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Mutual prodrugs for colon targeting: A review

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The goal of targeting drugs to a specific site or organ in the body is to achieve an ideal therapeutic effect with minimal harmful effects on the other components of the human body. In an effort to develop a unique drug delivery system with the capacity to release drugs precisely into the colon in a reproducible and predictable manner, a mutual prodrug design targeting the colon has attracted a great deal of attention in recent years. The colon is an interesting area for both local and systemic medication delivery. A mutual prodrug is made up of two chemotherapeutic drugs: the first is considered as an original drug and the other is regarded as its transporter, both of which have an inherent synergistic or an additive therapeutic activity. Therefore, utilizing a mutual prodrug reduces the necessary dose, minimizing the adverse systemic effects, and consequently producing a more efficient therapy system. The goal of this review is to comprehend the importance of mutual prodrugs in the treatment of colon diseases, and also mention the most significant and efficient prodrugs in this field.

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Introduction

The large intestine is the final section of the gastrointestinal tract (GIT) and consists of the caecum, colon, rectum, anal canal, and anus. The colon is the longest portion of the large intestine which extends from the cecum to the rectum [1]. There are many diseases that may affect the colon, such as colonic cancer, colonic polyps, and irritable bowel disease. Treatment of these diseases needs high concentrations of drugs at the site of damage. Hence, the colon-specific drug delivery system (CDDS) has been used to diminish the systemic side effects [2]. Drug targeting is not only used for local treatment of different bowel diseases that affect the colon, but is also used for systemic delivery of peptide drugs, which are degraded in the GIT's upper part by digestive enzymes and proteins [3].

There are numerous methodologies through which targeting drugs to the colon can be achieved; one of them is prodrug (P-drug) design [4]. The term "prodrug" is defined as pharmacologically inactive drug derivatives that could be used, in a temporary manner, to alter the physicochemical properties of drugs to increase their usefulness and/or to reduce associated adverse effects. A P-drug undergoes spontaneous or enzymatic hydrolytic biotransformation to release the active form when it reaches the desired site of action [5].

For colonic delivery, the prodrugs (P-drugs) are designed to undergo a minimal hydrolysis in the GIT's upper part and when they reach the colon undergo enzymatic hydrolysis, thereby releasing the active original drug [6].

The P-drugs are conventionally divided into two major classes; the first is biosubstrate P-drugs, and the second is transporter-connected P-drugs. For the first class, the P-drugs are substrates for specific metabolic biotransformation reactions that generate and subsequently release the original drugs. Members of the first glass are constituted of an original drug attached to a harmless transporter with special properties that alter the physicochemical properties of the original drug, reducing its undesirable side effects. The transporter may be inert and used only to translocate the original drug to a defined site, or it may have biological activity in addition to its role as a transporter resulted in the production of a mutual prodrug (MP) [7].

MP is defined as a combination of two covalently connected compounds which are pharmacologically active and each one acts as a transporter for the other. If the transporter has the same properties as the original drug, its effect may be synergistic. Otherwise, it may have an additional effect if it has a new biological action that the original drug lacks [8].

Mutual prodrugs (MPs) can be categorized depending on their composition as biosubstrates MPs or transporter-connected MPs, which can be further classified as bipartate or tripartite P-drugs (9). The MP of the initial subcategory, bipartite, has an active transporter connected directly to the drug molecule. While in the tripartite type, a linker has a dual connection with the drug and transporter. When the transporter-connected MPs reach their site of action, they split enzymatically or spontaneously from the original drug. In contrast, the bioprecursor prodrugs rely on chemical modification processes such as oxidative or reductive activation processes to produce their effects [9].

Mutual colon-specific drug delivery systems (MCDDs) have gained popularity in recent years due to the distinctive and potent pharmacological effects they have on the treatment of colonic diseases. Due to the synergistic or additional biological effects, MCDDs are also useful for reducing systemic side effects, enhancing drug bioavailability, and lowering the concentration of the required dose [8].

5-Aminosalicylic acid (5-ASA) MPs

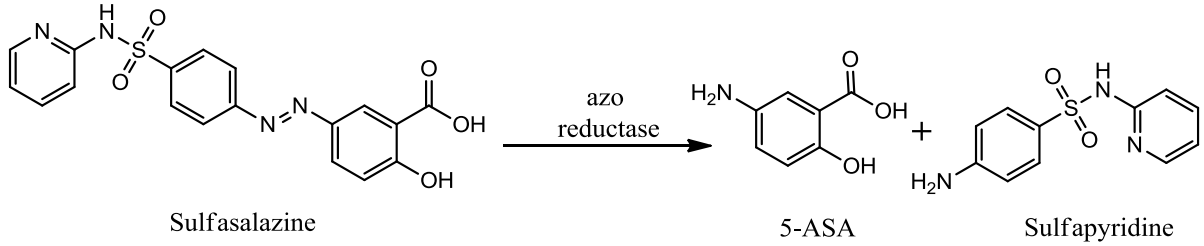
Ulcerative colitis (UC) and Crohn's disease (CD) are the main two abnormalities that constitute the chronic inflammatory medical condition called inflammatory bowel disease (IBD). Patients with this medical condition have a higher risk of developing colon cancer. Thus, it is critical to treat the condition to reduce inflammation and stop the progression of the disease, which calls for taking anti-inflammatory medications on a routine basis in massive doses [10].

The most effective and traditional treatments for IBD are 5-ASA, also known as mesalazine or salamine, and its derivatives. By inhibiting three correlated enzymes, 5-LOX, COX1, and COX2, and preventing leukocyte chemotaxis into inflamed areas, 5-ASA exerts its anti-inflammatory effect. Furthermore, 5-ASA has the ability to trigger the peroxisome proliferator-activated receptor, cytoprotective, and free-radical scavenging properties [11].

Although 5-ASA is very efficacious in the IBD management, there is indeed a risk of significant side effects because of the quick absorption of the drug in the upper GIT, which prevents it from reaching the colon. Utilizing MCDDs can help to resolve this issue by preventing GIT destructive environments and by producing an efficient supplemental or synergistic effect [12].

