Ligandi I_1-Imidazolinskih receptora sa centralnim antihipertenzivnim dejstvom

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Kratak sadržaj

Antihipertenzivi sa centralnim dejstvom, poput klonidina, rilmenidina i moksonidina, ostvaruju svoj farmakološki efekat aktivacijom presinaptičkih α_2-adrenergičkih receptora (α_2-AR) i imidazolinskih receptora (IR) u *Rostral Ventrolateral Medulla* (RVLM), dok njihovo sporedno sedativno dejstvo nastaje usled aktivacije samo α_2-AR u *locus coeruleusu*-u. Imidazolinski receptori su na osnovu farmakološkog efekta podeljeni na I_1-IR, I_2-IR i I_3-IR podtip. Ustanovljeno je da selektivna aktivacija I_1-IR podtipa imidazolinih receptora dovodi do dozno zavisne centralne inhibicije simpatikusa i sniženja krvnog pritiska. Najnovija istraživanja ukazuju da je optimalana ravnoteža u aktivaciji i I_1-IR i α_2-adrenergičkih receptora neophodna za postizanje snažnog centralnog hipotenzivnog dejstva imidazolinskih liganada, uz minimalne sporedne efekte. Druga generacija antihipertenziva sa centralnim dejstvom, kao što su rilmenidin i moksonidin, pokazala je veću I_1-IR/α_2-AR selektivnost pa samim tim i manje neželjenih efekata nego klonidin koji u najvećoj meri aktivira α_2-AR. Pored centralnog hipotenzivnog dejstva, selektivniji I_1-IR/α_2-AR ligandi dovode do antiaritmičkog efekta, i podstiču pojačanu renalnu cirkulaciju, diurezu i natriurezu, kao i inhibiciju aktivnosti renalnog simpatikusa. U ovom preglednom radu prikazana je analiza strukturnih karakteristika i farmakofora I_1-IR liganada, kao i najnovije eksperimentalne i teorijske studije koje su najviše doprinele napretku u istraživanju I_1-imidazolinskih receptora i selektivnijih I_1-IR liganada.

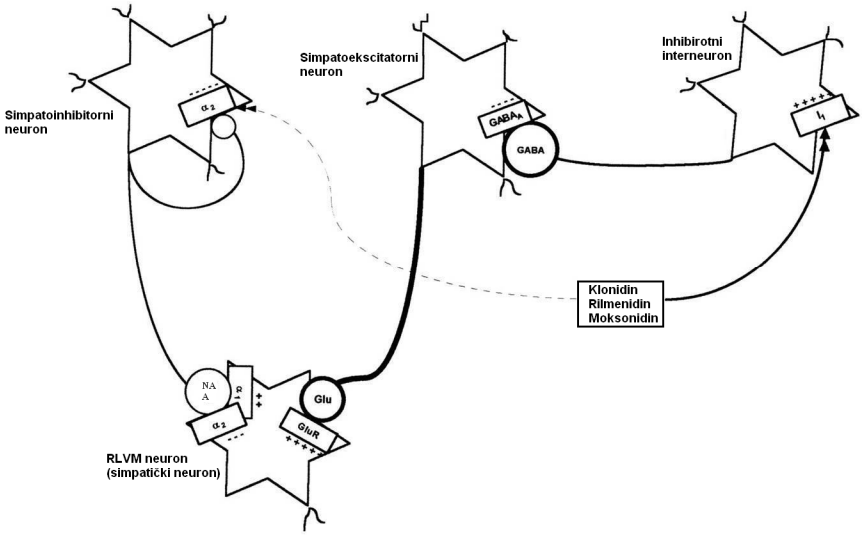
Ključne reči: I_1-imidazolinski receptori, alfa$_2$-adrenergički receptori, *QSAR*, farmakofore, moksonidin, rilmenidin, klonidin, hipertenzija, centralni antihipertenzivi.

Uvod

Pre više od dve decenije je ustanovljeno da klonidin i njemu srodni centralni antihipertenzivi ostvaruju svoje farmakološko dejstvo aktivacijom ne samo α_2-adrenergičkih receptora (α_2-AR) nego i aktivacijom imidazolinskih receptora (IR) [1-3].

