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REVIEW ON PYRIMIDINE ANALOGS AS POTENTIAL ANTIHYPERLIPIDEMIC AGENTS

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ABSTRACT

Hypercholesterolemia is considered as one of the most important risk factors and thereby a primary therapeutic target. Measurement of serum lipid concentration helps in identifcation of the subject with cardio metabolic abnormalities or risk of cardiovascular diseases. Although, the benefits of lowering cholesterol level has been widely known for the prevention of heart diseases. AcetylCoenzyme A: cholesterol acyltransferase (ACAT) and cholesteryl ester transfer protein (CETP) are the new targets which are directly or indirectly involved in hyperlipidemia. The rising tide of obesity, diabetes and hypertension are collectively attributed to our reluctance to exercise and desire for fast food. Cessation of smoking, control of blood pressure and blood levels of glucose, low density lipoprotein cholesterol (LDLC), as well as elevation of high density lipoprotein cholesterol (HDLC) levels remain the most effective long-term options for controlling atherosclerosis. Raised Cholesterol Situation and trends in india and globally is described. A variety of drugs used in the therapy belong to the classes of fibrates, statins, bile acid sequestrants, niacin derivatives, as well as, some newer drugs like ezetimibe, avasimibe, eflucimibe, lapaquinstat acetate, lomitapide mesylate, etc., are available in the present antihyperlipidemic therapy, but still there are problems associated with most of these currently available lipid lowering drugs. Current new drug discovery efforts to develop new molecules for antihyperlipidemic research involve focussing on various new molecular mechanisms of hyperlipidaemia and thereby several attractive molecular targets involved thereof in this process are being exploited. Peroxisome proliferation activated receptors (PPARs) [agonists of PPARs] is one of the most important target identified as antihyperlipidemic agents. This review deals with many new molecules may offer an insight for developing new leads for antihyperlipidemic therapy to budding researchers in this field.

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INTRODUCTION

Cardiovascular diseases are the major cause of morbidity and mortality worldwide and responsible for 30-35% of death in industrialized countries. Hypercholesterolemia is considered as one of the most important risk factors and consequently a primary therapeutic target. Measurement of serum lipid concentration helps in identifcation of the subject with cardio metabolic abnormalities or risk of cardiovascular diseases. Atherosclerosis is considered as the major cause of more than half of all deaths in the western world whereas; hyperlipidemia is the known cause of coronary heart disease and ischemic heart disease. Although, the benefits of lowering cholesterol level has been widely known for the prevention of heart diseases.

Alternative modes of treatment of CVS diseases are being investigated. Due to various limitations in the available therapies, there is extreme need to explore some new targets against hyperlipidemia. AcetylCoenzyme A: cholesterol acyltransferase (ACAT) and cholesteryl ester transfer protein (CETP) are the new targets which are directly or indirectly involved in hyperlipidemia. ACAT supposed to converts the free cholesterol into cholesterylesters whereas CETP mediates the net transfer of cholesteryl esters from atheroprotective high density lipoproteins to atherogenic low density lipoproteins or very low density lipoproteins. Hence, ACAT and CETP can be entitled as “entwined twins” and simultaneous targeting of both the enzymes can yield best therapeutic results. Cardiovascular diseases (CVD's) are among the major causes of deaths in the world today and shall continue to be so even by 2020. Hyperlipidaemia, leading to atherosclerosis is the major underlying factor for CVD's. Elevated low-density lipoprotein cholesterol (LDLC) levels are the best indicators of the atherosclerotic risk. Many novel molecular targets, on which new drugs could act and control hyperlipidaemia, are being identified and evaluated for new antihyperlipidemic drug discovery research.

