Discovery Approaches for Novel Dyslipidemia Drugs

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Abstract: *Introduction*: Dyslipidemia is increased fasting level of total cholesterol (TC), LDL cholesterol (LDL-C), and triglycerides (TG), along with decreased levels of HDL cholesterol (HDL-C). Owing to effect on the cardiovascular system and increased chances of metabolic diseases, it is needed to review novel under development drugs and new approaches in drug discovery for dyslipidemia. *Areas Covered*: This article reviews all phases I to IV clinical trials and preclinical trials with results associated with novel treatment of dyslipidemia. Drug discovery for dyslipidemia, toward newer targets has been addressed. *Findings*: Statins are, currently available, best choice of drugs for treating dyslipidemia and coronary diseases. In addition to this, lipid lowering drugs support treatment to a great extent, either as monotherapy or in combinations with other groups. Pravastatin used in combination with cholesteryl ester, transfers protein inhibitors (CETP) to produce efficient results. Peroxisome proliferator-activated receptor agonists (PPAR) like muraglitazar, aleglitazar and tesaglitazar are PPAR α/γ receptor agonist, dual in action performs better in phase 3 clinical study and reduces renal and cardiovascular events. By targeting both receptors, a better treatment for cardiovascular and diabetic problems can be achieved. Proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors like humanized monoclonal antibodies, are newly discovered inhibitors that reduce the risk of cardiovascular diseases. During the past few years, nucleic acid–based therapies targeting lipid and lipoprotein metabolism, such as microsomal TG transfer protein (MTP) may be a promising therapeutic approach to treat vascular diseases. Gene regulating transcription factors involved in bile acids and cholesterol metabolism can be controlled by FXR agonists in dyslipidemia. To overcome these drawbacks, many thyroid hormone analogues have been developed to lower down cholesterol level by targeting specifically thyroid hormone β receptors abundantly present in the liver without severe side effects. Virtual screening, an important tool in screening databases of the lead compounds, provides a good platform to access new compounds. In this review, examples of novel FXR modulators, thyromimetic agents, cholesterol absorption inhibitors and other new anti hyperlipidemia scaffolds have been addressed.

Keywords: Cardiovascular disease, diabetes mellitus, dyslipidemia, FXR modulators, PCSK9 inhibitors, statins, synthetic drugs, virtual screening.

1. INTRODUCTION

Since the very beginning of the nineteen century, there has been a great concern about infectious diseases responsible for the high mortality rate [1].

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The development of vaccines and antibiotics helped in the management of such diseases and decreased mortality rate. However, in the recent years, mortality rate from metabolic and cardiovascular diseases has reached to alarming level [2, 3]. Dyslipidemia has been reported as the main cause for metabolic and cardiovascular diseases causing increase in death rate. Dyslipidemia is described usually by raised fasting levels of TC, low density lipoproteins-cholesterol (LDL-C), and TG, along

with low levels of high density lipoproteins-cholesterol (HDL-C) [4]. Dyslipidemia is a major cause of such disorders which in turn need objective treatment. In order to address the disorders associated with dyslipidemia, cholesterol and lipid profile, a number of drug therapies have been considered up till now. Many drugs have undergone preclinical and clinical trials, and some new drugs are currently under investigation. As contemporary health hazard cardiovascular disease has been nominated as the main cause of death, and among these, coronary heart disease is being two third of all cardiovascular problems [5].

It has been reported that the primary cause of death in American women is cardiovascular disease. This accounts for more than 500,000 deaths each year [6]. There is a strong association between LDL-C and cardiovascular disorders. Moreover, it has been evidenced that clinical events of cardiovascular problems decrease when LDL-C level is lowered down [5, 7-9]. Recent guidelines from the National Cholesterol Education Program (NCEP), Adult Treatment Panel (ATP), as well as American Heart Association (AHA) support the LDL-C as the main target for therapy [1].

All available evidence shows that dyslipidemia is a risk factor for diabetes as it increases mortality rate in diabetic patients. One Finnish study has reported that patients with type 2 diabetes, having no history of cardiovascular diseases, have similar probabilities of death from cardiovascular diseases as non-diabetic patients having a history of myocardial infarction [10]. Moreover, the same results have been reported in another study carried on 6 different populations of the world [11]. Furthermore, Isomaa *et al.* have reported a high level of TG and LDL-C level in most diabetic patients. This establishes a close association between dyslipidemia and the occurrence of diabetes [12].

The main objective of this review is to analyze all fresh approaches employed for the treatment of dyslipidemia. Many lipid lowering drugs helps in decreasing the mortality rate due to dyslipidemia linked disorders like cardiovascular and diabetes. We have also explained some preclinical and clinical trials at different stages in Table **1**. In this review, the main focus was on new approaches and well-known targets in dicovery of dyslipidemia drugs. Meanwhile, all possible treatments including statins and non-statin therapies and their mechanism of

action have been described along with their beneficial and toxic effects (Fig. **1**, Table **2**).

2. SEARCH STRATEGY

Data are obtained from different scientific databases like PubMed, Google Scholar, ClinicalTrials.gov, Cochrane Central Register of Controlled trials of all clinical trials (Phase I to IV) and case reports which investigates fresh drugs of dyslipidemia. The search terms were "treatment of dyslipidemia", "case reports for dyslipidemia treatment", "mechanisms of dyslipidemia drugs", "dyslipidemia drugs awaiting FDA approval", "monoclonal antibodyasPCSK9 inhibitors", "nucleic acid–based therapies", "FXR modulators", "dual agonists of FXR/GP-BAR1", "thyromimetic agents", "synthetic cholesterol absorption inhibitors" and "synthetic anti-hyperlipidemic agents". The reference studies of retrieval cases were also analyzed for further study and their applicability in research for new drugs of dyslipidemia.

3. OVERVIEW OF CURRENT NOVEL DRUGS VIA DIFFERENT MECHANISMS

3.1. Statins

Atorvastatin

Hypercholesterolemia is one of the main factors controlling lipid profile changes in cardiac patients. Dyslipidemia with induction of atherosclerosis in such cases may increase mortality rate. In cholesterol synthesis 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase plays important role for the formation of mevalonate. A current study has proved that HMG-CoA reductase inhibitors can decrease occurrence of coronary heart disease by 31% and mortality rate by 21%. A major reason for selection of statins like atorvastatin is because of marked reduction in low density lipoproteins (LDL) level in cardiac abnormalities [1]. In order to analyze the difference between the adverse effects of all statins in comparison to atorvastatin was conducted. It is concluded that all statins have same intensity of adverse effects like myalgia, followed by pain, dyspepsia rhabdomylosis and sometime abdominal pain [13]. Atorvastatin effect has also been checked in cardiac patients with type 2 diabetes mellitus undergoing hemodialysis, where it gave same static results to decrease mortality rate [14]. Atorvastatin in study

Table 1. **Summary of randomized controlled trials of different drugs for treatment of dyslipidemia.**

Reference	Study Design/Phase	Drug	Dose	Duration	Mechanism of Action	Route of Administration	Results
[17]	Preclinical	Rosuvastatin	10 mg/kg, 5-15 µM	14 days, 18 hours	HMG-CoA reductase inhibitor	Oral	Cholesterol ↓ Triglycerides↓
[18]	Phase 3	Rosuvastatin and ABT-335	5 mg and 135 mg daily	12 weeks	HMG-CoA reductase inhibitor	Oral	Cholesterol ↓HDL ↑
[20]	Double blind	Pravastatin or placebo	40 mg daily	Variable	HMG-CoA reductase inhibitor	Oral	↓plasma cholesterol levels by 20% and low-density lipoprotein cholesterol levels by 26%.
[23]	Double blind	Pravastatin with placebo or JTT-705	40 mg and 300 mg or 600mg	4 weeks	HMG-CoA reductase CETP inhibitors	Oral	Combination therapy increases HDL cholesterol levels and is safe and well tolerated
[27]	Phase 3	Simvastatin, ezetimibe and rosuvastatin	10 mg-40mg	9 weeks	HMG-CoA reductase and PCSK9 inhibitors	Oral	Changes in HDL, triglycerides and apolipoprotein B levels
[30]	Double blind	Niacin or placebo	375-3000 mg/day	26 weeks	Apo lipoprotein A1	Oral	Better results in entire lipid profile, except side effects of flushing.
[31]	Open label	Niacin and lovastatin	500/10-2000/40	52 weeks	Apo lipoprotein A1 and HMG-CoA reductase inhibitor	Oral	Improved lipid profile with side effects of GIT flushing and rashes.
[19]	Double blind	Atorvastatin and placebo, atorvastatin and fenofibrate or fenofibrate and placebo	10 mg atorvastatin and placebo, and 10 mg atorvastatin plus 200 mg fenofibrate or 200 mg fenofibrate and placebo	2 months	HMG-CoA reductase inhibitor and PPARs agonists	Oral	Lipoproteins were stabilized to a high extent with combined therapy in comparison to atorvastatin or fenofibrate alone.
[96]	Phase 3	Rosuvastatin and Fenofibrate	10 mg and 160 mg	8 weeks	HMG-CoA reductase inhibitor and PPARs agonists	Oral	Caused mean percent change of LDL-C, HDL-C, VLDL-C, TG, TC, Apo-AI, Apo-B, primary outcomes expected in 2016.
[42]	Double blind	Simvastatin and ezetimibe	Simvastatin 20 mg plus ezetimibe 10 mg daily versus matching placebo	Follow up about 4.9 years	Target absorption of cholesterol in stomach and HMG-CoA	Oral	LDL-C↓ Atherosclerotic events↓ in chronic kidney patients.