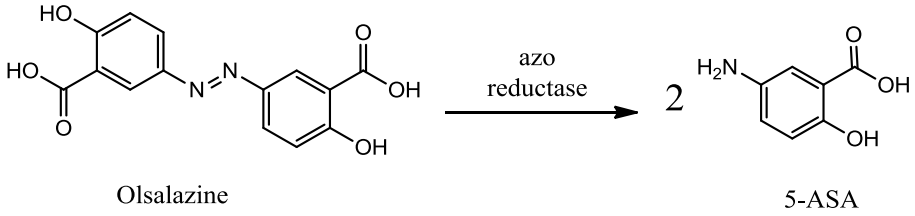
The most popularly utilized 5-ASA derivative for the IBD treatment is sulfasalazine, which is an azo-linked conjugate of 5-ASA, a powerful anti-inflammatory, sulfapyridine, and an antibiotic. As depicted in Scheme 1, whenever

sulfasalazine enters the colon, it is broken down by the colon's normal flora, releasing enzymes called azoreductases that are mostly found there. As a result, the colon receives 85% of the sulfasalazine oral dose [13].



SCHEME 1 The breakdown of sulfasalazine in colon to release the active moieties

Olsalazine, a 5-ASA P-drug made up of two molecules of mesalazine, was given FDA approval in 1990 for the treatment of ulcerative colitis. When olsalazine enters the colon, as depicted in Scheme 2, it is stimulated by the microflora action in a similar manner to that of sulfasalazine, producing two molecules of 5-ASA. The released drug can act regionally by reducing the emergence of prostaglandins and leukotrienes, which are directly to blame for inflammation and pain perception [14].



SCHEME 2 The breakdown of olsalazine in colon to release two 5-ASA molecules

Procainamide (PA), a local anesthetic, is one of the active transporters that have been used to increase the anti-inflammatory effectiveness of 5-ASA. In order to create 5-(4-[2-(diethylamino) ethyl] carbamoyl] phenylazo) salicylic acid (5-ASA-azo-PA), Kim *et al.* merged PA to 5-ASA via an azo bond. This MP can be steady when it travels through the gut wall, as displayed in Figure 1. However, it dissociates into 5-ASA and PA once it attains the colon, converting roughly 76% of the P-drug into its active form in just 10 hours. Nuclear factor-kappaB (NFκB), which plays a vital role in the IBD evolution and inflammatory mediators are both decreased by the use of 5-ASA-azo-PA, which has an additive curative effect [15].

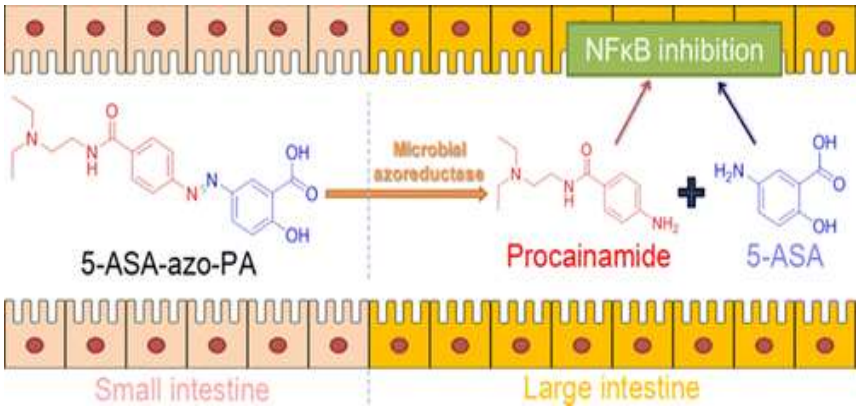
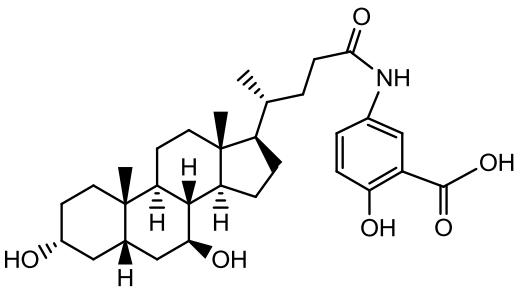


FIGURE 1 The journey of 5-ASA-azo-PA through the GIT, its cleavage, and its action

An epimer of chenodeoxycholic acid, named ursodeoxycholic acid (UDCA), can be used to treat cholestatic liver disease, dissolve gallstones, and more recently, has shown some promising results in reducing colonic polyps. One of the complications that can happen to a patient with UC is primary sclerosing cholangitis, and UDCA is effective in treating it. Conjugated 5-ASA has a synergistic cytoprotective and anti-inflammatory effect when combined with UDCA. The resultant MP is called (UDCA-5-ASA), with the chemical structure depicted in Figure 2, and cleaves in the colon to produce both UDCA and 5-ASA simultaneously [16].



UDCA-5-ASA

FIGURE 2 The molecular skeleton of MP named UDCA-5-ASA

Joo *et al*. delivered 5-aminosalicyltaurine (5-ASA-Tau) as a colon-specific P-drug of 5-ASA. The results indicate that taurine is just as effective as well-known transporters like aspartic acid and glycine, indicating that it could be used to improve 5-ASA colonic delivery, increase treatment effectiveness, and lessen adverse effects. The ability of p-drug to inhibit IL-1β-mediated NFκB activation is what caused it to have an anti-inflammatory effect on an exploratory colitis model. Taurine served as both an active therapeutic agent and a promoter by amplifying the inhibitory effect of 5-ASA, resulting in a mutual potency [17].

As depicted in Figure 3, Kim *et al*. created an MP that functions as CDDs and is composed of 5-ASA and cysteine. One of the most crucial intracellular safeguards against peroxidation overload in the GIT is glutathione, and cysteine is an amino acid that serves as its substrate. 5-ASA and cystine are combined to deliver both substances to the colon, acting as a prodrug with dual therapeutic effects to reduce colorectal inflammatory responses [18].

