Cimetna kiselina i njeni derivati

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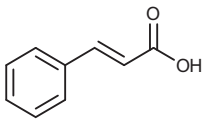
Cimetna kiselina u prirodi

Cimetna kiselina (3-fenilprop-2-enska ili fenilakrilna kiselina, slika 1.) i njeni derivati široko su raširena u biljnom svijetu. Naziv je dobila po biljnim vrstama iz roda *Cinnamomum* iz porodice Lauraceae u kojima je prisutna u značajnim količinama (1). Najvažniji predstavnik roda je *Cinnamomum verum*, J. Presl. (slika 2.). Nekoliko vrsta iz roda *Cinnamomum* uzgaja se komercijalno za dobivanje začina cimeta (pulvis dobiven iz kore, slika 3.).

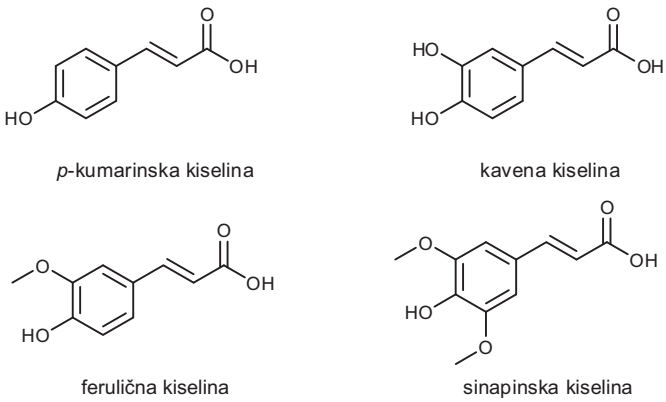


Slika 1. Cimetna kiselina

Cimetna kiselina pripada skupini biljnih hormona auksina koji reguliraju rast i diferencijaciju stanica. Biosinteza cimetne kiseline polazi iz aminokiseline L-fenilalanina, a njenom hidroksilacijom nastaju njeni fenolni derivati: *p*-kumarinska, kavena, ferulična i sinapinska kiselina (slika 4.) (4).

Slika 2. *Cinnamomum verum* (ili *Cinnamomum zeylanicum*, J. Presl., Lauraceae) (2)

Slika 3. Cimet, začin dobiven od kore *Cinnamomum* vrsta (3)



Slika 4. Fenolni derivati cimetne kiseline

Cimetna kiselina je ključni intermedijer u biosintezi važnih spojeva kao što su derivati šikimata, fenilpropanoida, stirena, stilbena, kumarina, lignina, izoflavonoida, flavonoida i antocijana, a prisutna je u različitim eteričnim uljima, gumama i balzamima kao slobodna kiselina ili esterificirana (1, 4). Šikiminska kiselina je prekursor u biosintezi mnogih alkaloida, aromatskih aminokiselina i derivata indola. Osim toga, cimetna kiselina je sirovina za sintezu komercijalno važnih spojeva, prije svega njenih estera, koji se koriste u prehrambenoj, farmaceutskoj i kozmetičkoj industriji.