↓: Reduction; ↑: Increase; HMG-CoA reductase: 5-hydroxy-3methylglutaryl-coenzyme A reductase; CETP: Cholesteryl ester transfer protein; LDL-C: Low density lipoproteins-cholesterol; HDL-C: High density lipoproteins-cholesterol; VLDL-C: Very low density lipoproteins-cholesterol; TG: Triglycerides; TC: Total cholesterol; Apo-A1 Apolipoprotein-A1; Apo-B: Apolipoprotein-B; PCSK9: Proproteinconverta-sesubtilisin/kexin type 9.
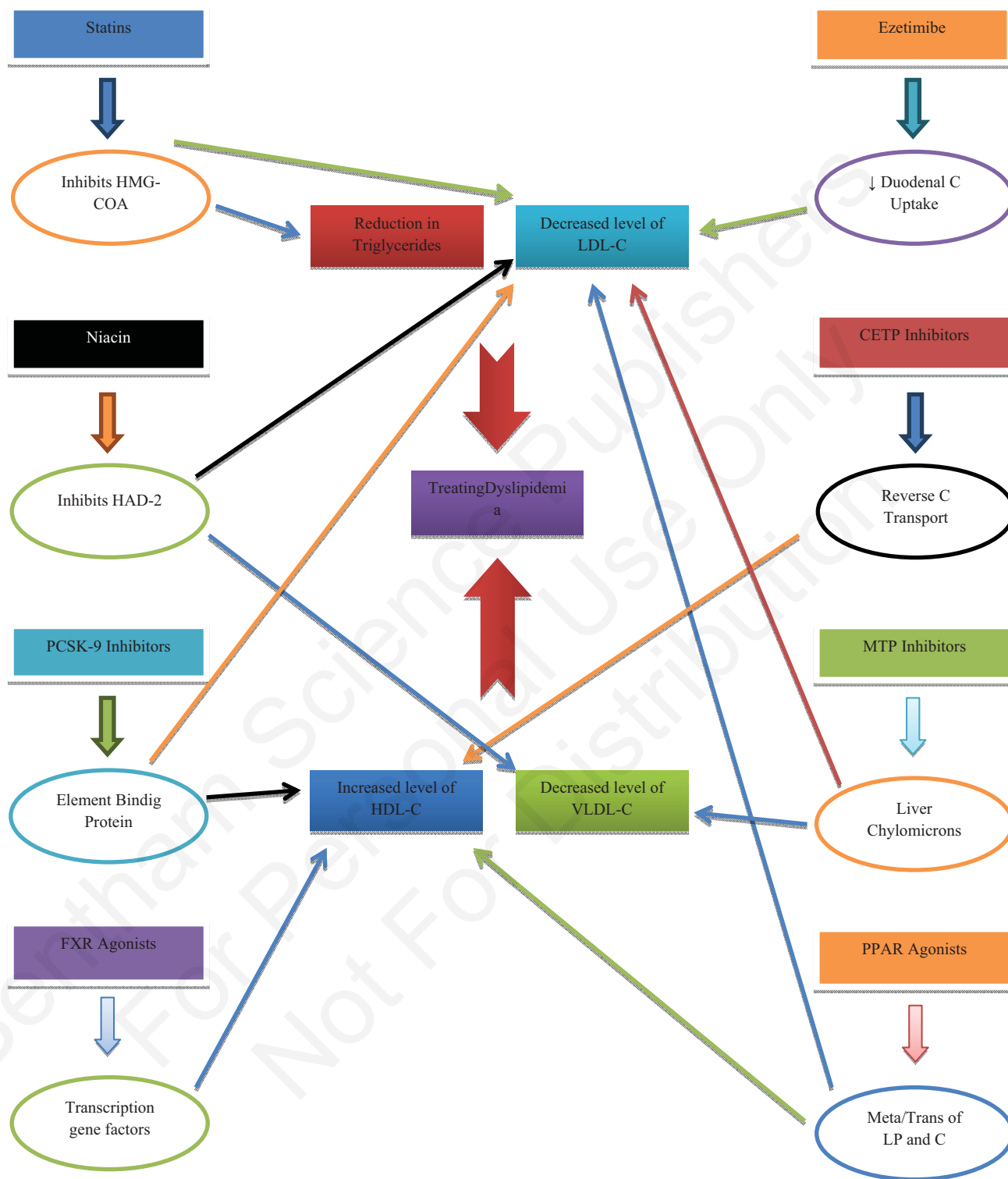
Fig. (1). Mechanism of action for different classes of drugs used in the treatment of dyslipidemia.

HMG-COA: Hydroxy-3methylglutaryl-coenzyme; LDL-C: Low density lipoproteins-cholesterol; VLDL-C: Very low density lipoproteins cholesterol; HDL-C: High density lipoproteins-cholesterol; LP: Lipoproteins; PPAR: Peroxisome proliferator activated receptor; FXR: Farnesoid X receptor; PCSK9: Proprotein convertase subtilisin/kexin type; HAD-2: Hepatocyte diacylglycerol acyltransferase-2; CETP: Cholesteryl ester transfer protein; MTP: Microsomal triglyceride transfer protein; Meta/Trans: Metabolism/Transport.

Table 2. Summary of different drug classes along with uses and toxic effects.

Drug Class	Mechanism/Uses	Adverse/Toxic Effects	Reference
Statins	Coronary heart diseases & hypertriglyceridemic patients.	Myopathy, rhabdomyolysis, acute renal failure	[136]
Hepatocyte diacylglycerol acyltransferase-2 inhibitors	Lipid disorders, cardiovascular diseases, target apo-B proteins	↑ Flushing	[137]
Cholesterol absorption inhibitors	Hyperlipidemic patients and & dyslipidemia.	Rare myopathy, ↑ liver transaminases	[138]
Cholesterylester transfer protein inhibitors	Atheroseclerosis ↑ HDL level ↓ LDL level	May ↑ blood pressure	[139]
Peroxisome proliferator activated receptor agonists	Lipid homeostasis and dyslipidemia	May stimulate antidiabetic effects	[140]
Proprotein convertase subtilisin/kexin type 9 inhibitors	Dyslipidemia and relevant cardiovascular diseases	Need more trials to study	[141]
Thyromimetic agents	Dyslipidemia, HDL and LDL cholesterol	Potentiate dangerous skeletal actions	[142]

has reduced serum uric acid level to significant level along with coronary heart diseases, so balancing an additional point with CHD [15].

Clinical evidence also proved that in a study where atorvastatin was given for coronary heart disease, it also improved liver functioning tests [16]. Mainly used statin therapy in history like atorvastatin has served as brand leader to other drugs for many years, later on other statins were developed. Single pill Gemini study was conducted for 14 weeks in patients for treating both dyslipidemia and hypertension in 1220 patients, out of which fifty eight were discontinued with therapy for serious adverse effects. So atorvastatin can be used as best drug in lipid profile abnormalities [17]. Comparing atorvastatin with other stains in a study it has been reported that atorvastatin produce more satisfactory results and more potent in lowering TG levels in body. Atorvastatin gave more beneficial effects as compared to simvastatin in patients having dyslipidemia in combination with impaired fasting glucose [18]. Low dose treatment with atorvastatin is also safe for dyslipidemia patients. It is observed in study that low dose reduced effectively total cholesterol, LDL-C and triglycerides in primary biliary cirrhosis (PBC) patients with minimal side effects, so it can be considered as first line therapy for dyslipidemia in PBC victims [19].

3.1.1. Rosuvastatin

Among the statins, rosuvastatinis one of the newest drugs, is employed as main drug therapy for lowering high lipoprotein levels. It is mainly used for treating elevated levels of TC, LDL-C and lowered levels of HDL-C in patients with mixed dyslipidemia conditions. Clinical evidences suggest that rosuvastatin also lowered down the risk factors of cardiovascular diseases in dyslipidemia patients [20]. Rosuvastatin acts by inhibiting 5-hydroxy-3methylglutaryl-coenzyme A (HMG-CoA) reductase. As a result decreased synthesis of cholesterol and exert maximum effect as compared to other statins [21]. Other possible mechanisms involved; rosuvastatin also reduces tumor necrosis factor and fibrinogen production along with increasing production of nitric oxide. Collectively, all these actions regulated by rosuvastatin improve vascular endothelial functions [22]. As far as side effects are concerned, rosuvastatin is a relatively safe and well tolerated drug rather than muscle weakness in body [20].

Clinical and preclinical studies have proved that rosuvastatin is the drug of choice for treating dyslipidemia associated with cardiovascular, diabetes and metabolic diseases. Some recent studies conducted in phase 2 and phase 3 by ClinicalTrials.gov show good results with the use

of rosuvastatin [23]. In the schizophrenic patients rosuvastatin has been used to treat dyslipidemia with maximum positive effect. Patients receiving rosuvastatin show a prominent effect on lipid profile, with decreased TG, LDL-C and increased HDL-C as compared to control [24]. In phase 3, randomized, double blind and active control study, patients with mixed dyslipidemia were treated with combined therapy with fenofibric acid (ABT-335) with 2 different doses of rosuvastatin. As a result of such combined treatment with a statin, lipid profile with all parameters of TG, LDL-C and HDL-C settled down to normal value more efficiently as compared to monotherapy [4]. In recently conducted phase 3 clinical trials (NCT00463606), rosuvastatin has been reported as a worthy drug for treating hypercholesterolemia [25]. It has been reported in recent study that, before or after cancer diagnosis statin use is linked to decrease in overall and cancer-specific mortality in colorectal cancer survivors [26]. Apart from clinical investigations, rosuvastatin showed promising results in many pre-clinical studies conducted on insulin resistant animal models [27]. A combination therapy used for diabetes 2 patients, having no cardiovascular threats, proved positive results. It was approved in another study of statin that from the single or combined treatment of simvastatin and fenofibrate for dyslipidemia patients, the best and reliable one is combined therapy [28].

3.1.2. Pravastatin

Pravastatin is another novel drug in the statin family, employed for the treatment of dyslipidemia and hypercholesterolemia. Recently, many studies performed to evaluate the efficacy of pravastatin in curing dyslipidemia in cardiac patients. Shepherd *et al.* reported a significant decrease in LDL-C and TG, with a prominent reduction of myocardial infarction and cardiovascular related mortality rate after pravastatin use [29].

A combination of statin therapy, simvastatin, atorvastatin, rosuvastatin and pravastatin have been used in dyslipidemia treatment. All of these statins produced suitable effects on lipid profile of patients with satisfactory clinical data [30]. The authenticity of pravastatin to treat hypercholesterolemia and cardiovascular problems cannot be denied, but along with this, the need was to evaluate effect on the development of diabetes mellitus. For this

purpose,the study was conducted on mice to evaluate the effect of pravastatin on adipocyte tissues and the occurrence of diabetes mellitus. This study concludes that pravastatin has beneficial effects on adipose tissue that also facilitates reduction of diabetes mellitus [31]. Likewise, other statins in combination form also have provided effective results, in a study conducted to treat dyslipidemia for Chinese's patient's that fenofibrate was used in combination with statins. In this study, patients with dyslipidemia and cardiovascular disease (NCT01462877) showed a visible change in serum TG, LDL and HDL level [32]. Pravastatin treatment for dyslipidemia was also analyzed for patients having liver problems. It is reported that pravastatin produced hepatotoxic effects in patients, so the need is to have safe measurements and cautions for treating patients with dyslipidemia as well as liver disease [33]. While treating patients for dyslipidemia, with a liver disorder, the use of statin sometime may not be rational, and there is a need for an alternative in special population. Recently in ClinicalTrials.gov phase 3 study (NCT01420549) where 3 drugs were used at different intervals in combination, for example, simvastatin 20 mg + ezetimibe 10 mg and simvastatin 40 mg + ezetimibe 10 mg to treat mixed dyslipidemia and hypercholesterolemia that gave satisfactory results [24].