Imidazolinski receptori se farmakološki razlikuju od α_2-AR po tome što se ne mogu aktivirati kateholaminima [4]. Veliki broj studija se bavio interakcijama i međusobnim uticajem I-IR i α_2-AR [3, 5-8] i ukazao da male promene u strukturi imidazolinskih liganada mogu prouzrokovati značajnu promenu u afinitetu i selektivnosti za I-IR i α_2-AR [9]. Imidazolinski receptori su podeljeni na I_1-IR, I_2-IR i I_3-IR podtip [10, 11], dok su alfa$_2$-adrenergički receptori klasifikovani na α_{2A}-AR, α_{2B}-AR i α_{2C}-AR podtip [3, 5-8]. Selektivna aktivacija I_1-IR podtipa imidazolinih receptora dovodi do dozno zavisne centralne inhibicije simpatikusa i sniženja krvnog pritiska, dok stimulacija α_{2A}-AR podtipa prouzrokuje hipotenziju, sedaciju i analgeziju [11-15].

Centralni hipotenzivni efekat klonidinu, rilmenidinu i moksinidinu-srodnih jedinjenja nastaje kao rezultat aktivacije i α_{2A}-adrenergičkih receptora (α_{2A}-AR) i I_1-imidazolinskih receptora (IR) u *Rostral Ventrolateral Medulla* (RVLM), dok njihovo sporedno sedativno dejstvo nastaje aktiviranjem α_{2A}-AR u *Locus Coeruleus*-u (Slika 1) [1, 3-8, 12-15].



Slika 1. Inhibicija simpatikusa u RVLM pomoću imidazolinskih liganada.
Figure 1. Inhibition of sympatic RVLM by imidazoline receptor ligands.

Detaljne farmakološke studije interakcija i međusobnog uticaja I-IR i α_2-AR su ukazale da je optimalana ravnoteža u aktivaciji I_1-IR i α_{2A}-AR važna za postizanje snažnog centralnog hipotenzivnog efekta I_1-imidazolinskih liganada [19, 20].

Druga generacija antihipertenziva sa centralnim dejstvom, kao na primer rilmenidin i moksonidin, pokazala je veću I_1-IR/ α_2-AR selektivnost pa samim tim i manje sporednih efekata (sedacije, bradikardije i suvoće usta) [16, 17], nego niskoselektivni antihipertenzivi prve generacije (klonidin) [5, 14, 18]. Pored centralnog hipotenzivnog dejstva, selektivniji I_1-IR/α_2-AR ligandi dovode do antiaritmičkog efekta, i podstiču pojačanu renalnu cirkulaciju, diurezu i natriurezu, kao i inhibiciju aktivnosti renalnog simpatikusa [37, 38], što sveukupno ima povoljan terapijski efekat. Novosintetisani visokoselektivni I_1-IR ligandi, poput S23515 [21], S23757 [21], LNP509 [22], LNP 906 [23] i LNP911 [24], su veoma korisni modeli za: ispitivanje I_1-imidazolinskog receptorskog sistema, istraživanje farmakoloških efekata baziranih samo na aktivaciji I_1-IR, eksperimentalno određivanje 3D-strukture I_1-IR, izvođenje detaljnijih teorijskih studija u cilju definisanja osnovnih farmakofora I_1-IR liganada i razvoj lekova sa manje izraženim sporednim efektima.

In vitro određivanje afiniteta vezivanja liganda za I_1-IR vršeno je metodom kompetitivne inhibicije vezivanja radioliganada, kao što su [^{3}H]-klonidin, [^{125}I] *p*-jodoklonidin ([^{125}I] PIC) [^{125}I] LNP 911, na plazma membranama ćelija [25-35]. Stimulacijom I_1-imidazolinskih receptora vrši se aktivacija signalnog puta fosfatidilholin-zavisne fosfolipaze C (*Phosphatidylcholine-sensitive Phospholipase C* (PC-PLC)) [31, 36, 37] i inhibicija aktivacije adenilciklaze [32]. Pored aktivacije ova dva glavna signalna puta, agonisti I_1-IR učestvuju i u mnogim drugim procesima u ćeliji izazivajući odgovarajuće promene u aktivnosti ćelije [21, 38-41].