Fizikalno-kemijska svojstva cimetne kiseline

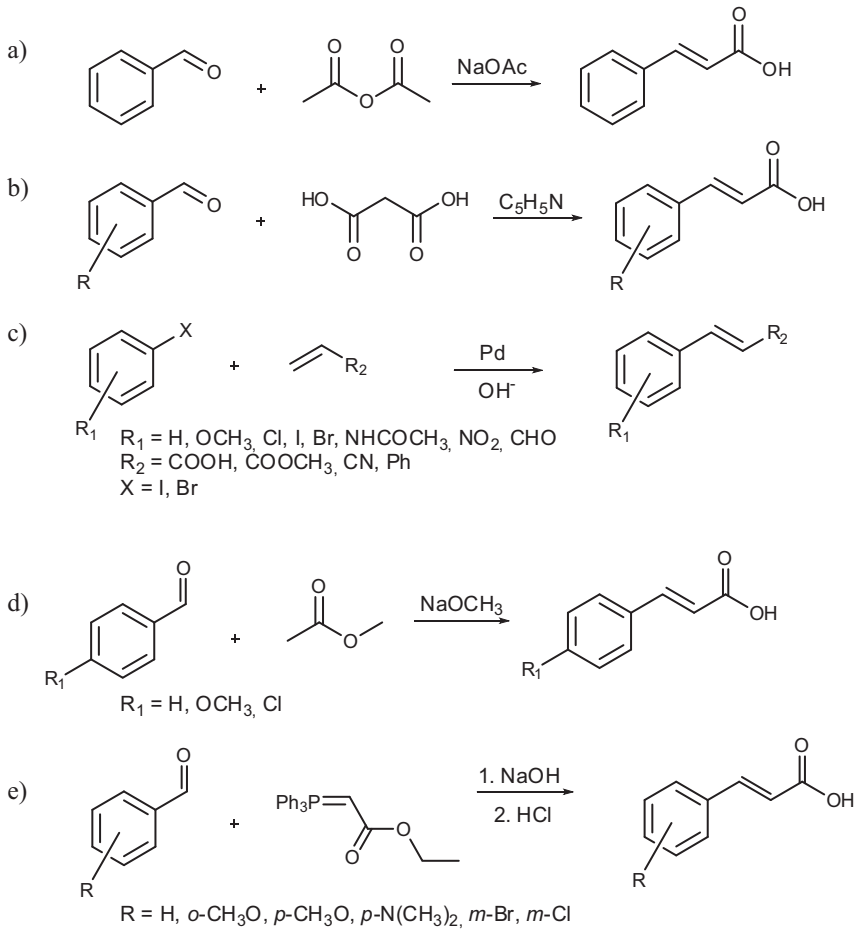
Cimetna kiselina je nezasićena aromatska kiselina. Može postojati kao *cis* i *trans* stereoizomer, a u prirodi je više zastupljen *trans* izomer. Bijela je kristalinična tvar, slabo topljiva u vodi, a dobro topljiva u mnogim organskim otapalima. Miriše po medu. Njena osnovna fizikalno-kemijska svojstva dana su u tablici 1. (5).

Tablica 1. Fizikalno-kemijska svojstva cimetne kiseline

Molekulska formula	$C_9H_8O_2$
Relativna molekulska masa	148,16
Kristalni sustav	monoklinski
Gustoća	1,2475 g cm^{-3}
Talište	133 °C
Vrelište	300 °C
Topljivost u vodi	500 mg L^{-1}
pK_a	4,44

Sinteza cimetne kiseline

Godišnja proizvodnja i potrošnja cimetne kiseline i njenih derivata kreće se od 1–10 tisuća tona (6). U shemi 1. prikazane su najvažnije metode njihove sinteze koje koriste: a) Perkinovu reakciju (6, 7), b) Knoevenagel-Hansovu kondenzaciju (8), c) Heckovu sintezu (9), d) Claisen-Schmidtovu kondenzaciju (10) ili e) Wittigovu reakciju (11).



Shema 1. Najvažnije metode sinteze cimetne kiseline i njenih derivata

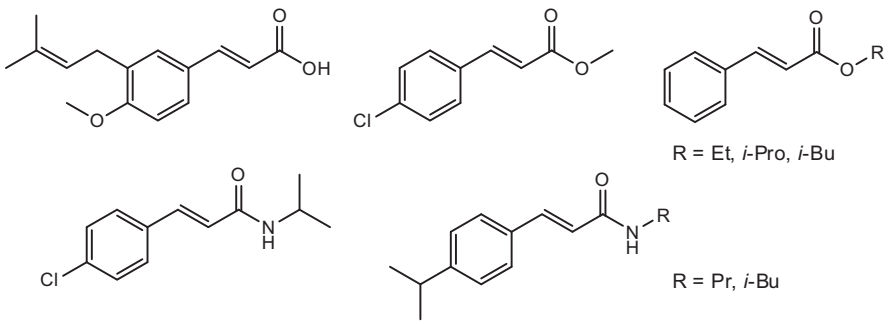
Upotreba cimetne kiseline i njenih derivata

