



# INFLAMMATORY BOWEL DISEASE



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# Drug Repurposing Opportunities for Inflammatory Bowel Disease

Supriya Roy; Suneela Dhaneshwar\*

Amity Institute of Pharmacy, Amity University Uttar Pradesh Lucknow Campus, India

## Corresponding Author: Dr. Suneela Dhaneshwar,

Professor & Director, Amity Institute of Pharmacy,  
Dy. Dean Research, Amity University Uttar Pradesh  
Lucknow Campus, Lucknow, U.P., India

Tel: 0522-2399606,

Email: sdhaneshwar1@lko.amity.edu

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**Keywords:** Inflammatory bowel disease; Drug repurposing; Ulcerative colitis; Crohn's disease; Tumor necrosis factor; Interleukin; Matrix metalloproteinases.

## Abstract

Inflammatory Bowel Disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract (GIT) characterized by typical symptoms such as diarrhea, abdominal pain, cramping, rectal bleeding, loss of appetite, weight loss and fatigue. The exact cause of IBD is not clearly understood, but it is known to involve an interaction between genes, environmental factors such as imbalance of the intestinal microbiota, changing food habits, ultra hygiene and inappropriate immune system. Several mediators such as tumor necrosis factor- alpha (TNF- $\alpha$ ), interleukin (IL)-1, matrix metalloproteinases (MMPs) and histamine play a significant role in the intensification and localization of inflammation associated with IBD. Poor understanding of pathogenesis of IBD hampers the development of new effective treatments. Cornerstone therapy includes aminosalicylates, corticosteroids and immunosuppressants, but their efficacy is outshined by multiple serious side effects associated with them. Thus, there is an extensive need for a significant increase in research efforts to address this unmet medical ailment and bring improvement in the treatment and management of IBD. Drug repurposing is an alternative, cost and time-effective drug development strategy that focuses on rediscovering new uses for old drugs. The approach includes identification of the new therapeutic potential of a drug either acting through originally known target or acting through a novel and unexplored target. Polypharmacology of drug molecule that interacts with multiple targets remains the central focus of drug repurposing as it can unveil various novel possibilities to design various effective and less toxic therapeutic agents. Since various IBD candidate genes and pro-inflammatory mediators such as IL, MMPs are implicated in pathogenesis of IBD, these targets can be further explored utilizing drug repurposing approach for the safe and effective management of IBD.

## Introduction

IBD is a group of idiopathic chronic intestinal diseases which is characterized by prolonged inflammation of the large or small intestine. Crohn's Disease (CD) and Ulcerative Colitis (UC) are the two principal types of IBD. The basic difference between the two is that CD affects the whole GIT from mouth to anus and is characterized by transmural or deeper mucosal inflammation throughout the GIT whereas UC primarily affects the colon and rectum and is characterized by inflammation limited to the superficial mucosal layer of the colon. The exact cause of IBD remains unknown, but enhanced intestinal permeability, imbalance of intestinal bacteria, genetic & environmental fac-

tors and inappropriate immune reaction are believed to play a substantial role in GIT injury. Common symptoms include diarrhea, fever and fatigue, abdominal pain and cramping, blood in stool, reduced appetite and unintended weight loss [1]. If left untreated, IBD patients may experience intestinal complications such as deep ulcerations, massive hemorrhage, bowel strictures and obstruction, fistulas and toxic megacolon. They also possess increased risk of colon cancer. Extraintestinal complications may include drug-induced arthropathies, hepatobiliary complications, renal and ocular complications. Malabsorption due to CD can have serious consequences such as vitamin B12 deficiency, steatorrhea, calcium oxalate and uric acid stone formation [2-4].



## Pathogenesis

### (i) Role of TNF- $\alpha$

TNF- $\alpha$  is a pro-inflammatory cytokine that mediates the local inflammatory immune response and induces the expressions of other pro-inflammatory cytokines and chemokines. Chemokines play an important role in maintaining homeostasis of mucosal immunity and enhances the recruitment and activation of lymphocytes that contributes to the pathogenesis of IBD. Cytokines are small peptides produced by immune cells that contribute to the disruption of normal physiological state of controlled inflammation of the gut [5].

