z 564.9 (M^+)

5.70. *N*-{4-[2-(3-Butylureido)-4-(4-methoxyphenyl)thiazol-5-yl]phenyl}acetamide (13s)

1-(5-(4-Aminophenyl)-4-(4-methoxyphenyl)-1,3-thiazol-2-yl)-3-butylurea **(12h)** (0.25 g, 0.631 mmol) was dissolved in THF (10 mL). Pyridine (2-3 drops) and acetic anhydride (0.09 mL, 0.657 mmol) were added drop-wise into the stirred solution at 0-5°C. The reaction was further carried out as described for compound **(13a)**. The desired compound **(13s)** was purified through column chromatography, (0.17 g, 69.47%), **m.p.** 159-161°C.

Anal:

TLC : R_f 0.17 (*n*-Hexane: Ethyl acetate) (7: 3)

IR (KBr, cm^{-1}) : 3405, 3247, 2953, 1668, 1529 and 837

PMR : 7.5 (bs, 1H), 7.37-7.39 (d, 2H), 7.25-7.27 (d, 2H), 7.09-7.11(d, 2H), 6.70-6.73 (d, 2H), 3.70 (s, 3H), 2.97-2.98 (t, 2H), 2.10 (s, 3H), 1.14-1.27 (m, 4H) and 0.81-0.93 (t, 3H).

MS : m/z 438.8 (M^+)

5.71. 3-Butyl-1-[5-(4-methanesulfonamidophenyl)-4-(4-methoxyphenyl)-1,3-thiazol-2-yl]urea (13t)

1-(5-(4-Aminophenyl)-4-(4-methoxyphenyl)-1,3-thiazol-2-yl)-3-butylurea **(12h)** (0.25 g, 0.631 mmol) was dissolved in dry pyridine (2 mL). Methanesulfonyl chloride (0.09 mL, 1.02 mmol) was added drop wise into the stirred solution at 0-5°C. The reaction was further carried out as described for compound **(13a)**. The crude product so obtained was purified through column chromatography to afford the pure compound **(13t)**, (0.16 g, 62.13%), **m.p.** 172-174°C.

Anal:

TLC : R_f 0.33 (*n*-Hexane: Ethyl acetate) (7: 3)

IR (KBr, cm^{-1}) : 3431, 3254, 3173, 1710, 1674, 1563 and 1299

PMR : 8.8 (bs, 1H), 8.5 (bs, 1H), 8.2 (s, 1H), 7.14-7.23 (m, 8H), 3.73 (s, 3H), 3.23 (t, 2H), 2.99 (s, 3H), 1.46-1.48 (m, 2H), 1.28-1.34 (m, 2H) and 0.87-0.94 (t, 3H).

5.72. 4-(4-Chlorophenyl)-2-methyl-5-(4-nitrophenyl)thiazole (14i)

2-Bromo-1-(4-chlorophenyl)-2-(4-nitrophenyl)ethanone **(9d)** (0.5 g, 1.413 mmol) was dissolved in ethanol (30 mL) in a 100 mL RBF. Thioacetamide (0.113 g, 1.686 mmol) was added into this reaction mixture and the reaction mixture was refluxed for 4 hr. Completion of the reaction was monitored by TLC. The solvent was distilled off and the residue so obtained was poured into ice cold water (250 mL). The precipitate was filtered off, dried and collected to obtain the desired product **(14i)**, (0.2 g, 42.82%), **m.p.** 147-149°C.

Anal:

TLC : 0.82 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}): 3242, 1633, 1528, 1335, 1220 and 835

5.73. 4-(4-Fluorophenyl)-2-methyl-5-(4-nitrophenyl)thiazole (14ii)

The title compound **(14ii)** was synthesized as per the method described for compound **(14i)** taking 2-bromo-1-(4-fluorophenyl)-2-(4-nitrophenyl)ethanone **(9e)** (0.5 g , 1.48 mmol) as the starting material. The crude product so obtained was purified through column chromatogaraphy to obtain the desired compound **(14ii)**, (0.2 g, 44.2%), **m.p.** 47-49°C.

Anal:

TLC : 0.84 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}): 3142, 1638, 1530, 1332, 1225 and 825

5.74. 4-(4-Methylphenyl)-2-methyl-5-(4-nitrophenyl)thiazole (14iii)

The title compound **(14iii)** was synthesized as per the method described for compound **(14i)** taking 2-bromo-2-(4-nitrophenyl)-1-(p-tolyl)ethanone **(9f)** (0.5 g, 1.413 mmol) as the starting material. The crude product so obtained was purified through column chromatography to obtain pure compound **(14iii)**, (0.2 g, 45.47%), m.p**.** 149-151°C.

Anal:

TLC : 0.78 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}): 3125, 1635, 1528, 1330, 1225 and 825

5.75. 4-(4-Methoxyphenyl)-2-methyl-5-(4-nitrophenyl)thiazole (14iv)

The title compound **(14iv)** was synthesized as per the method described for compound **(14i)** taking 2-bromo-1-(4-methoxyphenyl)-2-(4-nitrophenyl)ethanone **(9g)** (0.5 g , 1.413 mmol) as the starting material. The crude product so obtained was purified through column chromatography to obtain the desired compound **(14iv)**, (0.2 g, 45.47%), m.p**.** 149-151°C.

Anal:

TLC : 0.78 (*n*-Hexane: Ethyl acetate) (8: 2)

IR (KBr, cm^{-1}): 3422, 1637, 1525, 1332 and 1256

5.76. 4-[4-(4-Chlorophenyl)-2-methylthiazol-5-yl]aniline (15i)

4-(4-Chlorophenyl)-2-methyl-5-(4-nitrophenyl)thiazole **(14i)** (1 g, 3.025 mmol) was refluxed in methanol (50 mL). Iron powder (5 g) and sodium chloride solution (50 %, 10 mL) were added together portion-wise into the refluxed solution. Completion of the reaction was monitored by TLC. After completion of the reaction, the iron powder was filtered off from the reaction mixture and the filtrate was concentrated *in-vacuo*. The resultant solid so obtained was filtered off, dried and purified by column chromatography (neutral aluminum oxide as stationary phase and n-hexane and ethyl acetate, 7: 3 as mobile phase) to obtain pure desired compound **(15i),** (0.7, 77.78%), **m.p.** 102-104°C.

Anal:

TLC : 0.38 (*n*-Hexane: Ethyl acetate) (7: 3)

IR (KBr, cm^{-1}): 3413, 3338, 3029, 1497 and 1292

PMR : 6.5 -7.5 (m, 8H), 2.75 (s, 3H) and 4.1 (s, 2H)

5.77. 4-[4-(4-Fluorophenyl)-2-methylthiazol-5-yl]aniline (15ii)

The title compound **(15ii)** was synthesized as per the method described for compound **(15i)** taking 4-(4-fluorophenyl)-2-methyl-5-(4-nitrophenyl)thiazole **(14ii)** (1 g, 3.184 mmol) as the starting material. The crude product so obtained was purified through column chromatography to afford the pure desired compound **(15ii)**, (0.7 g, 77.78 %), **m.p.** 135-138°C.

Anal:

TLC : 0.37 (*n*-Hexane: Ethyl acetate) (7: 3)

IR (KBr, cm^{-1}): 3414, 3340, 1493 and 1294

MS : m/z 284.01(M^+)

5.78. 4-[4-(4-Methylphenyl)-2-methylthiazol-5-yl]aniline (15iii)

The title compound **(15iii)** was synthesized as per the method described for compound **(15i)** taking 4-(4-methylphenyl)-2-methyl-5-(4-nitrophenyl)thiazole **(14iii)** (1 g, 3.225 mmol) as the starting material. The crude product so obtained was purified through column chromatography to afford the pure product **(15iii)**, (0.7 g, 77.78%), **m.p.** 151-153°C.

Anal:

TLC : 0.36 (*n*-Hexane: Ethyl acetate) (7: 3)

IR (KBr, cm^{-1}): 3408, 3352, 1509 and 1285

NMR : 6.5 -7.5 (m, 8H), 2.75 (s, 3H), 2.46 (s, 3H) and 3.87 (s, 2H).

5.79. 4-[4-(4-Methoxyphenyl)-2-methylthiazol-5-yl]aniline (15iv)

The title compound **(15iv)** was synthesized as per the method described for compound **(15i)** taking 4-(4-methoxyphenyl)-2-methyl-5-(4-nitrophenyl)thiazole **(14iv)** (1 g, 3.067 mmol) as the starting material. The crude product so obtained was purified through column chromatography to afford the pure product **(15iv)**, (0.7 g, 77.78%), m.p**.** 138-140°C.

Anal:

TLC : 0.38 (*n*-Hexane: Ethyl acetate) (7: 3)

IR (KBr, cm^{-1}): 3362, 3309, 3034, 1510 and 1288

NMR : 6.5 -7.5 (m, 8H), 2.81 (s, 3H), 3.92 (s, 3H) and 3.75 (s, 2H)

5.80. 1-{4-[4-(4-Chlorophenyl)-2-methylthiazol-5-yl]phenyl}-3-phenylurea (16a)

Compound **(15i)** (0.2 g, 0.605 mmol) was dissolved in toluene (10mL) in a 50mL RBF. Phenyl isocyanate (0.086 g, 0.726 mmol) was added drop-wise into the stirring solution of amine **(15i)** at room temperature. The stirring was continued for 4 hours and completion of the reaction was monitored by TLC. A solid was separated out during the reaction and the resultant solid was filtered off followed by thorough washing by toluene to remove excess of isocyanate if present. The precipitate so obtained was dried and collected to afford the pure desired compound **(16a),** (0.15 g, 60%), **m.p.** 228-230°C.

Anal:

TLC : 0.34 (*n*-Hexane: Ethyl acetate) (7: 3)

IR (KBr, cm^{-1}): 3318, 1649, 1592,1552,1316,1231 and 837

NMR : 7.0-7.9 (m, 13H), 6.51 (s, 2H) and 2.61 (s, 3H).

5.81. 1-{4-[4-(4-Chlorophenyl)-2-methylthiazol-5-yl]phenyl}-3-(2,4-difluorophenyl)urea (16b)

Compound **(15i)** (0.5 g, 1.663 mmol) was dissolved in toluene (10 mL) in a 50 mL RBF. 2,4-Difluorophenyl isocyanate (0.5 mL) was added dropwise into the stirring solution of the amine **(15i)** at room temperature. The reaction was further carried out as described for compound **(16a)** to obtain the pure compound **(16b),** (0.3 g, 40%), **m.p.** 187-190°C.

Anal:

TLC : 0.32 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 256 nm

IR (KBr, cm^{-1}) : 3326, 1636, 1587, 1549 and 1228

PMR : 8.41 (bs, 1H), 8.91 (bs, 1H), 8.21-8.41 (m, 1H), 7.21-7.42 (m, 4H), 7.42-7.62 (m, 4H), 6.71- 7.05 (m, 2H) and 2.81(s, 3H).

5.82. 1-{4-[4-(4-Chlorophenyl)-2-methylthiazol-5-yl]phenyl}-3-(2,6-diethylphenyl)urea (16c)

Compound **(15i) (**0.2 g, 0.605 mmol) was dissolved in toluene (10 mL) in a 50 mL RBF. 2,6-Diethylphenyl isocyanate (0.13 mL, 0.726 mmol) was added drop wise into the stirring solution of amine **(15i)** at room temperature. The reaction was further carried out as described for compound **(16a)** to obtain the pure compound **(16c),** (0.1 g, 35%), **m.p.** 248-250°C.

Anal:

TLC : 0.35 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 259 nm

IR (KBr, cm^{-1}) : 3285, 1637, 1588, 1548 and 1228

NMR : 7.01-7.51 (m, 8H), 7.62-7.81 (m, 2H), 7.82-7.91 (m, 1H), 2.72 (s, 3H), 2.61-2.67 (q, 4H) and 1.2-1.4 (t, 6H).