Kao što je već rečeno, derivati cimetne kiseline koriste se u velikim količinama u prehrambenoj, kozmetičkoj i farmaceutskoj industriji. Prvenstveno se koriste kao dodatak pekarskim proizvodima, bezalkoholnim napitcima,

žvakaćim gumama, zubnim pastama i sredstvima za privlačenje insekata. Nadalje, koriste se u proizvodnji sapuna, parfema, šampona, dekorativnih kozmetičkih proizvoda te pripravaka za zaštitu od sunca i vjetra (6). Osim toga, cimetna kiselina važna je sirovina za sintezu L-fenilalanina iz kojeg se proizvodi zaslađivač aspartam.

Biološko djelovanje cimetne kiseline i njenih derivata

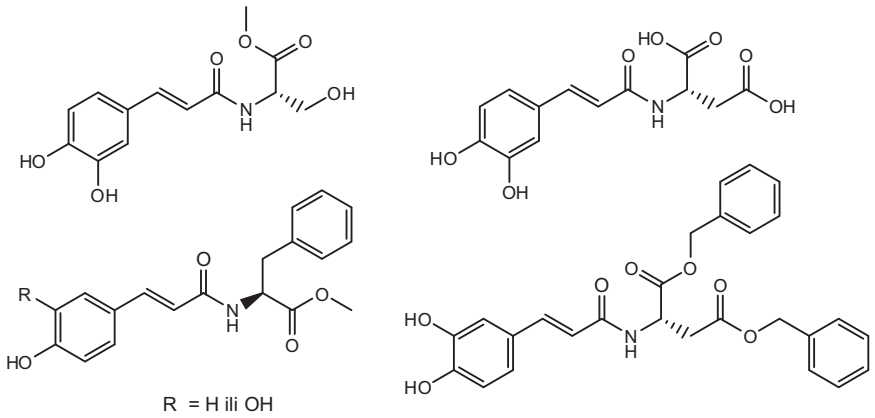
Prirodni i sintetski derivati cimetne kiseline imaju raznoliko farmakološko djelovanje. Postoje bogati literaturni izvori o njihovom antimikrobnom, antituberkulotskom, antioksidativnom, antimikotskom, antidijabetičkom, hepatoprotektivnom, antidepresivnom, hipolipemičkom, antimalarijskom, antivirusnom, anksiolitičkom, protuupalnom i citostatskom djelovanju. Publikacije autora Sharme i Lone i njihovih suradnika daju pregled bioloških djelovanja cimetne kiseline i njenih derivata (6, 12). Metilni ester kavene kiseline ima antimikrobno djelovanje te antitumorsko djelovanje na sarkom (13). Esterski i amidni derivati cimetne kiseline pokazali su značajno antimikrobno (14), a fenilakrilamidni derivati antituberkulotsko djelovanje (15). O antimikrobnom djelovanju derivata cimetne kiseline napisan je i pregledni članak s velikim brojem literaturnih citata (1). Nadalje, objavljeno je antioksidativno djelovanje feniletilnih estera fenolnih derivata cimetne kiseline (16, 17). Spojevi s najjače izraženim djelovanjem na rast i razvoj gljivica prikazani su na slici 5. (18, 19).



