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5-FTORURATSILNING METIL-4-(2-XLOROASETAMIDO)BENZOAT ASOSIDAGI YANGI HOSILASINI SINTEZ QILISH VA SARATON HUJAYRALARIGA QARSHI BIOLOGIK FAOLLIGINI O’RGANISH

Annotatsiya: Ushbu ishda metil-4-aminobenzoatning xloratsetillash mahsulotining 5-Ftoruratsil bilan reaksiyasi yordamida yangi birikma sintez qilingan. Jarayon 2 bosqichda amalga oshirilgan bo’lib, dastlab metil-4-aminobenzoatning xloratsetillash reaksiyasi amalga oshirilgan va ikkinchi bosqichda olingan birikmaning 5-Ftoruratsil bilan reaksiyasi

asosida yangi mahsulot sintez qilingan. Mahsulotning tuzilishi ^{1}H, ^{13}C YaMR, IQ- va Mass- spektrometriya usullari yordamida tasdiqlangan. Olingan mahsulotning suyuqlanish harorati, reaksiya unumi, eruvchanligi aniqlangan va biologik faolligi 3 xil saraton hujayralari: Hela (bachadon bo'yni saraton hujayrasi), HT-29 (yo'g'on ichak saraton hujayrasi) va MCF-7 (ko'krak saratoni hujayrasi) da o'rganilgan.
Kalit so'zlar: 5-Ftoruratsil (5-Fu), xloratsetilxlorid, metil-4-aminobenzoat.

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СИНТЕЗ НОВОГО ПРОИЗВОДНОГО 5-ФТОРУРАЦИЛА НА ОСНОВЕ МЕТИЛ-4-(2-ХЛОРАЦЕТАМИДО) БЕНЗОАТА И ИЗУЧЕНИЕ БИОЛОГИЧЕСКОЙ АКТИВНОСТИ ПРОТИВ РАКОВЫХ КЛЕТОК

Аннотация: В данной работе синтезировано новое соединение в результате реакции продукта хлорацетилирования метил-4-аминобензоата с 5-фторурацилом. Процесс осуществлялся в две стадии: сначала проведена реакция хлорацетилирования метил-4-аминобензоата, а на второй стадии – проведен синтез нового продукта в реакции метил-4-(2-хлорацетамидо) бензоата с 5-фторурацилом. Строение продукта

подтверждено методами ЯМР ^{1}H, ^{13}C, ИК и масс-спектрометрии. Определены температуру плавления, выход и растворимость полученного продукта и изучена его биологическая активность на 3 раковых клетках: Hela (клетка рака шейки матки), HT-29 (клетка рака толстой кишки) и MCF-7 (клетка рака молочной железы).

Ключевые слова: 5-Фторурацил (5-Фу), хлорацетилхлорид, метил-4-аминобензоат.

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SYNTHESIS OF A NEW DERIVATIVE OF 5-FLUOROURACIL BASED ON METHYL-4-(2-CHLOROACETAMIDO) BENZOATE AND EVALUATION OF ITS BIOLOGICAL ACTIVITY AGAINST CANCER CELLS

Abstract: In this work, a novel product was synthesized by the reaction of the chloroacetylation product of methyl-4-aminobenzoate with 5-fluorouracil. The process was carried out in 2 steps, firstly, the chloroacetylation reaction of methyl-4-aminobenzoate and in the second step, the synthesis of a new product with 5-Fluorouracil from the intermediate compound. The structure of the product was confirmed using ^{1}H, ^{13}C NMR, IR and Mass spectrometry methods. The liquefaction temperature, reaction yield,

solubility of the obtained product were determined and the biological activity was tested in 3 cancer cells: Hela (cervical cancer cell), HT-29 (colon cancer cell) and MCF-7 (breast cancer cell).
Key words: 5-Fluorouracil (5-Fu), chloroacetyl chloride, methyl-4-aminobenzoate.