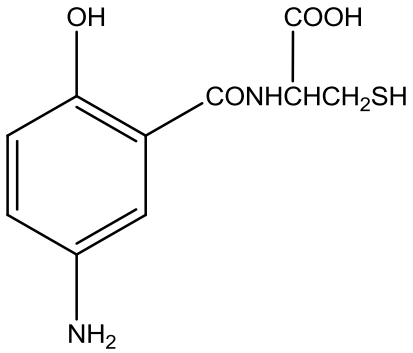
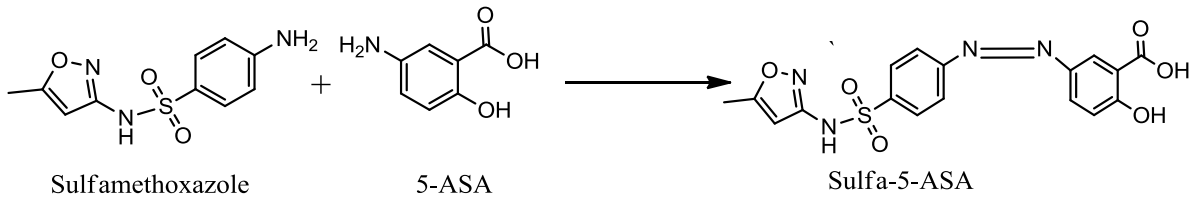


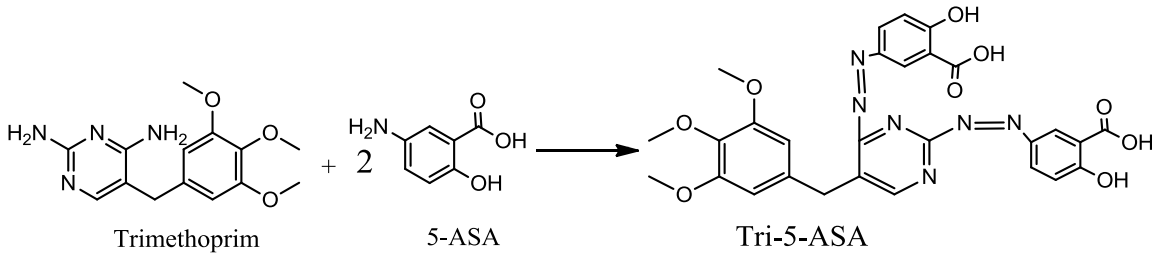
FIGURE 3 The Chemical structure of the MP created by Kim *et al*.

Two MPs were synthesized by Mustafa YF for colon targeting to treat diverticulitis. The first (Sulfa-5-ASA) was produced, as depicted in Scheme 3, by coupling an equal mole of sulfamethoxazole and 5-ASA, while the second (Tri-5-ASA) was manufactured, as

depicted in Scheme 4, by coupling one mole of trimethoprim with two moles of 5-ASA. Diverticulitis is typically brought on by aerobic gram-negative bacteria, which are responsive to trimethoprim and sulfamethoxazole. To address this medical issue, CDDs for the topical treatment of diverticulitis have been created. It was suggested that the azo-reductase activity of the colon would break down both MPs' azo linkages. An in vivo release study for these two MPs in rat feces was carried out to support that. The results showed a near-complete release of the active moieties adhering to the kinetic model of the first order [19].

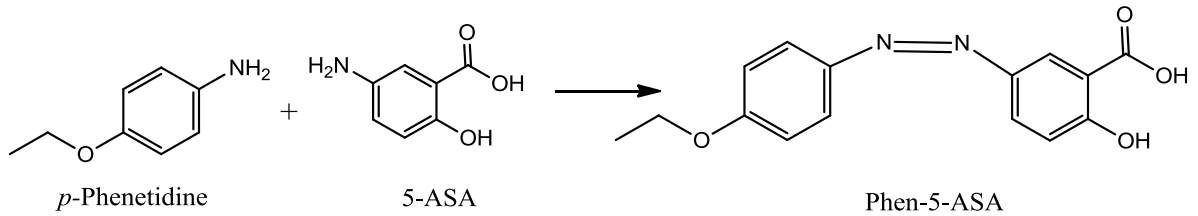


SCHEME 3 The MP synthetic pathway created by coupling sulfamethoxazole and 5-ASA



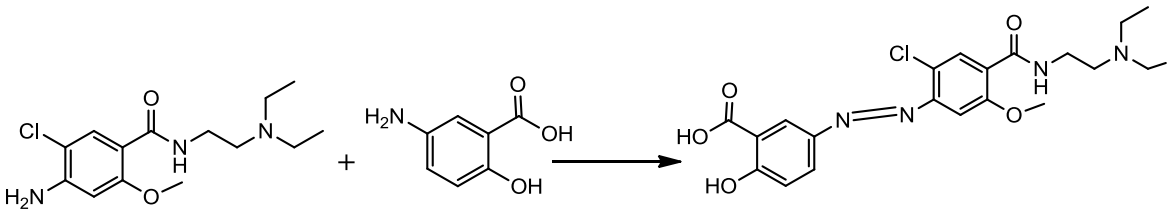
SCHEME 4 The MP synthetic pathway created by coupling trimethoprim and 5-ASA

Mustafa YF designed and synthesized a novel azo MP, abbreviated here as Phen-5-ASA, by coupling *para*-phenetidine with 5-ASA, as demonstrated in Scheme 5. The former is a minor metabolite of phenacetin, a nonsteroidal anti-inflammatory drug with a more potent prostaglandin synthesis inhibitor activity and greater selectivity for COX2 inhibition than indomethacin. When ingested orally, a huge proportion of *para*-phenetidine is soaked up from the upper portion of the GIT, resulting in systemic side effects. Thus, conjugating *para*-phenetidine with 5-ASA via amide or azo linkage may be beneficial for preferential delivery of both prescription medications to the colon, while reducing the administered dose and harmful side effects [20].