Slika 5. Derivati cimetne kiseline s antimikotskim djelovanjem

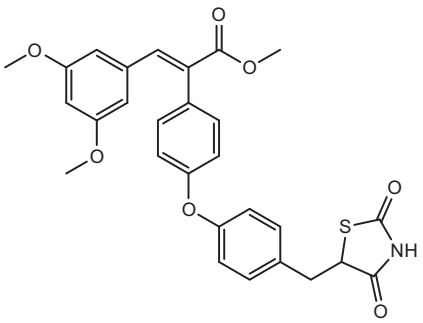
Fenolni derivati cimetne kiseline opisani su kao učinkoviti hepatoprotektivi (20, 21), dok halogenirani derivati djeluju kao depresori središnjeg živčanog sustava (22). Kim i suradnici opisali su hipolipemički učinak derivata kavene kiseline amidirane s aminokiselinama serinom, odnosno asparaginskom kiselinom (23), dok dibenzilester L-asparaginske kiseline amidiran s

kavenom kiselinom i metilni ester L-fenilalanina amidiran s *p*-kumarinskom kiselinom ili kavenom kiselinom inhibiraju pohranu kolesterola i tako djeluju kao antiaterosklerotici (slika 6.) (24, 25).



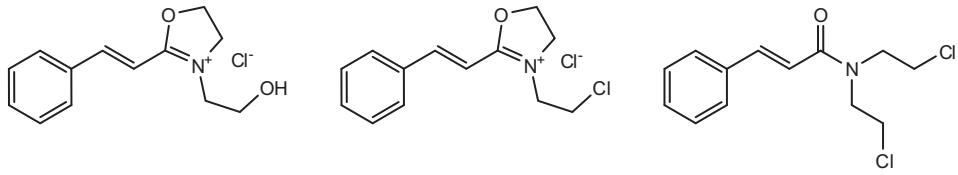
Slika 6. Amidi hidroksicimetne kiseline s aminokiselinama – antihiperlipemici

Derivati ferulične kiseline potiču izlučivanje inzulina (26, 27), a tiazolidinski derivat prikazan na slici 7. vrlo je učinkovit u snižavanju povišene koncentracije glukoze u krvi (28). Nadalje, neki prirodni i sintetski derivati cimetne kiseline potencijalni su protuupalni agensi (29, 30).



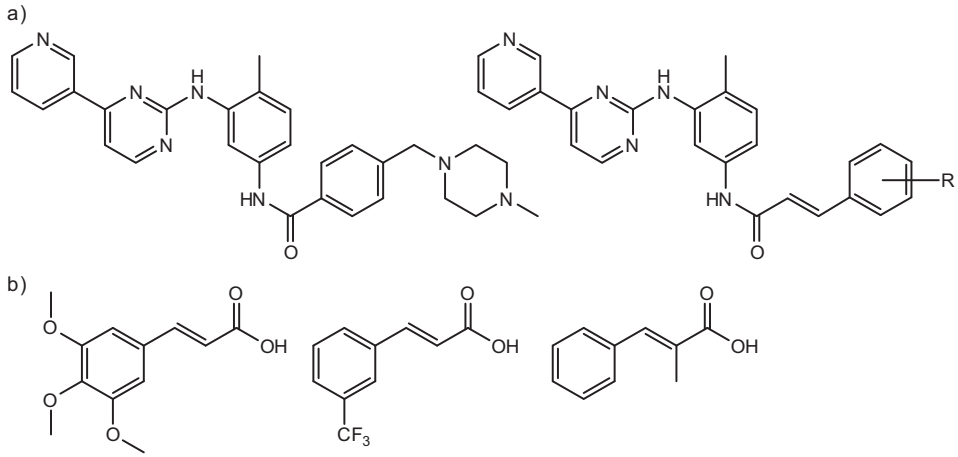
Slika 7. Tiazolidinski derivat cimetne kiseline s antihiperglikemijskim djelovanjem

U literaturi je opisano i virustatsko djelovanje derivata cimetne kiseline (31). Osim toga, derivati s oksazolinijem i dušikovim iperitom pokazali su citotoksični učinak i mogu poslužiti kao vodeći spojevi za razvoj citostatika (slika 8.) (32).