5.83. 1-Butyl-3-{4-[4-(4-chlorophenyl)-2-methylthiazol-5-yl]phenyl}urea (16d)

Compound **(15i)** (0.2 g, 0.605 mmol) was dissolved in toluene (10 mL) in a 50 mL RBF. *n*-Butyl isocyanate (0.1 mL, 0.786 mmol) was added drop wise into the stirring solution of the above amine **(15i)** at room temperature. The reaction was further carried out as described for compound **(16a)** to afford the pure compound **(16d)**, (0.15 g, 62.5%) **m.p.** 140-142°C.

Anal:

TLC : 0.35 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 252 nm

IR (KBr, cm^{-1}) : 3326, 1636, 1585, 1560 and 1229

NMR : 8.4 (s, 1H), 7.2-7.7 (m, 8H), 5.9 (s, 1H), 3.2-3.5 (q, 2H), 2.7(s, 3H), 1.2-1.4 (m, 4H) and 0.9-102 (t, 3H).

5.84. 1-Heptyl-3-{4-[4-(4-chlorophenyl)-2-methylthiazol-5-yl]phenyl}urea (16e)

Compound **(15i) (**0.2 g, 0.605 mmol) was dissolved in toluene (10 mL) in a 50mL RBF. *n*-Heptyl isocyanate (0.12 mL, 0.723 mmol) was added drop wise into the stirring solution of the above mentioned amine **(15i)** at room temperature. The reaction was further carried out as described for compound **(16a)** to afford the pure compound **(16e)**, (0.15 g, 55.97%) **m.p.** 168-170°C.

Anal:

TLC : 0.36 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 252 nm

IR (KBr, cm^{-1}) : 3321, 1633, 1586, 1555, 1235 and 833

NMR : 8.4 (s, 1H), 7.2-7.7 (m, 8H), 5.9 (s, 1H), 3.2-3.4 (q, 2H). 2.7 (s, 3H), 1.2-1.4 (m, 10H) and 0.9-1.02 (t, 3H).

5.85. 1-Dodecyl-3-{4-[4-(4-chlorophenyl)-2-methylthiazol-5-yl]phenyl}urea (16f)

Compound **(15i) (**0.2 g, 0.605 mmol) was dissolved in toluene (10 mL) in a 50 mL RBF. *n*-Dodecyl isocyanate (0.166 g, 0.784 mmol) was added drop-wise into the stirring solution of the

above amine **(15i)** at room temperature. The reaction was further carried out as described for compound **(16a)** to obtain the pure compound **(16f)**, (0.12 g, 40%), **m.p.** 182-184°C.

Anal:

TLC : 0.4 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 252 nm

IR (KBr, cm^{-1}) : 3320, 1634, 1556, 1231 and 834

NMR : 7.2-7.7 (m, 8H), 6.4 (s, 1H), 4.5 (s, 1H), 3.2 (t, 2H), 2.7 (s, 3H), 1.2-1.4 (m, 20H) and 0.9 (t, 3H)

5.86. 1-{4-[4-(4-Fluorophenyl)-2-methylthiazol-5-yl]phenyl}-3-phenylurea (16g)

Compound **(15ii) (**0.2 g, 0.605 mmol) was dissolved in toluene (10mL) in a 50mL RBF. Phenyl isocyanate (0.1 mL, 0.726 mmol) was added drop-wise into the stirring solution of amine **(15ii)** at room temperature. The reaction was further carried out as described for compound **(16a)** to obtain the pure compound **(16g)**, (0.15 g, 60%), **m.p.** 202-204°C.

Anal:

TLC : 0.34 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 252 nm

IR (KBr, cm^{-1}) : 3299, 1641, 1594, 1552, 1229 and 837

NMR : 7.0-7.9 (m, 13H), 6.5 (s, 2H) and 2.6 (s, 3H)

5.87. 1-{4-[4-(4-Fluorophenyl)-2-methylthiazol-5-yl]phenyl}-3-(2,4-difluorophenyl)urea (16h)

Compound **(15ii) (**0.2 g, 0.605 mmol) was dissolved in toluene (10 mL) in a 50 mL RBF. 2,4-Difluorophenyl isocyanate (0.134 mL, 0.865 mmol) was added drop wise into the stirring solution of the amine **(15ii)** at room temperature. The reaction was further carried out as described for compound **(16a), (**0.3 g, 40%), **m.p.** 216-218°C.

Anal:

TLC : 0.32 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 254 nm

IR (KBr, cm^{-1}) : 3291, 1640, 1556, 1505, 1226, 1096 and 842

NMR : 8.8 (s, 1H), 8.4 (s, 1H), 6.8-8.2 (m, 11H) and 2.8 (s, 3H).

5.88. 1-{4-[4-(4-Fluorophenyl)-2-methylthiazol-5-yl]phenyl}-3-(2,6-diethylphenyl)urea (16i)

Compound **(15ii) (**0.2 g, 0.605 mmol) was dissolved in toluene (10 mL) in a 50 mL RBF. 2,6-Diethylphenyl isocyanate (0.165 mL, 0.865 mmol) was added drop-wise into the stirring solution of amine **(15ii)** at room temperature. The reaction was further carried out as described for compound **(16a)**, **(**0.1 g, 35 %), **m.p.** 252-254°C.

Anal:

TLC : 0.32 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 253 nm

IR (KBr, cm^{-1}) : 3294, 1641, 1554, 1403 and 1222

MS : m/z 459 (M^+)

5.89. 1-Butyl-3-{4-[4-(4-fluorophenyl)-2-methylthiazol-5-yl]phenyl}urea (16j)

Compound **(15ii) (**0.2 g, 0.605 mmol) was dissolved in toluene (10 mL) in a 50 mL RBF. *n*-Butyl isocyanate (0.077 g, 0.786 mmol) was added drop-wise into the stirring solution of the amine **(15ii)** at room temperature. The reaction was further carried out as described for compound **(16a)**, **(**0.15 g, 62.5%), **m.p.** 178-180°C.

Anal:

TLC : 0.35 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 252 nm

IR (KBr, cm^{-1}) : 3314, 3117, 1634, 1514, 1403 and 1224

NMR : 8.4 (s, 1H), 7.2-7.7 (m, 8H), 5.9 (s, 1H), 3.2-3.4 (q, 2H), 2.7 (s, 3H), 1.2-1.4 (m, 4H) and 0.9-1.02 (t, 3H).

5.90. 1-Heptyl-3-{4-[4-(4-fluorophenyl)-2-methylthiazol-5-yl]phenyl}urea (16k)

Compound **(15ii) (**0.2 g, 0.605 mmol) was dissolved in toluene (10 mL) in a 50mL RBF. *n*-Heptyl isocyanate (0.102 g, 0.723 mmol) was added drop-wise into the stirring solution of the amine **(15ii)** at room temperature. The reaction was further carried out as described for compound **(16a)**, (0.15 g, 55.97 %), **m.p.** 154-156°C.

Anal:

TLC : 0.36 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 256 nm

IR (KBr, cm^{-1}) : 3279, 1638, 1590, 1547, 1402 and 1225.

PMR : 8.4 (s, 1H), 7.2-7.7 (m, 8H), 5.9 (s, 1H), 3.2-3.4 (m, 2H). 2.7 (s, 3H), 1.2-1.4 (m, 10H) and 0.9-1.04 (t, 3H).

5.91. 1-Dodecyl-3-{4-[4-(4-fluorophenyl)-2-methylthiazol-5-yl]phenyl}urea (16l)

Compound **(15ii) (**0.2 g, 0.605 mmol) was dissolved in toluene (10 mL) in a 50mL RBF. *n*-Dodecyl isocyanate (0.102 g, 0.723 mmol) was added drop wise into the stirring solution of amine **(15ii)** at room temperature. The reaction was further carried out as described for compound **(16a)**, **(**0.12 g, 40%), **m.p.** 182-184°C.

Anal:

TLC : 0.4 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 254 nm

IR (KBr, cm^{-1}) : 3320, 1634, 1556, 1403, 1222 and 836.

PMR : 8.01 (s, 1H), 7.2-7.7 (m, 8H), 5.5 (s, 1H), 3.2 (q, 2H), 2.7 (s, 3H), 1.2-1.4 (m, 20H) and 0.9-1.03 (t, 3H).

5.92. 1-{4-[4-(4-Methylphenyl)-2-methylthiazol-5-yl]phenyl}-3-phenylurea (16m)

Compound **(15iii)** (0.5 g, 1.785 mmol) was dissolved in toluene (10 mL) in a 50 mL RBF. Phenyl isocyanate (0.09 mL, 0.726 mmol) was added drop-wise into the stirring solution of the above solution of **15iii** at room temperature. The reaction was further carried out as described for compound **(16a)**, (0.3 g, 42%), **m.p.** 204-206°C.

Anal:

TLC : 0.32 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 257 nm

IR (KBr, cm^{-1}) : 3310, 1647, 1594, 1548, 1234 and 822

PMR : 8.2-8.3 (s, 2H), 6.9-7.4 (m, 13H), 2.7 (s, 3H) and 2.30 (s, 3H)

MS : m/z 400.0 (M+1)

5.93. 1-{4-[4-(4-Methylphenyl)-2-methylthiazol-5-yl]phenyl}-3-(2,4-difluorophenyl)urea (16n)

Compound **(15iii)** (0.5 g, 1.785 mmol) was dissolved in toluene (10 mL) in a 50 mL RBF. Phenyl isocyanate (0.086 g, 0.726 mmol) was added drop-wise into the stirring solution of the amine (**15iii**) at room temperature. The reaction was further carried out as described for compound **(16a)** to obtain the desired compound **(16n)**, (0.3 g, 40%), **m.p.** 212-214°C.

Anal:

TLC : 0.32 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 254 nm

IR (KBr, cm^{-1}) : 3322, 1634, 1586, 1554 and 833

NMR : 8.4 (bs, 1H), 8.8 (bs, 1H), 6.8-8.2 (m, 11H), 2.9 (s, 3H) and 2.52 (s, 3H).

MS : m/z 436.0 (M^+)

5.94. 1-{4-[4-(4-Methylphenyl)-2-methylthiazol-5-yl]phenyl}-3-(2,6-diethylphenyl)urea (16o)

Compound **(15iii)** (0.5 g, 1.785 mmol) was dissolved in toluene (10 mL) in a 50 mL RBF. 2,6-Diethylphenyl isocyanate (0.086 g, 0.726 mmol) was added drop-wise into the stirring solution of the amine (**15iii**) at room temperature. The reaction was further carried out as described for compound **(16a)** to obtain the desired compound **(16o)**, (0.1 g, 35%), **m.p.** 240-242°C.

Anal:

TLC : 0.35 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 250 nm

IR (KBr, cm^{-1}) : 3309, 1647, 1596, 1550, 1245, 1027 and 835

NMR : 8.2 (bs, 1H), 8.7 (bs, 1H), 6.8-8.2 (m, 11H), 2.62 (s, 3H), 2.30 (s, 3H), 2.61-2.67 (q, 4H) and 1.2-1.4 (t, 6H)

5.95. 1-Butyl-3-{4-[4-(4-mehtylphenyl)-2-methylthiazol-5-yl]phenyl}urea (16p)

Compound **(15iii)** (0.5 g, 1.785 mmol) was dissolved in toluene (10 mL) in a 50 mL RBF. *n*-Butyl isocyanate (0.08 g, 0.786 mmol) was added drop wise into the stirring solution of the amine **(15iii)** at room temperature. The reaction was further carried out as described for compound **(16a)** to obtain the desired compound **(16p)**, (0.15 g, 62%), **m.p.** 158-159°C.

Anal:

TLC : 0.35 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH): 252 nm

IR (KBr, cm^{-1}) : 3318, 1639, 1596, 1313, 1273 and 829

NMR : 7.0-7.5 (d, 8H), 6.3(s, 1H), 4.9(s, 1H), 2.62(s, 3H), 3.2-3.4 (q, 2H), 2.30 (s, 3H), 1.2-1.4 (m, 4H) and 0.9-1.02 (t, 3H).