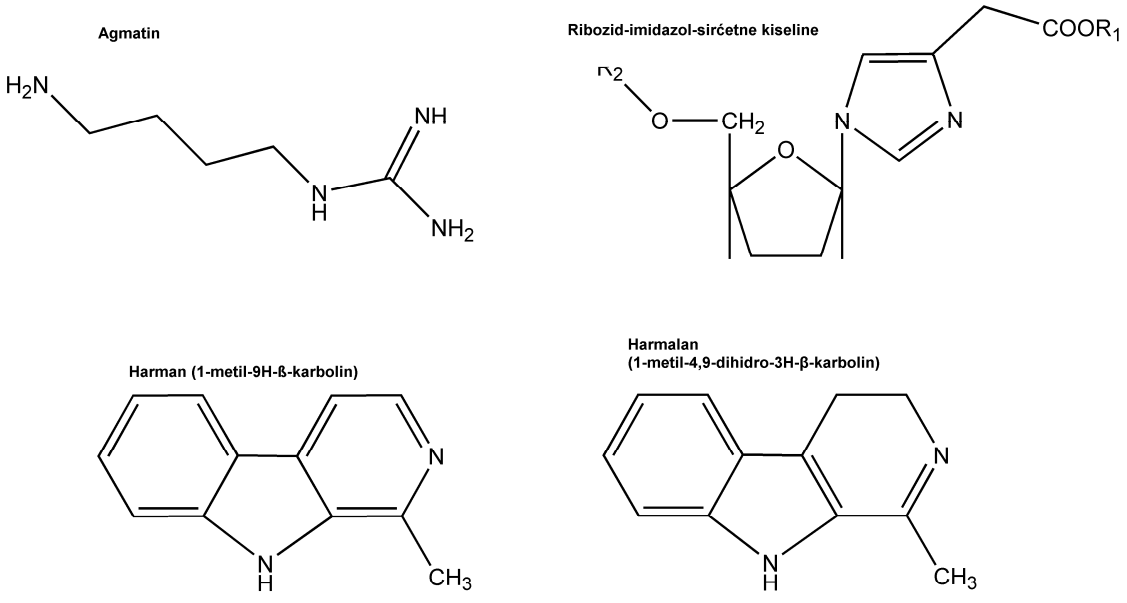
Do sada nije utvrđena 3D-struktura I_1-IR proteina, ali je uspešno kloniran *Imidazoline Receptor Antisera-Selected* (IRAS) gen koji je odgovoran za sintezu I_1-IR [42]. Prenos IRAS cDNA u PC 12 i *Chinese Hamster Ovary* (CHO) ćelije je doveo do ekspresije I_1-IR [42, 43]. Humani IRAS protein, nazvan *nischarin*, uspešno je identifikovan i kloniran [42, 44-46]. Pošto je ekspresija *nischarin*-a u ćeliji od ključnog značaja za očuvanje aktivnosti I_1-IR [46-49], pretpostavlja se da je *nischarin* zapravo I_1-IR [46-51]. Precizne *docking* studije liganada na I_1-IR nisu moguće zbog toga što 3D-struktura I_1-IR proteina nije eksperimentalno određena, pa su analize kvantitativnih odnosa strukture i dejstva (*Quantitative Structure Activity Relationship*, *QSAR*)) I_1-IR liganada optimalna metoda u razvoju novih I_1-IR liganada.

U ovoj preglednoj studiji analizirane su strukturne karakteristike liganada neophodnih za selektivnu aktivaciju I_1-imidazolinskih receptora.

Ligandi I_1-Imidazolinskih receptora

Prirodni endogeni ligandi imidazolinskih receptora poput agmatina [52] i ribozid-imidazol-sirćetne kiseline (*imidazol-4-acetic acid riboside* (IAA-RP)) [53, 54], harmana [55, 56] i harmalana [57] (Slika 2) pokazuju dobru selektivnost ka IR, pa stoga

predstavljaju dobra polazna jedinjenja u razvoju novih aktivnijih i selektivnijih imidazolinskih liganada.