The rising tide of obesity, diabetes and hypertension are collectively attributed to our reluctance to exercise and desire for fast food. Atherosclerosis may be defined as degenerative changes in the intima of medium and large arteries. This degeneration includes accumulation of lipids, complex carbohydrates, blood and blood products, as well as, cellular debris leading to plaque formation. As more plaques build up in the intima, arteries become narrow and stiffen. Eventually, enough plaques may build up to reduce blood flow through the arteries. This results in blocking a blood vessel or vessels that feed the heart, precipitating a heart attack. If plaques block blood vessels that feed the brain, it can cause a stroke. On the other hand if blood supply to the arms or legs is reduced, it can lead to gangrene or paralysis. Treatment of the atherosclerotic conditions of cardiovascular systems with procedures such as coronary artery by-pass graft (CABG), insertion of stents as well as use of various pharmaceutical agents to treat hypertension, diabetes, dyslipidaemia, pose an enormous economic, as well as, social burden on the society.

Cessation of smoking, control of blood pressure and blood levels of glucose, low density lipoprotein cholesterol (LDLC), as well as elevation of high density lipoprotein cholesterol (HDLC) levels remain the most effective long-term options for controlling atherosclerosis. More emphasis has been focused on the management of cholesterol, primarily through lifestyle and drug therapy. Drug therapy offers numerous options, with each drug class dealing with the disease state through its own unique mechanism of action. In addition, different cholesterol lowering drugs or non pharmacological treatments can significantly reduce morbidity from CVDs and the related coronary events [1-3].

Two different classifications for hyperlipidaemias are; the Fredrickson classification and the WHO classification, both based on the levels of lipoproteins, triglycerides and chylomicron in the blood. Lipoproteins are small spherules that transport fats in the body and consist of cholesterol, triglycerides and phospholipids. Lipoproteins are classified as chylomicrons, very low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL), LDL and HDL based on their electrophoresis, density and composition, the HDL being the smallest, but most dense amongst various lipoproteins. Apolipoproteins found on the outer surface of lipoprotein, make them soluble in plasma. The terms “good” and “bad” cholesterol refer to HDL and LDL, respectively. High levels of LDL are associated with coronary atherosclerosis, whereas, high levels of HDL appear to protect against CVD's.

Raised Cholesterol Situation and trends:

Raised cholesterol increases the risks of heart disease and stroke. Globally, a third of ischaemic heart disease is attributable to high cholesterol. Overall, raised cholesterol is estimated to cause 2.6 million deaths (4.5% of total) and 29.7 million disability adjusted life years (DALYS), or 2.0% of total DALYS. Raised total cholesterol is a major cause of disease burden in both the developed and developing world as a risk factor for Ischemic heart disease and stroke. A 10% reduction in serum cholesterol in men aged 40 has been reported to result in a 50% reduction in heart disease within 5 years; the same serum cholesterol reduction for men aged 70 years can result in an average 20% reduction in heart disease occurrence in the next 5 years. In Ireland, a 30% reduction in the heart disease death rate has been attributed to 4.6% reduction of the population mean for total cholesterol. In Finland, 50% of the decline in IHD mortality has been explained by the reduction of population blood cholesterol level.

In 2008 the global prevalence of raised total cholesterol among adults (≥ 5.0 mmol/l) was 39% (37% for males and 40% for females). Globally, mean total cholesterol changed little between 1980 and 2008, falling by less than 0.1 mmol/L per decade in men and women.

The prevalence of elevated total cholesterol was highest in the WHO Region of Europe (54% for both sexes), followed by the WHO Region of the Americas (48% for both sexes). The WHO African Region and the WHO South East Asian Region showed the lowest percentages (22.6% for AFR and 29.0% for SEAR) as described in **figure 1.**

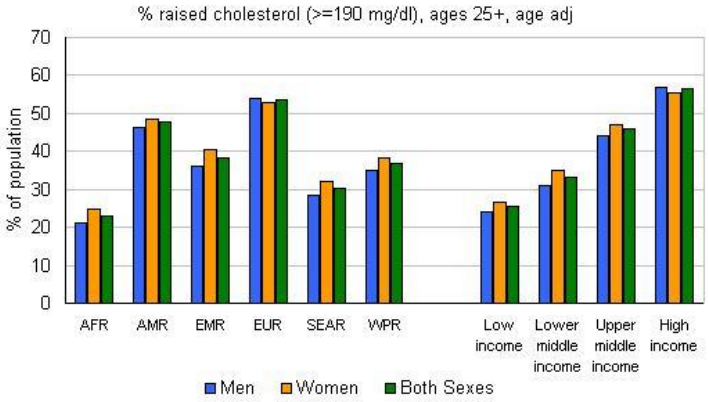


Figure 1.The prevalence of elevated total cholesterol.