Kirish

Bugungi kunda tibbiyot sohasida turli kasalliklarning paydo bo’lishi va ularning ba’zilari o’lim bilan tugayotganligi hammamizga ma’lum. Ularga misol qilib saraton kasalliklarini keltirishimiz mumkin. 5-Ftoruratsil (5-Fu) va uning hosilalari o’sma kasalliklar (oshqozon-ichak, yo’g’on ichak, bosh, bo'yin va ko'krak saratoni)ini davolashda uzoq yillardan buyon foydalanib kelinadi. 5-Fu saraton kasalliklarga qarshi kuchli vosita bo’lib, shu bilan bir vaqtda ko’plab salbiy xossalari mavjud. 5-Fu dan foydalangan bemorlarda og’iz va ichakning yallig’lanishi, soch to’kilishi, markaziy nerv sistemasi shikastlanishi va ko’ngil aynishi kabi salbiy ta’sirlar keltirib chiqargan. Ammo, 5-Fu asosida olingan hosilalarning biologik faolliklari, 5-Fu ga nisbatan ancha yaxshiroq ekanligi o’rganilgan. 5-Fu organik sintez uchun pirimidin asosidagi geterosiklik birikmadir. 5-Fu ning tanlab ta’sir qiluvchan, yangi, barqaror, zararli xossalari kam bo’lgan hosilalarini sintez qilish, biologik faolliklarini o’rganish va tibbiyot sohasida foydalanishga tadbiq etish organik kimyoning dolzarb vazifalaridan biri hisoblanadi.

Adabiyotlar tahlili

Saraton butun dunyo bo'ylab hayot uchun eng xavfli kasalliklardan biri bo'lib, inson salomatligiga jiddiy xavf tug'diradi [1,2]. Jarrohlik, radioterapiya, kimyoviy dori-darmonlar, biologik immunizatsiya terapiyalari asosiy davolash strategiyalari bo'lib, ular orasida kimyoterapiya saraton kasalligini davolashda muhim rol o'ynaydi [3–7]. 5-Fu kimyoterapiyada eng ko'p qo'llaniladigan antimetabolitlardan biridir u qattiq o'smalarning ko’plab turlariga qarshi ijobiy ta'sir ko'rsatadi [8]. 5-Fu kabi an'anaviy kimyoterapiyalar tez ko'payadigan saraton hujayralarini ingibirlovchi sitotoksik vositalardir. 5-Fu selektivligi past bo'lganligi sababli, uni klinik qo'llash paytida miyelosupressiya, shilliq qavat yallig’lanishi, dermatit va diareya kabi nojo'ya ta'sirlar kuzatiladi[9]. Bundan tashqari, 5-Fu juda qisqa yarim parchalanish davriga ega bo’lib taxminan 20 daqiqa va u

qabul qilingandan keyin tezda chiqariladi. Og‘iz orqali noto‘g‘ri so‘rilish va biologik o‘zlashtirilishning sustligi ko‘pincha klinik davolash natijalarining yomonlashishiga olib keladi [10]. Yuqorida aytib o‘tilgan muammolarni bartaraf etish maqsadida, tadqiqotchilar 5-Fu preparatining samaradorligini oshirish va zaharliligini kamaytirish uchun turli usullarni qo‘llaganlar. Bular qatoriga kimyoviy tuzilishni o‘zgartirish, preparat tarkibini takomillashtirish strategiyalari va dorini etkazib beruvchi yangi tizimlar kiradi. 5-Ftor-2-deoksiuridin, 1-(2-tetragidrofuril)-5-ftoruratsil va 3,5-dioktanoil 5-ftor-2-deoksiuridin kabi 5-Fu ning bir nechta kichik molekulyar massali propreparatlari ishlab chiqilgan [11-12]. Bundan tashqari Yosuke Ota va Arisa Nakamuralar tomonidan 5-ftoruratsilning trans-2-fenilsiklopropilamin(FSPA) va tert-butoksikarbonil(Bok) bilan N-gidroksi metil guruhi yordamida hosilalari sintez qilingan. Dastlab aminlar xlormetil xlorformiatlar bilan reaksiyaga kirishib karbamatlar olingan va olingan birikmalar 1,8-diazobisiklo-[5.4.0]undekan-7-en (DBU) yoki N,N-diizopropiletilamin ishtirikoda, CH_2Cl_2 va DMFA erituvchilari yordamida 5-Fu bilan nukleofil almashinish reaksiyalaridan kutilgan mahsulotlar olingan[13]. 5-FU ning to'rt xil farmakologik xavfsiz so-formerlar: karbamid, tiokarbamid, asetanilid va aspirin bilan rangsiz so-kristallari metanol erituvchida hosil qilingan. Bu so-kristallar olishda sodda metod, haroratni saqlashni talab qilmaslik, qimmat erituvchilar va ko’plab kimyoviy jihozlarga ehtiyoj yo’qligi, oraliq birikmalar hosil bo’lmasligi, mahsulotlarni izolyatsiya qilish va tozalashni osonligi bilan ajralib turadi. 5-Fu ning IQ- spektroskopiya analiz tahlilida N-H guruhi 3409.02 cm^{-1} va C=O esa 1647.77 cm^{-1} sohadagi nur yutilishi kuzatilgan. Bu ko’rsatkichlar 5-Fu-Asp so-kristalida mos ravishda 3499.40 va 1649.77 cm^{-1} sohada kuzatilgan [14]. Ko'pgina 5-ftoruratsilning hosilalari sintez qilingan va aniqlangan bo'lsada, 5-Fu ning turli antikanserogen hosilalari bilan dezoksiribonuklein kislotasining (DNK) o'zaro ta'sir qilishi haqida ko’plab ma’lumotlar mavjud. Shuningdek 5-Fu ning beshta yangi antikanserogen hosilalari sintez qilingan, ya'ni 5-FU-Asp, 5-Fu-Trp, 5-FU-Ser, 5-FU-Tyr va 5-FU-Fen va ularning DNKni bog'lash o'ziga xos xususiyatlari elektrokimyoviy usullar yordamida o’rganilgan[15]. Hozirgi kunda ham 5-Fu ning turli xil yangi hosilalari tadqiqotchilar tomonidan sintez qilinmoqda.