SCHEME 5 The synthetic pathway of MP created by conjugating *para*-phenetidine with 5-ASA

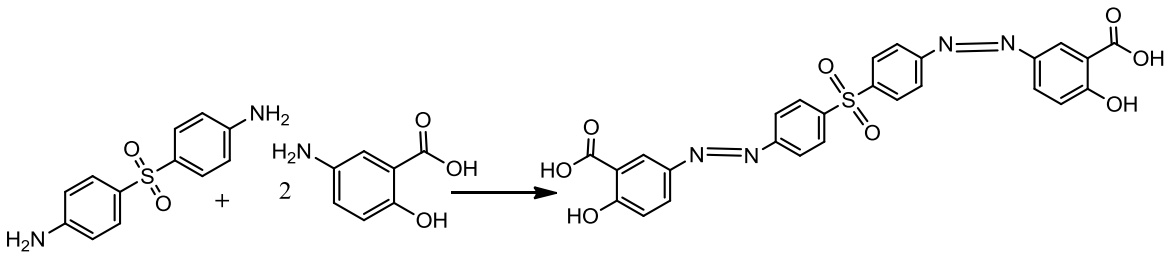
Metoclopramide azo 5-ASA (MCP-azo-ASA) MP was synthesized, as depicted in Scheme 6, by Yang *et al*. By limiting the levels of inflammatory mediators in the inflamed colon, this MP can reduce the colon inflammatory response to dinitrobenzene sulfonic acid hydrate in a dose-dependent manner in a rat model [21].



Metoclopramide 5-ASA MCP-azo-5-ASA

SCHEME 6 The synthesis of MP named MCP-azo-ASA as described by Yang *et al.*

Kang *et al*. designed and created, as depicted in Scheme 7, a colon-specific MP abbreviated as AS-DpS-AS by conjugating two molecules of 5-ASA with one molecule of dapsone through an azo bond. Dapsone is an antibacterial and antiprotozoal agent and has anti-inflammatory properties that can be used to treat autoimmune illnesses. In comparison to sulfasalazine, AS-DpS-AS MP showed better efficacy in colonic drug delivery and exhibited greater anti-colitic efficiency in a colitis rat model. Furthermore, intra-colonic therapy with AS-DpS-AS MP demonstrated that it was more effective against rat colitis than either dapsone or 5-ASA alone. These findings proposed that, due to the combined anti-colitic properties, this MP may be a good alternative to sulfasalazine with higher therapeutic efficacy [22].

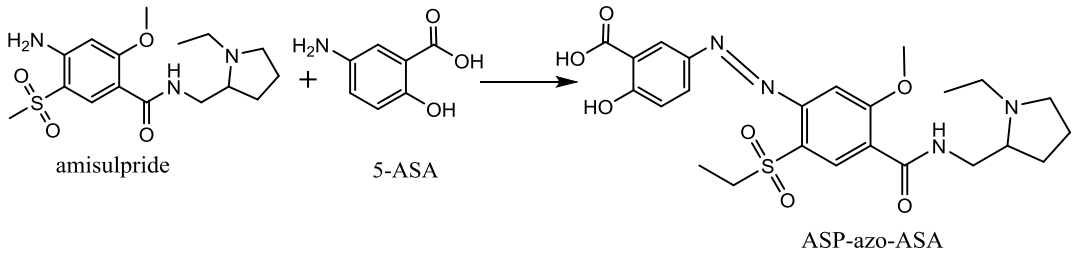


Dapsone 5-ASA AS-Dps-AS

SCHEME 7 The synthesis of the MP named AS-DpS-AS as described by Kang *et al*.

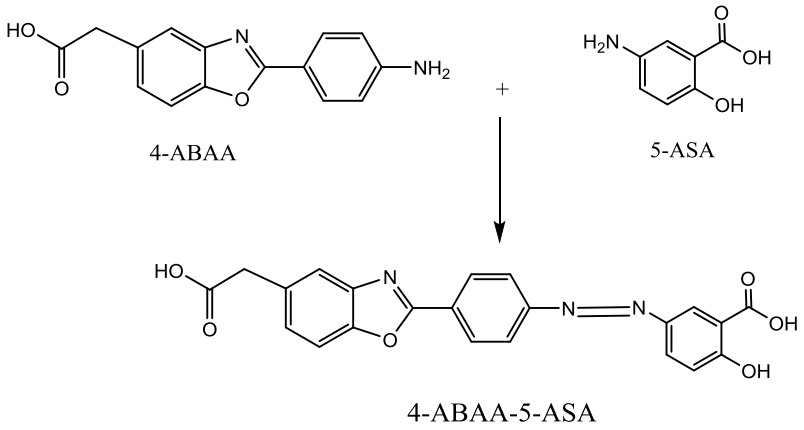
Jeong *et al*. developed ASA-azo-NA, a colon-targeted azo MP composed of 5-ASA and 5-[(3-carboxy-4-hydroxy phenyl) diazenyl] nicotinic acid. This MP was designed to transport 5-ASA and 5-aminonicotinic acid selectively to the infected portion of the colon. In addition, it improved mouse colitis more effectively than sulfasalazine from a therapeutic standpoint. ASA-azo-NA can be thought as a colon-targeted MP and may be successful in treating IBD in patients who are sulfasalazine resistant as a direct consequence [23].

A colon-targeted MP made, as displayed in Scheme 8, by Kim *et al*., is referred to as ASP-azo-ASA and contains 5-ASA conjugated to amisulpride via an azo bond. When combined with 5-ASA, amisulpride (ASP), an antipsychotic drug with anti-ulcer, anti-colitic, and anti-ulcer properties, can have additive or synergistic therapeutic effects. This MP has the potential to deliver 5-ASA to the colon at concentrations comparable to those of sulfasalazine. Furthermore, the MP can reduce the inflammatory mediator levels in the inflamed colon and alleviate colitis in a rat model more efficiently than sulfasalazine. Treatment with 5-ASA and ASP together via the rectal route corrected the colonic damage more successfully than treatment with either of them alone. As a result, ASP-azo-ASA may be a MP with a colon-specific effect that increases the anti-colitic efficacy of 5-ASA for treating colon inflammations [24].



SCHEME 8 The synthetic route for ASP-azo-ASA as described by Kim *et al*.

Jilani *et al.* used 4-aminophenylbenzoxazol-2-yl-5-acetic acid (4-ABAA) and 5-ASA to create a novel mutual azo P-drug with the chemical name 5- [4-(benzoxazol-2-yl-5-acetic acid) phenylazo]-2-hydroxybenzoic, as depicted in Scheme 9. Benoxaprofen, a well-known NSAID, demonstrates rapid healing properties, and 4-ABAA is its novel analogue. The MP was found to be just as effective as 5-ASA to treat UC after being tested for IBD in a rat model of colitis. According to the findings, this MP may offer UC patients a promising pharmacological option [25].