The prevalence of raised total cholesterol increased noticeably according to the income level of the country. In low income countries around a quarter of adults had raised total cholesterol, in lower middle income countries this rose to around a third of the population for both sexes. In high-income countries, over 50% of adults had raised total cholesterol; more than double the level of the low-income countries. Globally, around 39% of adults aged 25 and over had raised cholesterol in 2008. The figures was adapted from the link http:// www.who. int/gho/ ncd/risk_ factors/cholesterol_text/en/

In India only limited studies exist on epidemiology of cholesterol and other lipoprotein lipids on large samples in the last 20 years. We reviewed all the recent large population based epidemiological studies that focused on cardiovascular risk factors including cholesterol levels and found that there were only six multisite studies with sample size ranging from 2000–15,000 as shown in **Table 1**. Prevalence of various cholesterol lipoprotein abnormalities after age-adjustment in men and women, respectively were, as shown in **figure 2** [4].

Table 1. Prevalence of hypercholesterolemia (200mg/dl) in multisite Indian studies.

Study and Sites	Year reported	Sample size	Prevalence (%)	
			Men	Women
Indian Industrial Population Surveillance Study: Urban	2006	10,442	25.1	–
India Migration Study: Rural	2010	1983	21.1	27.8
ICMR Integrated Disease Surveillance Project: Urban	2010	15,223	31.7	32.8
ICMR Integrated Disease Surveillance Project: Rural	2010	13,517	19.5	26.4
ICMR Integrated Disease Surveillance Project: Periurban/Urban Slum	2010	15,751	18.1	23.4
Indian Women's Health Study: Urban	2013	2008	–	27.7
Indian Women's Health Study: Rural	2013	2616	–	13.5
India Heart Watch: Urban	2014	6123	25.1	24.9
ICMR INDIAB Study: Rural & Urban	2014	2042	13.9	?
FitHeart Study: Urban	2014	46,919	29.0	30.8

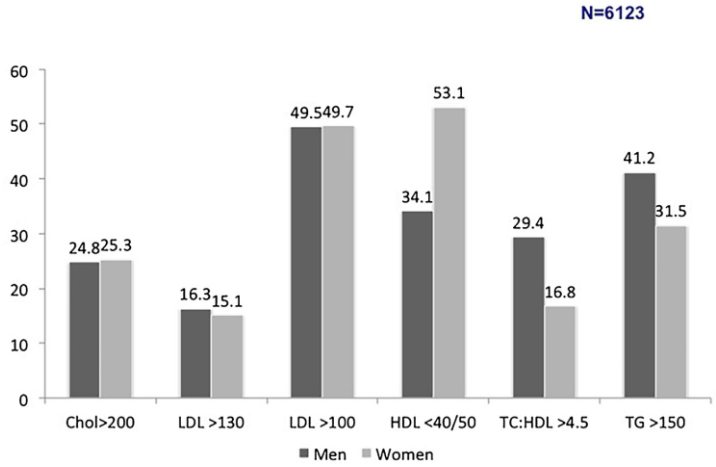


Figure 2. Prevalence of various dyslipidemias in India Heart Watch multisite study.

Cardiovascular diseases have assumed epidemic proportions in India as well. The Global Burden of Diseases (GBD) study reported the estimated mortality from coronary heart disease (CHD) in India at 1.6 million in the year 2010. A total of nearly 64 million cases of CVD are likely in the year 2015, of which nearly 61 million would be CHD cases (the remaining would include stroke, rheumatic heart disease and congenital heart diseases). Deaths from this group of diseases are likely to amount to be a staggering 3.4 million [5].

The burden of CVD and its risk factors in India calls for a sound public health approach to stem the epidemic. Efforts to put in place an intervention programme should be complemented with a robust surveillance mechanism so as to monitor, evaluate and guide policies and programmes. It has been demonstrated in a pilot mode that it is feasible to establish surveillance for CVD risk factors at community levels. It has been scaled up to the national level, and is now included in the National Programme for Prevention and Control of Diabetes, Cardiovascular Diseases and Stroke. The future of surveillance systems lies in its timeliness, systems approach and enduring partnerships. Consolidating on the gains should pave the path for the way forward [6].