3.2. Hepatocyte Diacylglycerol Acyltransferase-2 Inhibitors

3.2.1. Niacin

Niacin known as vitamin B3 or nicotinic acid exerts its action, possibly via inhibition of hepatocyte diacylglycerol acyltransferase-2 (DGAT-2), a key enzyme for TG synthesis. Thus, it affects the lipolysis through the FM-70 receptor. Inhibition of TG synthesis ultimately cause decreased secretion of VLDL and LDL particles. Other possible suggested mechanism of niacin to decrease TGs; hydroxyl-carboxylic acid (HCA) receptor2 (GPR109A) that are predominantly expressed in adipocytes [35].

In clinical trials, an extended release niacin given in different doses for a long time; showed significant effect on lipid profile without any serious toxicity except flushing [36]. In another clinical trial, combination of one a day niacin and lovastatin administered to almost 814 patients for 52 weeks. In this study 4 escalating doses were used (niacin/lovastatin in milligrams): 500/10 in

the first month, 1,000/20 in the second, 1,500/30 in the third, and 2,000/40 in the fourth month. It was concluded that this combination of drugs is effective and relatively safer for patients with dyslipidemia and reliable, because only in 10% of the patients flushing was seen [37]. But, there is one more study about combining niacin with statins, reporting less effect on lipid profile with enhanced side effects [38]. Apart from above, some clinical trials (NCT00659321) conducted by ClinicalTials.gov, showed that niacin at a dose of 500 mg or 1000 mg exerted satisfactory effects on lipid profile as compared to placebo [39].

Niacin has been a drug of choice for a long time, to decrease the mortality rate in patients with coronary heart diseases [40] but its use in the management of dyslipidemia has decreased because of flush caused by activation of prostaglandin E synthesis and potential liver toxicity. It is being anticipated that this major side effect would be subsidized with the development of non-flush niacin derivatives and fortunately a non-flush niacin derivative (ARI-3037 MO) has successfully reached human clinical trial [41]. It has been reported antisense oligonucleotide reduction of DGAT-2 expression in obese animals can reduce hepatic lipogenesis and hepatic steatosis as well as attenuate hyperlipidemia [42].

3.3. Cholesterol Absorption Inhibitors

3.3.1. Ezetimibe

Ezetimibe is an effective antihyperlipidemic drug that works by inhibiting the duodenal uptake of cholesterol or by inhibiting absorption of cholesterol in the intestine [43]. It has been observed that statin monotherapy works to decrease LDL-cholesterol production within liver, but simultaneously the absorption of cholesterol is increased in the duodenum. So the combination of statins along with ezetimibe showed better effects on LDL-C lowering as compared to conventional bile acid sequestrants [44]. Ezetimibe's use in combination with statin therapy not only causes LDL-C lowering effect, but also shows additional anti-inflammatory and antioxidant effects [45]. Ezetemibe when added to statins in recent study, then it was observed that it not only lower LDL cholesterol level but also improve effects on cardiovascular system. Combination can be preferred for additional benefits in cardiac patients [46].

Moreover, Ezetimibe alone or in combination with statins, has been used in heart transplanted patients to treat dyslipidemia causing significant reduction in cholesterol, LDL cholesterol, and TG concentrations with no consequence on HDL cholesterol concentrations. Ezetimibe was found more effective in these patients as only two patients out of total 36 developed hand edema or asymptomatic reappearance of rhabdomyolysis [47]. Yoneda *et al.* have evaluated the effect of ezetimibe in nonalcoholic steatohepatitis. Patients received 10 mg/day of ezetimibe for 6 months showed major improvement in histological parameters along with significant effect on liver biomarkers, lipoprotein, cholesterol and high sensitivity C-reactive proteins [48]. There is another clinical study reported by Baigent *et al.* evaluating the combined effect of simvastatin and ezetimibein patients suffering with chronic kidney disease. After using the combined therapy, both liver and kidney functions were significantly improved in these patients [49]. A study conducted by ClinicalTrials.gov showed that a combination therapy of rosuvastatin and ezetimibe or simvastatin and ezetimibe showed marked satisfactory effects on LDL-cholesterol levels for mixed dyslipidemia patients [50]. Nevertheless, combination therapy of statins and ezetimibe is highly tolerated, but elderly patients are required to be monitored for developing hepatotoxicity. The serum transaminases level should routinely be measured along with titration of dosage if required, or complete withdrawal in case of alarming symptoms [51].

3.4. Cholesterylester Transfer Protein Inhibitors

CETP is a water loving glycoprotein, formed mainly in liver and combined to HDL cholesterol and some part is conjugated with plasma [52]. It shows a significant role in reverse cholesterol transport as well as in the management of cholesterol homeostasis. Inhibition of CETP induces many positive effects in the body and paves the way for the treatment of dyslipidemia. Dalcetrapib, torcetrapib, evacetrapib and anacetrapib are some of main CETP inhibitors, which have entered phase 3 clinical trials and have shown beneficial therapeutic effects on lipid profile of dyslipidemia patients [53]. Evacetrapib has been used in combination with statins to control HDL and LDL cholesterol level in body [54]. A large number of experimental and also

human trials support the use of CETP inhibitors for dyslipidemia patients. Although, torcetrapib has been withdrawn recently in phase 3 because of the increased mortality rate in patients [55]. CETP is normally a protein present in every human. In healthy individuals the level of CETP varies between 1 and 3µg/mL, but in dyslipidemia patients its concentration reaches up to two or three folds of the normal value [56].

In many studies, as monotherapy and sometimes in combination with a statin, CETP inhibitors, JTT-705 and torcetrapib have been proved effective for increasing HDL cholesterol level in dyslipidemia patients [57]. In a study conducted on torcetrapib for patient's facing cardiovascular problems, different outcomes were observed. It was clear that at 12 months of treatment in combination of torcetrapib with atorvastatin, HDL cholesterol level was increased to 72.1% and low density lipoproteins were decreased to 24.1%. A study conducted by ClinicalTrials.gov (NCT00134264) also showed that there is an evidence of off-target effect of torcetrapib so far owing to increase in the mortality rate; its adverse effects cannot be avoided [58].

Another important drug of this class is anacetrapib. It is better tolerated and retains less adverse effects. Anacetrapib, as compared to torcetrapib, showed clear effects on lipid profile as well as no influence was observed on blood pressure. Bloomfield *et al.* have reported the use of anacetrapib alone or in combination with atorvastatin causing a significant effect on LDL cholesterol and increased in HDL cholesterol level [59]. Another study has found anacetrapib with equivalent results. Although, many investigations have found anacetrapib with good efficacy in the management of dyslipidemia in cardiovascular patients, it is still not registered for use in Canada and USA. Moreover, there are other ongoing studies (NCT01760460)(NCT01860729) conducted by ClinicalTrials.gov and the preliminary results have shown positive effects on HDL-C and LDL-C [60, 61].

Dalcetrapibis another drug of CETP inhibitor class used to treat dyslipidemia. The use of dalcetrapib has been reported to significantly increase the HDL-C level. A study recently conducted to assess the safety and tolerability of dalcetrapib in comparison to torcetrapib proved that it is comparatively more effective drug in cardiovascular patients [62]. In contrary to torcetrapib, dalcetrapib did not produce any effect on blood pressure, while it decreased HDL-C level with maximum effect [63]. A similar study performed on dalcetrapib for its safety concerns showed that 900 mg of this drug administered in patients inhibited any harmful actions. Clinically no effect and relevant change were observed in lymph nodes, blood pressure and other safety parameters in treatment with dalcetrapib[64]. Dalcetrapib added to pravastatin in the therapy of dyslipidemia patients with cardiovascular diseases showed satisfactory results with low mortality rate. As a result of both drug treatment 600 mg torcetrapib produced better results with pravastatin. HDL-C was increased with required limit, in addition to this Apolipoproteins level and CETP mass was increased with decreased CETP activity. Use of dalcetrapib in cardiovascular patients has not shown good results, although it has increased HDL-C level, it did not reduce LDL-C [65]. A study conducted by clinicaltrials.gov (NCT01516541) showed that in cardiovascular patients, dalcetrapib effects HDL-C and lipoprotein in different concentrations [66]. A phase 2 study (NCT00688896) conducted by combining pravastatin and dalcetrapib showed therapeutic effects on both HDL-C and LDL-D alongwith treatment of type II hyperlipidemia [67].

3.5. Peroxisome Proliferator Activated Receptor Agonists

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptor proteins regulating the expression of genes; involved in glucose homeostasis and lipid metabolism. PPARα is most abundant with high catabolism of fatty acids. Contrary to this, PPARβ/γ receptors have high expression in particular tissues that exhibit a high rate of cell proliferation and differentiation [68]. It has been evidenced from many studies that PPARs are one of important receptors that can control many metabolic disorders, like dyslipidemia, hyperlipidemia, diabetes, obesity and cardiovascular disease. Most important functions of PPARs recently uncovered how they control the level of TGs by regulating LDL-C near to optimum concentration [29]. The significance of PPARs agonists in treating a number of diseases by targeting different receptors cannot be avoided.

In previous decades, these types of drugs have served for many metabolic diseases, further research is going on to discover more novel mechanisms and drugs [69].

PPARα receptor activation controls expression of proteins utilized for transport of cholesterol, metabolism of lipoprotein, and oxidation of fatty acids. PPARα agonists like gemfibrozil and fenofibrate directly control the level of HDL-C, LDL-C and TG in the body. In order to find out the best of fibrates, ClincalTrials.gov is also involved to bring novelty in treatment. A recent study (NCT01539616) conducted on fenofibrate as compared to ZHY7 has shown better results to lower down TGs level in the human body [70]. Mixed dyslipidemia in recent year by ClinicalTrials. gov has been treated with a combination of rosuvastatin and fenofibrate. In a randomized study (NCT02262143), 10 mg of rosuvastatin along with a combination of 160mg fenofibrate versus rosuvastatin was used to treat dyslipidemia, that overall gave satisfactory results in combination rather than monotherapy and primary outcomes are expected until 2016 [71]. PPARγ receptors regulate transcription of high number of genes controlling insulin response effect. It is common and known that diabetes and cardiovascular disease co-exist. Therefore a drug controlling both PPARα and PPARγ receptors for regulating lipid profile might be beneficial for controlling both conditions [7]. Muraglitazar and tesaglitazar are PPAR α/γ receptor agonists that have shown better results in phase 3 clinical studies and reduced renal and cardiovascular events [72].