SCHEME 9 The synthesis of the MP prepared by Jilani *et al*.

4-Aminosalicylic acid (4-ASA) MPs

Since the initial description of the anti-inflammatory effects of the antitubercular drug 4-ASA by Lover in 1984, many clinical studies have been initiated since then to ascertain its effectiveness in UC. In comparison to 5-ASA, its anti-inflammatory potency is 50%, and it does not cause immune-allergic acute pancreatitis like 5-ASA. Although 4-ASA is a more stable and effective alternative to 5-ASA, it still has the disadvantage of not attaining the colon unchanged due to its rapid absorption in the upper GIT. To avoid the pitfalls affiliated with using 4-ASA alone, synthesis of 4-ASA P-drugs may be a good option [26].

Zhao's team was the first to create a colon-targeting amide P-drug of 4-ASA with a molecular skeleton shown in Figure 4, to treat IBD using the non-essential amino acid glycine. The P-drug was created by adapting glycine with an acyl chloride derivative of the amino-hydroxyl dual protected 4-ASA, which was then deprotected. Glycine is converted in the colon to glycine chloramine, which inhibits the NFκB, which is involved in the production of inflammation in IBD. In rat trials, 4-aminosalicylglycine was found to have higher therapeutic effects than 4-ASA [27].

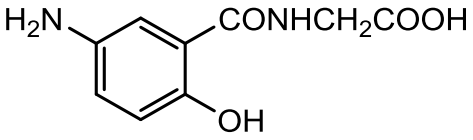


FIGURE 4 The structural framework of the MP prepared by Zhao *et al.*

Wallace *et al.* have patented the L-arginine salts of 4-ASA and 5-ASA, as can be seen in Figure 5, for large intestine inflammation. The primed salts were very successful in reducing edema caused by colitis and granulocyte infiltration and had significant free-radical quenching activity. The synergistic impact of L-arginine can be attributed to its capacity to act as a nitrogenous source, which is a powerful mediator of vasodilation that aids in the recovery of broken colonic mucosa [28].

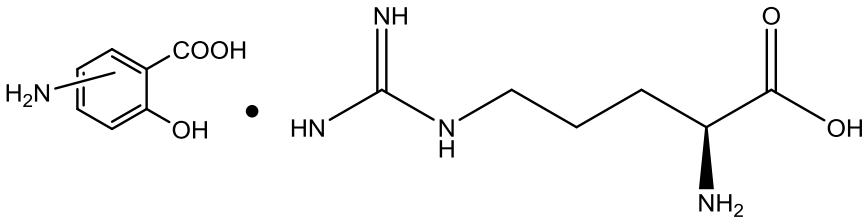
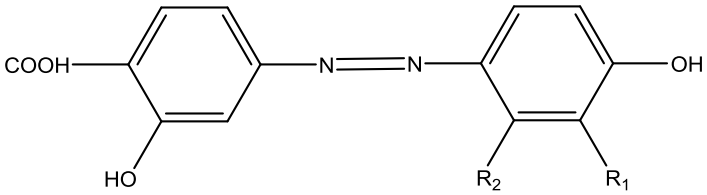


FIGURE 5 The general structural skeleton of the L-arginine salts of 4-ASA and 5-ASA prepared by Wallace *et al.*

Oxidative overload is a key risk factor in the IBD development, causing cellular damage and inflammation of colon mucosal cells. As depicted in Figure 6, Sheng *et al.* synthesized azo-linked colon-specific MPs of 4-ASA with a variety of multisubstituted phenolic derivatives with free-radical quenching properties, including salicylamide, 2-methyl-phenol, 2-nitrophenol, 3-nitrophenol, 3-methylphenol, and 2-dihydroxybenzene. The primary goal of this research team was to attain a synergistic dual antioxidant effect between 4-ASA and phenolic derivatives to boost reducibility and free-radical hunting [29].



where R_1=-H, R_2= -CH_3, R_2= -NO_2
R_2= -H, R_1= -$CONH_2$, R_1= -Cl, R_1= -CH_3, R_1= -NO_2

FIGURE 6 The general building framework of the MPs prepared by Sheng *et al.*

Dhaneshwar *et al.* investigated a mutual amide P-drug approach for 4-ASA with various amino acids, including D-phenylalanine and L-tryptophan, yielding MP1 and MP2, respectively. The amino acids are nontoxic transporters with tissue regeneration and anti-inflammatory properties, and they release (86–91%) of 4-ASA in rat feces in about 24 hours. These MPs with chemical structures displayed in Figure 7 were found to have a significantly better safety profile than sulfasalazine, 5-ASA, 4-ASA, and an equivalent effectiveness to sulfasalazine [30].

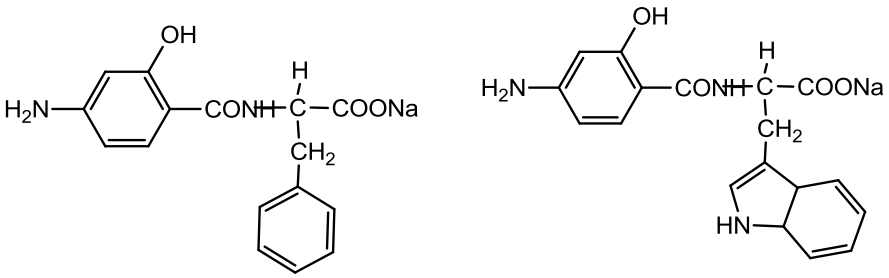


FIGURE 7 The molecular skeletons of the MP1 and MP2 as described by Dhaneshwar *et al.*

Suneela *et al.* developed four azo MPs of 4-ASA and 5-ASA, utilizing the same two salicylate derivatives as transporters. These MPs were made by combining diazo salt of 4-ASA or 5-ASA with either 4-ASA or 5-ASA as a transporter in all feasible combinations. These MPs were created to target the colon, where activation by azo reductase occurs, leading to the release of approximately 68–91% of the original active medications. The azo MP, abbreviated here as 4A-azo-4A and structurally described in Figure 8, consisting of two molecules of 4-ASA, was indicated to alleviate all the measurable markers of colitis in the rat model among the four synthesized MPs studied. Due to fewer side effects in the other parts of GIT, 4A-azo-4A P-drug could be a good alternative for patients with IBD that are intolerant to sulfasalazine [31].