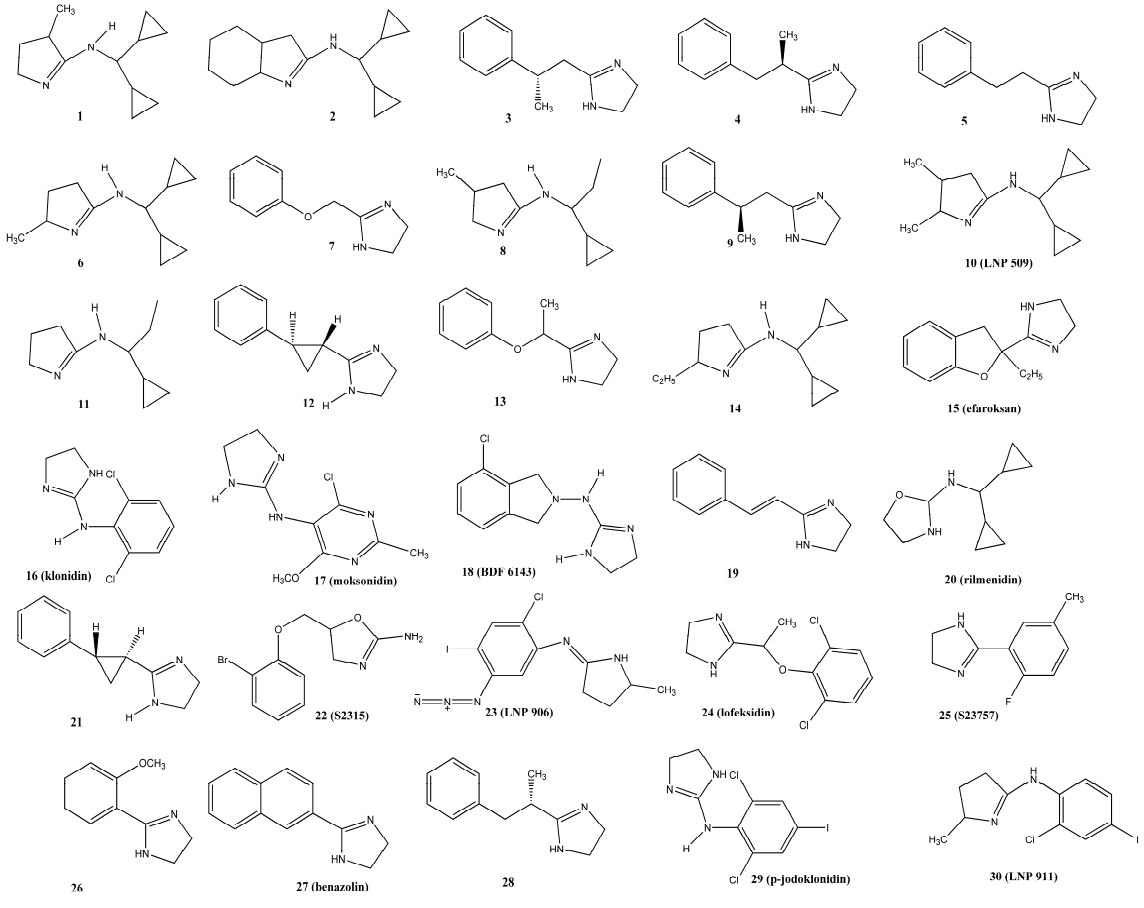
Slika 2. Hemijske strukture najznačajnijih endogenih I-IR liganada.
Figure 2. Chemical structures of endogenic I-IR ligands.

Agonisti I_1-imidazolinskih receptora, poput moksonidina, rilmenidina i benazolina, potstiču aktivaciju PC-PLC [31, 36, 37] i inhibiraju adenilat-ciklazu u ćeliji [32]. Parcijalni I_1-IR agonisti, kao na primer efaroksan i BDF-6143, blokiraju aktivaciju PC-PLC signalnog puta i istovremeno inhibiraju adenilat-ciklazu [31, 32, 36]. Antagonisti I_1-IR, poput S23757 [21], LNP 906 [23] i LNP911 [24], blokiraju aktivaciju PC-PLC signalnog puta i istovremeno ne inhibiraju adenilat-ciklazu. Ovi rezultati su ukazali na nove aspekte ispitivanja uloge I_1-IR u fiziološkim aktivnostima ćelije.

Različiti farmakološki efekti I_1-IR agonista, I_1-IR antagonista i I_1-IR parcijalnih agonista posledica su različitih mehanizama interakcije liganada sa aktivnim mestima receptora. Radi boljeg razumevanja agonističkog, antagonističkog i parcijalnog agonističkog mehanizma dejstva potrebno je formirati 3D-strukturu farmakofore odgovorne za I_1-IR agonističku aktivnost i 3D- farmakofore specifične za I_1-IR antagonističku aktivnost. Na ovaj način bi se razjasnile i definisale strukturne karakteristike koje uslovljavaju različite tipove interakcije sa receptorom. Pored toga,

potrebno je razviti odgovarajuće *QSAR* modele za predviđanje aktivnosti I_1-IR agonista i I_1-IR antagonista.