### (ii) Role of IL-1

IL-1 along with TNF- $\alpha$  plays an important role in the pathogenesis of IBD due to its pro-inflammatory activity. IL-1 such as IL-1 $\alpha$  and IL-1 $\beta$  induce the production of type 2 cyclooxygenase, phospholipase A and Inducible Nitric Oxide Synthase (iNOS) leading to inflammation of the intestinal mucosa [6].

### (iii) Role of mast cells

Mast cells are involved in chronic inflammation of the gut. The increased number of mast cells, histamine secretion and degranulation of mast cells in the colorectal mucosa, submucosa and lamina propria are found to be associated with patients with CD and UC. It is accompanied by increased expression of IL-6, TNF $\alpha$ , prostaglandins, leukotrienes, substance P and tryptase levels [7-9].

### (iv) Role of MMPs

MMPs, a family of Zn-containing endopeptidases are the key mediators responsible for the degradation of the extracellular matrix and mucosa which include collagenases (MMP-1, -8, and -13), gelatinases (MMP-2 and -9), stromelysins (MMP-3 and -10), matrilysin (MMP-7) and macrophage elastase (MMP-12) [10-12].

## Pharmacotherapy

IBD management involves drug treatment (Table 1), nutrition supplementation, surgery or a combination of all. The goals are to maintain remission and to improve quality of life. Immunomodulators, anti-inflammatory drugs such as 5-aminosalicylic acid (5-ASA) derivatives and corticosteroids are considered as the conventional therapy for IBD. 5-ASA and corticosteroids help to lessen inflammation quickly and are useful both for treating colitis flare-ups and maintenance of remission. Examples of aminosalicylates include sulfasalazine, balsalazide, mesalamine, olsalazine and that of corticosteroids are hydrocortisone and budesonide. Immunomodulators or immunosuppressive agents such as azathioprine block TNF and prevent the immune system from attacking the bowel and causing inflammation. A new type of biologic treatment using biosimilars has been approved by the Food and Drug Administration (FDA) for the possible use in IBD such as Infliximab-dyyb (Inflixtra). Antibiotics and anti-diarrheal drugs are also used to treat IBD symptoms. Sometimes surgery such as small bowel resection, colectomy and proctocolectomy is required for IBD patients [13].

## Drug repurposing

As the drug discovery pipeline is drying up and due to the high cost and time investment involved in new drug discovery, pharmaceutical companies and research organizations are focusing towards innovative ways for drug development. Drug

repurposing aims to speed up drug development process by rediscovering new uses for old drugs. Drug repurposing or drug repositioning approach explores new therapeutic applications for already existing drugs that were neither formerly referenced nor currently prescribed or explored. It has many advantages over traditional de novo drug discovery process in many ways:

(i) Detailed information on existing drug such as their pharmacology, dose, formulation, and potential toxicity is available as they have already been tested in humans.

(ii) The drug repurposing approach focuses on the fact that conjoint molecular pathways contribute to the pathophysiology of many different diseases.

(iii) As already approved compounds have demonstrated safety in human beings in phase I clinical trials, it significantly reduces the cost and drug development time.

Repurposing may combine an older drug with a newer drug in order to increase the efficacy of newer drug. There may be a combination of an available drug with a non-drug treatment option, such as radiation, for better working of non-drug treatment or to make the drug work better. The approach also allows the combinations of existing drugs that are already used in a specific disease but are not currently prescribed together. The concept of drug repurposing originated due to polypharmacology of drug molecules which means that drugs can have an activity on more than one target and metabolic pathway connections so that changes in the activity in a given target can exert additional effects by altering the overall activity of other targets. On this basis drug repositioning can be of two types:

a) On target drug repositioning: Exploring new therapeutic applications of drug acting through the originally known target and mechanism.

b) Off target drug repositioning: Exploring new uses of a drug acting through a novel or unanticipated target. This approach is largely exploited as a drug hits 6 to 13 targets on an average.