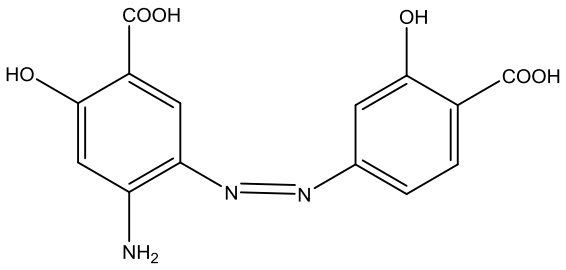


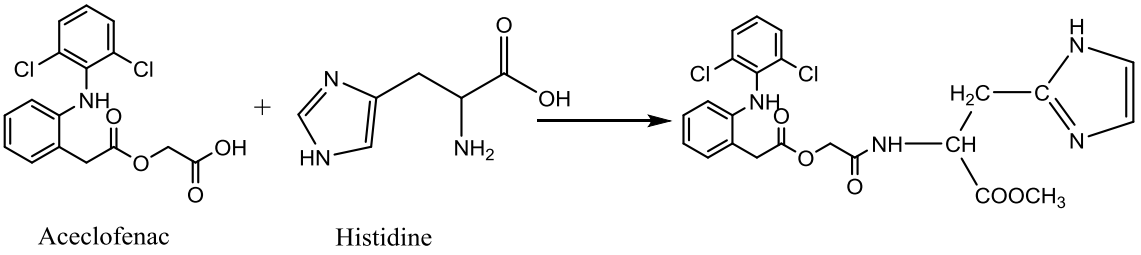
FIGURE 8 The structural framework of the 4A-azo-4A as displayed by Suneela *et al.*

Non-steroidal anti-inflammatory MPs

Non-steroidal anti-inflammatory drugs, which are globally abbreviated as NSAIDs, are powerful anti-inflammatory medications that are rapidly absorbed in the stomach. This fast absorption prevents these drugs from reaching the colon to reduce inflammation and produce analgesic effects in the affected area. NSAIDs cause a number of side effects due to the local irritation caused by the NSAIDs' free carboxylic group and the decrease production of prostaglandin in the GIT. These issues can be addressed by using CDDS, which also has the advantages of requiring fewer doses, being more effective, and limiting the side effects [32]. Different amino acids such as L-histide, L-glycine, and L-tyrosine that act as spacers or transporters can be used to synergize the therapeutic effect of NSAIDs due to their intrinsic pharmacological activity [33].

Aceclofenac, a newer diclofenac-based congener, is an NSAID with the same GIT harmful drawbacks as other representatives of this category. Rasheed *et al.* created new derivatives, as displayed in Scheme 10, by combining aceclofenac with amino acids having methyl ester groups, such as L-alanine methyl ester, L-glycine methyl ester, and L-histidine methyl ester, to obscure the carboxylic group effect of this NSAID. The P-drug of aceclofenac-L-histidine was evaluated as CDDS to get non-toxic MP. When this MP

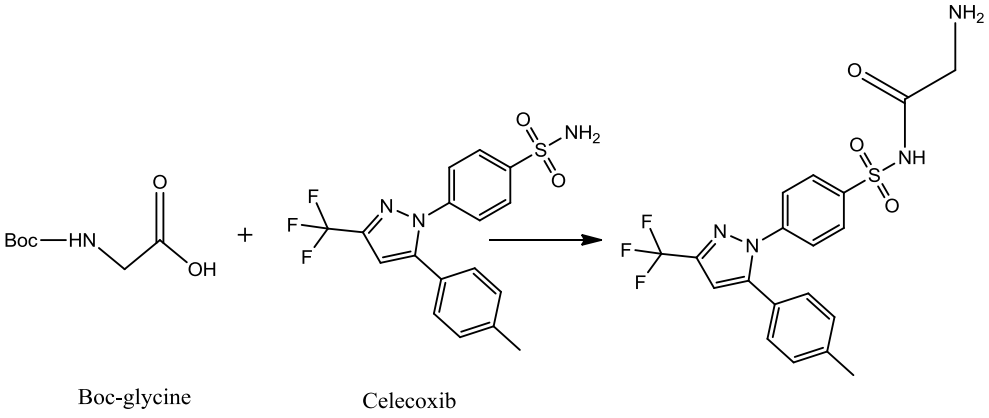
enters the colon, the initial entities are released due to the impact of the amidase enzyme. This high availability of MP is due to its low binding affinity to proteins compared with the high percentage of the original drugs (75%) [34].



Aceclofenac Histidine

SCHEME 10 The synthesis of the aceclofenac-L-histidine MP as depicted by Rasheed *et al.*

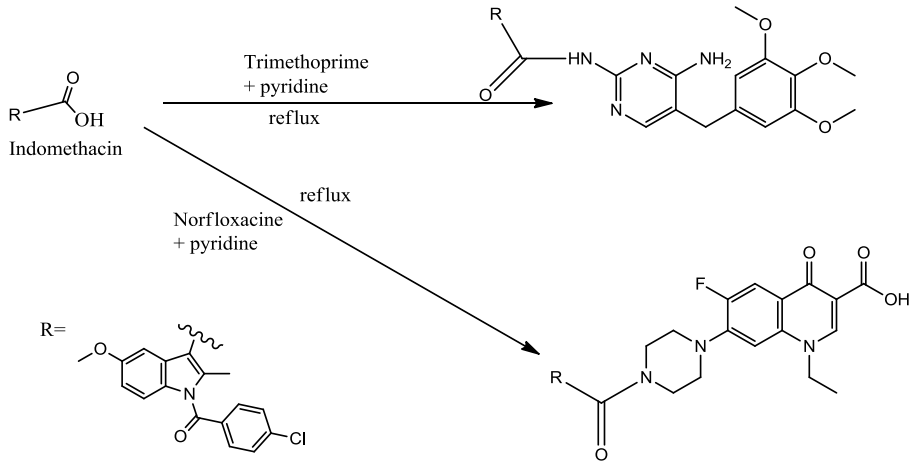
Celecoxib, a selective COX2 antagonist, has some less GIT complications than other non-selective NSAIDs, but its customers are more likely to experience cardiovascular events. Utilizing Boc-protected L-glycine, Lee *et al.* created a MP of celecoxib, as depicted in Scheme 11, and assessed its effectiveness as MCDDS that acts on NFκB. According to the research, a synthesized celecoxib MP may improve the anti-colitic effect of this medication and cardiovascular toxicity by concentrating more of this selective COX2 antagonist in the area that is inflamed and reducing its absorption throughout the body. In the large intestine, this MP was broken down to release the therapeutic effects of glycine and celecoxib [35].