MS : m/z 380.1(M^+)

5.96. 1-Heptyl-3-{4-[4-(4-methylphenyl)-2-methylthiazol-5-yl]phenyl}urea (16q)

Compound **(15iii) (**0.2 g, 0.71 mmol) was dissolved in toluene (10 mL) in a 50 mL RBF. *n*-Heptyl isocyanate (0.102 g, 0.72 mmol) was added drop-wise into the stirring solution of above amine **(15iii)** at room temperature. The reaction was further carried out as described for compound **(16a)** to obtain the desired compound **(16q)**, (0.15 g, 53.97%), **m.p.** 168-170°C.

Anal:

TLC : 0.35 (*n*-Hexane: ethyl acetate) (7:3)

UV_{max} (MeOH) : 250 nm

IR (KBr, cm^{-1}) : 3321, 1633, 1596, 1565, 1313, 1240 and 829

5.97. 1-Dodecyl-3-{4-[4-(4-methylphenyl)-2-methylthiazol-5-yl]phenyl}urea (16r)

Compound **(15iii) (**0.2 g, 0.714 mmol) was dissolved in toluene (10 mL) in a 50 mL RBF. *n*-Dodecyl isocyanate (0.102 g, 0.723 mmol) was added drop wise into the stirring solution of amine **(15iii)** at room temperature. The reaction was further carried out as described for compound **(16a)**. to obtain the desired compound **(16r)**, (0.12 g, 40%), **m.p.**115-117°C.

Anal:

TLC : 0.4 (*n*-hexane: ethyl acetate) (7:3)

UV_{max} (MeOH) : 250 nm

IR (KBr, cm^{-1}) : 3318, 1637, 1568, 1315 and 1240

PMR : 7.2-7.7 (m, 8H), 8.25 (s, 1H), 5.5 (s, 1H), 2.9 (s, 3H), 0.9-1.01 (t, 3H), 1.2-1.4 (m, 20H), 3.2-3.4 (q, 2H) and 2.4 (s, 3H).

5.98. 1-[4-{4-(4-Methoxyphenyl)-2-methylthiazol-5-yl]phenyl}-3-phenylurea (16s)

Compound **(15iv) (**0.5 g, 1.68 mmol) was dissolved in toluene (10 mL) in a 50 mL RBF. Phenyl isocyanate (0.086 g, 0.72 mmol) was added drop-wise into the stirring solution of the amine **(15iv)** at room temperature. The reaction was further carried out as described for compound **(16a)**, to obtain the desired compound **(16s)**, (0.3 g, 42%), **m.p.** 180-182°C.

Anal:

TLC : 0.32 (n-hexane: ethyl acetate) (7:3)

UV_{max} (MeOH) : 256 nm

IR (KBr, cm^{-1}) : 3321, 1633, 1596, 1550, 1221 and 835

NMR : 8.5 (s, 2H), 6.9-7.4 (m, 13H), 2.82 (s, 3H) and 3.82 (s, 3H).

5.99. 1-{4-[4-(4-Methoxyphenyl)-2-methylthiazol-5-yl]phenyl}-3-(2,4-difluorophenyl)urea (16t)

Compound **(15iv)** (0.5 g, 1.68 mmol) was dissolved in toluene (10 mL) in a 50mL RBF. 2,4-Difluorophenyl isocyanate (0.34 g, 2.163 mmol) was added drop-wise into the stirring solution of the amine **(15iv)** at room temperature. The reaction was further carried out as described for compound **(16a)** to obtain the desired product **(16t)**, (0.3 g, 40%), **m.p.** 188-190°C.

Anal:

TLC : 0.34 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 250 nm

IR (KBr, cm^{-1}) : 3309, 1647, 1596, 1550, 1292 and 835

NMR : 8.4 (s, 1H), 8.8 (s, 1H), 6.8-8.2 (m, 11H), 3.75 (s, 3H) and 2.92 (s, 3H).

5.100. 1-{4-[4-(4-Methoxyphenyl)-2-methylthiazol-5-yl]phenyl}-3-(2,6-diethylphenyl)urea (16u)

Compound (**15iv**) (0.5 g, 1.68 mmol) was dissolved in toluene (10mL) in a 50 mL RBF. 2,6-Diethylphenyl isocyanate (0.34 g, 2.163 mmol) was added drop-wise into the stirring solution of the amine **(15iv)** at room temperature. The reaction was further carried out as described for compound (**16a**) to obtain the desired product **(16u)**, (0.3 g, 35%), **m.p.** 248-250°C.

Anal:

TLC : 0.35 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 252 nm

IR (KBr, cm^{-1}) : 3322, 1634, 1554, 1251, 1028 and 828

NMR : 7.01-7.91 (m, 11H), 3.75 (s, 3H), 2.72 (s, 3H), 2.67-2.72 (q, 4H) and 1.2-1.4 (t, 6H).

5.101. 1-Butyl-3-{4-[4-(4-methoxyphenyl)-2-methylthiazol-5-yl]phenyl}urea (16v)

Compound (**15iv**) (0.5 g, 1.689 mmol) was dissolved in toluene (10 mL) in a 50 mL RBF. *n*-Butyl isocyanate (0.34 g, 2.163mmol) was added drop wise into the stirring solution of the amine **(15iv)** at room temperature. The reaction was further carried out as described for compound (**16a**) to afford the desired compound **(16v)**, (0.15 g, 62%), **m.p.** 178-180°C.

Anal:

TLC : 0.37 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 254 nm

IR (KBr, cm^{-1}) : 3321, 2927, 1633, 1596, 1222, 1179 and 829

NMR : 8.3(s, 1H), 6.8-7.5(d, 8H), 6.1(s, 1H), 3.75 (s, 3H), 3.2-3.4(q, 2H), 2.7 (s, 3H), 1.2-1.4 (m, 4H) and 0.9-1.02 (t, 3H).

5.102. 1-Heptyl-3-{4-[4-(4-methoxyphenyl)-2-methylthiazol-5-yl]phenyl}urea (16w)

Compound (**15iv**) (0.5 g, 1.689 mmol) was dissolved in toluene (10 mL) in a 50 mL RBF. *n*-Heptyl isocyanate (0.34 g, 2.163 mmol) was added drop wise into the stirring solution of the amine **(15iv)** at room temperature. The reaction was further carried out as described for compound (**16a**) to obtain the desired product **(16w)**, (0.15 g ,53.97%), **m.p.** 168-170°C.

Anal:

TLC : 0.35 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 251nm

IR (KBr, cm^{-1}) : 3309, 2927, 1647, 1550, 1220, 1116 and 822

NMR : 8.5 (s, 1H), 6.8-7.5 (d, 8H), 5.62 (s, 1H), 3.9 (s, 3H), 3.41-3.51 (q, 2H), 2.8 (s, 3H), 1.2-1.4 (m, 10H), and 0.9-1.01 (t, 3H).

5.103. 1-Dodecyl-3-{4-[4-(4-methoxyphenyl)-2-methylthiazol-5-yl]phenyl}urea (16x)

Compound (**15iv**) (0.5 g, 1.68 mmol) was dissolved in toluene (10 mL) in a 50 mL RBF. *n*-Dodecyl isocyanate (0.17 g, 0.784 mmol) was added drop wise into the stirring solution of the amine **(15iv)** at room temperature. The reaction was further carried out as described for compound (**16a**) to afford the desired compound **(16x)**, (0.12 g, 40%), **m.p.** 108-110°C.

Anal:

TLC : 0.4 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH): 251nm

IR (KBr, cm^{-1}) : 3291, 1638, 1555, 1227, 1138 and 846

NMR : 6.8-7.4 (m, 8H), 6.8 (s, 1H), 5.1 (s, 1H), 3.2-3.4(q, 2H), 3.8 (s, 3H) 2.7 (s, 3H), 1.2-1.4 (m, 20H) and 0.9-1.01(t, 3H).

5.104. 1-(4-Chlorophenyl)-2-(4-nitrophenyl)ethanedione (17i)

A mixture of 1-(4-chlorophenyl)-2-(nitrophenyl)ethanone **(8d)** (5.0 g, 20.7 mmol), selenium dioxide (3.5 g, 31.5 mmol) and dimethylsulphoxide (DMSO) (25 mL) in a loosely stoppered conical flask (100 mL) was exposed to microwave irradiations for 30 sec intermittently. The hot reaction mixture was filtered to remove precipitated selenium metal and washed with hot

dioxane (15 mL) and the combined filtrate was poured into crushed ice (150 g)and the solid so obtained was filtered, washed with water followed by chilled methanol to afford the desired compound **(17i)**, (4 g, 75%), **m.p.** 196-197°C (Lit[139]199-200°C).

Anal:

TLC : 0.82 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 268 nm

IR(KBr, cm^{-1}) : 1670, 1659, 1528, 1349, 1099 and 847.

5.105. 1-(4-Fluorophenyl)-2-(4-nitrophenyl)ethanedione (17ii)

The title compound **(17ii)** was synthesized as described in method for compound **(17a)** starting with 1-(4-fluorophenyl)-2-(4-nitrophenyl)ethanone **(8e)(**5.0 g, 19.3 mmol) to yield compound **(17ii)**, (4.5 g, 86%), **m.p.** 155-156°C.(Lit[140]154-155^{0}C)

Anal:

TLC : 0.82 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH): 268 nm

IR(KBr, cm^{-1}) : 1673, 1658, 1532, 1351, 1242,1205 and 850.

5.106. 1-(4-Methylphenyl)-2-(4-nitrophenyl)ethanedione (17iii)

The title compound **(17iii)** was synthesized as described in method for compound **(17i)** starting with 1-(4-methylphenyl)-2-(4-nitrophenyl)ethanone **(8f) (**5.0 g, 19.3 mmol) to yield compound **(17iii)**, (4 g, 76%), **m.p.** 180-181°C. (Lit[140]178-179^{0}C)

Anal:

TLC : 0.67 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 270 nm

IR(KBr, cm^{-1}) : 1670, 1660, 1521, 1348, 1205 and 846.

5.107. 1-(4-Methoxyphenyl)-2-(4-nitrophenyl)ethanedione (17iv)

The title compound **(17iv)** was synthesized as described in method for compound **(17i)** starting with 1-(4-methoxyphenyl)-2-(4-nitrophenyl)ethanone **(8g) (**5.0 g, 18.3 mmol) to yield compound **(17iv)**, (4.7 g, 89%), **m.p.** 150-152°C. (Lit[140]148-150^{0}C)

Anal:

TLC : 0.60 (*n*-Hexane: Ethyl acetate) (7:3)

UV_{max} (MeOH) : 275 nm

IR(KBr, cm^{-1}) : 1675, 1648, 1524, 1348, 1266 and 847.

5.108. 1-(4-Chlorophenyl)-2-(4-nitrophenyl)ethanedione dioxime (18i)

A mixture of 1-(4-chlorophenyl)-2-(4-nitrophenyl)ethanedione **(17i)** (2.0 g, 6.9 mmol), hydroxylamine hydrochloride (4 g, 57.14 mmol) and pyridine (10 mL) was refluxed in an oil bath for 7 hr. The reaction mixture was poured into crushed ice (150 g) containing conc HCl (10 mL). The product was filtered, washed with water and dried to yield compound **(18i)**, (1.8 g, 80%), **m.p.** 208-210°C.

Anal:

TLC : 0.19 and 0.21 (5% methanol in $CHCl_3$)

UV_{max} (MeOH): 255 nm

IR (KBr, cm^{-1}) : 3274, 1594, 1525, 1346, 1090, 985 and 732.