Značajne razlike u rezultatima *in vitro* određivanja afiniteta vezivanja za I_1-IR, koje su izvedene pomoću različitih radioliganada ([^{125}I] PIC) i [^{125}I] LNP 911) i na različitim ćelijama (PC 12 i humani trombociti) [24, 32, 34, 58], ukazuju na otežano poređenje rezultata različitih *in vitro* studija, kao i na mogućnost formiranja više specifičnih aktivnih centara na I_1-IR [59]. Do danas je sintetisan i ispitan veliki broj različitih hemijskih grupa I_1-IR liganada kao što su derivati gvanidina, 2-aminoimidazolina, 2-aminooksazolina, aminopirolina, 2-arilimidazolini, 2-fenilimidazolini, 2-imidazolini, endogeni amini i karbolini [21-24, 32, 33, 60-62] (Slika 3 i Tabela I).



Slika 3. Hemijske strukture I_1-IR liganada.
Figure 3. Chemical structures of I_1-IR ligands.

Tabela I Eksperimentalno određeni afiniteti I_1-IR liganada ka I_1-IR [21-24, 32, 33, 60], I_2-IR [21-24, 32, 33, 60, 75] i α_2-AR [21, 22, 24, 32, 33, 58, 60]. (p*K*i = log(1/*Ki*)).

Table I Experimentaly determined affinities of I_1-IR liganads for I_1-IR [21-24, 32, 33, 60], I_2-IR [21-24, 32, 33, 60, 75] and α_2-AR [21, 22, 24, 32, 33, 58, 60]. (p*K*i = log(1/*Ki*)).

Jedinjenje	I_1-IR: upotrebljen radioligand, membrana/ćelija	p*Ki* (I_1-IR)	p*Ki* (I_2-IR)	p*Ki* (α_2-AR)
1	[^{3}H] klonidin, *chromaffin* ćelije ovce	4.00	<5]	<5
2	[^{3}H] klonidin, *chromaffin* ćelije ovce	4.00	<5	<5
3	[^{125}I] PIC, PC 12	5.14	7.00	5.80
4	[^{125}I] PIC, PC 12	5.20	4.90	5.40
5	[^{125}I] PIC, PC 12	5.43	8.60	5.70
6	[^{3}H] klonidin, *chromaffin* ćelije ovce	5.80	<5	<5
7	[^{125}I] PIC, PC 12	6.15	9.05]	7.28
8	[^{3}H] klonidin, *chromaffin* ćelije ovce	6.19	<5	<5
9	[^{125}I] PIC, PC 12	6.23	5.60	5.90
10-LNP 509	[^{3}H] klonidin, *chromaffin* ćelije ovce	6.27	<5	<5
11	[^{3}H] klonidin, *chromaffin* ćelije ovce	6.29	<5	<5
12	[^{125}I] PIC, PC 12	6.46	8.22	6.92
13	[^{125}I] PIC, PC 12	6.51	5.75	7.01
14	[^{3}H] klonidin, *chromaffin* ćelije ovce	6.77	<5]	<5
15-Efaroksan	[^{125}I] PIC, PC 12	6.84	-	8.01 α_{2A}-AR, 8.00 α_{2B}-AR, 8.01 α_{2C}-AR
16-Klonidin	[^{125}I] PIC, PC 12	6.90	6.02	8.06 α_{2A}-AR, 7.50 α_{2B}-AR, 8.03 α_{2C}-AR
17-Moksonidin	[^{125}I] PIC, PC 12	7.47	<5	5.44 α_{2A}-AR, 5.59 α_{2B}-AR, 5.03 α_{2C}-AR
18-BDF 6143	[^{125}I] PIC, PC 12	7.55	-	8.55 α_{2A}-AR, 8.31 α_{2B}-AR, 8.96 α_{2C}-AR
19	[^{125}I] PIC, PC 12	7.72	8.72	4.85
20-Rilmenidin	[^{125}I] PIC, PC 12	7.90	<5	7.44 α_{2A}-AR, 7.37 α_{2B}-AR, 7.90 α_{2C}-AR
21	[^{125}I] PIC, PC 12	7.93	6.91	6.62
22-S23515	[^{3}H] klonidin, plazma membrana *chromaffin* ćelija	8.19	<4	6.39
23-LNP 906	[^{125}I] PIC, PC 12	8.22]	3.88	5.65 α_{2A}-AR, 5.43 α_{2B}-AR, 5.08 α_{2C}-AR

