

Carbamate group as structural motif in drugs: a review of carbamate derivatives used as therapeutic agents

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[Received in July 2020; Similarity Check in July 2020; Accepted in December 2020]

Due to their very good chemical and proteolytic stability, ability to penetrate cell membranes, and resemblance to a peptide bond, carbamate derivatives have received much attention in recent years and got an important role in modern drug discovery and medicinal chemistry. Today, carbamates make structural and/or functional part of many drugs and prodrugs approved and marketed for the treatment of various diseases such as cancer, epilepsy, hepatitis C, HIV infection, and Alzheimer's disease. In drugs they can play a role in drug-target interaction or improve the biological activity of parent molecules. In prodrugs they are mainly used to delay first-pass metabolism and enhance the bioavailability and effectiveness of compounds. This brief review takes a look at the properties and use of carbamates in various fields of medicine and provides quick insights into the mechanisms of action for some of them.

KEY WORDS: anticonvulsants; antiepileptics; cholinesterase inhibitors; neurodegenerative diseases; prodrugs; protease inhibitors

Carbamates are derivatives of carbamic acid, whose amino and carboxyl termini are substituted by a variety of structurally diverse alkyl, aryl, or alkyl-aryl substituents and are identified by the presence of the -O-CO-NH- linkage (1). Carbamates are integral part of many drugs and prodrugs approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Many compounds that contain a carbamate group are currently in various stages of preclinical and clinical trials (1, 2). An example of a carbamate compound recently approved by the FDA is cenobamate (3), indicated for the treatment of partial-onset seizures in adults (4).

The research of carbamates as potential drugs began with the discovery of physostigmine, a methyl carbamate ester isolated in pure form from the seeds of Calabar beans (*Physostigma venenosum*) in 1864 (5). Initially, physostigmine was used to treat high eye pressure and glaucoma, but today, it is also used to treat delayed gastric emptying and myasthenia gravis (5, 6). Broader utilisation of carbamate compounds began in 1959, when carbaryl was registered as first carbamate pesticide for use in the USA (5). Today, carbamate compounds are widely used as pesticides (insecticides, fungicides, and herbicides), as starting materials in the production of paints and polyurethanes, and as protecting groups of amines in organic synthesis (7).

Studies have shown that the carbamate group increases the biological activity of active pharmacophores of structurally different natural or synthesised compounds (7,

8). By varying the substituents at the amino and carboxyl termini of the carbamate group, it is possible to modulate their biological and pharmacokinetic properties and improve their stability (7, 8).

The chemical properties of carbamates, their conformational and metabolic stability, the ability to pass through cell membranes, and some through the blood-brain barrier, have made the carbamate group a desirable part of the structure of many pharmacologically important compounds and a structural motif of many drugs and prodrugs.

Moreover, strong growth of carbamate use in the pharmaceutical industry is additionally boosted by the fact that the carbamate group can be considered a structural analogue of the amide bond (8–10). Amide-based molecules make a very good starting point for developing many drugs, enzyme inhibitors in particular. However, their inadequate pharmacokinetic properties, most notably poor *in vivo* stability and low bioavailability, limit their broader use and development. These limitations of amide-based compounds have recently been addressed by the use of carbamates as amido- or peptidomimetics to improve drug potency, duration of action, or target specificity (2, 9–11).

Today, the carbamate group makes part of many approved drugs which act as chemotherapeutic agents (mitomycin C, irinotecan), cholinesterase inhibitors in the treatment of neurodegenerative disorders (rivastigmine, neostigmine, physostigmine, pyridostigmine), human immunodeficiency virus (HIV) protease inhibitors (ritonavir, amprenavir, atazanavir, darunavir), anticonvulsants (felbamate, retigabine, cenobamate), anthelmintics (febendazole, albendazole,

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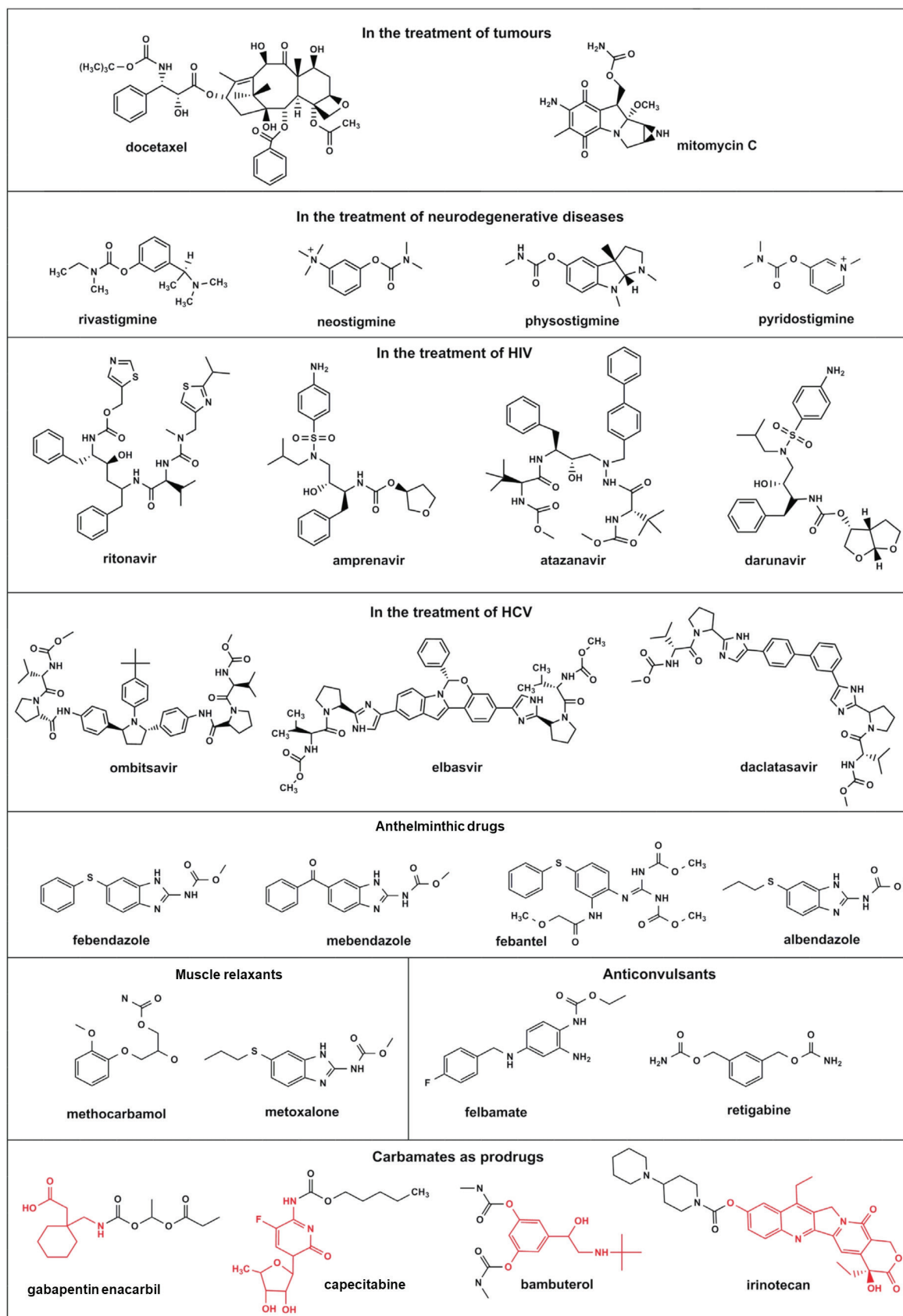