Employing this pathway, by targeting both receptors, we can have better treatment for cardiovascular and diabetes. PPARγ also plays very important role in fatty acid metabolism for several tissues. In nuclear receptors its activation facilitates, burning of fatty acids within skeletal muscle as well as adipose tissue via upregulation of fatty acid uptake, β-oxidation and energy utilization. So these can also decrease triglycerides and LDL-C level in dyslipidemia patients [73]. Toxicity concerns about some PPAR agonists like carcinogenicity, cardiac abnormalities and renal impairments are under more trials that need more discussion in future inorder to avoid health risks. Aleglitazar is another drug having dual functions; agonist for both PPARα/γ receptors, also has

shown better effects in patients with type 2 diabetes mellitus, with improvement in LDL-C, HDL-C and TG level [74]. TZD18 is a potent agonist of both receptors and caused normalization of cardiovascular and diabetic condition [75]. Recently in clinicaltrials (NCT00240383), it has been reported that muraglitazar shows promising results in treating type 2 diabetes mellitus [76].

3.6. Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors have been recently emerged therapy line for lowering LDL-C level. PCSK-9; protein that stabilizes the cholesterol concentration and maintains homeostasis. The exact mechanism is still unknown, but it is believed that PCSK-9 attaches to LDL receptors (LDLR) and thus enhancing access inside hepatocytes for degradation. Inherited PCSK-9 deficiency is directly connected with low LDL-C level and ultimately marked reduction of risk factors in cases of cardiovascular diseases. It is concluded from the Atherosclerosis Risk in Communities (ARIC) study that individuals with mutations in PCSK-9 have clear reduction of LDL-C up to 28% and 88% reduction in cardiovascular diseases in comparison to individuals without any change in PCSK-9 activity [77].

Level of PCSK-9 and LDL-C controlled by steel regulating element binding protein 2 that is further controlled by treatment with statins [78]. Use of PCSK-9 inhibitors along with statin therapy for such condition may be a better treatment option to reduce LDL-C level. Increase in PCSK-9 activity in case of statin treatment, is one of the major drawbacks of already mentioned therapy. Statins decreased the LDL-C level in the body, but on the other hand prominently PCSK-9 activity is increased leading to degradation of LDLR. A study employing combined therapy of statins and ezetimibe concluded that both of these drugs increase PCSK-9 activity with increased cardiovascular risk [79]. Different mechanisms of actions can be utilized to target the PCSK-9 receptors like antisense oligonucleotides, small interfering RNA, and antibodies against PCSK-9 [80].

The purpose of the initial approach to inhibit PCSK9 secretion was to provide a method to target its mRNA. Antisense RNA or small

interfering RNA (siRNA) technologies were used to induce silencing mRNA [81]. An antisense oligonucleotide, primarily used against PCSK-9 in mice, may be used an option to reduce LDL-C level as well as TC [82]. It has been observed that synthetic peptides mimicking the epidermal growth factor-A (EGF-A) domain of the LDLR interact with PCSK9 and dose-dependently reduce the cellular degradation of the LDLR [83].

3.7. Microsomal Triglycerides Transfer Protein Inhibitors

Microsomal triglyceride transfer protein (MTP) involved in the synthesis of VLDL-C in liver, and chylomicrons within the intestine. Inhibition of such proteins might help in decreasing hypertension, dyslipidemia and atherosclerosis via decreasing VLDL-C and LDL-C in the body. MTP inhibition a significant pathway and play important role in treating lipid and metabolic disorders. Many MTP inhibitors have been discovered till now and proved beneficial effects for treating dyslipidemia. Implitapide an excellent working MTP inhibitor has been studied recently in mice. Implitapide at 3.2 mg/kg dose administered for 8 weeks showed reduction in the triglycerides LDL-C and atherosclerotic about 83% in comparison to control [84]. In another study familial hypercholesterolemia patients were treated with BMS-201038 an MTP inhibitor, which caused reduction in LDL-C level and apolipoprotein B production in the human body. MTP inhibition can be caused via different mechanisms. The adverse effects seen with treatment were related to increase liver aminotransferase concentration and liver fat accumulation [85]. In guinea pigs, MTP inhibitor JTT-130 avoids hepatic accumulation of triglycerides and thus avoid hepatic toxicity. It was obvious after treating with a specific MTP inhibitor that it not only lowers plasma LDL and triglycerides, but also drops down the accumulation of triglycerides inside the liver [86]. Lomitapide is a selective inhibitor of MTP that is developed for treatment of lipid profile disorders. FDA has approved this as an orphan drug to treat hypercholesterolemia in 2011. It has been used in hypercholesterolemia patients in phase 3 study and caused a reduction in LDL and triglyceride level. But gastrointestinal irritations and problems were abundantly present among its side effects [87]. In future more MTP inhibitors may be discovered to fulfill the desire to treat dyslipidemia and lipid disorders.

4. NEW THERAPEUTIC APPROACHES IN THE DYSLIPIDEMIA DRUG DISCOVERY

Several high-profile failures of dyslipidemia drugs in clinical trials have led to indispensable interest in preclinical prioritization of potential targets and improved discovery. Some new therapeutic approaches in the dyslipidemia drug discovery with considering newer targets, antihyperlipidemic agents without known mechanisms, and also an older target such as NPC1L1 would be addressed.

4.1. Discovery of Monoclonal Antibody as PCSK9 Inhibitors

Evolocumab (AMG145), a monoclonal antibody, is newly discovered PCSK-9 inhibitor that reduces the risk of cardiovascular diseases. A recent phase 2 study (NCT01380730) conducted on population from the US, Canada, and Hungary in which AMG 145 was administered with different week's intervals and it was reported the incidence of cardiovascular risk was recorded as minimal. Therefore AMG 145 may be considered in future studies to assess its health benefits [88]. In another phase 1 study, AMG 145 with addition to statin decreased the LDL-C up to 75% in 39 individuals and was well tolerated over 6-8 weeks [89]. There is one more monoclonal antibody alirocumab (SAR236553/REGN727) which has caused a significant reduction in LDL-C level after combining with different doses of statins in Phase II clinical study [90]. Another similar study comprising 12 week period, utilizing REGN727, has documented reduction in LDL-C level in the body [91]. RN316/PF04950615, a humanized IgG2a monoclonal antibody, binds to PCSK9 and prevents LDLR degradation. RN316 lowered LDL-C in hypercholesterolaemic subjects in phase I and II studies [92]. Other PCSK9 monoclonal antibodies in clinical trials include LGT209 against the C-terminal residues 680–692 ofPCSK9 and RG7652 against the catalytic domain of PCSK9 [93].

Several pharmaceutical companies support the use of new antibodies to target PCSK-9 for treatment of dyslipidemia, cardiovascular and other diseases [94]. Merck Research Laboratories developed a monoclonal antibody (1D05-IgG2)

that structurally mimics the EGF-A domain of LDLR. The crystal structure of PCSK9/1D05-Fab complex showed that 1D05-Fab binds to an epitope on the PCSK9 catalytic domain which includes the entire LDLR EGF-A domain binding site which disrupted the PCSK9:LDLR interaction with an IC_{50} of 3.7 ± 0.1 nM [95]. Researchers at Merck reported the other anti-PCSK9 monoclonal antibody 1B20, similar to antibody 1D05 binds to PCSK9 with high affinity and inhibits PCSK9:LDLR interaction with a calculated IC50 of 11.4 ± 1.5 nM [96].

Pfizer-Rinat has recently reported a humanized monoclonal J16 binds to a three-dimensional epitope mapping to the catalytic domain of PCSK9 that almost perfectly overlaps with the LDLR EGF-A domain binding site on PCSK9 and also, in part, to the C-terminus of the prodomain. J16 blocked the PCSK9:LDLR interaction with an IC_{50} 1.4 nM. Mouse antibodies to human PCSK9 were generated by immunizing mouse with recombinant human PCSK9 and then mouse antibody J10 was humanized and affinity-matured to antibody J16 by using standard humanization and affinity maturation strategies [97].

In order to increase the pharmacokinetic and efficacy of this antibody, J16 was modified to bind PCSK9 in a pH-sensitive manner by introducing histidines into complementarity determining regions. The resultant J17 antibody shows prolonged half-life and increased duration of cholesterol lowering properties [98].

Moreover, it has been suggested that combination therapy of antibodies with synthetic drugs such as statins, ezetimibe, bile-acid sequestrants, or niacin produces additively reduced LDL-C levels.

4.2. Discovery of Nucleic Acid–based Therapies Targeting MTP

In the last decade a new class of small RNA molecules, microRNAs (miRs), have emerged as key regulators of gene expression at the post-transcriptional level. MiRNAs usually function by targeting the 3′untranslated region (3'UTR) of a mRNA and reduce protein synthesis by enhancing mRNA degradation, interfering with mRNA translation or both [99]. Several studies demonstrated that miRNA sdysregulation have a key role in the lipid homeostasis [100-102]. In that

regard, nucleic acid–based therapies targeting miRNAs and potentially opening new avenues for the treatment of dyslipidemias. At present, several antisense therapies for the treatment of dyslipidemia are in preclinical or clinical studies.

A miRNA that has gained a lot of attention in the last few years is miR-33 that is involved in regulation of HDL synthesis and cholesterol transport. Inhibition of miR-33 using an 2' fluoro/methoxyethyl–modified phosphorothioate backbone antisense oligonucleotide in mice promote reverse cholesterol transport to the plasma, liver, and feces and increased circulating HDL levels. Indeed, anti-miR–treated mice showed reductions in lipid content and plaque size [103]. In nonhuman primates fed with a high carbohydrate diet, the inhibition of miR-33b with 2' fluoro/methoxyethyl–modified phosphorothioate-backbone, for 12 weeks reduced VLDL triglyceride levels and elevated plasma HDL levels [104]. Furthermore, studies of miR33 targeting oligonucleotides revealed microRNA-30c (miR-30c) interacts with the 3′UTR region of MTP mRNA and causes faster degradation, leading to suppression of MTP which mediates the packaging of VLDL particles with triglycerides in the liver and small intestine, an essential step in apolipoprotein B secretion. MTP activity, as well as mRNA and protein expression, were increased or decreased by hepatic delivery of anti-miR-30c or miR-30c, respectively [105, 106]. The Soh *et al.* findings hold great potential for drug targeting in treating hyperlipidemias and associated disorders. MTP inhibitors such as miR-30c agonists or miR-30c mimics, reduces MTP-associated lipid production without side effects relative to other MTP inhibitors.