Early identification and treatment of cardiovascular risk factors (CVRFs) is essential to prevent excess morbidity, mortality and healthcarerelated costs. We sought to investigate whether an
active screening programme at pharmacies could identify a significant proportion of patients with previously undetected CVRFs [7].

Antihyperlipidemic agents currently used in therapy like clofibrate, nicotinic acid, D-thyroxine etc. The most widely used "Statins" suffer from limitations like, intolerance and adverse effects, often achieving only 40% risk reduction and sometimes even ineffective. Therefore, novel potential molecular targets for new drug discovery research (NDDR) for antihyperlipidemic therapy are being searched and investigated. New drugs, able to block the stimuli responsible for the formation of an atherosclerotic lesion need to be developed. Furthermore, specific drugs, which could bring about regression of the already existing atherosclerotic lesions, in the blood vessels are the need of the hour.

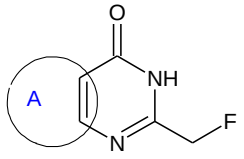
Pharmacophore of Pyrimidine is an important integral part of DNA and RNA and play an essential role in several biological processes and also have considerable chemical and pharmacological utility. The pyrimidine core is a structural constituent of vital Biomolecules like DNA and of critically important drugs like Fluorouracil, Etravirine, Risperidone, Iclaprim, Avanafil, and Rosuvastatin.

Current drug targets for antihyperlipidemic therapy:

1. Molecular entities involved in absorption of cholesterol [inhibition of cholesterol absorption] **2**. Peroxisome proliferation activated receptors (PPARs) [agonists of PPARs] **3.** Acyl-CoA cholesterol acyl transferase (ACAT) [inhibitors of ACAT] **4**. Coenzyme Q10 (CoQ10) [stimulators of CoQ10] **5.** ATP citrate lyase (ACL) [inhibition/antagonist of ACL] **6.** Concentration of HDL levels [enhancers of HDL] **7.** Microsomal triglyceride transfer protein (MTP) [inhibitors ofMTP] **8.** Cholesteryl ester transfer protein (CETP) [inhibition of CETP] **9.** C-reactive protein (CRP) [inhibition of CRP] **10.** Molecular entities involved in lipid oxidation [inhibition of lipid oxidation; antioxidants] **11.** Diacylglycerol O-acyl transferase (DGAT) [inhibition of DGAT] **12.** Lanosterol 14a-demethylase (LDM) [inhibition of human LDM(CYP51)] **13**. HMG-CoA synthase [inhibition of HMG-CoA synthase] **14.** Squalene synthase (SqS) [inhibition of SqS] **15.** Squalene epoxidase (SQLE) [inhibition of SQLE] **16**. 2,3-Oxidosqualene lanosterol cyclase (OSC or squalene 2,3-oxide-lanosterol cyclase) [inhibition of OSC] **17.** Farnesoid X receptoreretinoid X receptor (FXReRXR) [activation of FXReRXR] **18.** Sterol regulatory element binding proteins (SREBPs)[inhibition of SREBPs] **19.** Plasma apo-E related peptides [stimulation of plasma apo-E] **20.** Proprotein convertase subtilisin/kexin type 9 (PCSK9) [inhibition of PCSK9] [1].

