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# Synthesis of heterocyclic scaffolds with anti-hyperlipidemic potential: A review

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**ABSTRACT**

*The biological potential of various heterocyclic scaffolds draw special attention of medicinal chemists and hence exhaustive efforts are being carried out in the search of lead molecules pertaining to it. The knowledge of such biologically important heterocycles and their methods of synthesis are discussed in this review. Especially, the focus is kept on the heterocycles that are effective to treat many significant lifestyle diseases such as atherosclerosis, diabetes, ischemic heart disease, myocardial infarctions, which are strongly associated with imbalance in lipid metabolism and plasma lipoproteins. As these conditions are responsible for one-third of deaths in industrialized nations, special emphasis is given on synthesis of recently reported heterocycles possessing anti-hyperlipidemic activity. Such derivatives have been extensively studied in the past few decades. The present review includes the rigorous literature survey on the methods of preparation along with the potential biological activities correcting lipid metabolism.*

**Keywords**: Anti-hyperlipidemic potential, Heterocycles, Synthesis, Biological activity, Microwave irradiation, Intermediate.

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## INTRODUCTION

Drug discovery and development is a multidisciplinary, creative, innovative and highly regulated process. Since decades, it has been a demanding task to find a successful lead with promising and optimized characteristics. This optimization of lead involves structural manipulations to improve its chemical stability, potency and biological or therapeutic effectiveness [1]. The chemistry of heterocyclic compounds is as logical and reasonable as that of aliphatic or aromatic compounds as various naturally occurring compounds and even many clinically used drugs are heterocyclic in nature.

The investigational approaches towards Structure-Activity Relationship focusing the search of optimized candidates have become immensely important. There are wide range of heterocyclic compounds such as pyrrole, quinoline, furan, thiophene, piperidine, pyridine, pyrimidine, thiazole and many more which have interesting applications and are important intermediates in organic synthesis [2]. As structural motifs in pharmaceuticals, considerable attention has been attracted by various substituted and fused heterocycles. The discovery of potent, selective, and bioavailable small molecules that modulate biological systems of interest continues to be one of the most important endeavors for contemporary organic and medicinal chemists [3]. As the world(s) population is increasing and health problems are expanding accordingly, the need to rediscover therapeutics has become even more challenging.

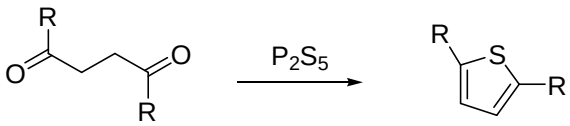
The most important challenge to be met today is the search for heterocycles that will combat with life style disorders which involve mostly the imbalance in endogenous chemicals. Hyperlipidemia is one of these imbalances involving elevation of lipids in plasma. Several studies have showed that an intimate correlation exists between coronary heart diseases and hyperlipidemia and consequently a rational approach to the treatment and prevention of coronary heart

diseases could be by decreasing any elevated levels of lipids in plasma. This review article covers different heterocyclic nuclei with their anti-hyperlipidemic potential. Considering the therapeutic potential of these nuclei, new drugs can be synthesized as hypolipidemic or anti-hyperlipidemic agents [4].

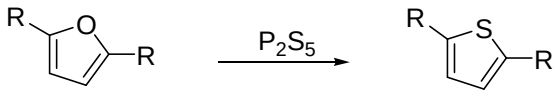
**A) THIOPHENE**

Thiophene belongs to a class of heterocyclic aromatic compounds containing a five membered ring made up of one sulphur as heteroatom [5]. Thiophene and its derivatives exist in petroleum or coal. Thiophene is taken from the word *theion*, the Greek word for sulfur and another Greek word *phaino* which means shining. Thiophene structure can be found in certain natural products and is also incorporated in several pharmacologically active compounds. In medicinal chemistry, thiophene derivatives have been very well known for their therapeutic applications. The simple thiophenes are stable liquids which closely resemble the corresponding benzene compounds in boiling point and even in smell. They occur in coal tar distillates. The discovery of thiophene in coal tar benzene provides one of the classic anecdotes of organic chemistry. Thiophene was discovered as a contaminant in benzene [6]. It was observed that isatin (1H-indole-2,3- dione) forms a blue dye if it is mixed with sulfuric acid and crude benzene. Victor Meyer was able to isolate the substance responsible for this reaction. The compound was found to be a heterocyclic compound- thiophene.