A recent study compared and contrasted the metabolic consequences of murine-specific apoB or MTP antisense oligonucleotides. Phosphorothioate oligonucleotides containing 2'-O-methoxyethyl groups at positions 1–5 and 15–20 targeting murine MTP (ISIS 144477) and apoB (ISIS 147764) were designed, synthesized and evaluated in preclinical pharmacology models. MTP (ISIS 144477) in primary mouse hepatocytes reduced MTP mRNA in a dose-dependent manner. MTP antisense oligonucleotides treatment consistently led to more hepatic triglyceride accumulation and more

biomarkers of hepatotoxicity relative to apoB antisense oligonucleotides [107].

4.3. Discovery of New FXR Modulators

4.3.1. Discovery of Non-steroidal FXR Modulators Using Virtual Screening

Virtual screening as a knowledge-based approach was used to discover new, potent non-steroidal FXR agonists. This computational technique automatically evaluates very large libraries of compounds and divided into two broad categories as structure-based and ligand-based methods. In a study, among well-established methods of ligand-based screening, including shape-based screening, ligand-based pharmacophore, 3D-QSAR, scaffold hopping and virtual library design, the ligand-based phase shape was combined with receptor based induced fit docking (IFD) to implement virtual screening. Two small molecule databases were prepared which one was used to validate the performance of phase shape and IFD. The official website of Enamine as the second one was for seeking new FXR modulators. This study benefited from structure-based and ligand-based virtual screening. Ligand-based virtual screening can not only find ligands which are similar to the known FXR modulators but, the use of IFD adjusts the binding pocket of FXR and thus accommodating various structural frameworks. Finally, among different X-ray co-crystal structures of FXR ligand binding domains with different legends, self- and cross-induced fit docking (IFD) was applied to bound ligands with PDB code 3DCT, 3FLI, and 3OKI. Based on these workflow 50 molecules were selected based on the docking pose and the hydrogen bond and hydrophobic interactions between the protein-ligand, so purchased from Enamine for bioassay. Homogeneous time-resolved fluorescence (HTRF) assays introduced 3 FXR active compounds, including 2 antagonists and 1 agonist. IC_{50} values of compound **1**, **2** were 8.23, 3.77 and EC_{50} value of compound **3** was 12.91 μM. The results of cell-based assay confirmed the results of HTRF method, so that compound **2** was found to have FXR antagonistic effect in a concentration dependent manner and compound **3** with an EC_{50} value of 2.60 μM had a potent agonistic effect on FXR [108].

Huang *et al.* screened an in-house library of 12480 compounds using ligand based virtual screening and 78 candidates was evaluated by HTRF assay. One nonsteroidal compound **4** was

identified as an FXR antagonist (IC_{50} =69.01 ± 11.75 μM), so 26 new derivatives were designed and synthesized accordingly. Synthetic compound **5** with IC50=8.96 ± 3.62 μM, showed antagonistic capability approximately 10 times and 8-fold higher than that of the control (Z-guggulsterone) and the prototype compound **4**, respectively. Compound **5** had more beneficial effects on lowering the contents of triglyceride and cholesterol contents in human hepatoma HepG2 cells and in the cholesterol-fed C57BL/6 mice than FXR natural antagonist Z-guggulsterone. The preliminary SARs showed changes of some substitutes of pyrazolone moiety, have a very important influence of antagonistic activity, and appropriate structural optimizations on these regions can substantially improve the antagonistic potency [109].

In the other study the hits were identified by virtual screening of a compound collection using an in silico model of FXR. The anthranilic acid derivative **6** was selected as a hit compound for optimization by medicinal chemistry and automated computational docking studies. Anthranilic acid derivatives were generated in a two-step synthesis with verification in two substitutes of the anthranilic acid core. The SAR study of anthranilic acid derivatives revealed replacing the acyl substitutes at the aniline nitrogen with larger lipophilic substitutes strongly improved the potency of compound **7**. Introduction of an additional aromatic moiety to the acidic head group at the 2-naphthoyl residue improved the EC_{50} value of the compounds. 3-Aminobenzoic acid derivative **8** showed the best overall characteristics with an EC_{50} of 1.5 ± 0.2 μM and 37 ± 1% maximal relative FXR activation in a cell-based full-length FXR transactivation assay with a firefly luciferase as a reporter gene [110].

This research group published optimization of the anthranilic acid scaffold by SAR and molecular docking studies. The first SAR study discovered two compounds **7** and **8** as FXR partial agonists with moderate potency. Recombination of **7** and **8** in compound **9** resulted in improved potency and provided the starting point of this SAR study. The SAR of the lipophilic acyl substituent, the acidic head group, and the anthranilic acid core structure were investigated in compound **9** as the starting compound. Introduction of a methoxy group in the 4-position

of the central aromatic ring showed even more potency on FXR and a very favorable docking pose. Among the 25 available cocrystal structures of the FXR-LBD with the benzimidazole-based partial agonistic ligand seemed most suited for docking studies on the here reported partial FXR agonists. Docking of compounds **9** and **10** into the FXR-LBD suggested prominent potent interactions with Arg335 and with Arg268 via near a water molecule from the water cluster [111].

4.3.2. Discovery of New FXR Modulators via Main Lead Compound GW4064 Scaffold

The discovery of FXR agonist GW4064 compound **11** was reported nearly 15 years ago. Among the non-steroidal FXR agonists, GW4064 and its derivatives are most potent and served as a model or reference compound in many experiments. Its limited pharmacokinetic profile, including clearance, short terminal half-life and limited oral exposure precludes any further testing in a clinical setting. Furthermore, the stilbene-mediated UV light instability and degradation could potentially lead to toxicity issues.

Novel analogs of GW4064 were developed based on the chemical structure of the potent FXR ligand GW4064 and the activity profile of these analogs was presented. Four possible naphthalene derivatives were synthesized via converting the stilbene to naphthalene. Fluorescent resonance energy transfer (FRET) and transient transfection (TT) assays revealed the 6-substituted 1-naphthoic acid (GSK8062) **12** was quite selective, full agonist and essentially equipotent to GW 4064. *In vivo* experiment showed GSK8062 was well absorbed in dog and monkey and despite poor oral exposure in rodents, reduced the severity of cholestasis in α-naphthyl-isothiocyanate (ANIT) chemically induced rat acute cholestasis model [112].

Several conformationally constrained analogs of GW4064 were prepared with replacement of the metabolically labile stilbene with either benzothiophene or naphthalene rings. Among two series of GW 4064 analogs, benzothiophene **13** and naphthalene **14** were potent and full FXR agonists. Pharmacokinetic studies in rats demonstrated benzothiophene **13** had a very high clearance, very short half-life (t1/2 = 15 min) and poorly bioavailable [113].

A follow-on GW4064 analogs revealed that replacement the naphthyl ring of GSK8062 with heteroaryl bicyclic systems could improve hydrophilicity, and improved aqueous solubility might increase rat exposure. Then a series of aza-naphthalene analogs of GSK8062 were synthesized and evaluated in *in vivo* and *in vitro* methods. The quinolone (GSK2324) **15** was an equipotent full FXR agonist to GSK8062 with good selectivity, water solubility and better rat pharmacokinetics. In addition, analog **15** lowered body weight gain, glucose, triglycerides, total cholesterol,and glycerol in diet-induced obese (DIO) mouse model of diabetes [114].

The discoveries of GSK8062 (TT EC_{50} = 68 nM, %Max = 104%) and GSK2324 (TT EC_{50} = 50 nM, % Max = 102%) proved that elimination of the stilbene moiety could improve the light stability of GW4064 analogs, while maintaining potency and efficacy.

The carboxylic acid groups on GW4064 form electrostatic interactions with [331]Arg in helix 5 of the FXR ligand binding domain. A strategy was implemented to further explore the optimal disposition of the carboxylic acid moiety relative to its interaction with [331]Arg, so a novel series of ring constrained analogs of GW4064 were prepared with different appendages of the carboxylate pharmacophore. The indole **16** and benzothiophene **17** display the optimal orientation of the carboxylate for enhanced FXR agonist potency and selectivity. The rat pharmacokinetic parameters showed none of these analogs had a pharmacokinetic profile superior to GSK2324 [115].

Molecular docking studies on co-crystal structure of GW4064 bound tothe active site of FXR demonstrated the isoxazole ring of GW4064 plays a crucial role in FXR activation through its edge-to-face stacking interaction with [454]Trp on helix 12, which is critical for recruiting accessory proteins for modulating gene transcription. A series of novel analogs of GW4064was designed and synthesized via replacement of the isoxazole ring by a 5-membered ring. The FRET andthe TT assays revealed oxazolidine **18** and pyrazole derivative **19** were very potent in both assays and also showed excellent agonist activity. It seems the isoxazolenitrogen atom in GW4064 accepts a key H-bonding interactionwith the backbone of FXR,

so nitrogen atom in the optimal position of heterocyclic ring is a key atom that leads to a significantly improved in potency. The most potent analogs in this study maintain a putativeH-bond acceptor, placed strategically in the ring [116]. Only few datasets have been published onanotherisoxazole-type synthetic FXR agonist, Px-102 and its eutomer, named Px-104 thatis currently being tested in patients with non-alcoholic fatty liver disease (NAFLD) [117].

4.3.3. Discovery of New Dual Agonists of FXR/GP-BAR1

Bile acids exert genomic and non-genomic effects by activating TGR5 (M-BAR, GP-BAR1 or BG37) a G-protein-coupled receptor, and farnesoid X receptor (FXR). Because the two receptors might have overlapping activities, ligands with dual activity might be beneficial in treating disorders of lipid and glucose homeostasis. Thus semisynthetic chenodeoxycholic acid derivative INT-767 **20**, acting on both FXR andGP-BAR1, attenuates signs and symptoms of liver injuries in rodent models of metabolic syndrome. INT-767 induces markedly decreases cholesterol and triglyceride levels in diabetic mice model [118, 119].

A new generation of dual GP-BAR1/FXR agonists was synthesized using INT-767asa template for dual bile acid receptor agonism. *In vitro* and *in vivo* pharmacological evaluation of the new generation of dual bile acid receptor agonists showed compound **21** stimulated the release of the potent insulinotropic hormone GLP-1 and transactivated both FXR and GP-BAR1 with an EC_{50} of ~1 μM and EC_{50} of ~0.2 μM respectively.To disclose the molecular basis of dual GP-BAR1/FXR agonism, the binding mechanism of the most potent dual agonists of the series to the two receptors was investigated, performing a series of computations. These simulations through a series of computations provided the molecular basis to achieve potent GP-BAR1/FXR dual organism [120]. Chemical structures and potency of some farnesoid X receptor (FXR) modulators are presented in Fig. (**2**).