Figure 1 Structures of carbamate-based drugs and prodrugs of different application (carbamate group is presented in blue; active substance of prodrugs is presented in red)

febantelmependazole), and muscle relaxants (methocarbamol, metoxalone) (Figure 1). They also make part of prodrugs with different therapeutic applications (irinotecan, bambuterol, gabapentin encabril, capecitabine) (2, 7, 12) (Figure 1).

The aim of this review is to take a brief look at carbamate properties that make them useful in drug design, discuss some of the carbamate-based drugs and prodrugs, and explain the mechanisms of action for some of them.

CARBAMATE PROPERTIES AND APPLICATIONS

Chemical properties of carbamates

The structure of biologically active carbamates is shown in Figure 2. The carbamate group consists of a carbonyl group (C=O) to which an alkoxy group (OR¹ in Figure 2, marked blue) and an amino group (R²NR³ in Figure 2, marked red) are attached. R¹, R², and R³ may be different alkyl, aryl, and alkyl-aryl or substituted alkyl, aryl, and alkyl-aryl groups (2, 7). Replacing the carbonyl oxygen atom with sulphur generates thiocarbamates, while additional replacement of the alkoxy oxygen with a sulphur atom generates dithiocarbamates (2).

The carbamate group owes its functionality to the structural similarity between amides (R²NR³-CO-R¹) and carbamates. Namely, carbamates can be structurally considered as “amide-ester” hybrids with chemical reactivity comparable to these two functional groups. Due to this amide-ester combination, carbamates are chemically stable and able to modify inter- and intramolecular interactions (13).

Carbamate stability stems from the resonance between the amide and carboxyl group, which has been studied theoretically and experimentally by estimating the C-N bond rotational barriers (14). Figure 2 shows three resonance structures obtained from carbamate group stabilisation. The carbamate rotational barrier of the C-N bond is about 3–4 kcal/mol (15–20 %) lower than the rotational barrier of structurally analogue amides due to steric and electron perturbations which result from the presence of additional oxygen of the carboxyl group (14–16) and which make carbamates more electrophilic than amides and sufficiently reactive to spontaneously react with nucleophiles (9).

Another important feature of carbamates is their conformation. Due to a pseudo double bond in their structure, carbamate molecules can exist as *cis* and *trans* isomers (Figure 3) (17, 18), but they show no preference for either isomeric form, as the difference in free energy of the isomers is small, about 1–1.5 kcal/mol due to the steric and electrostatic properties of the substituents.

However, this difference in free energy and consequently the ratio of the two conformations can change with

conditions like type and/or composition of the solvents, concentration of salts, and pH of the reaction mixture (17, 18). For example, decreasing the pH of a reaction mixture in which amino acids are protected by the *tert*-butyl carbamate (*Boc*) group, increases the concentration of *cis* isomers, while increasing the temperature increases the concentration of *trans* isomers (19). One study (20) which used a carbamate group to connect different ammonium groups to the entrance of the gramicidin ion channel, demonstrated that the ratio of *cis/trans* isomers depended on combined electrostatic and steric effects of the carbamate linker on cation flux through the channel. This suggests that a compound able to change the carbamate *cis/trans* ratio may also be used to regulate ion channel flux (13). R and R¹ (Figure 3) substituents must also be taken into account, as the steric effects of R and electronegativity of R¹ influence the difference in free energy and therefore the *cis/trans* ratio.

Five-, six-, and seven-membered cyclic carbamates can only exist as *trans* conformers. Five- or six-membered carbamates are quite stable because they generally do not undergo metabolic ring opening (17).

Furthermore, carbamates are semi-polar compounds that can form hydrogen bonds, both as hydrogen donors and as hydrogen acceptors, and various interactions can take place at their O- and N-termini. Carbamates contain C=O and N-C dipoles arising from covalent bonding of electronegative oxygen and nitrogen atoms with electroneutral carbon atoms. Because of the π -bonding arrangement of carbonyl and greater electronegativity of oxygen, carbonyl is a stronger dipole than the N-C dipole. The presence of a C=O dipole allows carbamates to act as H-bond acceptors, whereas the N-C dipole allows them to act as H-bond donors, but to a lesser extent (9).

Unlike amides, carbamates are proteolytically stable against various proteases (9), and can even inhibit them as discussed later. Thanks to these properties – proteolytic, chemical, and conformational stability and ability to pass through the cell membrane and blood brain barriers (not all) – carbamates are increasingly replacing peptides in pharmaceuticals (7).

Their pharmacological activity mostly depends on the speed and intensity of their hydrolysis (21), and their major hydrolysis pathway in physiological conditions is base hydrolysis. The mechanisms of base hydrolysis of monosubstituted and disubstituted carbamates are shown in Figure 4 (22). The difference between these two mechanisms is in the intermediate, which is an isocyanate anion in monosubstituted carbamates and a carbonate anion in disubstituted carbamates. Following basic hydrolysis, parent alcohol and carbamic acid are released, and carbamic acid rapidly decomposes to the corresponding amine and carbon dioxide (21, 22). Carbamate derivatives could be used as prodrugs for amines or alcohols and phenols to delay first-pass metabolism and enhance hydrolytic stability of compounds (23).

