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AXE-DEZOKSIPEGANIN KOMPLEKSINI MOLEKULYAR MODELLASHTIRISHDA LIGAND ATOMLARIDAGI ZARYAD TAQSIMOTLARINING O‘RNI

Annotatsiya: *Maqolada dezoksipeganin (DOP) alkaloidi atomlari uchun AM1-BCC, Gasteiger va RESP2(0.5) zaryad taqsimotlarini qo‘llagan holda atsetilxolinesteraza-dezoksipeganin kompleksining molekulyar dinamik (MD) tadqiqotlari natijalari keltirildi. AMBER99SB-ILDN kuch maydonlari usulida MD modellashtirish ishlarida AM1-BCC va RESP2 zaryad taqsimotlarini qo‘llash orqali Gasteiger zaryad taqsimotiga nisbatan ustuvor natijalarga erishish mumkinligi aniqlandi.*

Kalit so‘zlar*: Atsetilxolinesteraza, dezoksipeganin, molekulyar dinamika, zaryad taqsimotlari, AM1-BCC, Gasteiger, RESP2(0.5).*

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Роль распределения заряда на атомах лиганда в молекулярном моделировании комплекса АХЭ-дезоксипеганин

Аннотация: *В статье представлены результаты молекулярно-динамических (МД) исследований комплекса ацетилхолинэстеразы и дезоксипеганина, с использованием распределений зарядов AM1-BCC, Gasteiger и RESP2(0.5) для атомов алкалоида дезоксипеганина (DOP). Было установлено, что лучшие результаты могут быть достигнуты по сравнению с распределением зарядов Гастайгера при использовании распределений зарядов AM1-BCC и RESP2 в МД-исследованиях с использованием метода силового поля AMBER99SB-ILDN.*
Ключевые слова*: Ацетилхолинэстераза, дезоксипеганин, молекулярная динамика, распределение заряда, AM1-BCC, Гастайгер, RESP2(0.5).*

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The role of charge distribution on ligand atoms in the molecular modeling of AChE-deoxypeganine complex

Abstract: *The paper presents the results of molecular dynamics (MD) studies of the acetylcholinesterase-deoxypeganine complex, using AM1-BCC, Gasteiger, and RESP2(0.5) charge distributions for the deoxypeganine (DOP) alkaloid atoms. It was found that superior results could be achieved compared to the Gasteiger charge distribution by using the AM1-BCC and RESP2 charge distributions in MD simulation studies with the AMBER99SB-ILDN force field method.*
Keywords*:*

Kirish

Klassik molekulyar dinamika usullariga asoslangan Gromacs [1], AMBER [2], NAMD [3], CHARMM [4] kabi kompyuter dasturlarida oqsil va ligand komplekslarining vaqt mobaynida harakatlarini fiziologik muhitda amalga oshirish va shu orqali oqsil-ligand kompleksining barqarorligini aniqlash mumkin. Ushbu MD modellashtirish (simulyatsiya) yordamida molekulyar doking natijasida topilgan, biologik faol bo‘lishi mumkin bo‘lgan ligand molekulalari skrining qilinadi [5]. Oqsil bilan kuchsiz bog‘langan ligand molekulalari simulyatsiya jarayonida oqsil faol markazidan chiqib ketishi mumkin. Ligand molekulalaridagi atomlar ketma-ketligi, fazoviy tuzilishi, atomlardagi zaryad taqsimotlari va boshqa

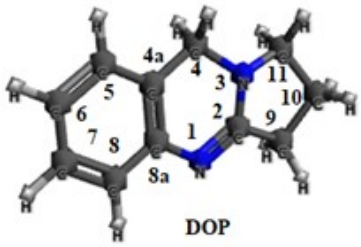
ko‘rsatkichlar (ligand topologiyasi) MD modellashtirish jarayonidagi asosiy omillardan biri hisoblanadi. Gromacs dasturidagi MD modellashtirishlar uchun ligandlar topologiyalari ACPYPE serverida [6,7] tayyorlanadi. Ushbu serverda dezoksipeganin (DOP) alkaloidining topologiyasi tayyorlanib, atsetilxolinesteraza –DOP kompleksi modellashtirildi.

Adabiyotlar tahlili

Ma’lumki, DOP antixolinesteraza faolligiga ega xinazolin alkaloidi hisoblanadi [8]. Ushbu faollikka ega birikmalar inson organizmida AXE fermentini ingibirlab, atsetilxolin neyromediyatori miqdorining oshishiga olib keladi va bir nechta kasalliklarni (Alsgeymer va b.) kasalliklarni davolashda qo‘llaniladi.