During recent years the increased prevalence of IBD has been reported due to changing food habits, fast food and hygiene. Although hundreds of genetic risk loci have been identified for IBD, little progress has been achieved in interpreting this knowledge into clinical practice for efficient drug development. Existing therapies for IBD consist of aminosalicylates, corticosteroids and immune suppressants which are associated with multitude of serious side effects (Table 1). Small molecules that specifically target pro-inflammatory pathways in the intestine are likely candidates for IBD treatment. Thus, investigation and integration of multiple targets implicated in pathogenesis of IBD by utilizing a drug repurposing approach presents a novel therapeutic opportunity for effective and safe management of IBD [14-15].

## Implications of drug repurposing approach in IBD

**Topiramate** (Figure 1) is an anticonvulsant agent which is primarily indicated for seizure disorders. Topiramate enhances the activity of Gamma-aminobutyric Acid (GABA)-A receptors, serves as an antagonist for Amino-3-hydroxy-5-methyl-4-isoxazole-proPionic Acid (AMPA)/kinate glutamate receptor subtypes and is a weak inhibitor of carbonic anhydrase isozymes II. Topiramate significantly reduced gross pathophysiological and histopathological events in the experimental model of IBD in rodents. Positive results of topiramate in rodent model of IBD have also

been supported by the computational predictions. The analysis revealed that topiramate acts on the genes related to Nuclear Factor- kappa B (NF- $\kappa$ B) signaling, inflammatory response, antigen presentation and other functional processes relevant to the pathophysiology of IBD. Another report compared gene expression profile of IBD with gene expression profiles from 164 drug compounds and then by identifying gene expression signature of topiramate with that of a disease signature, the group concluded that topiramate can be a good candidate for the management and treatment of IBD [16].

**Quinacrine** (Figure 2) has multifaceted antimalarial, antiprotozoal, anticancer, antirheumatic, antiprion, and intrapleural sclerosing activities. Quinacrine suppresses the induction of iNOS in vitro and successfully suppresses clinical disease index (CDI), histological changes of the colon, levels of inflammatory markers (iNOS, Cox-2, p53) in vivo when tested on two independent mouse models of UC - the dextran sulfate sodium and oxazolone without any sign of toxicity or side-effects. Another study has shown that quinacrine interrupts additional inflammatory mediators such as arachidonic acid cascade, phospholipase A2, formation of prostaglandins. In addition, it also inhibits NF- $\kappa$ B, TNF $\alpha$ , and IL-1 $\beta$  suggesting the possible use of quinacrine in UC and also giving insight into the potential mechanisms of anti-TNF therapy in the treatment of moderate to severe forms of IBD [17].

**Thioguanine** (Figure 3) has been approved for use by FDA in leukemia. Mucosal immune system activation has been found to play a major role in the chronic stage of IBD. Thiopurines are immunosuppressive drugs that act by deactivating T lymphocytes and thereby inflammation. Extensive clinical trials were conducted to evaluate the efficiency of thioguanine in treatment of IBD and observed that about 80% of patients experienced clinical benefit from its use, but this repurposed clinical benefit was eclipsed by the nodular regenerative hyperplasia advancement in liver associated with the high dose of thioguanine. Consequently, several trials were carried out to demonstrate that thioguanine in adequate dose of 0.2–0.3 mg/kg (not exceeding 25 mg per day), does not cause any liver abnormalities and was therapeutically repositioned as an immunosuppressive drug for the treatment of patients with IBD in the year 2001 [18].

**Aldesleukin**, an IL2 analogue, is used in the treatment of metastatic renal cell carcinoma. Previous research studies have shown that IL2 regulates the immune system and is one of the important mediators implicated in the pathogenesis of IBD and other autoimmune disorder. Presently clinical trial is being carried out in patients with autoimmune disorders like IBD, rheumatoid arthritis, primary sclerosing cholangitis to determine the probable effects of low dose of aldesleukin [19].