4.4. New Thyromimetic Agents

Novel thyromimetics with high TRβand liver selectivity, based on the structure of eprotirome **22** and molecular modeling were designed and structure–activity relationships (SARs) of new derivatives investigated (Fig. **3**). A docking model of eprotirome was constructed from the crystal structure of human TRβ-T3. The docking model suggested some interactions such as the interaction between Arg-320β and COOH of the ligand play a central role in hTRβ selectivity. So, the other indane derivatives with other acids and ring spacers were synthesized to obtain further SAR information. The evaluation by radioligand binding assay and cholesterol-fed rat model demonstrated KTA-439 **23**, a representative indane derivative, is a potent and dual selective thyromimetic expected to avoid hypothyroidism in some tissues as well as heart toxicity [121].

In other study, among several electron deficient heterocyclic modifications that were investigated, the pyridazinone analogues have been identified as potent selective inhibitors for TRβ.Optimization of these analogues by replacement of the acetic acid substituent with a cyanoazauracil,improved both the potency andselectivity and led to MGL-3196 **24**, which is 28-fold selective for THR-β over THR-α in an *in vitro* functional assay. **24** exhibited reasonable plasma exposures and oral bioavailability in preclinical animal models and in humans. When dosed orally to diet induced obese mice, **24** was efficacious in the reducing cholesterol levels and liver size without any impact on the central thyroid axis. In healthy volunteers, **24** exhibited significant reductions relative to placebo of up to 30% for LDL-C and up to 60% for TG at once daily oral doses of 50 mg or higher for 2 weeks [122].

4.5. New Synthetic Cholesterol Absorption Inhibitors

In addition to new targets, the attention could be focused on old approach such as cholesterol absorption inhibitors in drug discovery. It is known that the molecular target of ezetimibe **25** is Niemann-Pick C1-Like 1 protein (NPC1L1) which is critical for intestinal cholesterol absorption. They identify that compounds functioning as cholesterol-absorption inhibitor, via a correlation between NPC1L1 binding affinity and inhibition of cholesterol absorption *in vivo,* is an improvement in the cholesterol absorption inhibitor discovery. Virtual screening was used with aims to discover new, potent NPC1L1 inhibitors. However, a previous study reported a spiroimidazolidinone by similarity-based virtual
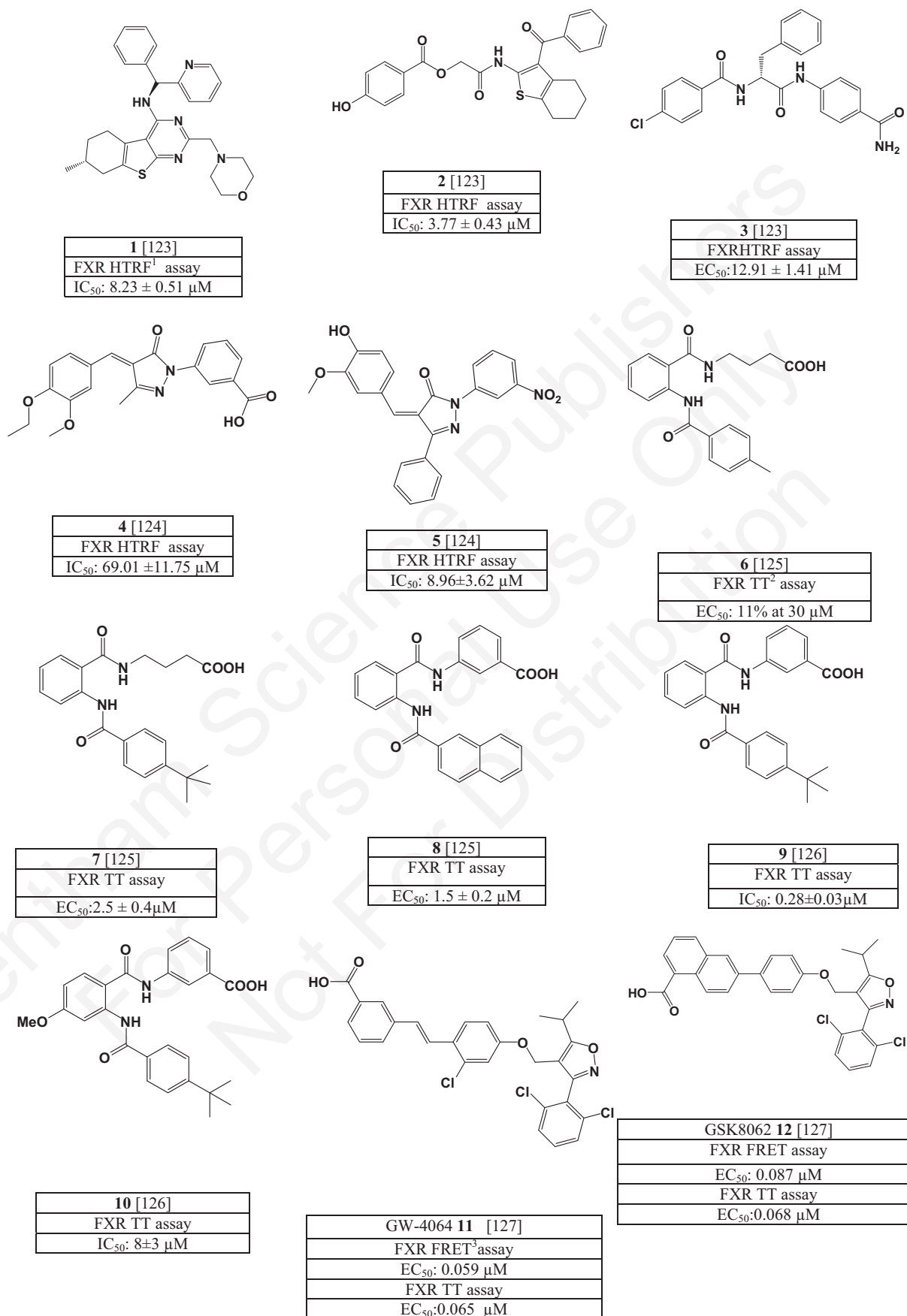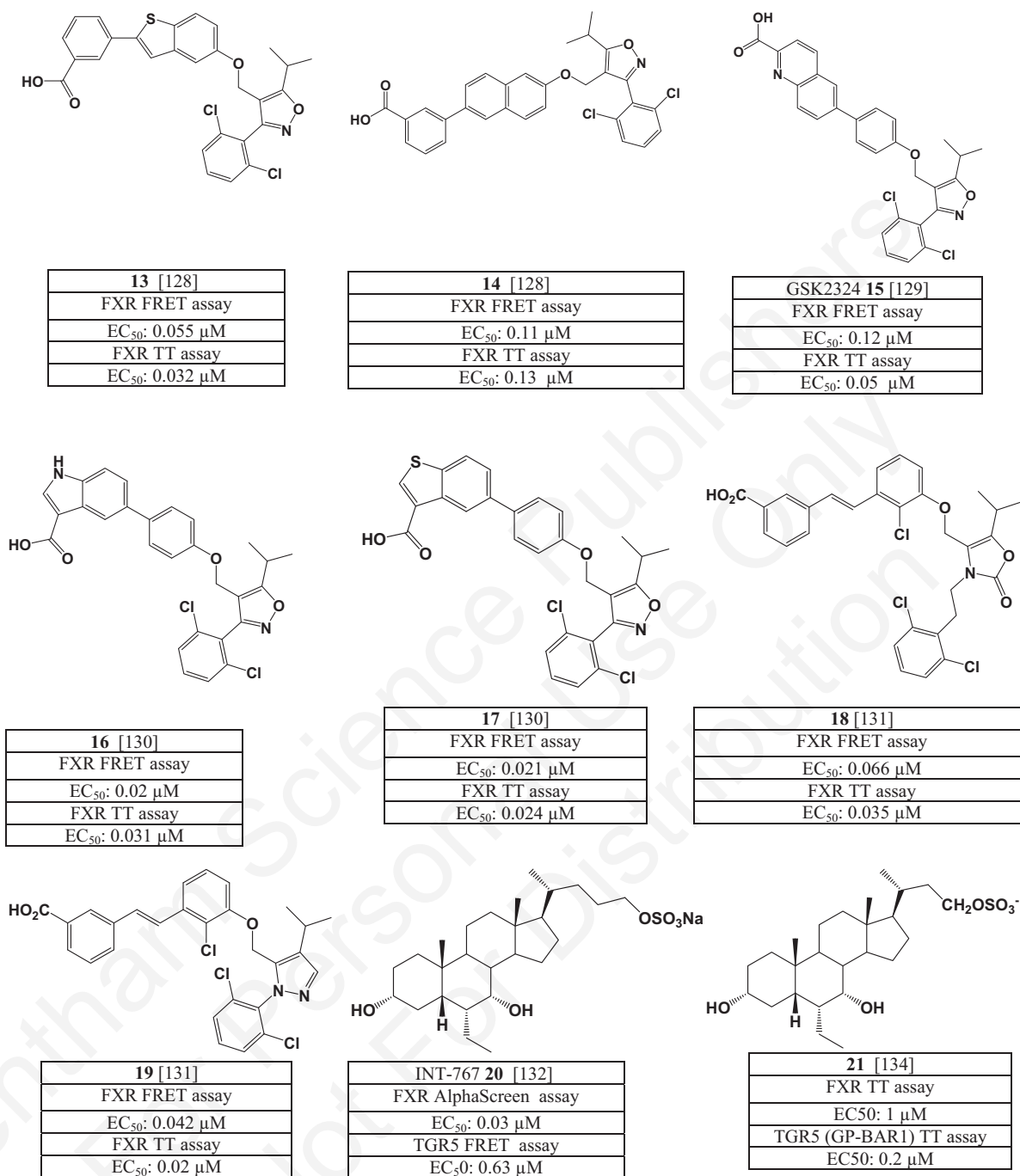
1 [123]
FXR HTRF[1] assay
IC$_{50}$: 8.23 ± 0.51 μM

2 [123]
FXR HTRF assay
IC$_{50}$: 3.77 ± 0.43 μM

3 [123]
FXRHTRF assay
EC$_{50}$:12.91 ± 1.41 μM

4 [124]
FXR HTRF assay
IC$_{50}$: 69.01 ±11.75 μM

5 [124]
FXR HTRF assay
IC$_{50}$: 8.96±3.62 μM

6 [125]
FXR TT[2] assay
EC$_{50}$: 11% at 30 μM

7 [125]
FXR TT assay
EC$_{50}$:2.5 ± 0.4μM

8 [125]
FXR TT assay
EC$_{50}$: 1.5 ± 0.2 μM

9 [126]
FXR TT assay
IC$_{50}$: 0.28±0.03μM

10 [126]
FXR TT assay
IC$_{50}$: 8±3 μM

GW-4064 **11** [127]
FXR FRET[3]assay
EC$_{50}$: 0.059 μM
FXR TT assay
EC$_{50}$:0.065 μM

GSK8062 **12** [127]
FXR FRET assay
EC$_{50}$: 0.087 μM
FXR TT assay
EC$_{50}$:0.068 μM

Fig. (2). contd….