5-Fu ning salbiy xossalarini kamaytirib, selektivlik, o’simtalarga qarshi yuqori biologik faollik va suvda oson eruvchan kabi xususiyatlarini yaxshilash uchun 5-Fu ning metil-4-aminobenzoat asosidagi yangi mahsulot sintez qilingan. Uning tuzilishi Mass, ^{1}H, ^{13}C YaMR va IQ-spektroskopiya usullari yordamida tasdiqlandi. Shuningdek mahsulotning suyuqlanish harorati, reaksiya unumi, eruvchanligi aniqlangan va MTT metodi yordamida biologik faolligini o’rganish uchun 3 ta saraton hujayrasi: Hela (bachadon bo’yni saraton hujayrasi), HT-29 (yo'g'on ichak saraton hujayrasi) va MCF-7 (ko'krak saratoni hujayrasi)ga ta’siri tekshirilgan.

Tajriba qismi

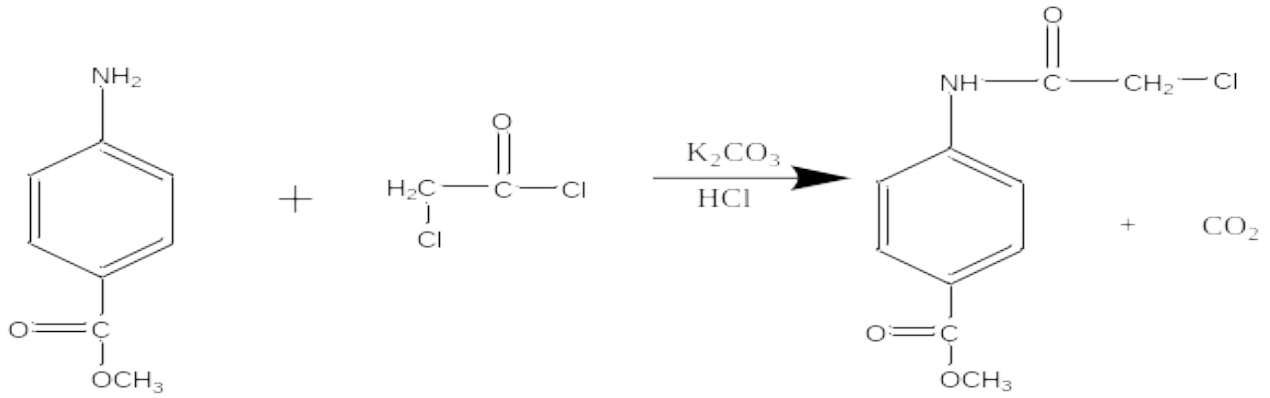
Olingan mahsulotning suyuqlanish haroratini o’lchash uchun M-560 jihozdan foydalanilgan. ^{1}H va ^{13}C YaMR spektrlari DMSO erituvchisida VARIAN MR 400 MHz spektrometrlarida olingan. Yuqori aniqlikdagi mass spektrometriyalari (HRMS) AB SCIEX QSTAR Elite yordamida mass analizi o’rganilgan. IQ spektrlari Fure-spektrometr Bruker Invenio S-2021 4000–400 $см^{-1}$ ATR jihozida o’rganilgan.