Reagents such as phosphorus pentasulfide ($P_2S_5$) or Lawesson's reagent act as sulfurizing agents as well as dehydrating agents, allowing a reaction pathway that could lead first to the formation of furans. This hypothesis was tested by Campaign and coworkers in 1952. They were able to prove that Paal thiophene synthesis could not proceed via furan as intermediate. Instead it went through the formation of a thione. To prove this they conducted parallel experiments where direct comparisons were made between the reactions of 2,5-hexanedione with $P_2S_5$ and the reactions of 2,5-dimethyl/diphenyl furan under the Paal thiophene synthesis conditions. Reactions utilizing the diketones provided a greater yield of the thiophene **(1)** suggesting that the furan is not an essential intermediate in the reaction pathway, but rather a byproduct [7].




(1)



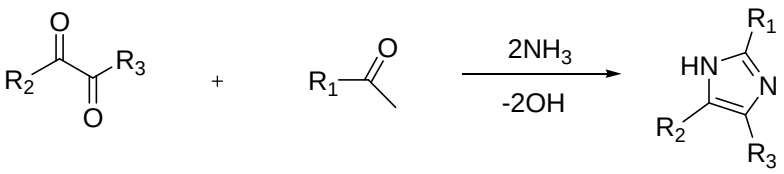

(1)

Thiophene heterocycle has been extensively studied and is found to possess various biological activities. Among these, the synthesized 4-(3-hydroperoxypentyl)-N-((5-octylthiophen-2-yl)methyl)benzenamine derivatives have shown good anti-atherosclerotic activity [8].

**B) IMIDAZOLE**

Imidazole is an aromatic heterocyclic also called '1,3-diazole' and is classified mainly as an alkaloid. Imidazole refers to the parent compound, whereas imidazoles are a class of heterocycles with similar ring structure, but varying substituents. This ring system is present in important biological building blocks, such as histidine, and the related hormone histamine. Imidazole can serve as a base as well as a weak acid.

Imidazole was first synthesized by Heinrich Debus in 1858, but various imidazole derivatives had been discovered as early as the 1840s, as shown below, using glyoxal and formaldehyde in ammonia to form imidazole. This synthesis, while producing relatively low yields, is still used for creating C-substituted imidazoles **(2)** [9]**.**




(2)

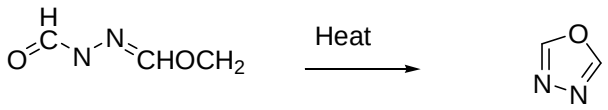
Various types of 2-imidazolines are biologically and pharmaceutically important and these possess antidiabetic, antihypertensive, and anti-inflammatory activities [10]. Many derivatives of 3-chloro-4(4-chloro-phenyl-1-(4-{1-[2'-(2H-tetrazol-5yl)-biphenyl-4-ylmethyl]-1H-benimidazol-2yl}phenyl)azetidin-2-ones have been prepared and screened for angiotensin(AII) receptor antagonistic activity. The compounds exhibited excellent activity and can be further used as anti-hypertensives and also as therapeutic agents in strokes and congestive heart failure [11].

**C) OXADIAZOLE**

1, 3, 4-oxadiazole is a thermally stable molecule. Oxadiazole is a very weak base due to the inductive effect of the extra heteroatom. The 1, 3, 4-Oxadiazole undergoes number of reactions including electrophilic substitution, nucleophilic substitution, thermal and photochemical. The electrophilic substitution in oxadiazole ring is extremely difficult at the carbon atom because of the relatively low electron density on the carbon atom which can be attributed to electron withdrawing effect of the nitrogen atom. If oxadiazole ring is substituted with electron releasing groups then the attack of electrophiles occurs at nitrogen. Oxadiazole ring is generally resistantto nucleophilic attack. Halogen substituted oxadiazole, however, undergo nucleophilic substitution similarly as occurring at an aliphatic sp2 carbon atom.