Boc-glycine Celecoxib

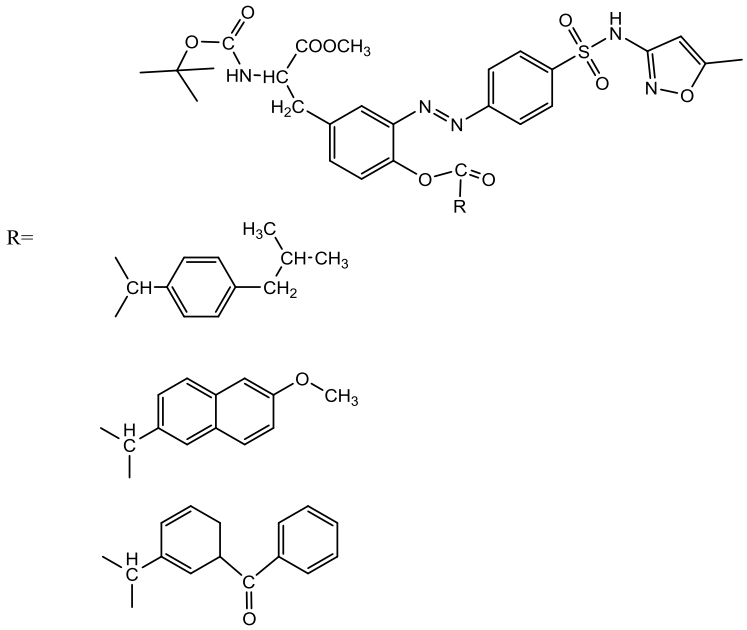
SCHEME 11 The synthesis of the celecoxib MP as described by its creators

The non-selective NSAID, indomethacin, has potent analgesic and anti-inflammatory properties. This drug was transformed into two MPs by Hussain *et al.*, as demonstrated in Scheme 12, through an amide linkage with trimethoprim and norfloxacin, serving as CDDSs. The use of antibacterial medications reduced the amount of local irritation in the GIT by acting as a transporter and masking the effects of indomethacin's free acidic group. To identify the anticipated hydrolysis of the synthesized amide conjugates in the GIT, release studies were conducted in a variety of simulation models. The research discovered that the initial entities released without any significant upper GIT absorption when these MPs reach the colon. Thus, doses could be decreased, which may enhance the therapeutic effectiveness of the initial entities [36].



SCHEME 12 The synthesis of the indomethacin MPs as displayed by Hussain *et al.*

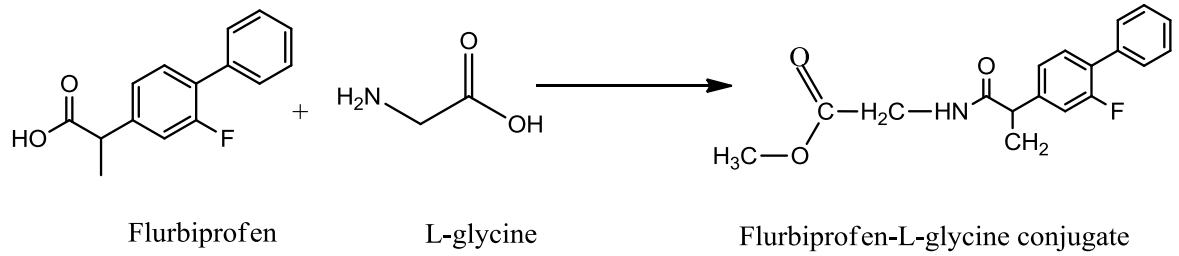
Abdulhadi *et al.* were synthesized derivatives of some NSAIDs (Ibuprofen, ketoprofen, or naproxen) with sulfamethoxazole as MPs by using tyrosine as spacer to act as CDDS, as displayed in Scheme 13. The prodrugs overcome the local irritation of NSAIDs due to free carboxyl group by ester linkage formation that remain intact in the stomach and hydrolyze in intestine. Furthermore, the synthetic derivatives are targeted to the colon by creating an azo group that only undergoes reduction by the colonic azo reductase enzyme. This reduction releases the original drugs to act locally for treatment of colonic inflammation and infections [37].



SCHEME 13 The synthesis of the some NSAIDs-sulfamethoxazole MPs as displayed by Abdulhadi *et al.*

An amide MP was synthesized by Philip *et al.* through coupling flurbiprofen with L-glycine, as indicated in Scheme 14. The latter is useful as a promoiety attached to the former for masking the carboxylic acid group effect of flurbiprofen. In comparison with the original drug, the synthesized MP showed higher solubility, reduced toxicity, and less

ulcerogenic activity. Thus, it not only solves flurbiprofen's formulation problem and minimizes side effects, but also permits targeted delivery of flurbiprofen to the colon [38].