5.109. 1-(4-Fluorophenyl)-2-(4-nitrophenyl)ethanedione dioxime (18ii)

The title compound **(18ii)** was synthesized as per the method described for compound **(18i)** starting with 1-(4-fluorophenyl)-2-(4-nitrophenyl)ethanedione **(17ii)** (2.0 g, 7.32 mmol) to yield compound **(18ii)**, (1.8 g, 81%), **m.p.** 193-195°C.

Anal:

TLC : 0.19 and 0.21 (5% methanol in $CHCl_3$)

5.110. 1-(4-Methylphenyl)-2-(4-nitrophenyl)ethanedione dioxime (18iii)

The title compound **(18iii)** was synthesized as per the method described for compound **(18i)** starting with 1-(4-methylphenyl)-2-(4-nitrophenyl)ethanedione **(17iii)** (2.0 g, 7.43 mmol) to offer compound **(18iii)**, (1.8 g, 81%), **m.p.** 191-193°C.

Anal:

TLC : 0.24 and 0.26 (5% methanol in $CHCl_3$)

IR (KBr, cm^{-1}): 3195, 1601, 1515, 1338, 1079 and 852.

5.111. 1-(4-Methoxyphenyl)-2-(4-nitrophenyl)ethanedione dioxime (18iv)

The title compound **(18iv)** was synthesized as per the method described for compound **(18i)** starting with 1-(4-methoxyphenyl)-2-(4-nitrophenyl)ethanedione **(17iv)** (2.0 g, 6.64 mmol) to offer compound **(18iv)**, (1.8 g, 81%), **m.p.** 191-193°C.

Anal:

TLC : 0.19 and 0.21 (5% methanol in $CHCl_3$)

IR (KBr, cm^{-1}): 3272, 1598, 1514, 1346, 1026 and 852.

5.112. 3-(4-Chlorophenyl)-4-(4-nitrophenyl)-1,2,5-oxadiazole (19i)

A mixture of finely powdered 1-(4-chlorophenyl)-2-(4-nitrophenyl)ethanedione dioxime **(18i)** (2.0 g, 8.34 mmol) and succinic anhydride (4 g) was fused in an oil bath at 180-185^{0}C for 10 min. The reaction mixture was cooled, suspended in water (200 mL) and the acid was neutralized by addition of sodium bicarbonate. The resulting suspension was extracted with successive quantities of chloroform (3x25 mL). The combined organic extract was washed with water (3x50 mL), dried and chloroform was distilled off. The crude product was crystallized from methanol to yield the compound **(19i)**, (0.82 g, 43%), **m.p.** 168-170°C.

Anal:

TLC : 0.85 (Benzene)

UV_{max} (MeOH): 257 nm

IR (KBr, cm^{-1}) : 1601, 1515, 1350, 1087 and 830.

5.113. 3-(4-Fluorophenyl)-4-(4-nitrophenyl)-1,2,5-oxadiazole (19ii)

The title compound **(19ii)** was synthesized as described for compound **(19i)** taking 1-(4-fluorophenyl)-2-(4-nitrophenyl)ethanedione dioxime **(18ii)** (2.0 g, 6.60 mmol) as the starting material. The product was recrystallised from methanol to yield compound **(19ii)**, (0.86 g, 45%), **m.p.** 137-138°C.

Anal:

TLC : 0.76 (Benzene)

UV_{max} (MeOH) : 266 nm

IR (KBr, cm^{-1}) : 1608, 1519, 1448, 1350, 1097 and 842.

5.114. 3-(4-Methylphenyl)-4-(4-nitrophenyl)-1,2,5-oxadiazole (19iii)

The title compound **(19iii)** was synthesized as described for compound **(19i)** taking 1-(4-methylphenyl)-2-(4-nitrophenyl)ethanedione dioxime **(18iii)** (2.0 g, 6.68 mmol) as the starting material. The product was recrystallised from methanol to yield compound **(19iii)**, (0.72 g, 38%), **m.p.** 113-114°C.

Anal:

TLC : 0.78 (Benzene)

UV_{max} (MeOH) : 257 nm

IR (KBr, cm^{-1}) : 1602, 1517, 1448, 1346, 1109 and 852.

5.115. 3-(4-Methoxyphenyl)-4-(4-nitrophenyl)-1,2,5-oxadiazole (19iv)

The title compound **(19iv)** was synthesized as described for compound **(19i)** taking 1-(4-methoxyphenyl)-2-(4-nitrophenyl)ethanedione dioxime **(18iv)** (2.0 g, 6.68 mmol) as the starting material. The product was recrystallised from methanol to yield compound **(19iv)**, (0.6 g, 32%), **m.p.** 125-126°C.

Anal:

TLC : 0.80 (Benzene)

UV_{max} (MeOH) : 266 nm

IR (KBr, cm^{-1}) : 1610, 1519, 1436, 1350, 1174 and 835.

5.116. 3-(4-Aminophenyl)-4-(4-chlorophenyl)-1,2,5-oxadiazole (20i)

Sodium chloride (1.0 g) and iron powder (1.0 g) were added in parts to a refluxing solution of 3-(4-chlorophenyl)-4-(4-nitrophenyl)-1,2,5-oxadiazole **(19i)** (0.5 g, 1.87 mmol) in aqueous methanol (200 mL, 95%). Refluxing was continued further for 7 hr. The reaction mixture was filtered through filtering aid (high flow supercel) and the filtrate was concentrated in *vaccuo* to remove methanol. The resulting aqueous solution was neutralized by adding sodium bicarbonate and extracted with chloroform (3x25 mL). The combine organic extract was dried and the solvent removed to obtain a residue which was crystallized from aqueous methanol to yield the compound **(20i)**, (0.4 g, 90%), **m.p.** 98-100°C.

Anal:

TLC : 0.28 (Benzene)

UV_{max} (MeOH) : 243 nm

IR (KBr, cm^{-1}) : 3482, 3382, 3230, 1624, 1446 and 835

PMR : 6.95-7.42 (m, 8H) and 3.75 (s, 2H)

5.117. 3-(4-Aminophenyl)-4-(4-fluorophenyl)-1,2,5-oxadiazole (20ii)

The title compound **(20ii)** was synthesized as per the method described for compound **(20i)** taking 3-(4-fluorophenyl)-4-(4-nitrophenyl)-1,2,5-oxadiazole **(19ii)** (0.5 g, 1.75 mmol) as the starting material. The product was crystallized from aqueous methanol to offer compound **(20ii)**, (0.4 g, 89%), **m.p.** 107-108°C.

Anal:

TLC : 0.3 (Benzene)

UV_{max} (MeOH) : 262 nm

IR (KBr, cm^{-1}) : 3477, 3378, 3228, 1624, 1446 and 835.

PMR : 6.51-7.91 (m, 8H) and 4.0 (s, 2H)

5.118. 3-(4-Aminophenyl)-4-(4-methylphenyl)-1,2,5-oxadiazole (20iii)

The title compound **(20iii)** was synthesized as per the method described for compound **(20i)** taking 3-(4-methylphenyl)-4-(4-nitrophenyl)-1,2,5-oxadiazole **(19iii)** (0.5 g, 1.75 mmol) as the starting material. The product was crystallized from aqueous methanol to offer compound **(20iii)**, (0.4 g, 89 %), **m.p.** 143-144°C.

Anal:

TLC : 0.3 (Benzene)

UV_{max} (MeOH) : 258 nm

IR (KBr, cm^{-1}) : 3469, 3134, 3224, 1620, 1446 and 835.

PMR : 6.51-7.91 (m, 8H), 2.40 (s, 3H) and 3.9 (s, 2H)

5.119. 3-(4-Aminophenyl)-4-(4-methoxyphenyl)-1,2,5-oxadiazole (20iv)

The title compound **(20iv)** was synthesized as per the method described for compound **(20i)** taking 3-(4-methoxyphenyl)-4-(4-nitrophenyl)-1,2,5-oxadiazole **(19iv)** (0.5 g, 1.75 mmol) as the starting material. The product was crystallized from aqueous methanol to offer compound **(20iv)**, (0.4 g, 89%), **m.p.** 95-96°C.

Anal:

TLC : 0.3 (Benzene)

UV_{max} (MeOH) : 262 nm

IR (KBr, cm^{-1}) : 3469, 3373, 3232, 1620, 1445, 1244 and 835.

PMR : 6.72-7.85 (m, 8H), 4.0 (s, 3H), and 4.53 (s, 2H)

5.120. 1-{4-[4-(4-Chlorophenyl)furazan-3-yl]phenyl}-3-(2,4-difluorophenyl)urea (21a)

3-(4-Aminophenyl)-4-(4-chlorophenyl)-1,2,5-oxadiazole **(20i)** (0.2 g, 0.46 mmol) was dissolved in toluene (25 mL). 2,4-Difluorophenyl isocyanate (1 mL) was added and the reaction mixture was stirred for 5 hr and the reaction was monitored by TLC. Solid precipitate so obtained

was filtered, washed with toluene to remove the excess isocyanate. The ppt was dried and collected to obtain the desired compound **(21a)**, (0.15 g, 70%), **m.p.** 221-223°C.

Anal:

TLC : 0.3 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 260 nm

IR (KBr, cm^{-1}) : 3292, 3182, 1656, 1603, 1551, 1423 and 1142

PMR : 8.41(s, 1H), 8.81 (s, 1H), 8.21-8.41 (m, 1H), 7.21-7.42 (m, 4H), 7.42-7.62 (m, 4H) and 6.71-7.05 (m, 2H).

5.121. 1-{4-[4-(4-Chlorophenyl)furazan-3-yl]phenyl}-3-(2,6-diethylphenyl)urea (21b)

The title compound **(21b)** was synthesized as per the method described for compound **(21a)** taking 3-(4-aminophenyl)-4-(4-chlorophenyl)-1,2,5-oxadiazole **(20i)** (0.2 g, 0.46 mmol) and 2,6-diethylphenyl isocyanate (1 mL) as the starting materials. The crude product was purified through column chromatography to obtain pure compound **(21b)**, (0.15g, 70%), **m.p.** 198-200°C.

Anal:

TLC : 0.32 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 260 nm

IR (KBr, cm^{-1}) : 3321, 1650, 1595, 1550, 1259 and 801

PMR : 7.01-7.51 (m, 8H), 7.62-7.81 (m, 2H), 7.82-7.91 (t, 1H), 2.61-2.67 (q, 4H) and 1.2-1.4 (t, 6H).

5.122. 1-Butyl-3-{4-[4-(4-chlorophenyl)furazan-3-yl]phenyl}urea (21c)

The title compound **(21c)** was synthesized as per the method described for compound **(21a)** taking 3-(4-aminophenyl)-4-(4-chlorophenyl)-1,2,5-oxadiazole **(20i)** (0.2 g, 0.46 mmol) and *n*-butyl isocyanate (1 mL) as the starting materials. The crude product was purified through column chromatography to obtain the pure desired product **(21c)**, (0.15 g, 70 %), **m.p.** 184-186°C.

Anal:

TLC : 0.30 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 260 nm

IR (KBr, cm^{-1}) : 3299, 1638, 1571, 1498, 1296, 1092 and 898

PMR : 8.41 (s, 1H), 7.2-7.7 (m, 8H), 3.37 (s, 3H), 3.21-3.45 (m, 2H), 1.2-1.4 (m, 4H) and 0.9-1.01 (t, 3H).

5.123. 1-Heptyl-3-{4-[4-(4-chlorophenyl)furazan-3-yl]phenyl}urea (21d)

The title compound **(21d)** was synthesized as per the method described for compound **(21a)** taking 3-(4-aminophenyl)-4-(4-chlorophenyl)-1,2,5-oxadiazole **(20i)** (0.2 g, 0.46 mmol) and *n*-heptyl isocyanate (1 mL) as the starting materials. The crude product was purified through column chromatography to obtain the pure desired compound **(21d)**, (0.1 g, 65 %), **m.p.** 160-162°C.