Oxadiazole derivatives have been extensively studied in the past few decades. It is a five membered heterocyclic ring that exists in four isomeric forms. Out of its four isomers 1, 3, 4-oxadizole exhibits a wide range of biological activities which includes antibacterial, antitubercular, vasodialatory, antifungal, cytotoxic, antiinflammatory, analgesic, hypolipidemic, anticancer and ulcerogenic activities. The present review deals with the various chemical aspects of 1,3,4-oxadiazoles [12].

Ainsworth prepared 1, 3, 4-oxadiazole **(3)** in 1965 by the thermolysis of ethylformate formyl hydrazine at atmospheric pressure [13-14].



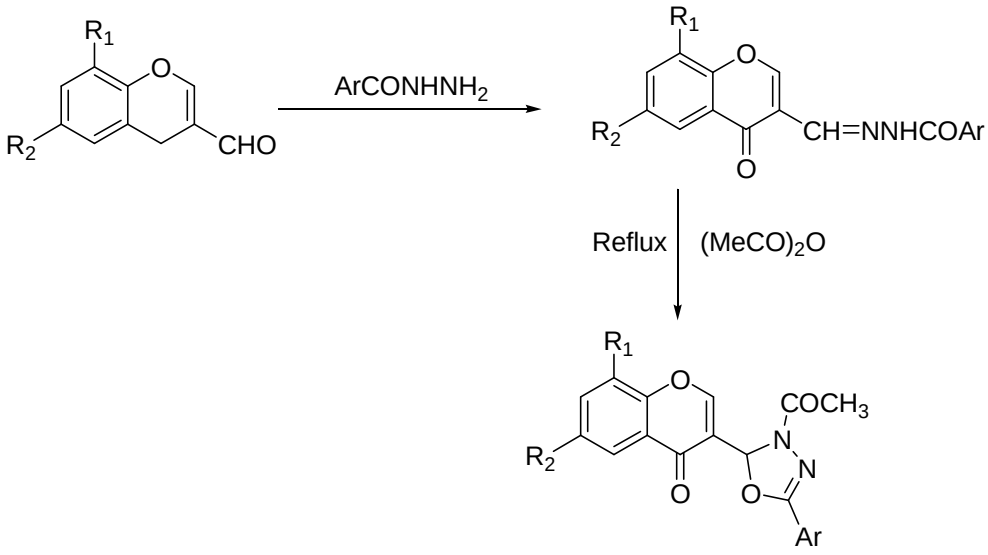

(3)

1,3,4-oxadiazole derivatives have been found to exhibit vasorelaxant activity by blocking L-type calcium channels which corrects the endothelial dysfunction and normalizes the high blood pressure levels [15].

**D) CROMONES**

Chromone is a derivative of benzopyran with a substituted keto group on the pyran ring. It is an isomer of coumarin. Derivatives of chromone are collectively known as chromones. Most, though not all, chromones are also phenylpropanoids.

The synthesis of the previously unknown 3-(3-acetyl-5-aryl-2,3-dihydro-1,3,4-oxadiazol-2 chromone has been carried out successfully using the available 3-formylchromones. The treatment of the 3-formylchromones with aroylhydrazines give the corresponding aroylhydrazones which in the presence of acetic anhydride causes heterocyclization to afford 3-(3-acetyl-5-aryl-2,3-dihydro-1,3,4-oxadiazol-2-yl) chromones **(4)** [16].




(4)

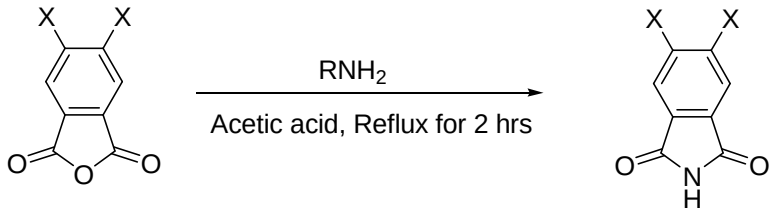
3-Heterylchromones exhibit a broad range of biological actions such as antiallergic, anticholesteremic, hypolipidemic, antimicrobial and fungicidal activities. They are also effective stimulators of the central nervous system [17]. For this reason much attention has been paid to the synthesis of novel compounds of this heterocycle in recent times [18]. 3-(5-aryl-1,3,4-oxadiazole-2yl) chromones have broad range of biological activity and display anti-cholesterol activity by lowering triglycerides and cholesterol in serum [19].