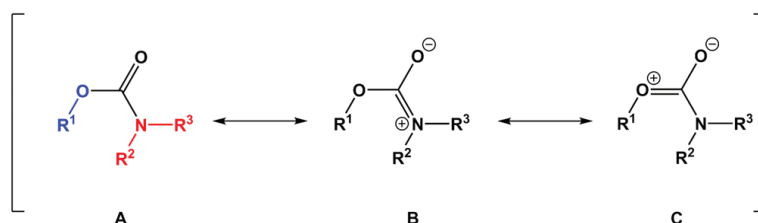


Figure 2 Possible resonance structures for the carbamate group (amino group is presented in red, and alkoxy group in blue) (adopted from ref. 14)

A recent review by Vacondio et al. (21) has compiled substantial data from recent studies of metabolic stability of therapeutic carbamates to evaluate the qualitative relationship between molecular structure of carbamates and their susceptibility to metabolic hydrolysis and has proposed the following order in metabolic resistance: aryl-OCO-NHalkyl >> alkyl-OCO-NHalkyl ~ alkyl-OCO-N(alkyl)₂ ≥ alkyl-OCO-N(endocyclic) ≥ aryl-OCO-N(alkyl)₂ ~ aryl-OCO-N(endocyclic) ≥ alkyl-OCONHArlyl ~ alkyl-OCO-NHacyl >> alkyl-OCO-NH₂ > cyclic carbamates (21).

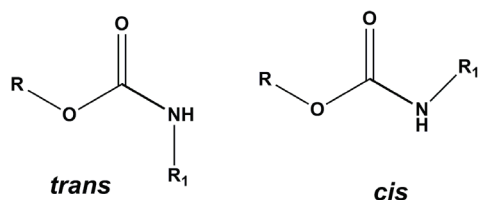


Figure 3 *Cis* and *trans* conformations of carbamates (adopted from ref. 14)

Application of carbamates

Carbamate derivatives have a wide range of applications. Their first massive use in agriculture as pesticides, fungicides, and insecticides in various crops all around the world started in the 1950s (25–27). They have been the second most common pesticides and a welcome replacement of poisonous organochloride pesticides since the 1970s. Even so, some of them are assumed to be potentially carcinogenic and mutagenic or display acute toxicity for mammals and aquatic organisms (28–30). Most carbamates used in agriculture represent an issue for the environment with more than 10,000 tonnes deployed each year, which makes their clean-up one of environmental priorities (30).

Mass use of carbamates in everyday life was expanded by the discovery of polyurethanes (PUs) – compounds with polymerised carbamate groups whose biological, chemical, and physical properties enabled carbamate application in surface coatings, synthetic fibres, elastomers, foams, and packaging (31). It must be mentioned that ethyl carbamate, also known as urethane, has no connection with polyurethanes in any way. Urethanes are commonly synthesised from an alcohol and an isocyanate, while carbamate synthesis usually does not involve isocyanate as reactant (32).

Carbamates are also used to protect amino groups, most notably tert-butoxycarbonyl (*Boc*), benzyloxycarbonyl

(*Cbz*), and allyloxycarbonyl (*Alloc*) (33). As starting material, carbamates have also a leading role in the paint industry (8, 34).

In recent years, carbamate derivatives, including urethanes (especially five- or six-membered cyclic and bicyclic fused carbamates) have seen an expansion to pharmaceutical industry as important structural and functional elements in the design of drugs and prodrugs (32, 35).

CARBAMATES AS DRUGS

The biological activity of a carbamate was first reported by European missionaries in West Africa in the 19th century. There a local tribe was using a white extract from Calabar beans (*Physostigma venenosum*) as an ordeal poison in witchcraft trials (36). These beans were imported to Great Britain in 1840, and in 1864, Jobst and Hesse isolated an active alkaloid component they named *physostigmine* (37). *Physostigmine* is a naturally occurring methyl carbamate ester initially used as a medicine to treat glaucoma, but its application broadened over the years. *Physostigmine* was reported to markedly improve muscle strength in patients with myasthenia gravis and had been the drug of choice for this condition for three decades, until it was replaced by a longer-acting oral agent *pyridostigmine*. Today, *physostigmine* is also used to treat delayed gastric emptying and anticholinergic poisoning caused by overdosing with atropine, scopolamine, and other anticholinergic drugs. Furthermore, *pyridostigmine* seems to improve long-term memory, which is why it was clinically studied for treatment of Alzheimer's disease but was abandoned due to moderate to severe side effects in favour of other acetylcholinesterase inhibitors (38, 39).

Because of their chemical and proteolytic stability, ability to create inter- and intramolecular interactions, and bond resembling that of amides, carbamates soon piqued the interest of pharmaceutical industry (2, 7, 9). Recent studies (2, 8) have shown that incorporating the carbamate group in a molecule increases the biological activity of active pharmacophores of structurally different natural or synthesised compounds. For example, replacing the unsaturated ester chain at C-6 in fumagillin (a natural antibiotic and endothelial cell proliferation inhibitor) with the *O*-(chloroacetyl) carbamoyl moiety resulted in a 50