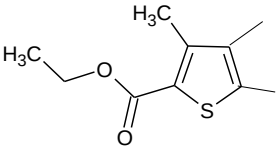
High blood lipid levels and thereby atherosclerosis, have been proven to be linked with incidences of CVDs and stroke which remain the leading cause of human mortality. A variety of drugs used in the therapy belong to the classes of fibrates, statins, bile acid sequestrants, niacin derivatives, as well as, some newer drugs like ezetimibe, avasimibe, eflucimibe, lapaquinstat acetate, lomitapide mesylate, etc., are available in the present antihyperlipidemic therapy, but still there are problems associated with most of these currently available lipid lowering drugs. These problems include intolerance, adverse effects, ineffectiveness or partial effectiveness, as well as cost. Besides this, no drug has been yet developed which could effectively control the formation of atherosclerotic plaques or further, bring about the regression of already developed plaques; thereby circumventing operative procedures like angioplasty or cardiac by-pass surgery. Current new drug discovery efforts to develop new molecules for antihyperlipidemic research involve focussing on various new molecular mechanisms of hyperlipidaemia and thereby several attractive molecular targets involved thereof in this process are being exploited. This review deals with many new molecules may offer an insight for developing new leads for antihyperlipidemic therapy to budding researchers in this field.

Muthu K. Kathiravan et al reported a series of novel condensed 2-fluoromethyl-pyrimidines which has been synthesized and evaluated for anti hyperlipidemic activity in high fat diet fed hyperlipidemic Sprague–Dawley rats. The aim of this study was to investigate the effect of the fluorine atom at the 2-methyl position of these compounds. Most of the synthesized compounds significantly affected the lipid profile of the test animals. Compound (Ring A is thiophene) exhibited remarkably best effects in lowering the serum cholesterol and triglyceride levels and elevating the serum HDL levels, of the test animals [8].

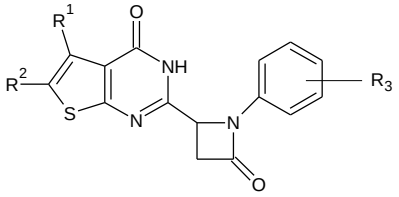


Ring A = diff.heterocyclic ring

Ring A =

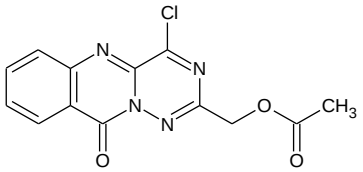


Nikhilesh Arya et al reported novel thienopyrimidine derivatives of azetidinone possessing the combined features of the cholesterol absorption inhibitor drug ezetimibe and potential antihyperlipidemic 2-substituted thienopyrimidin-4-ones were synthesized and characterized by spectroscopic data and elemental analysis. These compounds were evaluated for their lipid-lowering activity in Wistar albino rats. Some of them showed significant lipid-lowering effects comparable to those of the standard drug, gemfibrozil, at the same dose levels [9].



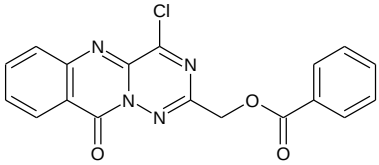
Thienopyrimidine derivatives of azetidinone

M.K. Kathiravan et al reported the synthesis and antihyperlipidemic activity of some novel 4-substituted-2-substituted methyltriazino [6, 1-b] quinazolin-10-ones and 2,4-disubstituted-6,7-dimethoxy quinazoline derivatives are described. Among the series 4-chloro-2-acetoxymethyl-3H,11H-[1,2,4]triazino[6,1-b]quinazoline-4,10-dione **5d** has shown better activity in case of % reduction in serum cholesterol level while 4-chloro-10-oxo-10H-[1,2,4]triazino[6,1-b]quinazolin-2-yl benzoate **5f** in reducing % serum triglyceride level than that of the standard. 4-Hydroxyquinazolin-2-yl nicotinate **6g** has significantly increased serum HDL level. Among the series compound **6g** has shown promising results over all in lipid profile. These molecules indeed have the potential to be developed as an antihyperlipaemic molecule [10].