**E) CYCLIC IMIDES**

Imides are derived from ammonia and containing the bivalent NH group combined with bivalent acidic group or two monovalent acidic groups. Imides are strongly basic because of lone pair of electrons.Imides belong to the class of aromatic heterocyclic compounds having nitrogen as hetero atom in it.

Certain new halogenated cyclic-imides related to N-substituted phthalimide moiety have been synthesized. Spacers of one or two carbon atom distances were inserted to connect the N-terminus of the cyclic-imide nuclei to the heteroaryl groups and biological evaluation was carried out to observe the alteration in activity. The activities of interest were hypoglycemic and anti-hyperlipidemic ones. Some of the tested compounds proved to be more potent than the reference drugs glibenclamide and clofibrate [20]. Those new cyclic-imides could be considered as useful template for future development to obtain more potent hypoglycemic and anti-hyperlipidemic agents.

The synthetic strategy to prepare the target isoindoline-1,3-diones is depicted. The halogenated acid anhydrides were reacted with the appropriate heteroaryl amines in glacial acetic acid to give the corresponding cyclic-imides **(5)** in reasonable yields [21-24].




(5)

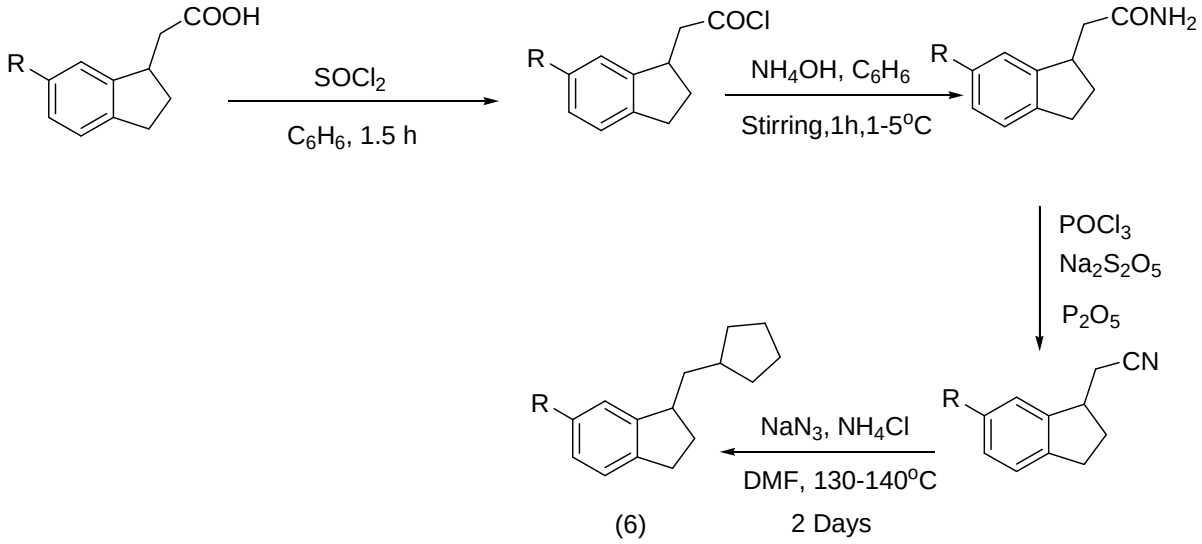
Compound 5,6-dichloro-2-(pyrimidin-2yl)isoindoline-1,3-dione related to cyclic imides significantly reduce serum cholesterol level by lowering serum level of low density lipoproteins (LDL) [20].

**F) INDANYL TETRAZOLES**

Indanyl tetrazole in its structure has indan nucleus fused with tetrazole. Indan nucleus contains 6-membered ring benzene fused with 5-membered ring. Tetrazole contain 4 nitrogen in it as hetero atoms. Indan acids, which belong to nonsteroidal aryl alkanoic acids class, have assumed a special significance primarily because of its stereospecific structural framework making it a highly sensitive ring moiety

The most common clinically useful non-steroidal anti-hyperlipidemic drugs are now in the market each having its own limitation for chronic administration in the treatment of patients suffering from hypercholesterolemia.. It has also been reported that the smaller alkyl group like methyl, ethyl at the alpha carbon in the acetic acid moiety exhibited good hypolipidemic activity [25]. It is already established that tetrazole, an aromatic azapyrrole group, is metabolically stable and encouraging anti-inflammatory activity has been noted for it. Also, indanyl tetrazoles have been screened for cholesterol lowering activity [26].