Anal:

TLC : 0.32 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 260 nm

IR (KBr, cm^{-1}) : 3321, 1650, 1573, 1499, 1295 and 875

PMR : 6.91 (bs, 1H), 7.51-8.1 (m, 8H), 5.2 (bs, 1H), 3.35-3.52 (m, 2H), 1.51-1.61(m, 10H) and 0.9-1.01 (t, 3H).

5.124. 1-{4-[4-(4-Chlorophenyl)furazan-3-yl]phenyl}-3-dodecylurea (21e)

The title compound **(21e)** was synthesized as per the method described for compound **(21a)** taking 3-(4-aminophenyl)-4-(4-chlorophenyl)-1,2,5-oxadiazole **(20i)** (0.2 g, 0.46 mmol) and *n*-dodecyl isocyanate (1 mL) as the starting materials. The crude product was purified through column chromatography to obtain the pure compound **(21e)**, (0.1g, 65%), **m.p.** 110-112°C.

Anal:

TLC : 0.35 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 260 nm

IR (KBr, cm^{-1}) : 3336, 1636, 1568, 1468, 1291 and 891

PMR : 8.2 (bs, 1H), 7.2-7.4 (m, 8H), 6.1 (bs, 1H), 3.1-3.3 (q, 2H), 1.3-1.5 (m, 20H) and 0.9-1.01 (t, 3H).

5.125. 1-{4-[4-(4-Fluorophenyl)furazan-3-yl]phenyl}-3-(2,4-difluorophenyl)urea (21f)

The title compound **(21f)** was synthesized as per the method described for compound **(21a)** taking 3-(4-aminophenyl)-4-(4-fluorophenyl)-1,2,5-oxadiazole **(20ii)** (0.2 g, 0.46 mmol) and 2,4-difluorophenyl isocyanate (1 mL) as the starting material. The crude product was crystallized from aqueous methanol to obtain compound **(21f)**, (0.1 g, 50 %), **m.p.** 212-214°C.

Anal:

TLC : 0.35 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 264 nm

IR (KBr, cm^{-1}) : 3301, 1654, 1453, 1294, 1229, 1102 and 848

PMR : 8.21 (bs, 1H), 8.81 (bs, 1H), 8.21-8.41 (m, 1H), 7.21-7.42 (m, 4H), 7.42-7.62 (m, 4H) and 6.71-7.05 (m, 2H)

5.126. 1-{4-[4-(4-Fluorophenyl)furazan-3-yl]phenyl}-3-(2,6-diethylphenyl)urea (21g)

The title compound **(21g)** was synthesized as per the method described for compound **(21a)** taking 3-(4-aminophenyl)-4-(4fluorophenyl)-1,2,5-oxadiazole **(20ii)** (0.2 g, 0.46 mmol) and 2,6-diethylphenyl isocyanate (1 mL) as the starting material. The crude product was crystallized from aqueous methanol to obtain pure compound **(21g)**, (0.1 g, 50 %), **m.p.** 210-212°C.

Anal:

TLC : 0.35 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 264 nm

IR (KBr, cm^{-1}) : 3286, 1639, 1401, 1310, 1225, 1096 and 810

PMR : 7.01-7.51 (m, 8H), 7.62-7.81 (m, 2H), 7.82-7.91 (m, 1H), 2.61-2.67 (q, 4H) and 1.2-1.4 (t, 6H).

5.127. 1-Butyl-3-{4-[4-(4-fluorophenyl)furazan-3-yl]phenyl}urea (21h)

The title compound **(21h)** was synthesized as per the method described for compound **(21a)** taking 3-(4-aminophenyl)-4-(4-fluorophenyl)-1,2,5-oxadiazole **(20ii)** (0.2 g, 0.46 mmol) and *n*-butyl isocyanate (1 mL) as the starting materials. The crude product was crystallized from aqueous methanol to obtain pure compound **(21h)**, (0.1 g, 50 %) **m.p.** 150-152°C.

Anal:

TLC : 0.36 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 264 nm

IR (KBr, cm^{-1}) : 3300, 1637, 1577, 1509, 1451, 1236 and 839

PMR : 8.41 (bs, 1H), 5.91 (bs, 1H), 7.21-7.61 (m, 8H), 3.62- 3.81 (q, 2H), 2.61-2.67(m, 4H) and 1.2-1.4 (t, 3H).

5.128. 1-Heptyl-3-{4-[4-(4-fluorophenyl)furazan-3-yl]phenyl}urea (21i)

The title compound **(21i)** was synthesized as per the method described for compound **(21a)** taking 3-(4-aminophenyl)-4-(4-fluorophenyl)-1,2,5-oxadiazole **(20ii)** (0.2 g, 0.46 mmol) and *n*-heptyl isocyanate (1 mL) as the starting materials. The crude product was crystallized from aqueous methanol to obtain compound **(21i)**, (0.1 g, 50%), **m.p.** 136-138°C.

Anal:

TLC : 0.35 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 260 nm

IR (KBr, cm^{-1}) : 3298, 1637, 1553, 1453, 1235 and 841

PMR : 8.41 (bs, 1H), 7.2-7.7 (m, 8H), 5.91 (bs, 1H), 3.37-3.45 (m, 2H), 1.37-1.45 (m, 10H) and 0.9-1.01 (t, 3H).

5.129. 1-4-[4-(4-Fluorophenyl)furazan-3-yl]phenyl-3-dodecylurea (21j)

The title compound **(21j)** was synthesized as per the method described for compound **(21a)** taking 3-(4-aminophenyl)-4-(4-fluorophenyl)-1,2,5-oxadiazole **(20ii)** (0.2 g, 0.46 mmol) and *n*-dodecyl isocyanate (1 mL) as the starting materials. The crude product was crystallized from aqueous methanol to obtain pure compound **(21j)**, (0.1 g, 50%), **m.p.** 82-85°C.

Anal:

TLC : 0.34 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 260 nm

IR (KBr, cm^{-1}) : 3336, 1636, 1401, 1096 and 810

PMR : 8.5 (bs, 1H), 7.8 (bs, 1H), 7.2-7.4 (m, 8H), 1.3-3.5 (m, 22H) and 0.9-1.02 (t, 3H).

5.130. 1-(2,4-Difluorophenyl)-3-[4-(*p*-tolyl)-1,2,5-oxadiazol-3-yl]phenylurea (21k)

The title compound **(21k)** was synthesized as per the method described for compound **(21a)** taking 3-(4-aminophenyl)-4-(4-methylphenyl)-1,2,5-oxadiazole **(20iii)** (0.2 g, 0.46 mmol) and 2,4-difluorophenyl isocyanate (1 mL) as the starting materials. The crude product was crystallized from aqueous methanol to obtain pure compound **(21k)**, (0.1 g, 50%), **m.p.** 198-200°C.

Anal:

TLC : 0.35 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 265 nm

IR (KBr, cm^{-1}) : 3446, 1650, 1400, 1262, 1021 and 805

PMR : 9.3 (bs, 1H), 8.4 (bs, 1H), 6.8-8.2 (m, 11H) and 2.3 (s, 3H).

5.131. 1-(2,6-Diethylphenyl)-3-[4-(*p*-tolyl)-1,2,5-oxadiazol-3-yl]phenylurea (21l)

The title compound **(21l)** was synthesized as per the method described for compound **(21a)** taking 3-(4-aminophenyl)-4-(4-methylphenyl)-1,2,5-oxadiazole **(20iii)** (0.2 g, 0.46 mmol) and 2,6-diethylphenyl isocyanate (1 mL) as the starting materials. The crude product was crystallized from aqueous methanol to obtain pure compound **(21l)**, (0.1 g, 50%), **m.p.** 205-207°C.

Anal:

TLC : 0.32 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 262 nm

IR (KBr, cm^{-1}) : 3286, 1639, 1400, 1262, 1021 and 805

PMR : 7.01-7.51 (m, 8H), 7.62-7.81 (m, 2H), 7.82-7.91 (m, 1H), 2.61- 2.67 (q, 4H), 2.37 (s, 3H) and 1.2-1.4 (t, 6H).

5.132. 1-Butyl-3-[4-(*p*-tolyl)-1,2,5-oxadiazol-3-yl]phenylurea (21m)

The title compound **(21m)** was synthesized as per the method described for compound **(21a)** taking 3-(4-aminophenyl)-4-(4-methylphenyl)-1,2,5-oxadiazole **(20iii)** (0.2 g, 0.46 mmol) and *n*-butyl isocyanate (1 mL) as the starting materials. The crude product was crystallized from aqueous methanol to obtain pure compound **(21m)**, (0.1 g, 50%), **m.p.** 165-168°C.

Anal:

TLC : 0.34 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 265 nm

IR (KBr, cm^{-1}) : 3301, 1654, 1453, 1401, 1229, 1025 and 804.

PMR : 8.41 (s, 1H), 7.2-7.7 (m, 8H), 5.91 (s, 1H), 3.37-3.40 (m, 2H), 2.37 (s, 3H), 1.2-1.4 (m, 4H) and 0.9-1.06 (t, 3H).

5.133. 1-Heptyl-3-[4-(*p*-tolyl-1,2,5-oxadiazol-3-yl]phenylurea (21n)

The title compound **(21n)** was synthesized as per the method described for compound **(21a)** taking 3-(4-aminophenyl)-4-(4-methylphenyl)-1,2,5-oxadiazole **(20iii)** (0.2 g, 0.46 mmol) and *n*-heptyl isocyanate (1 mL) as the starting materials. The crude product was crystallized from aqueous methanol to obtain pure compound **(21n)**, (0.1 g, 50%), **m.p.** 142-145°C.

Anal:

TLC : 0.32 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 263 nm

IR (KBr, cm^{-1}) : 3321, 1650, 1511, 1401, 1255 and 810

PMR : 7.52-8.12 (m, 8H), 6.92 (bs, 1H), 5.21 (bs, 1H), 3.32 (m, 2H), 1.52-1.81 (m, 10H), 2.37 (s, 3H) and 0.91-1.02 (t, 3H)

5.134. 1-Dodecyl-3-[4-(*p*-tolyl)-1,2,5-oxadiazol-3-yl]phenylurea (21o)

The title compound **(21o)** was synthesized as per the method described for compound **(21a)** taking 3-(4-aminophenyl)-4-(4-methylphenyl)-1,2,5-oxadiazole **(20iii)** (0.2 g, 0.46 mmol) and *n*-dodecyl isocyanate (1 mL) as the starting material. The crude product was purified through column chromatography to obtain compound **(21o)**, (0.12 g, 62%), **m.p.** 162-165°C.

Anal:

TLC : 0.34 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 265 nm

IR (KBr, cm^{-1}) : 3336, 1636, 1524, 1290, 1024 and 814.

PMR : 8.5 (s, 1H), 7.2-7.4, (m, 8H), 7.8 (s, 1H), 2.3(s, 3H), 1.3-3.5 (m, 22H) and 0.9-1.05 (t, 3H).

5.135. 1-(2,4-Difluorophenyl)-3-[4-(4-methoxyphenyl)-1,2,5-oxadiazol-3-yl]phenylurea (21p)

The title compound **(21p)** was synthesized as per the method described for compound **(21a)** taking 3-(4-aminophenyl)-4-(4-methoxyphenyl)-1,2,5-oxadiazole **(20iv)** (0.2 g, 0.46 mmol) and 2,4-difluorophenyl isocyanate (1 mL) as the starting materials. The crude product was crystallized from aqueous methanol to obtain compound **(21p)**, (0.13 g, 66 %), **m.p.** 210-212°C.

Anal:

TLC : 0.35 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 262 nm

IR (KBr, cm^{-1}) : 3401, 3124, 1654, 1504, 1220, 1027 and 836.