**Adalimumab** was originally approved for clinical use in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. In randomized, double-blind trial it was found that adalimumab binds TNF- $\alpha$  and is safe and effective for inducing and maintaining remission in up to 36% of patients with moderate-to-severe UC who does not respond to conventional therapies used in IBD, such as steroids or immunosuppressants [20].

**Interferon beta 1b** was originally used for the autoimmune disorder- multiple sclerosis. Although the therapeutic profile of this drug is not yet clear, several research studies have suggested that Interferon beta 1b has anti-inflammatory effect and may have promising effects in other inflammatory disorders including IBD [21].

In clinical practice **vitamin D analogues** (Figure 4) are used to prevent a common symptom osteoporosis mostly associated with IBD patients. Animal studies revealed that since vitamin D is one of the chief regulators of the immune system, it could be a potential drug for autoimmune disorders like IBD. In one of the randomized clinical trial of CD, patients who were administered with vitamin D3 had shown a reduced risk of clinical relapse from 29 % to 13 % as compared to the CD patients receiving no treatment [22].

**Thalidomide** (Figure 5) is a controversial drug due to its severe side effect of polyneuropathy. The drug is not listed in the treatment protocol for IBD. However, in cases where patients do not respond to steroids or other known therapies for IBD, physicians do prescribe thalidomide. Also thalidomide has shown to be effective in patients with CD in a small open label clinical trial study. Therefore, intensive research needs to be done to scrutinize the genetic information that supports the use of thalidomide in the treatment of IBD [23].

Recruitment of monocytes in the intestinal wall is being carried out via C-C Chemokine Receptor 2 (CCR2) which mediates colon damage and aids in progression of IBD pathogenesis. The role of CCR2 in IBD has been explored by correlating resection ileum samples of CD patients with resection ileum samples of non-IBD conditions and studies have found that CCR2 expression is 30 times higher in ileum samples of CD patients than that of non-IBD. The investigators established that a CCR2 antagonist could be an effective therapeutic target for the treatment of CD. INCB3284 and MLN120 are the two experimental CCR2 antagonist drugs that are being currently investigated for the possible treatment of IBD.

**Cluster of Differentiation (CD) 30-ligand (CD30L)** is a membrane-associated glycoprotein that belongs to the tumor necrosis factor family. Animal studies have investigated that the serum level of soluble CD30 is increased in IBD patients signifying that CD30L/CD30 signaling might play a role in the pathogenesis of IBD. Another investigational drug SGN30 has great affinity for the CD30 receptor, suggesting that if a drug can decrease serum CD30 level in IBD patients, it could be very beneficial in treating IBD patients [24].

**Angiotensin-Converting Enzyme 2 (ACE2)** has been shown to play a critical role in gastrointestinal tissue and enhanced expression of ACE2 has been observed in IBD patients. A potent and selective ACE2 inhibitor GL1001 significantly decrease colon pathology and myeloperoxidase activity and revealed anti-inflammatory activity that might produce favorable effects and therapeutic effectiveness in IBD [25].

Various experimental data and clinical studies have recommended that **statins** can attenuate both acute and chronic inflammatory processes. In a clinical study, administration of atorvastatin (Figure 6) in patients with CD reduced significantly decreases C-reactive protein which is a major marker of inflammation in gastrointestinal diseases. Other markers that are known to be elevated during ongoing inflammation in CD were also reduced by atorvastatin. It downregulated tissue chemokine (C-C motif) ligand (CCL)2 and 8 that have chemoattractant property for monocytes and mast cells. Atorvastatin also potently suppresses the expression of C-C chemokine Receptor type 2 (CCR2) in all monocytes and macrophages, thus further investigation can be made to explore statin-mediated defensive effects in IBD patients especially for maintenance therapy [26].

Recent meta-analysis demonstrated that administration of high dose of extended colon-release tablet of Low-Molecular-Weight-Heparin (LMWH) prevented clinical remission and improved histological features of colon and suggested that further randomized controlled studies may be carried out to confirm the effectiveness of LMWH in the treatment of UC. However, while administering LMWH in patients with active UC, increased risk of rectal bleeding should be taken care of [27].