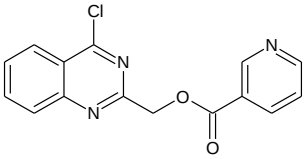
5d

(4-chloro-10-oxo-10*H*-[1, 2, 4] triazino [6, 1-*b*] quinazolin-2-yl) methyl acetate



5f

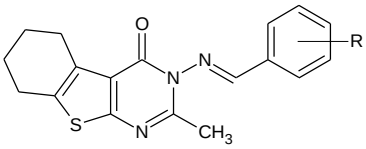
(4-chloro-10-oxo-10*H*-[1, 2, 4] triazino[6, 1-*b*] quinazolin-2-yl) methyl benzoate



6g

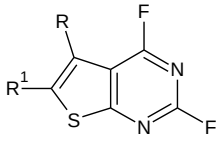
(4-chloroquinazolin-2-yl) methyl pyridine-3-carboxylate

Rangappa Srinath et al reported the present study, aimed to evaluate some newly synthesized thieno – [2, 3-d] - pyrimidin-4-(3H)-ones namely SR-C1 to SR-C12 for their anti-hyperlipidemic activity. The findings of the present study clearly demonstrates that methyl, methoxy, chloro,dimethylamino, dimethoxy and trimethoxy functional groups possess cholesterol-suppressive capacities and has an ability to attenuate the accelerated development of atherosclerosis in hypercholesterolemic models. However, hydroxyl and nitro derivatives did not show any hypolipidemic activity [11].



SR -- 1 to SR -- 12

R.P. Devale et al reported the sysnthesis of condensed 2- substituted pyrimindes were found to be highly potent as anti hyperlipidemic. Substitution at 4th position by hydroxyl group is found to have potent anti-hyperlipidemic activity. A series of five novel molecules, 2-flouroromethyl-4-flouro-pyrimidines are synthesized using two methods and biological evaluation was performed on Spargue dawley rats with high fat diet. The standard drug used was ezetimibe, which is a cholesterol absorption inhibitor. The compounds **II** and **IV** were found to be the most significant in lowering serum total cholesterol, triglycerides and increasing the serum HDL levels [12].

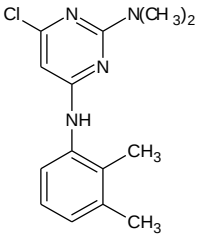


comp. I -- IV

Condensed 2- substituted pyrimindes

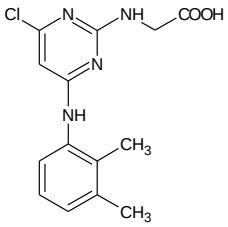
Shaukat Tamboli et al reported a novel series of substituted thieno [3, 2-d] pyrimidin-4(3H) ones has been synthesized and evaluated for in vivo antihyperlipidemic activity using Triton WR 1339. Out of the 16 compounds synthesized and tested, 8 compounds have shown significant effect on total lipid profile. These compounds are several times more potent than gemfibrozil, the standard drug used for comparison. The superior activity of compounds may be because of their esterase mediated metabolism into active metabolites. These compounds may serve to be ideal leads to provide newer antihyperlipidemic agents [13].

Gaetano d'AtriNew et al reported compounds, were synthesized by changing the substituents of a trisubstituted pyrimidine, i.e., [[4-chloro-6-[(2,3-dimethylphenyl)amino]-2-pyrimidinyl] thio]acetic acid, a potent hypolipidemic agent, impaired, however, by a marked hepatomegaly-inducing effect. The structural variations led to the subsidence (**14b**, i.e., 4-chloro-2- (di methylamino)-6-[(2,3-dimethylphenyl)amino]pyrimidine) or to the reduction (**18b**, [[4-chloro-6-[(2,3-dimethyl-phenyl)amino]-2-pyrimidinyl]amino]acetic acid) of said untoward effect but still maintained the hypolipidemic effect that, although markedly decreased, still proves significant for serum cholesterol and triglycerides (18b) or for serum triglycerides only (14b) [14].



14b

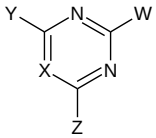
6-chloro-N^4-(2,3-dimethylphenyl)-N^2,N^2-dimethyl pyrimidine-2,4-diamine



18b

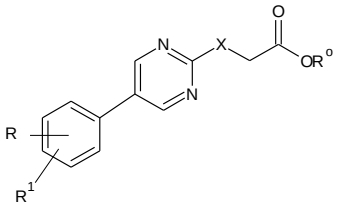
({4-chloro-6-[(2,3-dimethylphenyl)amino] pyrimidin-2-yl}amino)acetic acid

Piero Gomaraska et al reported pyrimidine and s-triazine derivatives of formula in which X = CH or N; Y = halogen, alkoxy; W = --CH2COOH, --OCH2—COO alkyl, --NHCH2—CONHCH2CH2OH; Z = 2, 3 xylidino and the methods for the preparation thereof are described. The compounds show high antilipemic activity [15].