DOP O‘zbekistonda dastlab O‘zR FA O‘MKI xodimlari tomonidan Peganum harmala o‘simligidan ajratib olingan, keyin X.M. Shahidoyatov tomonidan sintez qilib olish yo‘li ishlab chiqilgan [9].

Xinazolin alkaloidlarining, shu jumladan DOPning AXE fermenti bilan ta’sirlashishi molekulyar darajada o‘rganilmagan. Ularni molekulyar doking va molekulyar dinamika (MD) usullari bilan o‘rganish orqali ular asosida yangi avlod antixolinesteraza preparatlarini yaratish imkoniyatini yuzaga kelishi mumkin. Shu sababli ushbu ishda DOP molekulasining AXE fermenti bilan ta’sirlashishi hamda AXE-DOP kompleksining MD simulyatsiyasi amalga oshirildi.



1-rasm. DOP molekulasi fazoviy tuzilishi va undagi atomlar raqamlanishi

Tadqiqot metodologiyasi

DOP alkaloidining uch o‘lchamli geometriyasi Avogadro [10] dasturida hosil qilindi. Atsetilxolinesteraza (AXE) oqsili sifatida 1DX6 fermenti oqsillar bazasidan (PDB [11], www.rcsb.org) yuklab olindi. AutoDock Vina [12] molekulyar doking dasturida oqsil (1DX6) va DOP ta’sirlashishi o‘rganilib, ularning energetik jihatdan maqbul komplekslari olindi. Doking natijasida olingan AXE-DOP kompleki Gromacs-2023 [1] dasturida molekulyar dinamik (MD) modellashtirish ishlarini bajarish uchun foydalanildi.

Natijalar va ularning tahlili

Modellashtirish AMBER99SB-ILDN kuch maydonlari usulida olib borildi. Modellshtirishdan oldin DOP molekulasi atomlari uchun AM1-BCC [13, 14] va Gasteiger [15] zaryad taqsimotlari ACPYPE serverida hisoblandi (1-jadval). DOP atomlaridagi RESP2(0.5) [16] zaryad taqsimoti MultiWFN [17] va ORCA 6.0 [18] dasturlari asosida hisoblab topildi.

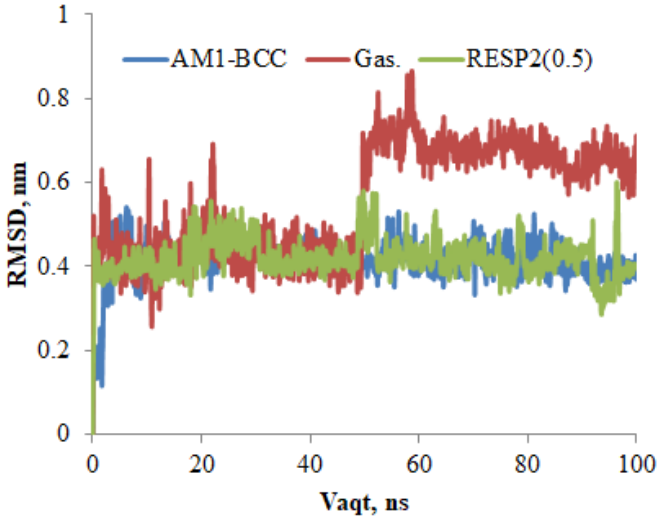
1-jadval

DOP molekulasi atomlaridagi AM1-BCC (BCC), Gasteiger (Gas) va RESP2 usullarida aniqlangan zaryad taqsimotlari