The compound indanyl tetrazole **(6)** was obtained by treatment of the respective acids with thionyl chloride in dry benzene refluxing for 1-5 hrs. The acid chlorides thus obtained were immediately added to ammonia solution at 125˚C to give respected substituted amines in good yield. The amines were then dehydrated with $P_2O_5$ in dry benzene or in a mixture of $POCl_3$ and $Na_2S_2O_5$ (10:1) ratio. Refluxing for 2-4 hrs after decomposing the reaction mixture and working up, the respective nitriles were obtained. Subsequently the nitriles were allowed to react with activated $NaN_3$ in presence of $NH_4Cl$ in DMF at 130-140˚C for 2 days to give target compounds [27].



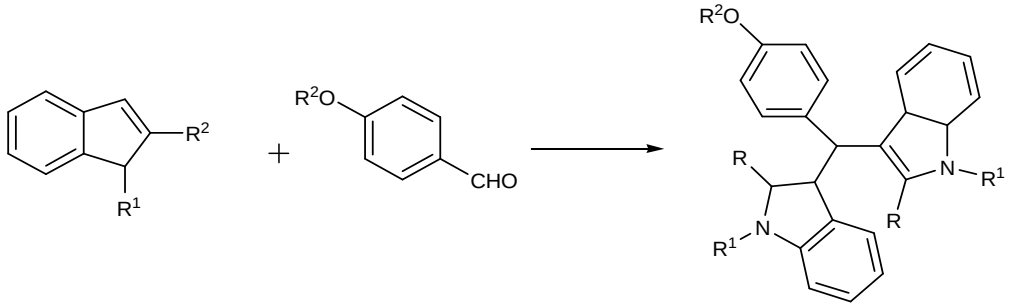

Compounds 5-((2,3-dihydro-5-methoxy-1H-inden-3yl)methyl-1H-tetrazole and 5-((2,3-dihydro-5,6-dimethoxy-1H-inden-3yl)methyl)-1H-tetrazole exhibit almost same significant level of cholesterol lowering and triglyceride lowering activity, also both compounds show anti-hyper-cholesterolemic activity [25].

**G) INDOLES**

Indole ring occurs widely in nature as alkaloids and alkaloids have medicinal values. In these compounds a benzene ring is fused with pyrrole ring and hence behaves as an aromatic heterocyclic compound. Because of the aromatic stability of benzene ring the most important contributing structure of indole to its resonance hybrid is its enamic form. Because of higher electron density in the hetero-ring, indole undergoes electrophilic substitution.

In the design of new drugs, the development of hybrid molecules through the combination of different pharmacophores may lead to compounds with interesting biological profiles. We have searched some coumarin based hybrids which have shown diverse biological properties such as anticancer, antiinflammatory and antithrombotic activities. A series of coumarin-bisindole hybrids have also been reported to show significant anti-hyperlipidemic activity in HFD (High fat diet)-fed hamsters [28]. The indole group is an essential pharmacophore for a number of compounds responsible for showing biological activity [29]. Some indole derivatives are well-known for their diverse pharmacological effects including a hypolipidemic effect [30-34].

Here in, we describe the synthesis of novel indole-fibrate hybrids and their utility as potential anti-obesity and anti-dyslipidemic agents. The target compounds substituted bis-Indoles (7) have been synthesized by an efficient electrophilic substitution of suitable indoles with substituted benzaldehyde derivatives using catalytic iodine in acetonitrile at room temperature [35].



(7)

where,

R= H

$R^1$= $C_2H_5$, $CH_3$

$R^2$=$CH(CH_3)COOC_2H_5$

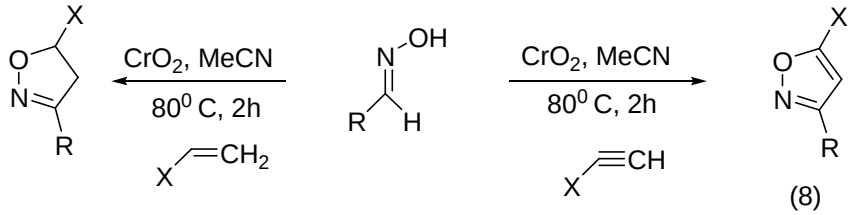
Of the many derivatives of this heterocycle, 2-(4-(bis(1-propyl-1H-indole-3yl)methyl)phenoxy)pentan-3-one has emerged as a promising agent for dislipidemia as this compound significantly modulates blood plasma lipids and reduces visceral body masses, increases catabolism of LDL and confirms its efficacy.