PMR : 8.4 (s, 1H), 9.3 (s, 1H), 6.8-8.2 (m, 11H) and 4.0 (s, 3H)

5.136. 1-(2,6-Diethylphenyl)-3-[4-(4-methoxyphenyl)-1,2,5-oxadiazol-3-yl]phenylurea (21q)

The title compound **(21q)** was synthesized as per the method described for compound **(21a)** taking 3-(4-aminophenyl)-4-(4-methoxyphenyl)-1,2,5-oxadiazole **(20iv)** (0.2 g, 0.46 mmol)

and 2,4-diethylphenyl isocyanate (1 mL) as the starting materials. The crude product was crystallized from aqueous methanol to obtain pure compound **(21q)**, (0.09 g, 45 %), **m.p.** 240-242°C.

Anal:

TLC : 0.38 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 264 nm

IR (KBr, cm^{-1}) : 3298, 3129, 1637, 1410, 1220, 1024 and 854

PMR : 7.01-7.51 (m, 8H), 7.62-7.81 (d, 2H), 7.82-7.91 (m, 1H), 2.61-2.67 (q, 4H), 4.0 (s, 3H) and 1.2-1.4 (t, 6H)

5.137. 1-Butyl-3-[4-(4-methoxyphenyl)-1,2,5-oxadiazol-3-yl]phenylurea (21r)

The title compound **(21r)** was synthesized as per the method described for compound **(21a)** taking 3-(4-aminophenyl)-4-(4-methoxyphenyl)-1,2,5-oxadiazole **(20iv)** (0.2 g, 0.46 mmol) and *n*-butyl isocyanate (1 mL) as the starting materials. The crude product was crystallized from aqueous methanol to obtain pure compound **(21r)**, (0.12 g, 61%), **m.p.** 150-152°C.

Anal:

TLC : 0.32 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 264 nm

IR (KBr, cm^{-1}) : 3321, 1650, 1450, 1222 and 1025

PMR : 8.45 (s, 1H), 7.2-7.7 (m, 8H), 5.9 (s, 1H), 3.37-3.40 (m, 2H), 4.05 (s, 3H), 1.2-1.4 (m, 4H) and 0.9-1.05 (t, 3H)

5.138. 1-Heptyl-3-[4-(4-methoxyphenyl)-1,2,5-oxadiazol-3-yl]phenylurea (21s)

The title compound **(21s)** was synthesized as per the method described for compound **(21a)** taking 3-(4-aminophenyl)-4-(4-methoxyphenyl)-1,2,5-oxadiazole **(20iv)** (0.2 g, 0.46 mmol) and *n*-heptyl isocyanate (1 mL) as the starting materials. The crude product was crystallized from aqueous methanol to obtain pure compound **(21s)**, (0.11 g, 49%) **m.p.** 135-138°C.

Anal:

TLC : 0.36 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 261 nm

IR (KBr, cm^{-1}) : 3446, 1650, 1545, 1409, 1225 and 1025

PMR : 7.5-8.1 (m, 8H), 6.91 (bs, 1H), 5.2 (bs, 1H), 3.3-3.5 (m, 2H), 3.8 (s, 3H), 1.5-1.8 (m, 10H) and 0.9-1.02 (t, 3H)

5.139. 1-Dodecyl-3-[4-(4-methoxyphenyl)-1,2,5-oxadiazol-3-yl]phenylurea (21t)

The title compound **(21t)** was synthesized as per the method described for compound **(21a)** taking 3-(4-aminophenyl)-4-(4-methoxyphenyl)-1,2,5-oxadiazole **(20iv)** (0.2 g, 0.46 mmol) and *n*-dodecyl isocyanate (1 mL) as the starting materials. The crude product was crystallized from aqueous methanol to obtain compound **(21s)**, (0.1 g, 50%), **m.p.** 121-123°C.

Anal:

TLC : 0.34 (*n*-Hexane: Ethyl acetate) (7: 3)

UV_{max} (MeOH) : 262 nm

IR (KBr, cm^{-1}) : 3336, 1636, 1547, 1410 and 1220

PMR : 8.5 (bs, 1H), 7.8 (bs, 1H), 7.2-7.4 (m, 8H), 4.0 (s, 3H), 1.3-3.5 (m, 22H) and 0.9-1.08 (t, 3H).

5.140. Biological studies

Screening of the synthesized compounds was performed as per the method of Largis et al[141, 142] with some modifications. The assay mixture consisted of potassium phosphate buffer (0.1 M), BSA (5 mg/ml), microsomal protein from rat liver (200 µg) and cholesterol solubilized in 45% w/v hydroxypropyl β-cyclodextrin (2 mM) and the reaction volume was made upto 850 µl with the help of potassium phosphate buffer (0.1 M). Vehicle or test/standard compounds were added having a final volume not exceeding 10 µl and incubated at room temperature for 15 mins to allow binding with the ACAT enzymes. The reaction was initiated by the addition of oleoyl CoA (200 µM, sigma). The reaction was allowed to proceed for 10 minutes at 37°C and was terminated by the addition of of chloroform: methanol mixture (6 mls, 2:1 v/v). This mixture was shaken in a separating funnel and phases were allowed to segregate. The organic phase was collected and evaporated to dryness. The residue was resuspended in of chloroform: methanol (500 µl, 2:1 v/v) and 25 µl of this solution was spotted on the aluminium backed silica gel $60F_{254}$ TLC plates (Merck) for separation of cholesteryl oleate and its quantification. Each sample was applied to the TLC plates at least in triplicate. Before sample application, chromatography plates were pre-washed using methanol as a mobile phase and dried for 10 minutes at 120°C to activate the plates. Samples were applied to the plate as 6 mm wide bands, 10 mm apart by means of Linomat V sample applicator (Camag, Switzerland) fitted with a 100 µl Hamilton syringe. A constant rate of application of 150 nl/s was used. After sample application, the plates were dried in a current of dry air and developed in a linear ascending manner using *n*-hexane-diethyl ether-glacial acetic

acid (90:10:1, v/v/v) as mobile phase. Mobile phase (18 ml) was used for development of each plate. Development was performed in a 10×10 twin-trough chamber (Camag, Switzerland) which was previously saturated with mobile phase for 30 minutes. All the steps were performed at 25±2°C and ambient relative humidity. The solvent front position was fixed at 80 mm from the point of application.

After running the mobile phase the plates were dried and dipped in a solution of anisaldehyde-sulphuric acid reagent. The plates were dried and heated at 120°C for 8 minutes. This led to the development of purple colored bands on the plates. Densitometric scanning was performed with Scanner III (Camag, Switzerland) in absorbance mode at 546 nm. The slit dimension was set at 6mm × 0.45mm and scanning speed was kept at 20 mm/s. Calculations were performed with the help of WinCats software (version 1.4.4, Camag). Percentage inhibition values were obtained by comparing the AUC of cholesteryl oleate in test compound lanes to that of vehicle lane.

6. Summary

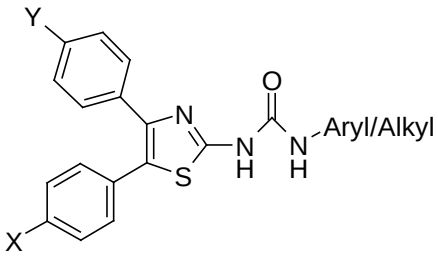
High serum cholesterol levels have been associated with cardiovascular diseases (CVD), a leading cause of death in the world. Atherosclerosis is a disease of medium and large arteries, characterized by progressive thickening of arterial intima. Occlusion of these vessels may ultimately lead to myocardial infarction. This is the leading cause of morbidity and mortality in the developed and developing countries.

Acyl-Coenzyme A: Cholesterol O-Acyltransferase (ACAT)

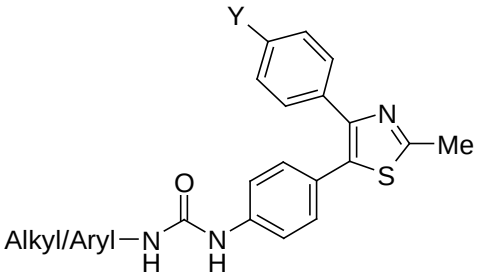
The acyl-coenzyme A: cholesterol O-acyltransferase (ACAT) family is a small enzyme family comprising three homologous members, acyl-coenzyme A: cholesterol O-acyltransferase 1 and 2 (ACAT1 and ACAT2), and acyl-coenzyme A: diacylglycerol acyltransferase 1 (DGAT1). These enzymes are responsible for *in vivo* neutral lipid synthesis. Among them, ACAT1 and ACAT2 catalyze the synthesis of cholesteryl esters using long-chain fatty acyl-coenzyme A and free cholesterol as substrates.

ACAT1 and ACAT2 are critical for *in vivo* cholesterol homeostasis. Under pathophysiological conditions, they convert excess cholesterol into cholesteryl esters in cholesterol-loaded macrophages. The macrophages are gradually converted into foam cells, which is a hallmark of early lesions of atherosclerosis.

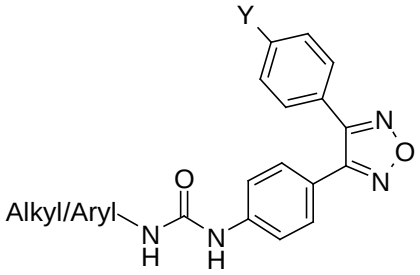
A review of literature revealed the existence of a plethora of compounds possessing ACAT inhibitory activity *in vitro* and *in vivo*. All of these have common characteristic features in their structures. They commonly possessed either an amide or urea moiety, one of the most essential functionality for ACAT inhibitory activity. Between the two functionalities, the urea derivatives have proved to be more potent than the amide derivatives. Other characteristic features included a polar head linked to a lipophilic tail and various heterocyclic and substituted carbocyclic rings. The heterocyclic ring systems were usually imidazole, oxazole, isoxazole, tetrazole and pyrazole. A disubstituted urea derivative with a thiazole or 1,2,5-oxadiazole rings possessing ACAT inhibitory activity could not be traced in the literature.



(I)



(II)



(III)

Y = Cl, F, Me, OMe etc.

X = Cl, F, Me, OMe, COMe, SO_2Me, $CH(Me)_2$

Aryl = Phenyl, 2,4-Difluorophenyl, 2,6-Diethylphenyl etc.

Alkyl = Butyl, Heptyl, Dodecyl etc.

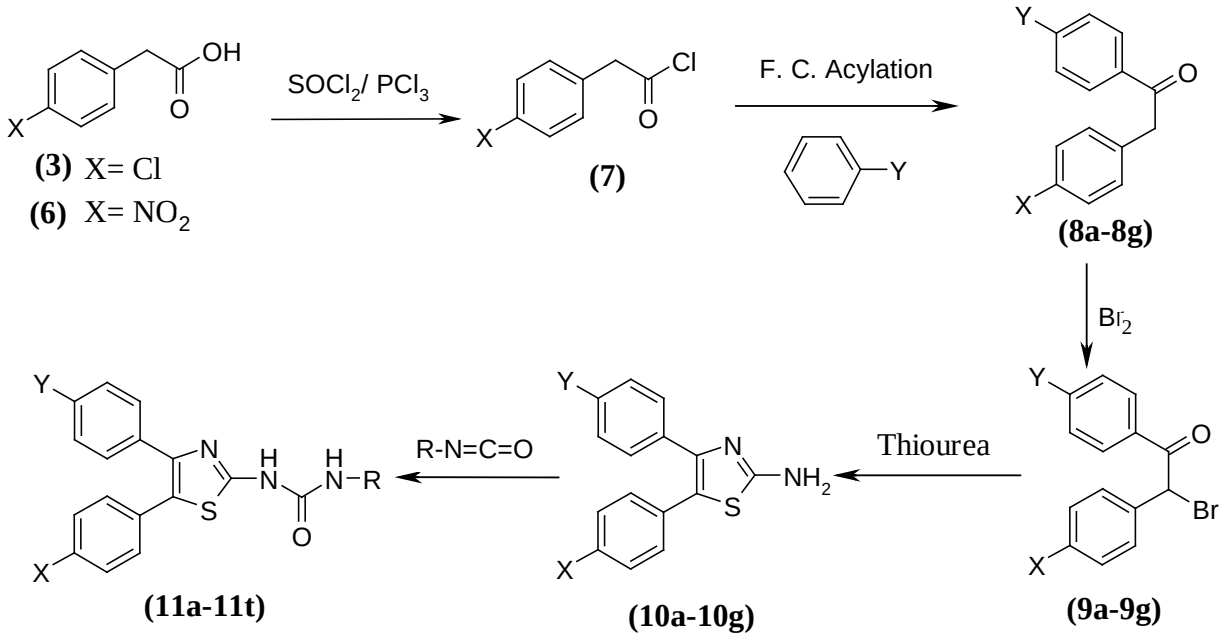
Keeping this fact in mind it was planned to design disubstituted ureas **(I-III)** incorporating all mandatory functionalities required for activity. The compounds **(I-III)** were synthesized by following various systematic schemes and characterised by various spectroscopic techniques. Further, the synthesized compounds were screened for their ACAT inhibitory activity *in vitro*.