One of the novel therapies that have been proposed for UC is thiazolidinedione ligands for Peroxisome Proliferator Activated Receptors- Gamma (PPAR- $\gamma$ ). In a randomized, double-blind clinical trial the effectiveness of rosiglitazone (Figure 7) at an oral dose of 4 mg twice daily for 12 weeks was studied in patients with mild-to-moderate UC and demonstrated that rosiglitazone can reduce colonic inflammation and that it can serve as a good candidate for the treatment of IBD patients. Rosiglitazone increases adipophilin levels and reinstated PPAR $\gamma$  activity in epithelial cells of exacerbated mucosa both in vitro and in vivo. Rosiglitazone reduced the Mayo ulcerative colitis score from 8.9 to 4.3. In another study rosiglitazone was administered along with mesalazine and achieved more effective results than mesalazine alone [28].

Omega-3 Poly-Unsaturated Fatty Acids (PUFA or  $\omega$ 3FA) such as epanova may be beneficial in IBD due to their anti-inflammatory action in experimental animals and ex vivo models of CD and UC. Antiinflammatory action is mainly due to reduced synthesis of the intestinal pro-inflammatory cytokines such as prostaglandin E2, leukotrienes as well as TNF- $\alpha$ , IL-6, IL-1 $\beta$ . It also reduces protein expression of intestinal apoptotic cells NF $\kappa$ B. Furthermore, these acids may reduce weight loss and intestinal permeability, thereby improving intestinal morphology and barrier function. Another study demonstrated that  $\omega$ 3FA lead to

the production of protectins, resolvins and maresins which mitigate the inflammatory processes profiting IBD patients [29].

Safety and efficacy of recombinant cholera toxin B subunit was evaluated in CD patients. An oral solution of 5 mg recombinant cholera toxin B subunit for 2 weeks showed significant decrease in CD Activity Index (CAI) score. Response rates were 42% in the per-protocol analysis, 40% in remission and 30% at 8 weeks post-treatment with no major side-effects. The results suggest that microbes and microbial products could be a safe and effective therapy in active IBD patients. However, further clinical study involving a large number of patients with different types of IBD needs to be conducted [30].

MAP kinase inhibitors such as semapimod and dorapimod are clinically being tested currently for the probable treatment of CD on the basis of the facts that they reduce the expression of many inflammation-associated gene such as cytokines, MMPs, endothelial adhesion molecules and also block the production of TNF- $\alpha$  [31].

### Conclusion

IBD is a chronic inflammatory GIT disorder for which few safe and effective therapies are available for long-term treatment and disease maintenance. Drug repositioning involves discovering new uses for existing drugs and is a time and cost-efficient approach due to availability of information on drug pharmacokinetics and safety. Various susceptible genes and mediators such as TNF- $\alpha$ , IL-1 have been found to play a significant role in IBD. These IBD candidate genes and mediators involved in the pathogenesis of the disease can be targeted by other FDA approved drugs and could possibly be repositioned for IBD treatment. Incorporating drug repurposing approach in IBD may eventually lead to the improvement of IBD treatment.