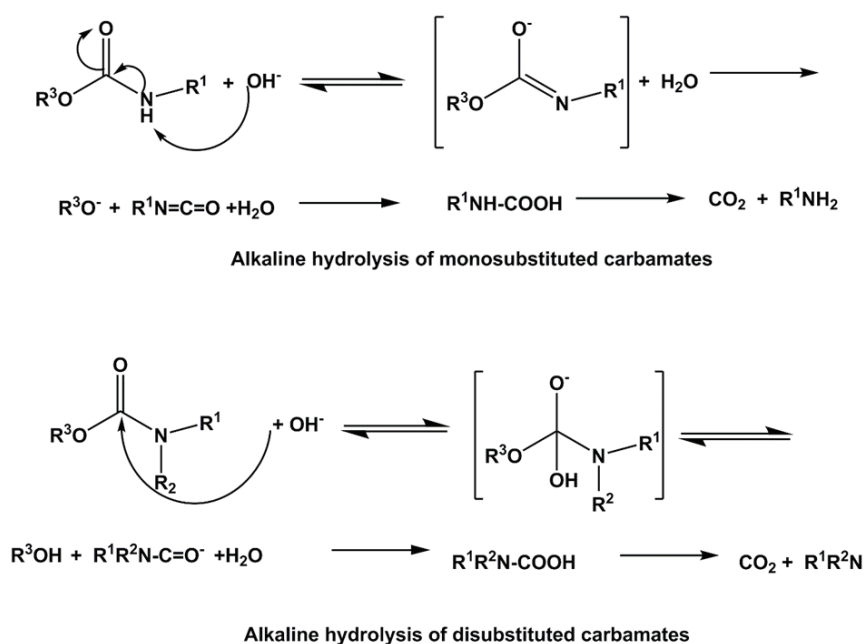
Table 1 Roles of the carbamate moiety in drugs and prodrugs

Drug	The role of the carbamate moiety in the drug	Reference
Docetaxel	prolongs drug action, increases drug potency, improves water solubility	39
Mytomicin C	participates in the formation of an alkylating compound during reaction with target	40
Rivastigmine, neostigmine, physostigmine, pyridostigmine	key element for interaction with the target	38
Ritonavir, amprenavir, atazanavir, darunavir	improves drug bioavailability and potency, engaged in a backbone interaction with protease	8
Ombitasvir, elbasvir, daclatasavir	improves drug stability and lipophilicity	41
Febendazole, mebendazole, febantel, albendazole	improves aqueous solubility and bioavailability, increases cytotoxicity	42
Mehocarabamol, metaxalone	inhibits acetylcholinesterase at synapses in the autonomic nervous system, neuromuscular junction, and central nervous system	43
Felbamate	improves drug stability and bioavailability	44, 45
Retigabine	major pharmacophore responsible for interacting with residues in the KCNQ2–5 channels	46
Gabapentin enacarbil	improves bioavailability	47
Capecitabine	improves selectivity and bioavailability	47
Bambuterol	delays first-pass metabolism	47
Irinotecan	improves aqueous solubility	47

times more potent antitumor compound. Another example is betulinic acid, a very promising anticancer drug (8), whose imidazole and triazole carbamate derivatives were 12 times more potent and less cytotoxic (2). This possibility to change the biological and pharmacokinetic properties and improve the stability of parent compounds by varying the substituents on the *O*- and/or *N*- termini of a carbamate group has recently boosted the interest in developing efficient and safe synthesis of carbamate esters (8). Today, many drugs incorporate the carbamate moiety, whose roles in some drugs and prodrugs are listed in Table 1.

Carbamates in tumour treatment

Two carbamate drugs, mitomycin C and docetaxel, have so far been approved for the treatment of various types of tumours (Figure 1). Both can be used alone or in combination to other antitumor drugs (48–50). Their antitumor activity stems from their ability to selectively inhibit the synthesis of DNA in a tumour cell or to inhibit the tubulin polymerisation, both resulting in the arrest of mitotic phase of cell division (48).

**Figure 4** Alkaline hydrolysis of monosubstituted (A) and disubstituted (B) carbamates (adopted from ref. 22)

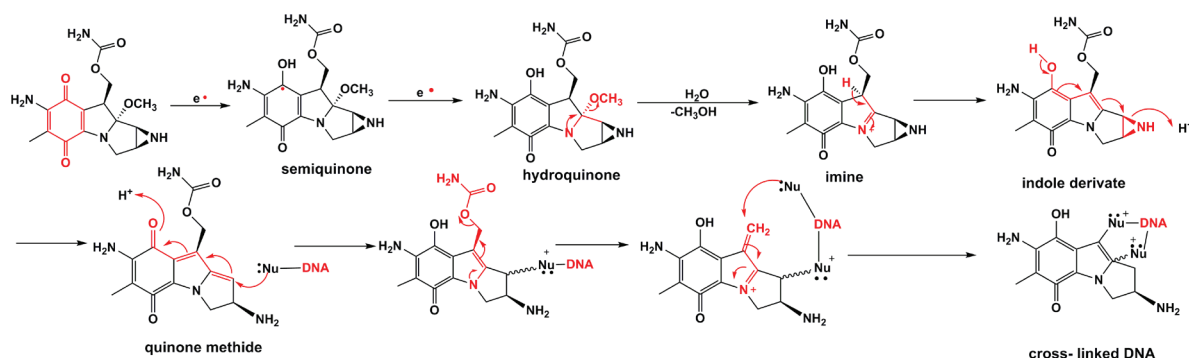


Figure 5 Mechanism of action of mitomycin C (adopted from ref. 40)

Mitomycin C is a miscellaneous antibiotic that selectively inhibits DNA synthesis in a tumour cell and is indicated for chemotherapy of gastrointestinal, anal, and breast cancers (49). Its mechanism of action is given in detail in Figure 5 (40). All starts with an *in situ* bioreductive activation of quinone that involves two consecutive reduction steps to the corresponding hydroquinone. The elimination of methanol from hydroquinone produces a reactive imine. Deprotonation of imine results in an indole derivative that undergoes rearrangement to produce a quinone methide, which then reacts with nucleophilic DNA groups, yielding an unstable intermediate that binds to complementary strands of double-stranded DNA coils. This binding inhibits DNA replication and causes tumour cell death. At high concentrations, mitomycin C has also been shown to suppress RNA and protein synthesis, inhibit proliferation of B-cells, T-cells, and macrophages *in vitro*, and to reduce the secretion of interferon gamma, tumour necrosis factor alpha (TNF α), and interleukin 2 (IL-2) (40, 51).

Docetaxel (Figure 1) is a chemotherapeutic used to treat breast, head/neck, stomach, prostate, and lung cancers. It binds to the β -subunit of tubulin and forms the docetaxel-

tubulin complex, which interferes with tubulin polymerisation and, in turn, leads to tumour cell cycle arrest and apoptosis, including the apoptosis of B-cells affected by leukaemia (50, 52).