Chemical Studies

It was envisaged to synthesize various disubstituted urea derivatives **(I-III)**. The various schemes as described below were followed for the synthesis of the designed compounds.

A. Synthesis of 2-thiazolylurea derivatives

Various substituted diaryl ethanones or desoxybenzoins **(8a-8g)** were important intermediates required for this work. Friedel-Craft acylation reaction was carried out between the 4-chloro/nitrophenylacetyl chloride **(7)** and substituted benzenes to obtain the substituted diaryl ethanones or desoxybenzoins, as common intermediates **(8a-8g)**. The common inter-



(3) X= Cl
(6) X= NO_2

(7)

(8a-8g)

(9a-9g)

(10a-10g)

(11a-11t)

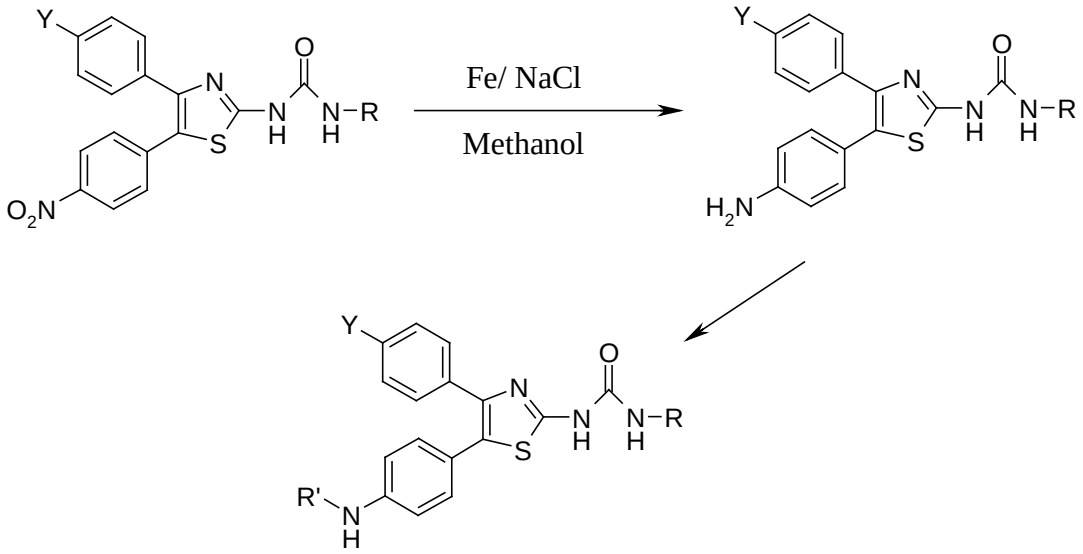
(8a, 9a, 10a)	X = Cl	Y = F
(8b, 9b, 10b)	X = Cl	Y = Me
(8c, 9b, 10c)	X = Cl	Y = OMe
(8d, 9d, 10d)	X = NO_2	Y = Cl
(8e, 9e, 10e)	X = NO_2	Y = F
(8f, 9f, 10f)	X = NO_2	Y = Me
(8g, 9g, 10g)	X = NO_2	Y= OMe

(a)	X = Cl	Y = F	R = 2,4-Difluorophenyl
(b)	X = Cl	Y = F	R = *n*-Butyl
(c)	X = Cl	Y = F	R = 2,6-Diethylphenyl
(d)	X = Cl	Y = F	R = *n*-Dodecyl
(e)	X = Cl	Y = Me	R = Phenyl
(f)	X = Cl	Y = Me	R = 2,4-Difluorophenyl
(g)	X = Cl	Y = Me	R = *n*-Butyl
(h)	X = Cl	Y = Me	R = 2,6-Diethylphenyl
(i)	X = Cl	Y = OMe	R = Phenyl
(j)	X = Cl	Y = OMe	R = 2,4-Difluorophenyl
(k)	X = Cl	Y = OMe	R = *n*-Butyl
(l)	X = Cl	Y = OMe	R = *n*-Dodecyl
(m)	X = NO_2	Y = Cl	R = 2,4-Diflurophenyl
(n)	X = NO_2	Y = F	R = 2,4-Diflurophenyl
(o)	X = NO_2	Y = Me	R = 2,4-Diflurophenyl
(p)	X = NO_2	Y = OMe	R = 2,4-Diflurophenyl
(q)	X = NO_2	Y = Cl	R = *n*-Butyl
(r)	X = NO_2	Y = F	R = *n*-Butyl
(s)	X = NO_2	Y = Me	R = *n*-Butyl
(t)	X = NO_2	Y = OMe	R = *n*-Butyl

Scheme I

mediates **(8a-8g)** were brominated by reacting them with bromine in glacial acetic acid medium to obtain the bromo derivatives **(9a-9g).** The bromo intermediates (**9a-9g**) and thiourea were refluxed for 3-4 hr in ethanol to obtain the corresponding substituted 4,5-diphenylthiazoles (**10a-10g**). All of the synthesized derivatives were characterized by their IR

and mass spectra. The respective 4,5-diaryl-thiazol-2-ylamines **(10a-10g)** were dissolved in dry toluene and were reacted with different substituted isocyanates to obtain the desired disubstituted urea derivatives **(11a-11t) (Scheme I)**. These disubstituted ureas were purified by column chromatography using different solvent systems and characterized on the basis of their IR, NMR and mass spectra.



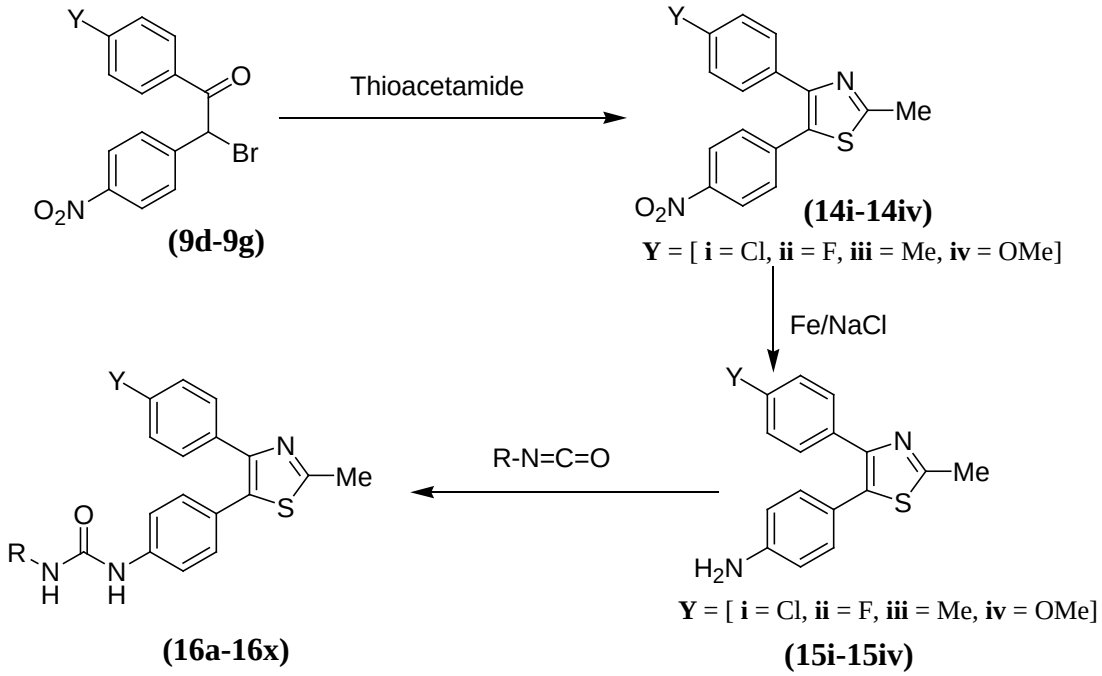
(a)	Y = Cl	R = 2,4-Difluorophenyl	R’ = COMe
(b)	Y = Cl	R = 2,4-Difluorophenyl	R’ = SO_2Me
(c)	Y = Cl	R = *n*-Butyl	R’ = COMe
(d)	Y = Cl	R = *n*-Butyl	R’ = SO_2Me
(e)	Y = F	R = 2,4-Difluorophenyl	R’= COMe
(f)	Y = F	R = 2,4-Difluorophenyl	R’ = SO_2Me
(g)	Y = F	R = *n*-Butyl	R’ = COMe
(h)	Y = F	R = *n*-Butyl	R’ = SO_2Me
(i)	Y = Me	R = 2,4-Difluorophenyl	R’ = COMe
(j)	Y = Me	R = 2,4-Difluorophenyl	R’ = SO_2Me
(k)	Y = Me	R = *n*-Butyl	R’ = COMe
(l)	Y = Me	R = *n*-Butyl	R’ = SO_2Me
(m)	Y = OMe	R = 2,4-Difluorophenyl	R’ = *i*-Propyl
(n)	Y = OMe	R = 2,4-Difluorophenyl	R’ = *n*-Dodecyl
(o)	Y = OMe	R = 2,4-Difluorophenyl	R’ = COMe
(p)	Y = OMe	R = 2,4-Difluorophenyl	R’ = SO_2Me
(q)	Y = OMe	R = *n*-Butyl	R’ = *i*-Propyl
(r)	Y = OMe	R = *n*-Butyl	R’ = *n*-Dodecyl
(s)	Y = OMe	R = *n*-Butyl	R’ = COMe
(t)	Y = OMe	R = *n*-Butyl	R’ = SO_2Me

Scheme II

The nitro group containing derivatives **(11m-11t)** were reduced in presence of iron powder (Fe) and NaCl solution in methanol to yield the amino derivatives **(12a-12h)**. The free amino group of derivatives **(12a-12h)** was converted to the targeted derivatives **(13a-13t)** by reacting them with acetic anhydride, mesyl chloride, isopropyl bromide and dodecyl bromide as shown in **scheme II**.

