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

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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, ...
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)
the ratio of the two conformations can change with and electrostatic properties of the substituents. The isomers is small, about 1–1.5 kcal/mol due to the steric for either isomeric form, as the difference in free energy of isomers (Figure 3) (17, 18), but they show no preference 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 R' (Figure 3) substituents must also be taken into account, as the steric effects of R and electronegativity of R' 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).
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) ≥ alkyl-OCO-N(endocyclic) ≥ aryl-OCO-N(alkyl) ~ aryl-OCO-NH(aryl) ˃˃ alkyl-OCO-NH(acyl) ˃≥ cyclic carbamates (21).

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
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).

### 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 |
| Mytomycin 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, daclatasvir | improves drug stability and lipophilicity | 41 |
| Febendazole, mebendazole, febantel, albendazole | improves aqueous solubility and bioavailability, increases cytotoxicity | 42 |
| Mechocarabamol, 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 |

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![Figure 4 Alkaline hydrolysis of monosubstituted (A) and disubstituted (B) carbamates (adopted from ref. 22)](image_url)
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 (TNFα), 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...
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<sub>A</sub>-receptor binding sites and thus enhances GABA-elicited Cl<sup>-</sup> 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<sup>-</sup> 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<sub>A</sub> 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
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 an 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 (Aβ) peptides in the cortex of patients with Alzheimer’s. Aβ-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 Aβ-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...
sulphonamide derivatives (B in Figure 9) have shown strong \(\gamma\)-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 ombitsavir (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 metaxalon (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 \(\beta\)-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 promoiety that masks the functional group within the parent drug (Figure 10). Typically, a promoiety 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 carboxylic, 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 \(N\)-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](image-url) A simplified illustration of the prodrug concept
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...
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 antimitabolite 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-fluourouridine 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).

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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 skupina koristi se uglavnom zbog mogućnosti smanjenja osjetljivosti spoja na metaboličke enzime, odnosno povećanja hidrolitičke stabilnosti samoga spoja. U ovom radu dan je 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