Carbamates in HIV infection treatment

HIV-1 protease is essential for viral maturation, as it cleaves newly synthesised polyproteins Gag and Gag-Po to create mature protein components of the HIV virion, the infectious form of the virus outside the host cell (53). There are ten HIV protease inhibitors approved by the FDA, four of which have the carbamate group in their structure (ritonavir, atazanavir, amprenavir, and darunavir). These bind directly to the active site of HIV-1 protease to prevent Gag and Gag-Po cleavage (53–58). One of them, ritonavir, was later found that not only it inhibits HIV protease but can also boost blood concentrations of other HIV protease inhibitors by inhibiting cytochrome P450 3A4, which would otherwise metabolise them and render inefficient (54–56). Another HIV protease inhibitor, atazanavir, shows good oral bioavailability allowing a once-a-day dosing. It is used only in combination with ritonavir and/or other antiviral

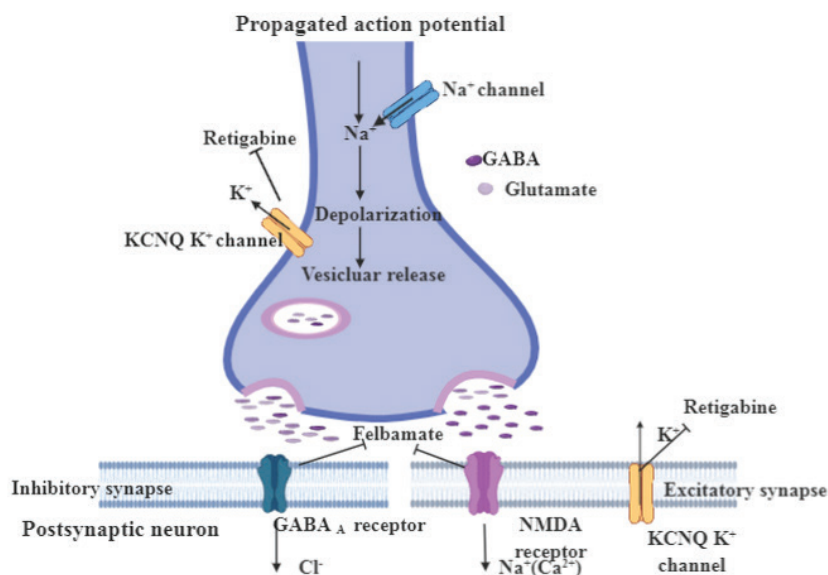


Figure 6 Proposed targets and mechanism of action of felbamate and retigabine in postsynaptic neuron (adopted from refs. 62 and 63)

drugs (55, 56) and as such currently makes the first-line antiretroviral treatment (56, 57).

Carbamates as antiepileptics and anticonvulsants

Carbamate anticonvulsants used in epilepsy treatment are felbamate and retigabine (Figure 1). Their exact mechanism of action is still unclear but what is known is that they inhibit *N*-methyl-D-aspartate (NMDA) receptors to some extent and slightly enhance gamma-aminobutyric acid (GABA) activity (59, 60).

Felbamate is potent and very effective anticonvulsant approved by FDA in 1993 for the management of focal seizures and Lennox-Gastaut syndrome. It is effective as monotherapy or add-on to phenytoin and carbamazepine in patients with uncontrolled focal epilepsy (61, 62). However, its approval has now been limited because its use is associated with the development of aplastic anaemia and hepatic failure. It is now available in the USA only for a very limited use, principally by neurologists in patients for whom potential benefit outweighs the risk (60). It is believed that felbamate acts as NMDA receptor-ionophore complex antagonist at the strychnine-insensitive glycine-recognition site (62), as it blocks the effects of excitatory amino acids, suppresses neuronal firing, and prevents seizure. As for GABA receptors, some studies suggest that felbamate weakly inhibits GABA_A-receptor binding sites and thus enhances GABA-elicited Cl⁻ currents in cultured cortical neurons. This may explain how felbamate dampens neuronal excitation and inhibits voltage-gated sodium and calcium channels (Figure 6) producing a barbiturate-like effect (63, 64). However, one *in vitro* receptor-binding study

reported that felbamate did not enhance GABA evoked ³⁶Cl⁻ influx in cultured spinal cord neurons (65). These discrepancies between reports may lie in varying regional and ontogenetic expression of GABA receptor subunits and varying properties of GABA receptors between central nervous system (CNS) regions and stages of development (66).

Retigabine is an anticonvulsant used as adjunct in the treatment of partial seizures in adult patients, tinnitus, migraine, and neuropathic pain (45, 46, 67). The mechanism of its action is unique among antiepileptic drugs and represents a new approach in the treatment of neurological conditions. Retigabine works primarily by opening a particular group of voltage-regulated potassium ion channels in brain cells – KCNQ2 and KCNQ3 (Figure 6) – which stabilises the resting membrane potential and regulates electrical neuron excitation to keep it below the threshold. This prevents the onset of epileptiform discharges (46, 67, 68).

Cenobamate is indicated for the treatment of partial-onset seizures in adults (3, 4). It selectively blocks the persistent sodium current of voltage-gated sodium channels (VGSCs) (3, 4). It also acts as a positive allosteric modulator of high-affinity GABA_A receptors to stabilise neural circuits of the epileptic hippocampus (69).

Carbamates in the treatment of neurodegenerative diseases

Neurodegenerative diseases are characterised by progressive structural and functional degeneration of the central and/or peripheral nervous system (70). One of their