B. Synthesis of 4-thiazolylphenylurea derivatives

The common intermediates **(9d-9g)** were reacted with thioacetamide in methanol to form intermediate diaryl thiazoles **(14i-14iv)**. Upon reduction, the diaryl thiazoles **(14i-14iv)** were



(9d-9g)

(14i-14iv)

Y = [**i** = Cl, **ii** = F, **iii** = Me, **iv** = OMe]

(15i-15iv)

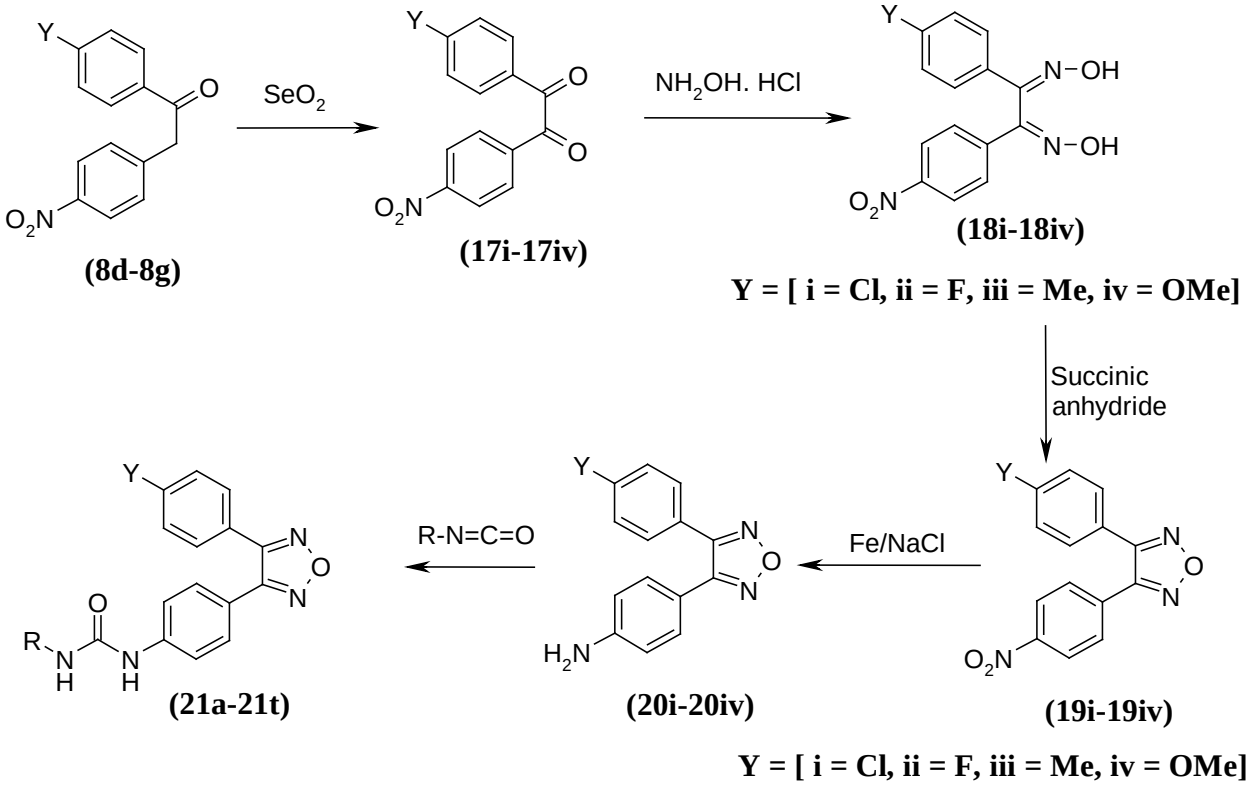
Y = [**i** = Cl, **ii** = F, **iii** = Me, **iv** = OMe]

(16a-16x)

(a)	R = Phenyl	Y = Cl	(m)	R = Phenyl	Y = Me
(b)	R = 2,4-Difluorophenyl	Y = Cl	(n)	R = 2,4-Difluorophenyl	Y = Me
(c)	R = 2,6-Diethylphenyl	Y = Cl	(o)	R = 2,6-Diethylphenyl	Y = Me
(d)	R = *n*-Butyl	Y = Cl	(p)	R = *n*-Butyl	Y = Me
(e)	R = *n*-Heptyl	Y = Cl	(q)	R = *n*-Heptyl	Y = Me
(f)	R = *n*-Dodecyl	Y = Cl	(r)	R = *n*-Dodecyl	Y = Me
(g)	R = Phenyl	Y = F	(s)	R = Phenyl	Y = OMe
(h)	R = 2,4-Difluorophenyl	Y = F	(t)	R = 2,4-Difluorophenyl	Y = OMe
(i)	R = 2,6-Diethylphenyl	Y = F	(u)	R = 2,6-Diethylphenyl	Y = OMe
(j)	R = *n*-Butyl	Y = F	(v)	R = *n*-Butyl	Y = OMe
(k)	R = *n*-Butyl	Y = F	(w)	R = *n*-Heptyl	Y = OMe
(l)	R = *n*-Dodecyl	Y = F	(x)	R = *n*-Dodecyl	Y = OMe

Scheme III

converted to the 4-thiazolylaniline derivatives **(15i-15iv)**. The 4-thiazolylphenylurea derivatives **(16a-16x)** (**Scheme II**) were synthesized by reacting 4-thiazolylaniline derivatives **(15i-15iv)** with various isocyanates. Selection of the isocyanates was based on literature reports



(a)	R = 2,4-Difluorophenyl	Y = Cl	**(k)**	R = 2,4-Difluorophenyl	Y = Me
(b)	R = 2,6-Diethylphenyl	Y = Cl	**(l)**	R = 2,6-Diethylphenyl	Y = Me
(c)	R = *n*-Butyl	Y = Cl	**(m)**	R = *n*-Butyl	Y = Me
(d)	R = *n*-Heptyl	Y = Cl	**(n)**	R = *n*-Heptyl	Y = Me
(e)	R = *n*-Dodecyl	Y = Cl	**(o)**	R = *n*-Dodecyl	Y = Me
(f)	R = 2,4-Difluorophenyl	Y = F	**(p)**	R = 2,4-Difluorophenyl	Y = OMe
(g)	R = 2,6-Diethylphenyl	Y = F	**(q)**	R = 2,6-Diethylphenyl	Y = OMe
(h)	R = *n*-Butyl	Y = F	**(r)**	R = *n*-Butyl	Y = OMe
(i)	R = *n*-Butyl	Y = F	**(s)**	R = *n*-Heptyl	Y = OMe
(j)	R = *n*-Dodecyl	Y = F	**(t)**	R = *n*-Dodecyl	Y = OMe

Scheme IV

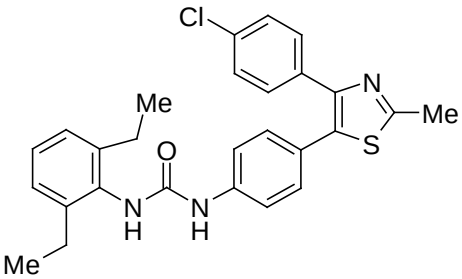
that suggested optimal ACAT enzyme inhibitory activity associated with these groups. Purity of all of the synthesized compounds was checked by TLC in different solvents systems. All of the synthesized derivatives were characterized by their spectral data.

The common intermediates **(8d-8g)** were oxidized in presence of selenium dioxide in different solvents to obtain the titled intermediates (**17i-17iv**). Oximation of the intermediates **(17i-17iv)** yielded the substituted diaryl dioximes **(18i-18iv)** which upon dehydration formed the substituted diaryl oxadiazole derivatives **(19i-19iv)**. IR spectra of all of the synthesized derivatives **(18i-18iv)** displayed characteristic IR peaks at 3253 (N-OH str), 1520 (N=O str), 1346 cm^{-1} (N=O str) and disappearance of C=O str in the region 1666-1668 cm^{-1}. All of the synthesized derivatives (**18i-18iv**) were dehydrated in presence of succinic anhydride to obtain the desired diaryl furazans (**19i-19iv**). All of the synthesized diarylfurazans or oxadiazoles (**19i-19iv)** displayed characteristic IR bands at 1230 (C-N str) and disappearance of peak at 3253 cm^{-1}(N-OH str). The nitro derivatives **(19i-19iv)** were reduced in presence of iron powder in acidic medium to obtain the 4-furazanylaniline derivavatives **(20i-20iv)**. The synthesized anilines **(20i-20iv)** were reacted further with desired isocyanates in toluene at room temperature to obtain the diaryl oxadiazole ureas **(21a-21t) (Scheme IV)**. All the synthesized compounds were characterized on the basis of their IR, NMR and Mass spectra.

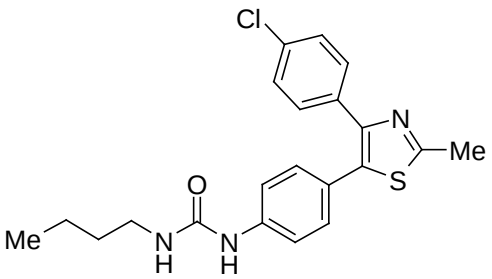
Biological Studies

The biological studies were carried out in the pharmacological division of this department. Some of the compounds were evaluated for their inhibitory potency towards the ACAT enzymes. Screening of test compounds was performed as per the method of Largis et al with some modifications.

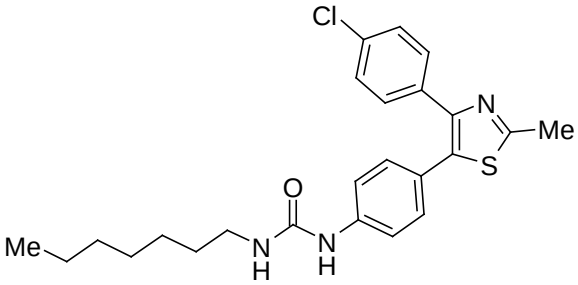
4-Thiazolylphenylurea derivatives with 2,6-diethylphenyl (**16c**, **16i**), *n*-butyl (**16d**, **16j**, **16p**) and *n*-heptyl (**16e**, **16k**) side chain exhibited good ACAT inhibitory activity (more than 60% inhibition at 10 µM conc.) in comparison to standard drug Avasimibe (73.63% at 10 µM conc). This was expected of them due to their moderate non-polar nature.



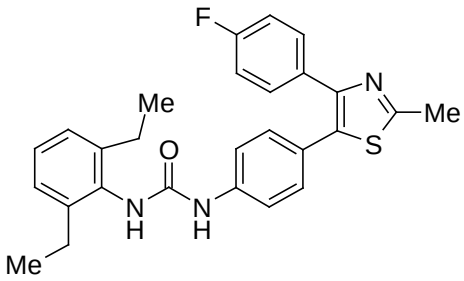
(16c, 63.32 %**)**



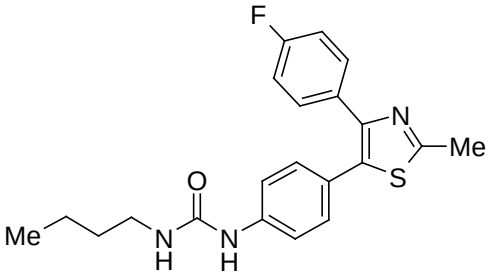
(16d, 60.71% **)**



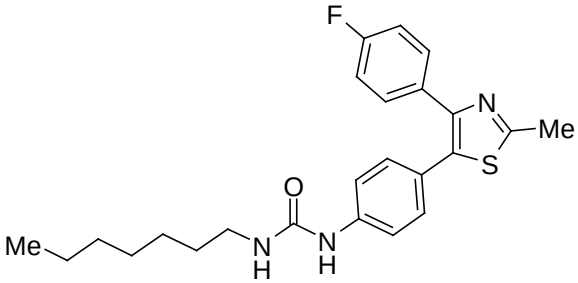
(16e, 52.18 %**)**



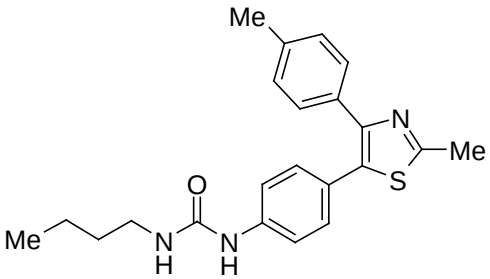
(16i, 46.68 %**)**



(16j, 59.91%**)**



(16k, 62.96 %**)**



(16p, 64.91%**)**

2-Thiazolylurea derivatives (**11a**, **11i** and **13m**) and 4-furazanylphenylurea derivatives (**21f**, **21g** and **21h**) showed moderate inhibition (more than 45% inhibition at 10 µM conc.) in comparison to the standard drug Avasimibe.

Rest of the compounds did not exhibit encouraging ACAT inhibitory activity.

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