### Tables

**Table 1:** Overview of drug therapy in IBD

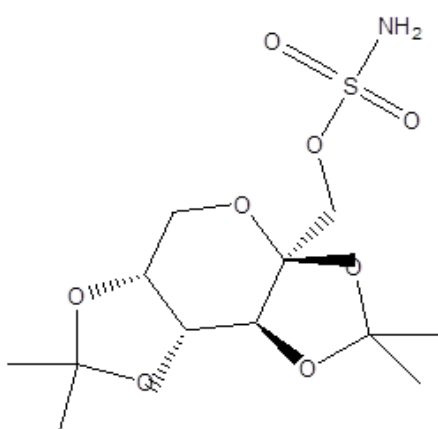
Category	Mechanism of action	Drugs	Side effects
5-Aminosalicylic acid and its derivatives	Inhibit the release of inflammatory cytokines and reactive oxygen species (ROS)	Mesalamine	Mild nausea, stomach cramps, diarrhea, liver dysfunction, sore throat, pancreatitis, myocarditis
		Sulfasalazine	Decreased appetite, stomach upset, pain, hypersensitivity
Corticosteroids	Inhibit various inflammatory pathways, suppress IL transcription and arachidonic acid metabolism, stimulate apoptosis of lymphocytes within the lamina propria of the gut	Hydrocortisone	Insomnia, immune suppression, mood changes, thinning skin, discoloration, slow wound healing
		Prednisone	Confusion, excitement, restlessness, cataract, osteoporosis
		Methylprednisolone	Insomnia, mood changes, acne, dry skin, discoloration, slow wound healing, increased sweating
Immunosuppressant agents	Inhibit proliferation of T and B lymphocytes	Azathioprine	Bone marrow suppression, increased risk of infections, leucopenia
		6-Mercaptopurine	Nausea and vomiting, poor appetite, diarrhea, bone marrow depression, hepatotoxicity
Antibiotics	Inhibitory effect on undetermined pathogen and bacterial overgrowth	Metronidazole	Stomach pain, dizziness, loss of balance, vaginal itching or discharge
		Rifaximin	Bloating, gas, stomach pain, feeling like you need to empty your bowel urgently

Antispasmodic agents	Inhibits gastrointestinal propulsive motility due to its antimuscarinic and musculotropic effects	Dicyclomine	Severe constipation, bloating, or stomach pain, worsening of diarrhea or other irritable bowel symptoms
		Hyoscyamine	Dizziness, drowsiness, feeling nervous, blurred vision, headache, insomnia
TNF- $\alpha$ inhibitors	Disrupts the interaction of TNF- $\alpha$ with its receptors, cause lysis of cells that produce TNF- $\alpha$ and inhibit pro-inflammatory cascade signalling.	Infliximab	Headache, stomach pain, nausea, stuffy nose
		Adalimumab	Numbness, vision problems, weakness, chest pain

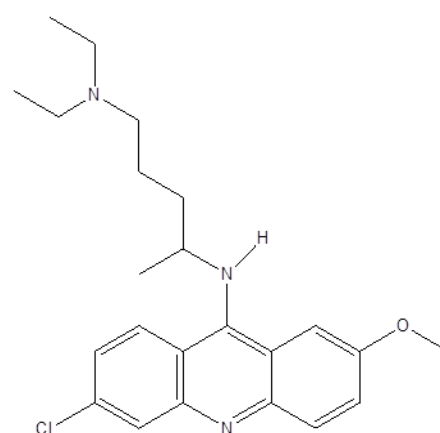
**Table 2:** Potential targets and drugs that could be repurposed for IBD

S.No.	IBD candidate gene	Target drugs	Approved uses
1.	IL1R1	Anakinra	Rheumatoid arthritis
2.	JAK2	Ruxolitinib	
3.	PTGS2	Etoricoxib	
4.	FCGR2A,FCGR2B,FCGR3A,FCGR3B	Alefacept	Psoriasis
5.	FCGR2A, FCGR2B,FCGR3A,FCGR3B	Alemtuzumab, Muromonab	Multiple sclerosis
6.	IFNAR1	Natural Alpha interferon, Interferon beta	
7.	IL5, NFKB1	Pranlukast	Asthma
8.	MAPK1	Arsenic trioxide	
9.	SELE	Carvedilol	CVS diseases
10.	VDR	Alfacalcidol	Osteoporosis
11.	IL10	Ibudilast	Allergic rhinitis
12.	NFKB1	Triflusal	Cerebral ischemia
13.	FCGR2A,FCGR2B,FCGR3A, FCGR3B	Cetuximab	Anticancer
14.	PTGS2	Pomalidomide	Multiple myeloma
15.	AHR	Nimodipine	Subarachnoid hemorrhage