Fig. (2). Schematic representation of chemical structure of some examples of the Farnesoid X Receptor (FXR) modulators. [1]HTRF: Homogeneous time-resolved fluorescence; [2]TT: Transient transfection; [3]FRET: Fluorescent resonance energy transfer

screening as NPC1L1 inhibitor, which showed moderate binding activity but was not efficacious in an *in vivo* rodent model of cholesterol absorption [123].

In order to investigate the structure–activity relationship of ezetimibe analogs eight new derivatives of the 2-azetidinone cholesterol absorption inhibitors were synthesized and their cholesterol absorption inhibition activities was evaluated in orally dosed seven day cholesterol fed hamsters. Some of the ezetimibe analogs such as **26**, which amide electron deficient pyridine ring and ester group were introduced to the C-(3) carbon chain of ezetimibe, showed comparable effects in lowering the levels of TC in the serum (Fig. **4**) [124].

Eprotirome **22** [135]	KTA-439 **23** [135]	MGL-3196 **24** [136]
hTRβ	hTRβ	hTRβ Rel % Activity of T3: 83.8%
Ki :0.43 nM	Ki :7.8 nM	
hTRα	hTRα	hTRα Rel % Activity of T3: 48.6%
Ki: 9.6 nM	Ki: 172 nM	
ED$_{50}$ Chol:9.06nmol/kg	ED50 Chol:21.9 nmol/kg	
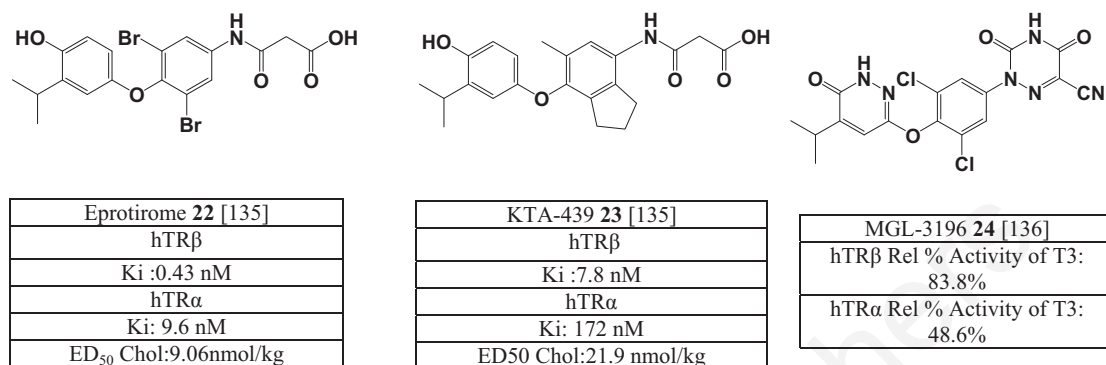
Fig. (3). Structure of some novel thyromimetics with high TRβ selectivity ED$_{50}$chol: Dose causing 50%greater lowering from the vehicle.
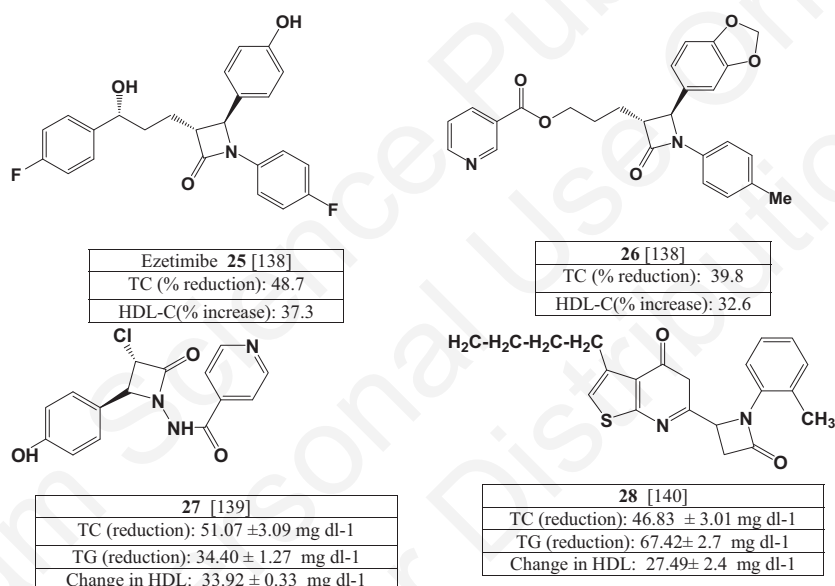

Ezetimibe **25** [138]	**26** [138]
TC (% reduction): 48.7	TC (% reduction): 39.8
HDL-C(% increase): 37.3	HDL-C(% increase): 32.6

27 [139]	**28** [140]
TC (reduction): 51.07 ±3.09 mg dl-1	TC (reduction): 46.83 ± 3.01 mg dl-1
TG (reduction): 34.40 ± 1.27 mg dl-1	TG (reduction): 67.42± 2.7 mg dl-1
Change in HDL: 33.92 ± 0.33 mg dl-1	Change in HDL: 27.49± 2.4 mg dl-1

Fig. (4). Structure and antihyperlipaemic activity data of some new potent synthetic cholesterol absorption inhibitors.

The eight new 2-azetidinone analogs of ezetimibe were designed and prepared through structure-based virtual screening (in silico docking studies) with the X-ray crystal structure of the Niemann-Pick C1-like 1 protein (NPC1L1). The antihyperlipdemic evaluation of the synthetic analogs in the Triton WR-1339-induced hyperlipidemic rat model showed some of these molecules to exhibit significant lipid-lowering effects which are comparable to ezetimibe. Correlation between the in silico molecular docking scores and experimental biological activity of the compounds was observed. Docking scores for compound **27** was the most favorable, due to the more significant interactions and higher proximity with the NPC1L1 active site residues.

Significant antihyperlipidemic activity in some of the synthetic compounds especially **27** was observed, which is comparable to the standard drug, ezetimibe [125].

Some novel thienopyrimidine derivatives of azetidinone possessing the combined features of the potential antihyperlipidemic 2-substituted thienopyrimidin-4-ones and cholesterol absorption inhibitor drug ezetimibe were synthesized and their lipid-lowering activities in Wistar albino rats were evaluated. Compound **28** showed promising lipid lowering activity like reducing serum levels of cholesterol and triglycerides in test animals, which is comparable to the standard drug, gemfibrozil [126].
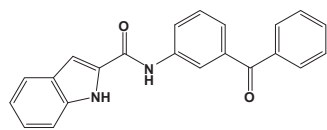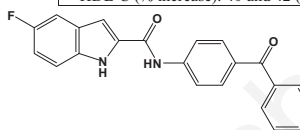
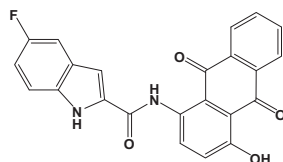| 29 [142] |
|---|
| TG (%reduction): 91 and 66 (7h and 24h) |
| TC (%reduction): 17 |
| LDL-C (%reduction): - |
| HDL-C (% increase): 24 and 34 (7h and 24h) |

| 30 [142] |
|---|
| TG (reduction): 72% and 64% (7h and 24h) |
| TC (%reduction): 27 |
| LDL-C (%reduction): 75 and 40 (7h and 24h) |
| HDL-C (% increase): 40 and 42 (7h and 24h) |
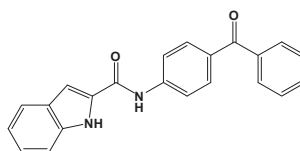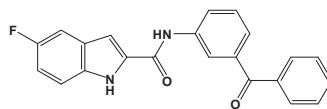
31 [143](
TG (%reduction): 90 (12h)
TC (%reduction): -
LDL-C (%reduction): 35 (12h)
HDL-C (% increase): 86 (12h)

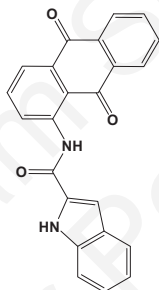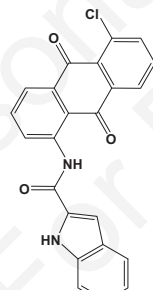| 32 [143] |
|---|
| TG (%reduction): 83 |
| TC (%reduction): - |
| LDL-C (%reduction):39 (12h) |
| HDL-C (% increase): 53 (12h) |

| 33 [144] |
|---|
| TG (%reduction): 86 and 33 (7h and 24h) |
| TC (%reduction): 46 (12h) |
| LDL-C (%reduction): 50 (12h) |
| HDL-C (% increase): 148 (12h) |
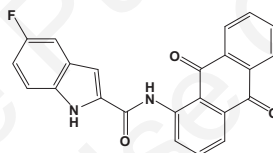
34 [144]
TG (%reduction): (80 and 33) (7h and 24h)
TC (%reduction): 20 (12h)
LDL-C (%reduction): 26 (12h)
HDL-C (% increase): 114 (12h)

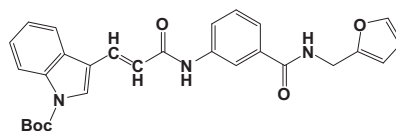| 35 [145] |
|---|
| TG (%reduction): 65 (8h) |
| TC (%reduction): 20 (8h) |
| LDL-C (%reduction): 24 (8h) |
| HDL-C (% increase): 62 (8h) |

36 [145]
TG (%reduction): 70 (8h)
TC (%reduction): 20 (8h)
LDL-C (%reduction): 29 (8h)
HDL-C (% increase): 60 (8h)
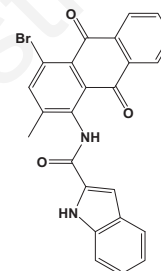
37 [145]
TG (%reduction): 71 (8h)
TC (%reduction): 17 (8h)
LDL-C (%reduction): 27(8h)
HDL-C (% increase): 60 (8h)

38 [146]
DGAT IC_{50}^{1}: 2.5 μM
hDGAT-1 IC_{50}^{2}: >100 μM
hDGAT-2 IC_{50}^{2}: 6.9 μM
TG synthesis, % of control: 33.2 ± 3.5 (10μM)
Control:100 ± 9.4

Fig. (5). Chemical structure and anti-hyperlipidemic effects of some Indole derivatives. [1]Rat microsomal DGAT inhibition; [2]Human recombinant DGAT1 and DGAT2 inhibition.