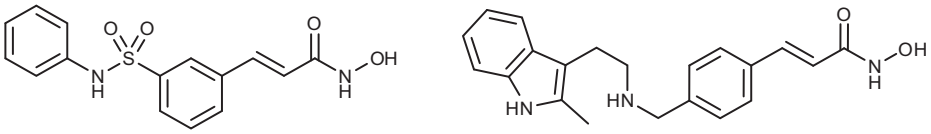
Slika 8. Derivati cimetne kiseline s citotoksičnim učinkom

Sama cimetna kiselina i njeni prirodni fenolni derivati imaju vrlo izraženo antiproliferativno djelovanje. Na slici 9. prikazane su strukture najaktivnijih spojeva koji su sintetizirani po uzoru na njih. Mehanizam antitumorskog djelovanja može uključivati izoprenilaciju proteina, inhibiciju tirozin-kinaze, regulaciju ekspresije metaloproteinaza, indukciju apoptoze, Michaelovu adiciju ili inhibiciju aldo-keto reduktaza (4, 7, 33–35).



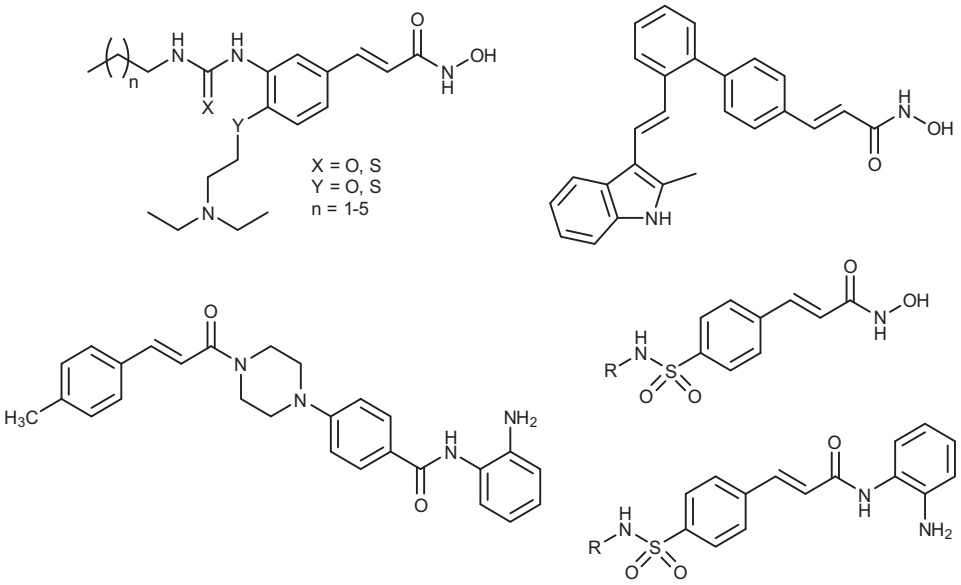
Slika 9. Derivati cimetne kiseline s antitumorskim djelovanjem:
a) inhibitori tirozin-kinaze, b) inhibitori AKR1C3

Derivati cimetne kiseline s hidroksamskom skupinom inhibitori su histonske deacetilaze (HDAC) (4). Najvažniji među njima su belinostat i panobinostat (slika 10.), koji su prije nekoliko godina odobreni za liječenje refraktornog perifernog limfoma T-stanica, odnosno za liječenje multiplog mijeloma (36, 37). Vežu se na aktivno mjesto enzima i keliraju cinkove ione, što dovodi do povećane koncentracije acetiliranih histona i drugih proteina potrebnih za ekspresiju gena nužnih za diferencijaciju stanice (38).