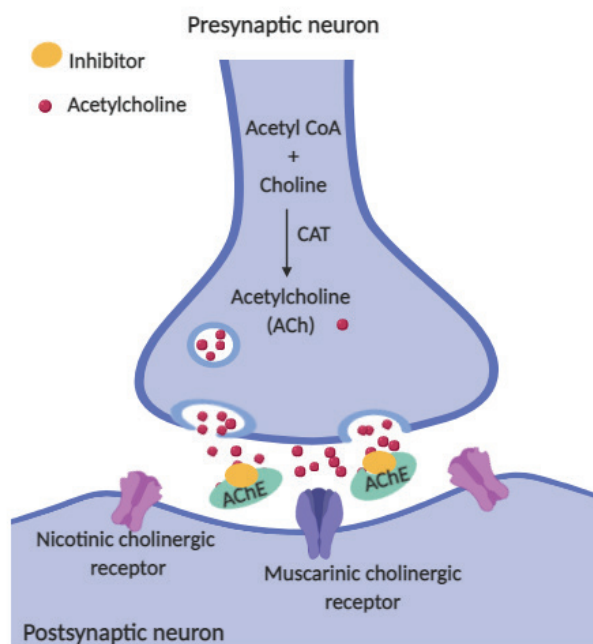


Figure 7 A proposed simplified mechanism for AChE inhibition by carbamates. Rapid formation of the covalent enzyme-carbamate intermediates, followed by slow regeneration of a free AChE prevents breaking down of acetylcholine in postsynaptic cleft by AChE (adopted from ref. 81)

clinical manifestations is the depletion of acetylcholine (ACh), a neurotransmitter in cholinergic synapses, caused by its excessive metabolism to choline and acetic acid mediated by cholinesterases. In humans, there are two cholinesterases: acetylcholinesterase (AChE), whose physiological role is to hydrolyse ACh, and butyrylcholinesterase (BChE), whose physiological role is still unclear, except that it hydrolyses ACh and other esters and scavenges some toxins by reacting with them before they reach AChE (70–72). Treatment of patients with neurodegenerative diseases who have low ACh levels (Alzheimer's disease) and disorders of the neuromuscular system (Parkinson's disease, myasthenia gravis) is focused on alleviating symptoms. Restoring the concentration of ACh by inhibiting AChE (Figure 7) is the primary treatment for cognitive deficits, although more recent studies point to BChE as a new possible target of cholinesterase inhibitors (73–75). To date, different types of cholinesterase inhibitors have been identified, designed, and synthesised. The first such cholinesterase inhibitor to be clinically approved was a natural carbamate physostigmine (76). Since then, many carbamates have been developed and tested for the treatment of various disorders of cholinergic neurotransmission. Four of them are currently approved for treating neurodegenerative diseases: physostigmine, pyridostigmine, rivastigmine, and neostigmine (Figure 1) (77).

Physostigmine acts by inhibiting AChE activity and preventing ACh hydrolysis, which in turn increases ACh levels at the synapse and indirectly stimulates nicotinic and muscarinic receptors. As it crosses the blood-brain barrier, it can also treat the effects of atropine and other anticholinergic drug overdoses on the CNS (78, 79).

Pyridostigmine and neostigmine are parasympathomimetics used in the treatment of myasthenia gravis and both inhibit AChE (78, 80). Rivastigmine inhibits both AChE and BChE and is used to treat mild to moderate Alzheimer's and Parkinson's dementia (77).

Cymserine is a physostigmine-based compound with a isopropylphenyl instead of a methyl group at the *N*-4' position, which makes it 15 times more selective for BChE than AChE (81–84). In clinical trials it has shown highly promising results in patients with Alzheimer's disease, but also unacceptable side effects caused by its toxic metabolites (85).

One of the pathological features of Alzheimer's is the formation of β -amyloid ($A\beta$) peptides in the cortex of patients with Alzheimer's. $A\beta$ -peptides are generated by sequential cleavage of β -amyloid precursor protein (APP) by β -secretase and γ -secretase. These two enzymes have therefore become important targets in designing drugs to treat Alzheimer's disease (8). To overcome the limitations imposed by cymserine metabolite induced side effects in clinical trials, several cymserine derivatives (Figure 8) have been tested *in vivo* and shown to increase ACh levels in the brain, produce nootropic effects, and reduce APP and $A\beta$ -peptide levels. They have the potential to become the first drugs capable of stopping and even reversing the progression of Alzheimer's disease (86).

Many other carbamate compounds have been designed as potential secretase inhibitors, but none have yet been approved for medical use. Some have shown great β -secretase inhibition potential, like the 16-membered macrocycle (compound A in Figure 9) containing a *trans*-olefin, amide, and carbamate functionalities. Others, like

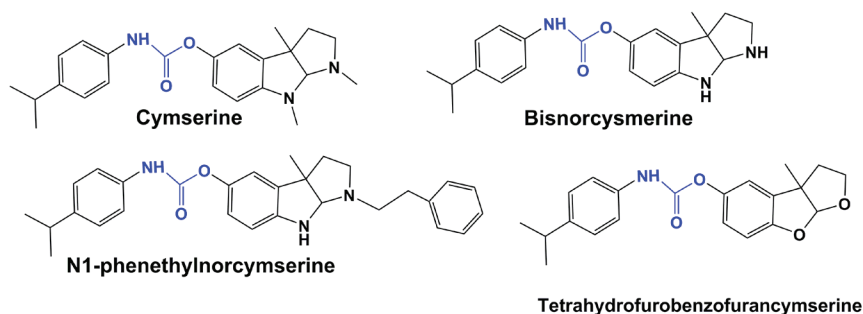


Figure 8 Cymserine and its derivatives (carbamate group in blue) (adopted from ref. 82)

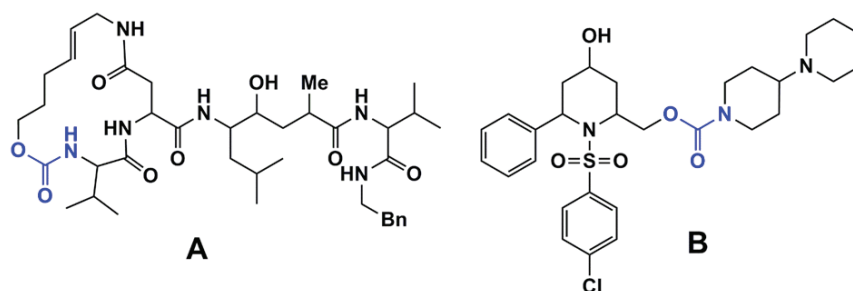


Figure 9 Chemical structure of secretase inhibitors tested with potential to be used in treatment of Alzheimer's disease A – a 16-membered macrocycle compound; B – sulphonamide compound (adopted from ref. 8)

sulphonamide derivatives (B in Figure 9) have shown strong γ -secretase inhibition (8).

Carbamates in the treatment of hepatitis C

Hepatitis C virus (HCV) causes acute and chronic mild to severe hepatitis. With time, a significant number of chronic patients develop cirrhosis or liver cancer (87).