**H) ISOXAZOLE**

Isoxazole is a five membered heterocyclic compound having one oxygen atom and one nitrogen atom at adjacent position. Due to the presence of lone pair it undergoes electrophilic substitution. Isoxazole refers to the parent compound, whereas isoxazoles are a class of heterocycles with similar ring structure, but varying substituents.

Atherosclerosis caused by lipid disorders that in turn results from high levels of cholesterol and oxidized LDL forms the major share of such diseases. As isoxazole forms a major component of various bioactive molecules, an easy Baylis-Hillman reaction of 5-isoxazolcarboxaldehyde has been carried out to provide a good platform to fight against such diseases [36].

A variety of isoxazoles **(8)** and isoxazolines have been synthesized via 1,3-dipolar cycloaddition of alkenes and alkynes with nitrile oxides generated *in situ* by treatment of aldoximes with chromium oxide in either toluene or MeCN at 80˚C [37].



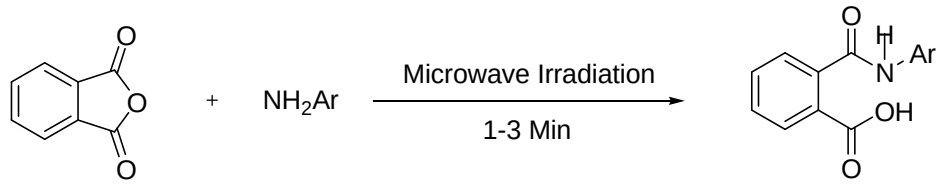
(8)

A series of (E)-N-sec-butyl-2-methyl-3-(3-phenylisoxazole-5yl)acrylamides have been synthesized and were found to lower phospholipid and triglyceride levels. There was a significant increase in the cholesterol lowering profile in nearly all derivatives of isoxazole [38].

**I) PHTHALAMIC ACID**

Phthalamic acids may be obtained by the ring-opening reaction of phthalic anhydride with amines by using conventional heating [39-41]. The use of microwaves has been reported for organic synthesis, in oxidation reactions [42], aromatic substitutions [43], N-alkylations [44-45], pericyclic reactions [46-47] and others [48-50], but very little work about microwave-mediated synthesis of phthalamic acids has been reported.

The reaction for obtaining N-arylphthalamic acids **(9)** is based on the principle that two solid reagents with low melting points or a solid and a liquid reagent are able to melt rapidly, giving a polar liquid that is more prone to microwave absorption. In these conditions, the temperature can be around 135˚C and the reaction can occur when phthalic anhydride dissolves in amines. Different acids were obtained by mixing an equimolar quantity of phthalic anhydride (1.35 mmol) and an appropriate aromatic amine or heterocyclic amines (1.35 mmol). The mixture was heated for 1-3 min in a domestic microwave oven operating at 1350 W and 2450 MHz [51].




(9)