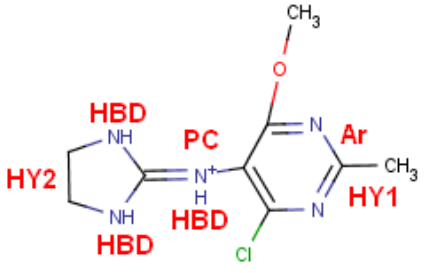
Jedinjenje	I_1-IR: upotrebljen radioligand, membrana/ćelija	*pKi* (I_1-IR)	*pKi* (I_2-IR)	*pKi* (α_2-AR)
24-Lofeksidin	[^{125}I] PIC, PC 12	8.25	-	-
25-S23757	[^{3}H] klonidin, plazma membrana *chromaffin* ćelija	8.28	<4	8.21
26	[^{3}H] klonidin, plazma membrana *chromaffin* ćelija	8.53	5	<5
27-Benazolin	[^{125}I] PIC, PC 12	8.89	9.07	5.45 α_{2A}-AR
28	[^{125}I] PIC, PC 12	8.97	6.84	5.30
29-*p*-Jodoklonidin (PIC)	[^{125}I] PIC, PC 12	9.10	<5	8.66 α_{2A}-AR, 8.13 α_{2B}-AR, 9.10 α_{2C}-AR
30-LNP 911	[^{125}I] PIC, PC 12	9.75	4.79	<4 α_{2A}-AR

Klonidin (Slika 3, jedinjenje **16**) pokazuje veći afinitet ka I_1-IR i α_2-AR, nego prema I_2-IR (Tabela I), dok *p*-jodoklonidin (Slika 3, jedinjenje **29**) poseduje veći afinitet i selektivnost ka I_1-IR u odnosu na klonidin, ali je zadržao i sposobnost aktivacije α_2-AR (Tabela I). Daljim modifikacijama molekula klonidina sintetisani su moksonidin i rilmenidin (Slika 3, jedinjenja **17** i **20**) kao centralni antihipertenzivi druge generacije koji su ispoljili snažan afinitet ka I_1-IR i visoku selektivnost ka I_1-IR u odnosu na I_2-IR and α_2-AR (Tabela 1). Izosterna zamena oksazolidina pirolinskim prstenom u molekulu rilmenidina (Slika 3, jedinjenja **1**, **2**, **6**, **8**, **10**, **11** i **14**) dovela je do značajnog pada afiniteta ka α_2-AR, dok je afinitet ka I_1-IR samo neznatno oslabio (Tabela I). Najnovija istraživanja su potvrdila da benazolin i srodna jedinjenja (Slika 3, jedinjenja **26** i **27**) poseduju snažan afinitet ka I_1-IR i I_2-IR, sa visokom selektivnošću u odnosu na α-AR [32, 60]. Ove studije su ukazale da I_1-IR pokazuju snažan afinitet ka 2-fenil-imidazolinima sa metil ili metoksi grupom na položaju 2' ili 3' (Slika 3, jedinjenja **26**) [60]. Strukturnim modifikacijama feniletilen-imidazolinskih derivata (Slika 3, jedinjenje **5**) došlo je do značajnog porasta selektivnosti za I_1-IR u odnosu na I_2-IR [33] (Tabela I). Snažniji I_1-IR afinitet i veća I_1-IR/α_2-AR i I_1/I_2-IR selektivnost jednog u odnosu na drugi enantiomer (Slika 3, jedinjenja **4** i **28**; **12** i **21**) ukazuje na stereospecifičnost interakcije sa aktivnim centrima I_1-IR, I_2-IR i α2-AR [33].

Derivati 2-aminoimidazolina su nastali povezivanjem strukture agmatina i imidazolinskog prstena. Ovim inkorporiranjem gvanidinske strukture u imidazolinski prsten došlo je do značajnog pojačanja afiniteta ka I_1-IR [62].