Slika 10. Strukturne formule odobrenih inhibitora HDAC: belinostata i panobinostata

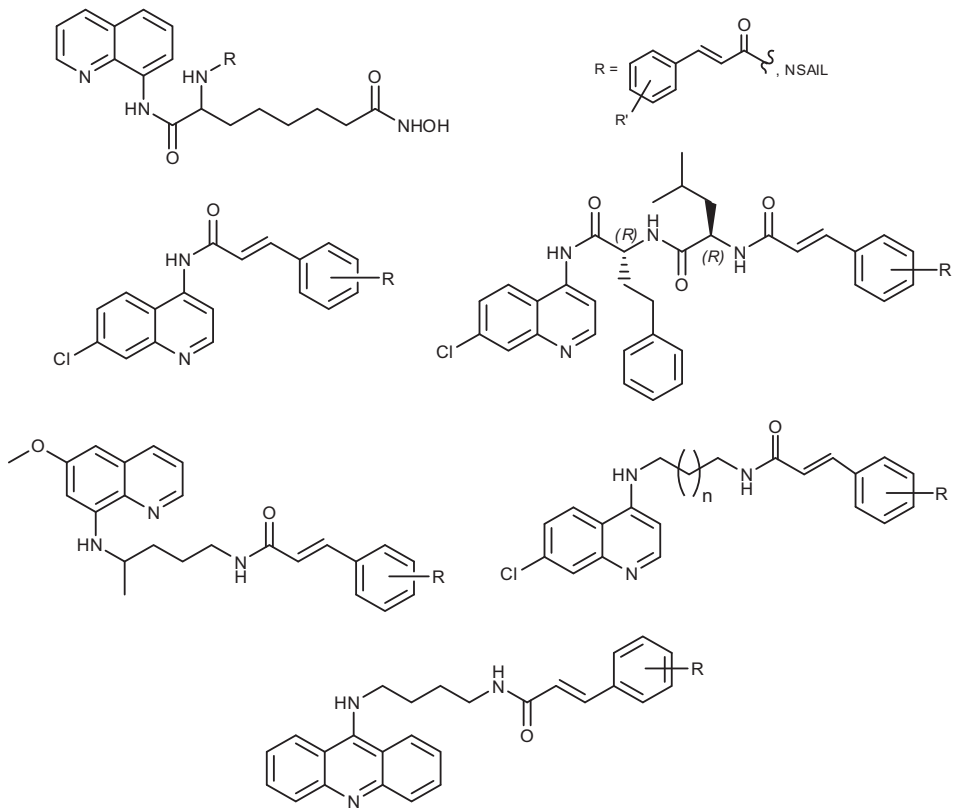
Razvoj novih derivata cimetne kiseline kao potencijalnih inhibitora HDAC vrlo je aktualno područje u farmaceutskoj kemiji. U posljednjih pet godina objavljeno je mnogo radova u kojima je evaluirano citostatsko djelovanje različitih derivata cimetne kiseline kao potencijalnih inhibitora HDAC, a neki od njih su karbamidni i tiokarbamidni derivati cinamohidroksamske kiseline (39), indolil-supstituirane 4-fenilcinamohidroksamske kiseline (40), piperazinski derivati kidamida (41), sulfonamidni derivati cinamohidroksamske kiseline i amidi cimetne kiseline (slika 11.) (42). Mnogi od njih pokazali su slično ili jače antiproliferativno djelovanje od vorinostata, prvog registriranog inhibitora HDAC (43).



Slika 11. Strukturne formule inhibitora HDAC

Inhibitori HDAC-a imaju i antimalarijsko djelovanje (44, 45). Među njima su hibridi aminosuberinske kiseline, 8-aminokinolina i derivata cimetne