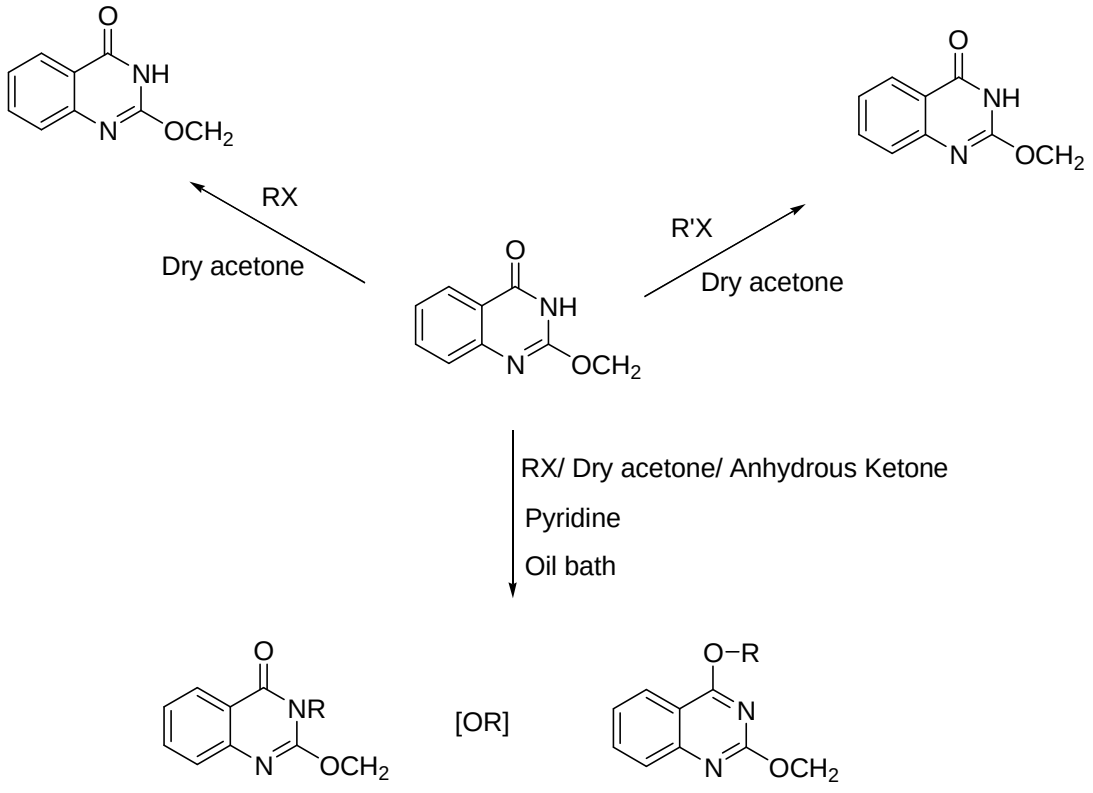
2-(phenylcarbamoyl)benzoic acid reduces body weight and also significantly reduces plasma cholesterol levels by lowering phospholipids and triglycerides [51].

**J) QUINAZOLINONE**

Quinazolinones are aromatic heterocycles with fused-ring system. They are fully unsaturated aromatic heterocycles. Quinazoline nucleus contains benzene ring fused with another 6-membered ring containing two nitrogens as hetero atoms. presence of lone pair made it to take part in electrophilic reactions.

Quinazolinone derivatives are known to possess a broad spectrum of biological activities and are used in pharmaceutical industry, in medicine and agriculture [52]. Quinazolinone derivatives have recently gained a growing interest owing to their varied spectrum of biological activities. Especially the chemistry of 4(3*H*)-quinazolinones is being studied extensively as it has been identified as an important pharmacophore [53-54]. Few of its important biological activities are antioxidant, antimicrobial and antihyperlipidimic activities [55]. Moreover, several industrial uses have been also reported for this class of compounds. Among their diverse uses, the extensive utility in the synthesis of dyes [56-57].

The synthesis of 2-ethoxy (4*H*)-3,1-quinazolin-4-one has been reported by the solvent free reaction of 2-ethoxy (4*H*)-3, 1-benzoxazin-4-one with ammonium acetate. This quinazolinone was further reacted with various organic halides in presence of dry acetone and anhydrous potassium carbonate to afford the corresponding *N*-substituted quinazolinones **(10)** [58].



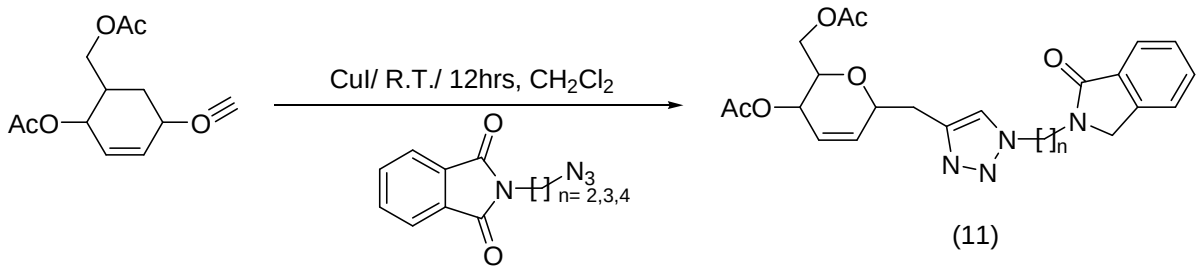

(10)