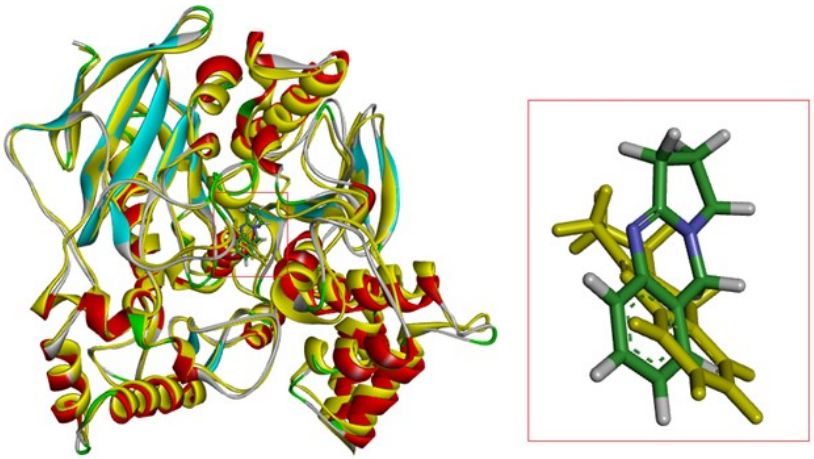
Atom	BCC	Gas	RESP2	Atom	BCC	Gas	RESP2
N1	-0.62	-0.23	-0.89	H(C4)	0.04	0.05	0.05
C2	0.61	0.09	0.65	H(C4)	0.04	0.05	0.05
N3	-0.75	-0.31	-0.23	H(C5)	0.13	0.06	0.13
C4	0.26	0.04	0.08	H(C6)	0.13	0.06	0.14
C4a	-0.13	-0.01	-0.16	H(C7)	0.13	0.06	0.14
C8a	0.15	0.07	0.55	H(C8)	0.15	0.06	0.16
C5	-0.11	-0.05	-0.15	H(C9)	0.08	0.03	0.09
C6	-0.14	-0.06	-0.19	H(C9)	0.08	0.03	0.09
C7	-0.12	-0.06	-0.13	H(C10)	0.06	0.02	0.02
C8	-0.11	-0.03	-0.30	H(C10)	0.06	0.02	0.02
C9	-0.12	0.01	-0.24	H(C11)	0.04	0.04	0.07
C10	-0.09	-0.03	0.04	H(C11)	0.04	0.04	0.07
C11	0.20	0.01	-0.08				

DOP molekulasining uchta topologiya fayllari uch xildagi zaryad taqsimotlarini (1-jadval) kiritgan holda ACPYPE serverida hosil qilindi. Keyin, 1DX6-DOP kompleksi uch marta bir xil sharoitda 100 nanosekunddan (ns) modellashtirildi. Gromacs dasturidagi MD modellashtirishning dastlabki bosqichida AXE-DOP kompleki kvadrat qutiga joylashtirilib, unga erituvchi sifatida suv molekulalari va ionlar (Na^+, Cl^-) qo‘shildi. Keyin, hosil qilingan tizim energiyasi maqbullashtirildi hamda ma’lum bir harorat va bosimda tizim muvozanat holatiga keltirildi. Undan keyin tizimdagi atom va molekulalar harakatlari 2 femtosekund (fs) qadam bilan 100 nanosekund (ns) davomida (t=310 K, P=100 kPa) MD simulyatsiya qilindi. Simulyatsiya davrida kompleksning barqarorligini tahlil qilish uchun o‘rtacha kvadratik og‘ish (RMSD) grafigi tuzildi (2-rasm). AM1-BCC, Gasteiger va RESP2(0.5) zaryad taqsimotlaridan foydalanib olib borilgan MD modellashtirish jarayonida DOP molekulasining 100 ns simulyatsiya davomida oqsil faol markazidan chiqib ketmaganligini RMSD grafigidan kuzatish mumkin (2-rasm). AM-BCC zaryad taqsimotini qo‘llagan holda olib borilgan MD simulyatsiya RMSD grafigidan (ko‘k rangli chiziq) 0-10 ns oralig‘ida DOP geometriyasini qisman o‘zgartirganligini (3-rasm), keyin kuchli

tebranishlar (fluktatsiyalar) kuzatilmasdan sistema muvozanat holatiga yetganini ko‘rish mumkin. RESP2(0.5) zaryad taqsimotini qo‘llagan holda olib borilgan MD simulyatsiyasi jarayonida (2-rasm, yashil rangli chiziq) ham tizim ayrim fluktatsiyalar bilan muvozanat holatiga intililishi kuzatiladi. Ammo, Gasteiger (Gas.) zaryad taqsimotini qo‘llagan holda olib borilgan MD modellashtirish jarayonida 50 ns atrofida DOP oqsil faol markazidagi holatini qisman o‘zgartirishi va buning natijasida fluktatsiyaning oralig‘i 0.3 – 0.5 nm dan 0.7 – 0.8 nm oralig‘iga o‘zgarishi kuzatiladi.