U cilju razvoja novih I_1-IR liganda pristupilo se izvođenju teorijskih ispitivanja strukturnih karakteristika I_1-IR liganada, *2D/3D-QSAR* (*dvodimenzionalne/trodimenzionalne-QSAR*) studijama i analizi 3D-strukture farmakofore I_1-IR liganada [61, 63-77]. *2D-QSAR* studije I_1-IR liganada su ukazale da porast lipofilnosti ($logD_{pH\ 7.4}$), molarne refractivnosti i dipolnog momenta, zajedno sa

sniženjem naelektrisanja na N-atomu u heterociklusu I_1-IR liganada, dovodi do snažnijeg afiniteta ka I_1-IR [63, 64], dok su lipofilnost (ClogP) i HOMO (*Highest Ocupied Molecular Orbital*) energija I_1-IR liganada važni parametri I_1-IR/α_2-AR selektivnosti [63]. Primenom *3D-QSAR* metoda odabrane su kombinacije elektrostatičkih i sternih deskriptora značajnih za afinitet na I_1-IR i kreirale farmakoforu I_1-IR liganada koja se sastoji iz dve grupe donora vodonične veze (*Hydrogen-Bond Donor Groups* (HBD)), dva hidrofobna regiona (HY1 i HY2), aromatičnog prstena (AR) i pozitivno naelektrisanog dela strukture (*Positively Charged moiety* (PC)) (Slika 4) [77].



Slika 4. Šematski prikaz farmakofore I_1-IR liganada na primeru moksonidina.
Figure 4. Pharmacophore of I_1-IR liganads, presented on moxonidine.

Zaključak

Istraživanje imidazolinskih receptora je veoma aktuelna tema za medicinske hemičare, farmakologe i biologe. Farmakološke studije I_1-imidazolinskih liganada su ukazale da je optimalna ravnoteža u aktivaciji I_1-IR i α_{2A}-AR neophodna za postizanje snažnog centralnog hipotenzivnog efekta. Smanjena incidenca sporednih neželjenih efekata, antiaritmička aktivnost, kao i povoljni metabolički i renalni efekti selektivnijih I_1-IR liganada ukazuju da njihove strukture predstavljaju dobru osnovu za razvoj novih, snažnijih i bezbednijih centralnih antihipertenziva.

Razvoj novih, snažnijih i selektivnijih I_1-IR liganada baziran je prvenstveno na *QSAR* studijama različitih grupa I_1-IR liganada zbog nepostojanja detaljnijih informacija o 3D-strukturi imidazolinskih receptora. Veoma različiti farmakološki efekti agonista, antagonista i parcijalnih agonista na I_1-IR ukazuju na potrebu razvoja 3D-strukture farmakofore odgovorne za I_1-IR agonističku aktivnost, 3D-farmakofore

specifične za I_1-IR antagonističku aktivnost, kao i *QSAR* modela za predviđanje agonističke i antagonističke aktivnosti na I_1-IR.

Zahvalnica

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I_1-Imidazoline Receptors Ligands as central antihypertensives

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Summary

The mechanism by which central antihypertensives, such as clonidine, rilmenidine, and moxonidine, lower blood pressure is activation of both α_2-adrenergic receptors (α_2-AR) and imidazoline receptors (IR) in *Rostral Ventrolateral Medulla* (RVLM), while sedation, as main side effect, is result of activation of only α_2-AR in *locus coeruleusu*. Three imidazoline receptor subtypes, I_1-IR, I_2-IR, and I_3-IR, have been characterized by extensive pharmacological studies. Selective activation of I_1-IR is responsible for dose dependant central inhibition of sympathicus and hypotensive effect of the I_1-IR ligands. Recent studies indicated that optimal balance between activation of both the I_1-IR and α_2-AR is crucial factor for strong central hypotensive effect. The second generation of centrally acting antihypertensives, such as rilmenidine and moxonidine, exert higher I_1-IR/α_2-AR selectivity and therefore induce fewer side effects than clonidine which mainly activate α_2-AR. Also, the selective I_1-IR ligands produce antiarrhythmic and diuretic effect too. In the present review we provide a brief update to the field of imidazoline research, highlighting some of the chemical diversity and progress made in the experimental and theoretical studies of the I_1-IR ligands.

Keywords: I_1-imidazoline receptors, alpha$_2$-adrenergic receptors, *QSAR*, pharmacophores, moxonidine, rilmenidine, clonidine, hypertension, centraly acting antihypertensives.