Recent years have seen the development of a number of new and effective hepatitis C drugs which specifically target viral NS3/4A protease, non-structural protein 5A (NS5A), or NS5A RNA polymerase to inhibit viral replication, and counter NS5A-associated interferon-resistance as the common cause of treatment failure (87–89). Today, there are ten carbamates targeting NS5A. Six have been approved for use (89) and the rest are in phase III of clinical trials (89, 90). They inhibit NS5A by blocking signalling interactions, redistributing NS5A from the endoplasmic reticulum to the surface of lipid droplets, and by inhibiting HCV replication (9, 92). Figure 1 shows the structures of three approved carbamate HCV inhibitors: daclatasavir, elbasvir, and ombitasvir (93).

Antiviral action is further increased by combining NS5A with NS3/4A protease inhibitors, as is the case with daclatasavir and sofosbuvir (92–95). Both daclatasavir and sofosbuvir and their combination have been included in the WHO model list of the most efficacious, safe, and cost-effective medicines for a specific condition, the so called essential medicines list (EML) (96).

Carbamates as muscle relaxants

The best known carbamate muscle relaxants are methocarbamol and metaxalone (Figure 1) (43). Although the exact mechanism of action of methocarbamol is still not clarified, it is believed to involve AChE inhibition at synapses in the autonomic nervous system, neuromuscular junction, and the CNS (97). Metaxalone is usually prescribed as adjuvant therapy that accompanies rest, physical therapy, and other measures to relieve acute musculoskeletal pain. Its mode of action is also not clear, but is most likely related to general CNS depression (98).

Carbamates as anthelmintics

The carbamates that act against parasitic worms or helminths in humans and animals are fenbendazole, febantel, mebendazole, and albendazole (Figure 1) (99). Mebendazole and albendazole are benzimidazole carbamate anthelmintics used to treat a broad range of parasitic

infections (100, 101). Their mechanism of action is analogous to that of docetaxel: they selectively inhibit microtubule synthesis by binding to β -tubulin and blocking the polymerisation of tubulin dimers in intestinal parasite cells. This disruption of cytoplasmic microtubules results in blocking glucose and other nutrient transport in parasites cells and their gradual immobilisation and death (101).

CARBAMATES AS PRODRUGS

Prodrugs are designed to undergo enzymatic and/or chemical metabolism in the body to release the active drug with a desired pharmacological effect (Figure 10) (47, 102). They serve as carriers to overcome physicochemical, biopharmaceutical, or pharmacokinetic limitations of active drugs by increasing their solubility in water and absorption, by delaying their first-pass metabolism, by delivering them to the brain, or by reducing their toxicity and local irritation (103). Prodrugs generally consist of a parent (active) drug and a promoity that masks the functional group within the parent drug (Figure 10). Typically, a promoity is attached to the active drug with bond(s) that break in certain conditions, such as the presence of an enzyme or a change in pH and releasing the active substance to do its job (103). Esters are used as prodrugs to improve lipophilicity and permeability through cell membranes, while phosphate esters, oximes, and amides are used to improve drug solubility in water and oral absorption (47, 103).

Carbamates are used in the design of prodrugs of carboxyl, hydroxyl, or amine functionalities to delay first-pass metabolism and enhance systemic hydrolytic stability (103) (Table 1). Their bioconversion for active drug release involves rapid hydrolysis mediated by metabolic enzymes, mainly cytochrome P450 and esterases, which usually occurs in the liver (22, 47, 103).

Carbamate prodrugs with a phenol as active substance

Carbamates are used as prodrugs of alcohols and phenols to achieve systemic hydrolytic stability and protection from first-pass metabolism (23). Carbamates of *N*-monosubstituted and *N,N*-disubstituted alcohols are chemically stable against hydrolysis (21), as are the carbamates of *N,N*-disubstituted phenols but not as much those of *N*-monosubstituted phenols (21, 24). Examples of carbamate prodrugs whose active substance is alcohol or phenol are irinotecan and bambuterol (Figure 1).

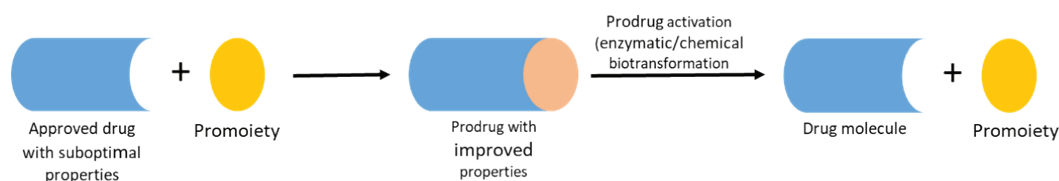


Figure 10 A simplified illustration of the prodrug concept

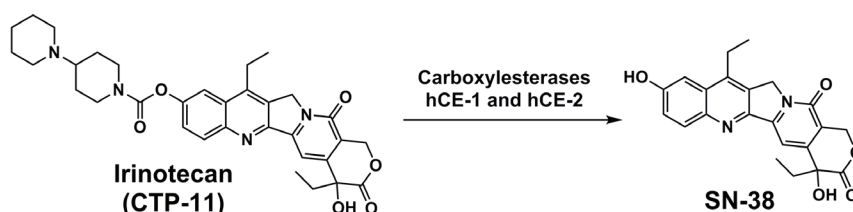


Figure 11 Irinotecan metabolism by carboxylesterases hCE-1 and hCE-2 (adopted from ref. 105)

Irinotecan (CPT-11) is a semisynthetic analogue of the natural alkaloid camptothecin, commonly used for the treatment of colon, rectal, and ovarian cancers (104, 105). In human body, irinotecan is metabolised by tissue and serum carboxylesterases to an active compound SN-38 (106), which has a 100–1,000 times higher antitumour activity than irinotecan. SN-38 inhibits topoisomerase I activity by stabilising the cleavable complex between topoisomerase I and DNA, which leads to DNA breaks, inhibition of DNA replication, and triggers apoptotic cell death (Figure 11) (106).