Of the various quinazolinones reported in the literature, 4-(3H)-quinazolinone and 6,8-dibromo-2-methyl-4-(3H)-quinazolinone derivative has been shown to effect significant reduction in serum total cholesterol and cholesterol ester levels. This effect was brought about by inhibition of dietary cholesterol absorption [59].

**K) ALKYL SUBSTITUTED PHTHALIMIDE TRIAZOLE**

Like other anhydrides, cyclic anhydrides react with ammonia to yield amides; in this case product contains both –$CONH_2$ and –COOH groups. If this acid amide is heated a molecule of water is lost, a ring forms, which contains two acyl groups attached to nitrogen. Triazole is heterocyclic ring in which three nitrogens are present as hetero atoms. Phthalimide derivatives **(11)** are an interesting class of compounds because they possess important biological activities, such as anti-inflammatory [60] and hypolipidemic ones [61-62].

Triazolo linked phthalimide derivatives have been reported to be synthesized from cyclohexene diester in presence of dichloromethane, copper iodide, triethylamine and using homologous series of azide-phthalimides [63].



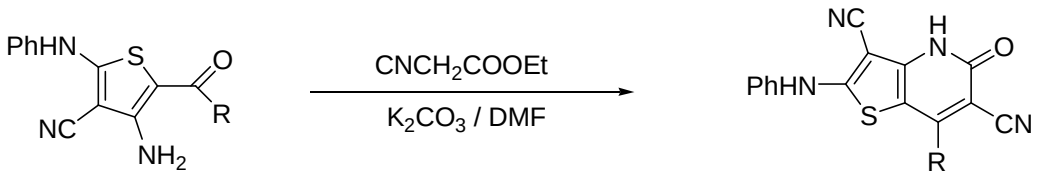

(11)

Literature survey revealed that a number of synthesized derivatives of 1-N-(1,8-naphthalimido)-butan-3-one and 1-N-3-methylphthalimidobutan-3-semicarbazone reduce plasma cholesterol and triglyceride levels. This particular activity has been exhibited by these compounds by lowering tissue lipid levels of liver, small intestine mucosa and aorta walls. These compounds also raise fecal excretion of cholesterol moderately and raise HDL cholesterol levels [64].

**L) THIENOPYRIDINES**

Thienopyridine belongs to a class of heterocyclic aromatic compounds containing a five membered and six membered ring made up of one sulphur as heteroatom in thieno nucleus and nitrogen as hetero atom in pyridine nucleus. Many thienopyridines have been evaluated pharmacologically and have been found to shown activity against, for example, diabetes mellitus [65-66], as analgesics and antiinflammatories, anticoagulants [67], antiartheroscleroties [68], and as gonadotropin releasing hormone antagonists.

Literature survey revealed that when amino substituted thiophene nitriles were allowed to react with ethyl cyanoacetate or with a variety of β-ketoesters in DMF and potassium carbonate, corresponding thieno[3,2-b]pyridine-2-ones **(12)** were obtained .




(12)

The compound **(12)** was further subjected to biological activity screening which revealed that it possessed cholesterol suppressive capacity and has an ability to attenuate the accelerated development of atherosclerosis [69].

## CONCLUSION

Heterocyclic compounds are also widely distributed in nature and are essential for life. Various compounds such as alkaloids, essential amino acids, vitamins, haemoglobin, hormones, large number of synthetic drugs and dyes contain heterocyclic ring systems. There are vast numbers of pharmacologically active heterocyclic compounds many of which are in regular clinical use. Heterocycles also form a part of vital elements of our body such as nucleic acids.

The present review summarizes the heterocycles possessing a great potential to interfere with lipid synthesis thereby exerting antihyperlipidemic activity. We have also tried to outline basic synthesis of such heterocycles which shall be helpful to the researchers to further carry out various structural modifications in these heterocycles in order to improve antihyperlipidemic potential.

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