4.6. Novel Indole Derivatives with Anti-hyperlipidemic Activity

Indoles derivatives are of wide interest because of their diverse biological activity and clinical applications. Some indole-2-carboxamides derivatives are well known to decrease lipid agents in Triton WR-1339-induced hyperlipidemic rats [127].

The six unsubstituted N-(Benzoylphenyl)-1H-indole-2-carboxamides were prepared and the lipid-lowering effect of the derivatives was tested in Triton WR-1339-induced hyperlipidemic rats. At a dose of 15 mg/kg body weight, synthetic compounds **29**, **30** (Fig. **5**) and bezafibrate as reference hypolipidemic drug significantly (p < 0.0001) reduced the elevated plasma triglyceride levels after 7 and 24 h compared to the hyperlipidemic control group. Moreover, HDL-C levels were significantly increased in all treated groups. However, only compounds **29** and **30** significantly decreased TC levels after 24h [128].

The five N-(benzoylphenyl)-5-fluoro-1H-indole-2-carboxamide derivatives were synthesized and studied in Triton WR-1339-induced hyperlipidemia rats. The results showed that both compounds **31** and **32** at a dose of 15 mg/kg and bezafibrate at a dose of 100 mg/kg body weight were able to significantly decrease serum triglyceride levels after 12 h. In addition, both compounds **31** and **32** increased HDL levels. The results indicated that compounds **31** and **32** at a dose of 15 mg/kg body weight was found to be more potent than the reduction induced by bezafibrate at a dose of 100 mg/kg body weight 12 h after Triton injection [129].

In the other study a novel series of 5-fluoro-N-(9,10-dihydro-9,10-dioxoanthracen-8-yl)-1H-indole-2-carboxamides were synthesized. At a dose of 15 mg/kg, compounds **33** and **34** obviously showed a significant reduction in elevated plasma triglycerides and plasma levels after 12 and 24 h compared to the hyperlipidemic control group. Moreover, HDL-C levels were significantly increased in all treated groups. Some synthetic compounds such as **33** and **34** at a dose of 15 mg/kg body weight showed the same potential in reducing TG levels and in increasing HDL-C levels compared to bezafibrate at a dose of 100 mg/kg body weight. Furthermore, TC levels did not differ significantly in the bezafibrate treated group which agrees with the mechanism of action of fibrates [130].

Other five derivatives of unsubstituted indole-anthraquinonecarboxamide were synthesized and 1 ml of 57 μM of them evaluated for anti-dyslipidemic activity in Triton WR-1339- induced hyperlipidemic rats after 8 h. Compounds **35**, **36** and **37** significantly reduced TC, TG and LDL-C levels and increased in the plasma level of HDL-C. Promisingly, in this study the reduction of the lipid level by compounds was higher than that induced by bezafibrateat at a dose of 1 ml of 276 mM [131].

The pharmacological effect of compounds in mentioned studies confirmed that the presence of the three structural components such as carboxamide linkage, aromatic heterocyclic ring and a lipophilic area for the lipid lowering activity of indoles derivatives are essential.

Screening of a library composed of various heterocyclic compounds led to the identification of indolyl acrylamide derivatives as DGAT inhibitors. A series of indolyl acrylamide derivatives was synthesized and the DGAT-2 inhibitory activity and selectivity evaluated. Among a series of indolyl acrylamide derivatives furfurylamine containing indolyl acrylamide derivative **38** was identified as a selective human DGAT-2 inhibitor. Further evaluation showed compound **38** inhibited triglyceride synthesis dose-dependently in HepG2 cell line [132].

CONCLUSION

We evaluated the available data for treatment of dyslipidemia and addressed the some new approaches in dislipidemia drug discovery. Different evidences suggest variability in therapy of cardiovascular and diabetic patients. However, statins are still proving to be the best treatment for dyslipidemia [133, 134].

Newly discovered statins with modified chemical structures proved best for treating lipid disorders. Despite such novel discoveries there still remain some limitations with regard to use of statins in some patients, owing to specific adverse effects. In such cases niacin, or other drugs like fibrates can be used for further therapy. DGAT-2catalyze final step of triglyceride synthesis, so drugs targeting this mechanism have been nominated as ideal molecules. Another class, CETP inhibitors acting via a different mechanism assisted in clinical trials to high extent. PPAR-α/β

agonists are agents with prominent effect on lipid profile both in cardiovascular as well as diabetic patients. The modulation of FXR receptor, MTP remains an attractive area in drug discovery to develop novel therapeutic opportunities for liver and metabolic disorders.

In addition to these, many other drugs are still needed to be discovered. Many agents are in the process of testing by ClinicalTrials.gov and hoped to have more promising drugs in the near future to be approved for lowering lipid profiles in humans. Newly discovered lipid lowering drugs with multiple mechanisms are supported for managing lipid disorders.

5.   Practical   Opinion: Treatment of dyslipidemia has been a main issue for long. Increasing mortality rate due to cardiovascular and diabetic problems requires a drug therapy which is relatively safe and effective. For a very long time ago, bile acid sequestrants like cholestyramine were first used to treat hypercholesterolemia, but after since the discovery of statins, now have only a minor role in this indication. Statins therapy at first glance is the main drug of choice in lipid profile disorders. Atorvastatin, rosuvastatin and pravastatin widespread use eradicated symptoms of dyslipidemia, as monotherapy and also in combination with other drugs like CETP inhibitors. Niacin give sustain released effects and is preferred in patients with liver diseases to avoid hepatic toxicity, but flushing in GIT is one of the minor side effect observed with this therapy [35]. Fenofibrate therapy in combination with statin can be used as the best tool for treating cardiovascular patients along with lipid profile disorders. Ezetimibe along with statins is best opted therapy in such cases when statin not alone gives better response.

PPAR α/γ receptor agonists are discovered newly for treating both cardiovascular and diabetic patients, muraglitazar and tesaglitazar are drugs targeting both these receptors and preferably lowering mortality rates because of both diseases.

The monoclonal antibody for PCSK9 is a novel approach that opens up the opportunity to target a protein, prevent it from binding to the LDL receptor, and therefore maintain greater LDL receptor up-regulation. AMG 145 newly discovered monoclonal antibody as PCSK-9 inhibitor, best treated dyslipidemia patients. Antibody J10 was

developed to the affinity-matured and humanized J16 which exhibited dose-dependent pharmaco-kinetic profiles. In order to improve pharmaco-kinetic and activity of this antibody pH-sensitive binding to mouse, cynomolgus, and human PCSK9 was engineered. The duration of maximum efficacy was increased 2.8-fold using engineered antibody J17, compared with the parental antibody J10 [97]. Monoclonal antibody are currently the most advanced approach in terms of clinical development, but putative benefit of new inhibitors and candidate populations for PCSK9 inhibition should be considered. However, cost/benefit ratio will be an important issue.

With the discovery of microRNAs as potential therapeutics for dyslipidemias, several miRNAs have been investigated for pharmacological activity in lipid dysregulation. Two strategies based on antisense technology and gene therapy approaches have been developed to target miRNA pathways. The first strategy aims to inhibit the function of miRNAs using antisense oligonucleotides (antimiRs, locked nucleic acids, or antagomiRs), sponges, masking, and erasers. The second strategy involves small-molecule activators or inductors of miRNA expression and miRNA mimics which aim to enhance the function of miRNAs. MTP inhibitors such as miR-30c agonists or miR-30c mimics and MTP antisense oligonucleotides reduces MTP-associated lipid production without serious side effects.

FXR agonists that are recently discovered for dyslipidemia, are supposed to serve in the future as important drugs. Activation of FXR by bile acids or synthetic FXR agonists lowers plasma triglycerides in conditions such as hypertriglyceridemia, type 2 diabetes, nonalcoholic steatohepatitis, metabolic syndrome and obesity. Discovery of new steroidal and non-steroidal FXR agonists or dual agonists of FXR/GP-BAR1 using computational technique and lead compounds may provide a promising structure for further optimization and make an attractive candidate to advance into clinical studies.

Virtual screening or computer-aided drug design aims to manage the synthesis and screening against biological targets, and could lead to potential drug candidates. ligand-based virtual screening uses 2D or 3D chemical similarity for analysis multiple large compound databases. Structure-based design applies different modeling techniques such as docking, which dock small

molecules into the structures of macromolecular targets and score their potential complementary to the binding sites.

Synthetically produced thyroid hormones that can best act on thyroid β receptors is newly used approach to avoid more adverse effects, but natural thyroid hormones can cause nervous system and cardiovascular problems. The new synthetic compounds may target older medicinal purposes such as NPC1L1 which is the molecular target of ezetimibe, or may show anti-hyperlipidemic activity without any known targets.

Furthermore, the effects of the synthetic peptides such as PRO–GLY–PRO peptide on hemostasis and lipid metabolism was evaluated in high fat diet male albino rats. The results of this study showed that administration of PGPrestored the normal cholesterol level, even if a high fat food contained a large amount of saturated fatty acids and cholesterol was consumed [135].

In the near future many synthetic agonists or antagonists, gene therapy techniques, humanized monoclonal antibody, peptidomimetics will be focused to have advancement in therapy. Still now many agents are in process of experiments on animals and humans and near to approval. Further research is required in this field to develop more novel drugs for improving treatment and in this way mortality rate can be decreased to very low level for patients facing cardiovascular problems. Although, drug therapy for dyslipidemia must be individualized and most patients often need treatment with multiple agents to achieve therapeutic goals.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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HIGHLIGHTS

- Treatment of dyslipidemia is of high importance as it can increase the quality of life of cardiac and diabetic patients and reduce socioeconomic burden.

- Currently available therapies for dyslipidemia include statins owing to some side effects and less efficacy, DGAT-2 (niacin) with flushing side effect, cholesterol absorption inhibitors (ezetimibe), CETP inhibitors, PPARs agonists and MTP inhibitors are mainly used.

- Discovery of monoclonal antibodies as PCSK9 inhibitors provided comprehensive evidence that causes inhibition of PCSK9 which is a very effective method to reduce low-density lipoprotein cholesterol (LDL-C).

- Discovery of nucleic acid–based therapies target MTP, which overcomes the steatosis associated with conventional MTP inhibitors, holds great potential for drug targeting to treat dyslipidemias and coronary artery disease.

- Discovery of new FXR modulators, thyromimeticagents, cholesterol absorption inhibitors and new compounds with anti-hyperlipidemic activity via virtual screening and main lead compounds scaffolds, using medicinal chemistry, led to a clinical candidate.

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