Bambuterol (Figure 1) is a bis-dimethyl carbamate prodrug of terbutaline, used to treat asthma and chronic obstructive pulmonary disease. Bambuterol belongs to long-acting drugs due to catecholic hydroxyl groups in its structure that are quite resistant to hydrolysis and first-pass metabolism. In the lung tissue, bambuterol is hydrolysed

to terbutaline by BChE (Figure 12), and in the liver, it is metabolised to terbutaline under the influence of cytochrome P-450-dependent oxidases (24, 107, 109). Terbutaline is an adrenergic agonist that predominantly stimulates β -2 receptors to relax the smooth muscle of the bronchus and dilate the airways (107–109).

Carbamate prodrugs with an amine as active substance

At physiological pH amine-based drugs or drugs having an amine group in the structure can undergo protonation and may not always be optimally distributed in the body (47, 102). Because of that, polar amino groups are often derivatised to make the compounds neutral or hydrophobic, i.e. more soluble in lipids (47, 102). One of the derivatisation strategies involves introduction of carbamate moiety into drug structure. Currently used amine-based carbamate

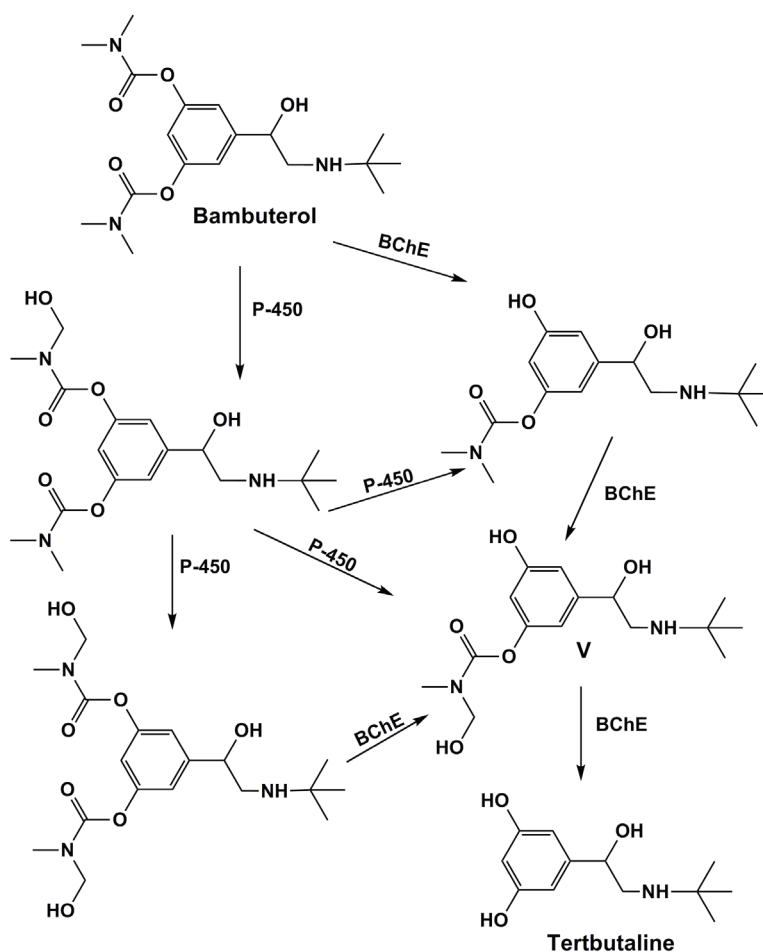


Figure 12 Bambuterol metabolism into terbutaline by cytochrome p450 and butyrylcholinesterase (BChE) (adopted from ref. 106)

prodrugs gabapentin enacarbil and capecitabine are presented in Figure 1.

Gabapentin enacarbil is a prodrug designed to increase oral bioavailability of gabapentin used to treat the restless legs syndrome (RLS) and postherpetic neuralgia (PHN) in adults (110). After oral administration gabapentin enacarbil gets strongly hydrolysed by non-specific carboxylesterases, primarily in enterocytes and to a lesser extent in the liver, to form the active drug gabapentin, carbon dioxide, acetaldehyde, and isobutyric acid (110).

Capecitabine is a fluoropyrimidine carbamate of the antimetabolite class of chemotherapeutics (111) that is selectively activated by tumour cells to produce cytotoxic 5-fluorouracil (5-FU) (112), which is then metabolised to its active components 5-fluoro-2-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). The first inhibits DNA synthesis and cell division by reducing normal thymidine production, and the second inhibits RNA and protein synthesis by competing with uridine triphosphate for incorporation into the RNA strand (111, 112).

Acknowledgment

This article was supported by the Croatian Science Foundation (project no. IP-2018-01-7683) and the Institute for Medical Research and Occupational Health (project no. IMI-IP-2017-2).

Conflict of interests

None to declare.

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Karbamatna skupina kao strukturni element lijekova – pregledni rad

Zbog svoje vrlo dobre kemijske i proteolitičke stabilnosti, sposobnosti prodiranja kroz stanične membrane i sličnosti s peptidnom vezom, derivati karbamata posljednjih godina sve više privlače pozornost medicinskih kemičara i dobivaju važniju ulogu u modernom načinu otkrivanja lijekova. Tako je u današnje vrijeme karbamatna skupina strukturni i funkcionalni element mnogih odobrenih lijekova, a mnogi se već i koriste kao lijekovi za liječenje raznih vrsta bolesti poput raka, epilepsije, hepatitisa C, infekcije HIV-om, Alzheimerove bolesti i mnogih drugih. U lijekovima, karbamatna skupina može biti važan dio molekule koji ima ulogu u interakciji lijek-meta ili je umetnuta u strukturu spoja kako bi se poboljšala biološka aktivnost temeljne molekule. U protulijekovima, karbamatna se skupina koristi uglavnom zbog mogućnosti smanjenja osjetljivosti spoja na metaboličke enzime, odnosno povećanja hidrolitičke stabilnosti samoga spoja. U ovom je radu dan ne samo kratki pregled karbamata koji se koriste kao lijekovi u raznim područjima primjene, kao i karbamata koji se koriste kao protulijekovi, nego i uvid u mehanizam djelovanja nekih od njih.

KLJUČNE RIJEČI: antiepileptici; antikonvulzanti; inhibitori kolinesteraza; inhibitori proteaza; neurodegenerativne bolesti; protulijekovi