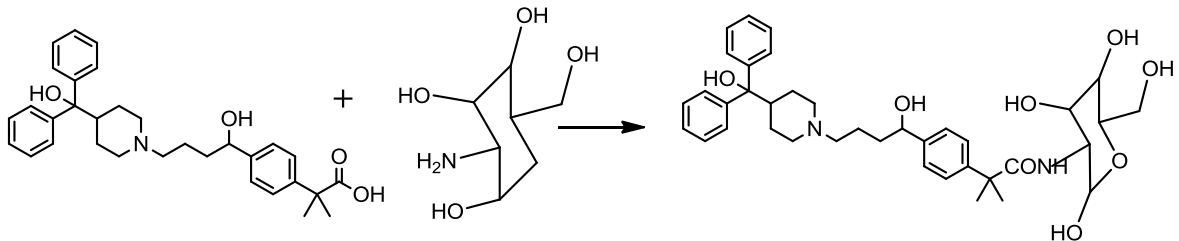
Flurbiprofen L-glycine Flurbiprofen-L-glycine conjugate

SCHEME 14 The synthesis of the flurbiprofen MP as depicted by its creators

Antihistaminic MPs

Immunological irregularities and elevated neutrophil, eosinophil, and mast cell inflammatory events are features of IBD, a chronic inflammatory condition. A number of pro-inflammatory cytokines, such as platelet activating factor, leukotriene, and histamine, are immediately released when a mast cell is stimulated. These mediators are crucial in the pathophysiology of the majority of IBD-related inflammatory diseases [39].

Patients with IBD benefit greatly from antihistamines like fexofenadine because they lower the high level of histamine released as a result of mast upregulation. In addition, they aid in lowering the increased levels of C-reactive protein and leukocytes, which helps to lessen inflammatory conditions and stop the spread of disease. In relation to drug safety and therapeutic response, the MP created by conjugating fexofenadine to D-glucosamine is extremely advantageous, as shown in Scheme 15. D-glucosamine is an amino-simple carbohydrate that acts as a transporter, encourages the formation of intestinal mucus and glycosaminoglycans, and has anti-inflammatory properties. These functions safeguard the gut wall. As a result of its polyhydroxy framework, fexofenadine becomes less lipophilic and can only be absorbed in the colon. When the MP reaches the aforementioned site, N-acyl amidase causes the MP to cleave, allowing the initial moieties to work together for reducing inflammation and protecting mucous membrane cells [40].



Fexofenadine D-glucosamine Fexofenadine-D-glucosamine conjugate

SCHEME 15 The synthetic pathway of the MP consists of fexofenadine and D-glucosamine

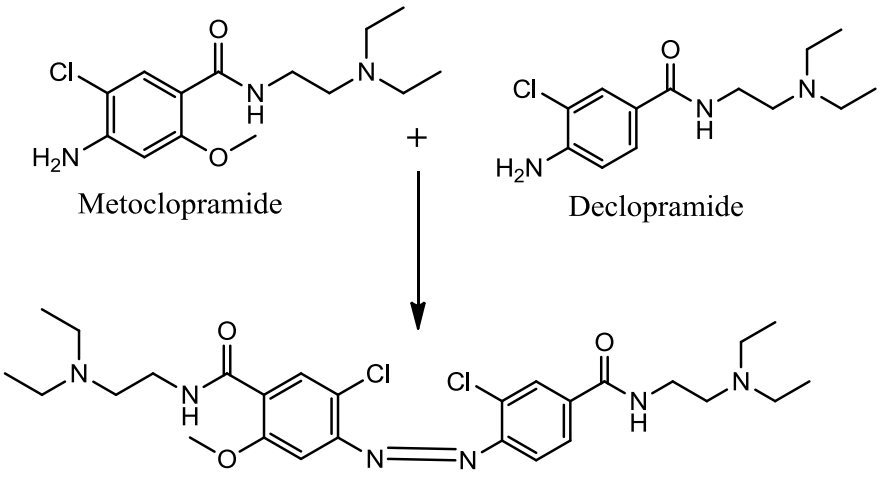
Anticancer MPs

5-Flurouracil (F-uracil), a 1957 discovery and FDA-approved antiproliferative drug, is highly effective in treating a variety of cancers, including those of the GIT, in general, and colorectal cancer, in particular [41]. Although it is therapeutically very effective in cancer treatment, the clinical applications of F-uracil are limited because it has a low cancer cell selectivity pattern and could have serious negative health effects. There have

been numerous attempts to address this issue, such as producing MPs by conjugating F-uracil to different natural, semisynthetic, and synthetic bioactive compounds [42].

In an ongoing effort to combat colon cancer, which is currently the third most common form of cancer globally, platinum-based drugs are combined with F-uracil to form highly potent antitumor MPs. Alkylating anticancer medications relying on platinum as a chelater have been widely used in the recent years. The therapeutic regime consists of platinum-based drug called oxaliplatin and F-uracil, is currently used as the first line drug regime of treatment for metastatic colorectal cancer. Oxaliplatin's high potential for severe systemic toxicity and innate or acquired resistance were remained its major clinical barriers. To get around the limitations of oxaliplatin, a group of platinum and F-uracil MPs known as fuplatins have been created and put through testing. Compared with administering the initial moieties individually, the fuplatins demonstrated increased therapeutic cytotoxic efficacy [43].

Descriptions of N-substituted benzamides with anticancer, anti-inflammatory, local anesthetic, and antiemetic properties include metoclopramide and declopramide. By hybridizing these two drugs through an azo bond, as depicted in Scheme 16, Mustafa YF created a new MP that can break down due to the action of the azo-reductase enzyme in the colon. By inhibiting the NFκB pathway, both of the released active moieties work in concert to treat the colon tumor. In addition, due to its local stimulating impact on the colonic smooth muscles, metoclopramide could treat complicated constipation, affording a dual action [44].



SCHEME 16 The synthesis of the MP that consists of metoclopramide and declopramide

Conclusion

A MP layout is one of the most effective ways to guarantee drug delivery to a particular site of action, which lowers systemic side effects and increases clinical benefit. In this review, the most significant MPs that specifically affect the bio-environment of the colon are discussed. The most influential currently available medications that act cooperatively and particularly in the colon are also highlighted, along with the significance of the discussed MPs in the treatment of colonic diseases and an illustration of the role of active transporter in enhancing therapeutic efficacy. The authors came to the conclusion that MCDDS could be used effectively to cure different colonic illnesses and that there are numerous MPs targeting the colon and offer a more successful treatment response than conventional drug delivery systems.

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