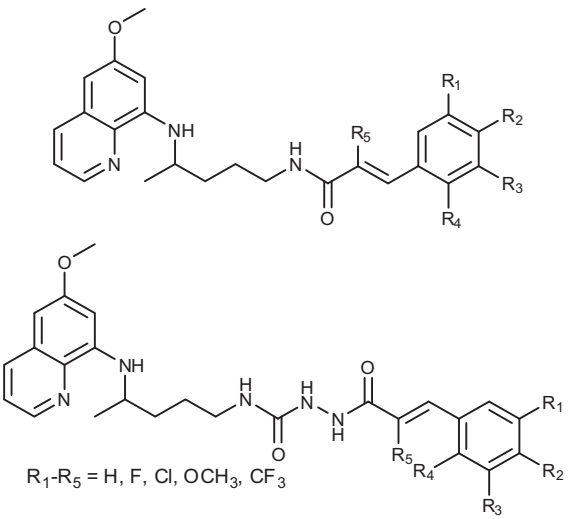
kiseline ili nesteroidnog antiinflamatornog lijeka (45) te hibridi cimetne kiseline i 4-aminokinolina ili primakina povezani izravno, dipeptidnom ili aminoalkilnom poveznicom (slika 12.) (46–49).



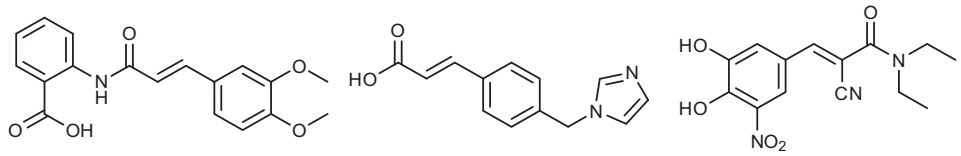
Slika 12. Konjugati aminokinolina i derivata cimetne kiseline s antimalarijskim djelovanjem

Pavić i suradnici objavili su sintezu serije konjugata primakina i cimetne kiseline i njenih derivata povezanih amidnom ili acilsemikarbazidnom skupinom (slika 13.) (50). Spojevi su testirani na antiproliferativno, antivirusno, antioksidativno te antimalarijsko i antituberkulotsko djelovanje (50–53).

Osim u ranije navedenom panobinostatu i belinostatu motiv cimetne kiseline pojavljuje se u nekoliko drugih lijekova iz različitih terapijskih skupina: u tranilastu, ozagrelu te entakaponu (slika 14., tablica 2.).



Slika 13. Konjugati primakina i cimetne kiseline povezani amidnom vezom ili preko acilsemikarbazidne skupine



Slika 14. Registrirani lijekovi koji sadrže motiv cimetne kiseline

Tablica 2. Registrirani lijekovi – derivati cimetne kiseline

Međunarodni nezaštićeni naziv	Farmakološko djelovanje	Zaštićeni naziv	Država u kojoj je registriran
panobinostat	citostatik	Farydak	EU
belinostat	citostatik	Beleodaq	SAD
tranilast	antialergik	Rizaben	Japan, Južna Koreja
ozagrel	antitrombotik	Donenan, Ozagrel, Athrombone	Japan
entakapon	antiparkinsonik	Comtan, Stalevo	SAD, EU, Hrvatska

Cinnamic acid and cinnamic acid derivatives

K. Pavić, B. Zorc

Abstract

Cinnamic acid (3-phenylpropenoic or phenylacrylic acid) and its derivatives occur naturally in a number of plants. They are precursors in the biosynthetic pathways of many alkaloids, aromatic amino acids, phenylpropanoids, styrenes, stilbenes, coumarins, lignins and flavonoids, and are present in various essential oils, gums and balsams. Cinnamic acid derivatives are used in large quantities in the food, cosmetic and pharmaceutical industries. In addition, they possess a variety of pharmacological activities: antimicrobial, antitubercular, antioxidative, antimicrobial, antimalarial, antiviral, antidiabetic, hepatoprotective, antidepressant, anxiolytic, hypolipemic, anti-inflammatory and cytostatic activities. Several drugs with cinnamic acid motifs are used in modern therapy (panobinostat, belinostat, cinanserin, tranilast, ozagrel and entacapone).

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