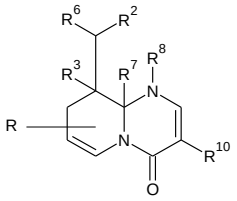
Pyrimidine and s-triazine derivatives

Goetz E. Hardtmann et al reported synthesis of 5-phenyl-2-oxy acetic and 2-mercaptoacetic acids and esters of pyrimidine compounds. Where x is oxygen or sulfur, R^0 is hydrogen or alkyl of 1 to 4 carbon atoms, and R and R' are hydrogen, halo, alkyl or alkoxy. The compounds are useful as hypolipidemic agents and prepared by reacting the corresponding 2-halo-5-phenylpyrimidine with a compounds of the formula $HXCH_2COOR$ [16].



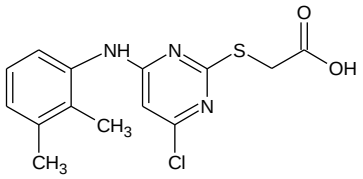
Acids and esters of pyrimidine compounds

Istvan Hermecz et al reported the synthesis of fused pyrimidine derivatives where R is hydrogen or C_1 to C_6 alkyl; R^2 and R^3 are each hydrogen or together form a valency bond;R^6 is carboxy or C_1 to C_6 alkoxycarbonyl;R^7 and R^8 are each hydrogen or together form a valency bond; R^{10} is carboxy or C_1 to C_6 alkoxycarbonyl and the dotted line represents two hydrogen atoms or a valency bond. The compounds are useful in the treatment of atherosclerosis [17].



Fused pyrimidine compounds.

Santilli et al reported the synthesis of Pirinixic acid is a peroxisome proliferator-activated receptor alpha (PPARα) agonist that is under experimental investigation for prevention of severe cardiac dysfunction, cardiomyopathy and heart failure as a result of lipid accumulation within cardiac myocytes. Treatment is primarily aimed at individuals with an adipose triglyceride lipase (ATGL) enzyme deficiency or mutation because of the essential PPAR protein interactions with free fatty acid monomers derived from the ATGL catalyzed lipid oxidation reaction. It was discovered as WY-14,643 in 1974 [18].



Pirinixic Acid (WY-14643)

CONCLUSION

Due to high lipid levels in blood it causes atherosclerosis and causes cardiovascular diseases and stroke which is the leading cause of human mortality. Many drugs used in the therapy belong to the classes of fibrates, statins, bile acid sequestrants, niacin derivatives, as well as, some newer drugs like ezetimibe, avasimibe, eflucimibe, lapaquinstat acetate, lomitapide mesylate, etc., are available in the present antihyperlipidemic therapy, but still there are problems associated with most of these currently available lipid lowering drugs. These problems include intolerance, adverse effects, ineffectiveness or partial effectiveness, as well as cost. Besides this, no drug has been yet developed which could effectively control the formation of atherosclerotic plaques or further, bring about the regression of already developed plaques; thereby circumventing operative procedures like angioplasty or cardiac by-pass surgery. Prevention through risk factor controls like smoking cessation and control of blood pressure, blood glucose, and LDL cholesterol, and raising of HDL cholesterol remains the most effective long-term option for the treatment. Current new drug discovery efforts to develop new molecules for antihyperlipidemic research involve focussing on various new molecular mechanisms of hyperlipidaemia and thereby several attractive molecular targets involved thereof in this process are being exploited. Twenty such molecular targets offer an insight for developing new leads for antihyperlipidemic therapy. Peroxisome proliferation activated receptors (PPARs) [agonists of PPARs] is one of the most important target identified as antihyperlipidemic agents.

This review is a detail account of recent developments and guideline for novel pyrimidine analogues as antagonists or agonists as antihyperlipidemic drug.

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Conflict of interests

Authors declare that they have no conflict of interest.

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