## Figures



**Figure 1:** Topiramate



**Figure 2:** Quinacrine

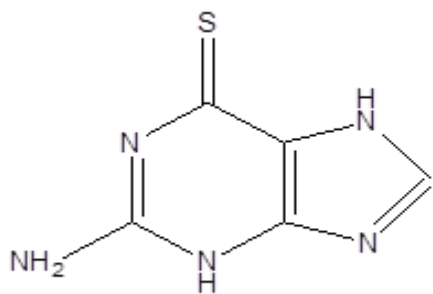


Figure 3: Thioguanine

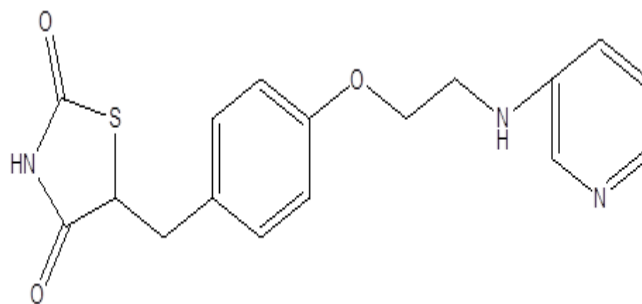


Figure 7: Rosiglitazone

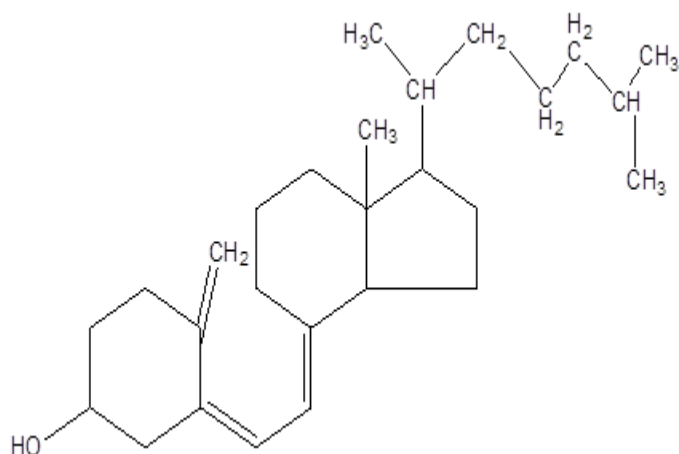


Figure 4: Vitamin-D

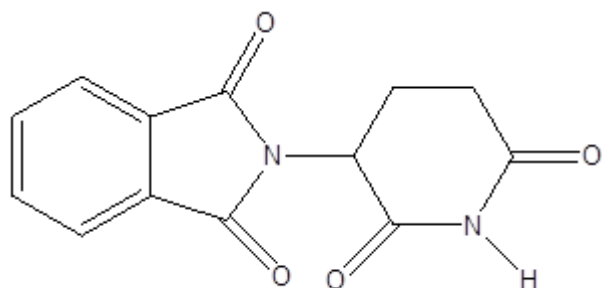


Figure 5: Thalidomide

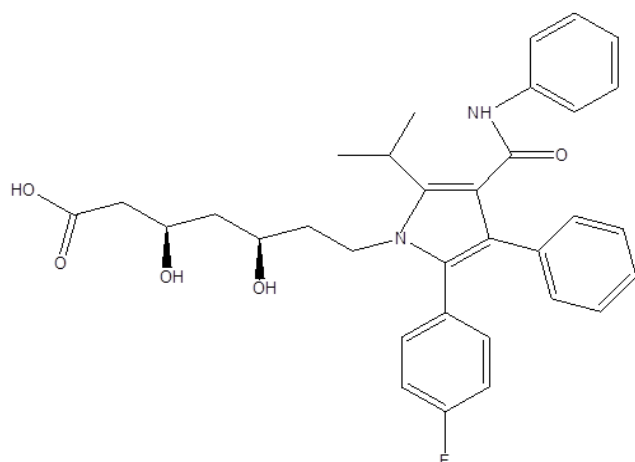


Figure 6: Atorvastatin

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