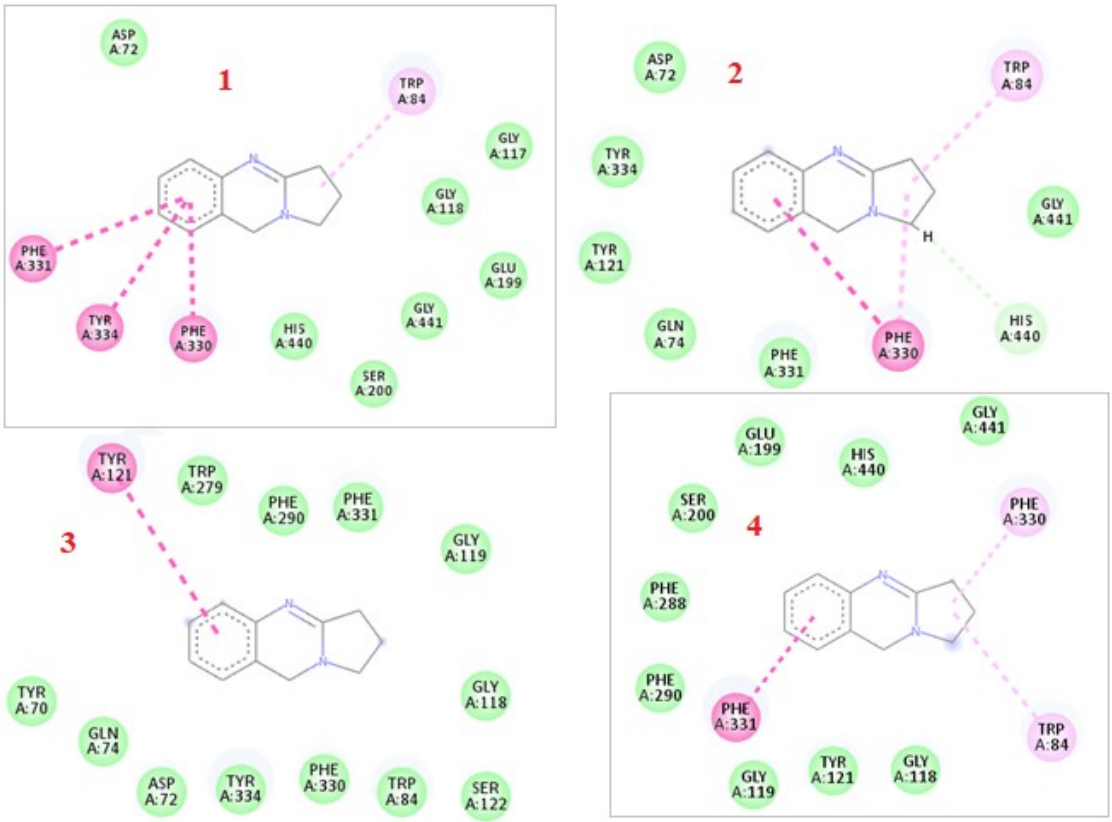
2-rasm. AXE-DOP kompleksi MD simulyatsiyasi RMSD grafigi



3-rasm. MD modellashtirishdan oldingi (sariq rangda) va keyingi kompleks geometriyalarinig taqqoslanishi

MD modellashtirish jarayonida DOP molekulasining oqsil faol markazidagi holatining o‘zgarishi uning oqsil aminokislotalari qoldiqlari bilan ta’sirlashishlariga ham ta’sir qiladi. Ushbu holatni 4-rasmda keltirilgan ma’lumotlardan ko‘rish mumkin. Dastlabki, MD modellashtirish uchun olingan kompleks faol markazida (4-rasm, 1) DOP triptofan (TRP84), fenilalanin (PHE330, PHE331) va tirozin (THYR334) aminokislotalari qoldiqlari bilan π – π(alkil) ta’sirlashishga ega. AM1-BCC zaryad taqsimotini qo‘llagan holda bajarilgan MD modellashtirish natijasida (4-rasm, 2) faqat triptofan (TRP84) va

fenilalanin (PHE330) bilan ta’sirlashish saqlanib qolgan. Gasteiger zaryad taqsimotini qo‘llagan holatda (4-rasm, 3) esa umuman yangi, tirozin (TYR121) bilan π –π ta’sirlashish yuzaga kelgan. Oldingi 2- va 3-holatdan farqli ravishda, RESP2(0.5) zaryad taqsimotini qo‘llagan holatdagi MD modellashtirish natijasida (4-rasm, 4) DOP triptofan (TRP84) va fenilalanin (PHE330, PHE331) aminokislotalari qoldiqlari bilan π –π(alkil) ta’sirlashishga ega.



4-rasm. DOP molekulasining AXE faol markazida MD modellashtirishdan oldin (1) va keyin (2-4) joylashishi

Xulosa

Izlanishlar natijasida AMBER99SB-ILDN kuch maydonlari usulida MD modellashtirish ishlarida AM1-BCC va RESP2 zaryad taqsimotlarini qo‘llash orqali Gasteiger zaryad taqsimotiga nisbatan ustuvor natijalarga erishish mumkinligi aniqlandi. Ammo, hamma holatda DOP molekulasi oqsil faol markazida saqlanib qolishi va MD simulyatsiya (100 ns) mobaynida oqsil margazidagi holatini qisman o‘zgartirishi aniqlandi.

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