Tadqiqot natijalari va muhokamalar

Sintez metodi

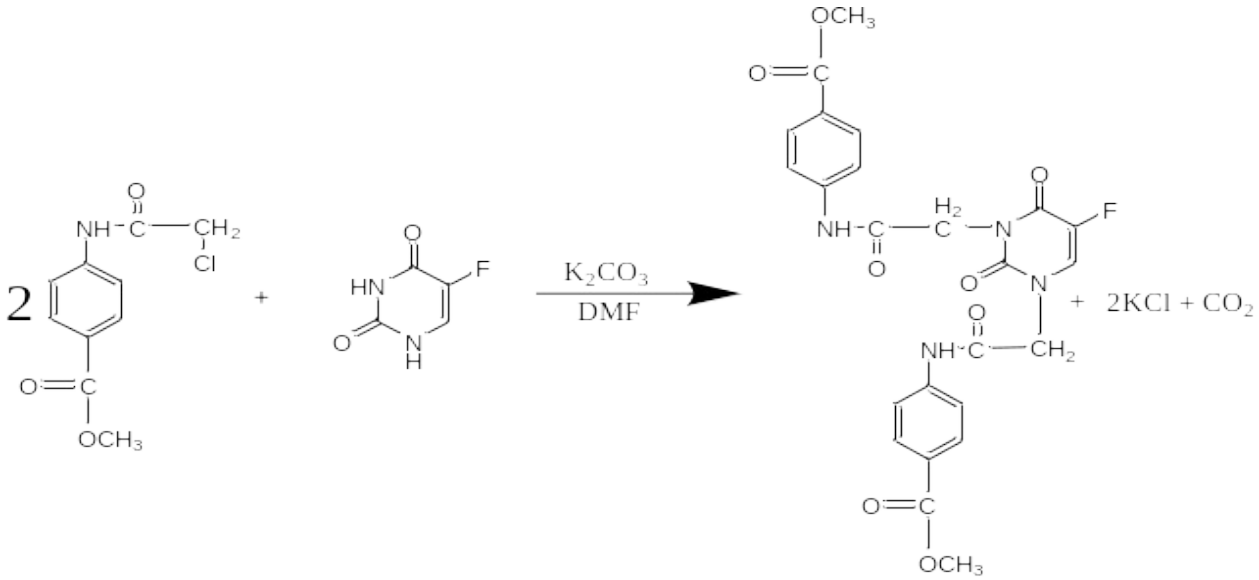
5-Fu ning metil-4-aminobenzoat asosida yangi hosilasini sintez qilish jarayoni ikki bosqichda amalga oshirilgan. Dastlab metil-4-aminobenzoatning (0,01 mol) miqdori 100 ml hajmli tubi yumaloq kolbaga solindi va u 50 ml atsetonitrilda eritildi. Aralashmaga K_2CO_3 0,01 mol, (1.38 gr) miqdori analitik tarozida tortib olindi va qo’shildi. Eritma harorati -1-3 ^{o}C sovuq muhitda 30 min davomida magnitli aralashtirgich yordamida aralashtirib turildi va unga xloratsilxloriddan 0,01 mol, (0.8 ml) miqdori tomchilatib qo’shildi. So’ngra 2 soat davomida ultra tovushli suv hammomida reaksiya olib borildi va undan keyin aralashma YuQX yordamida (geksan:atseton,1-1.5) identifikatsiya qilindi.

Sxema-1. Reaksiya tenglamasining birinchi bosqichi



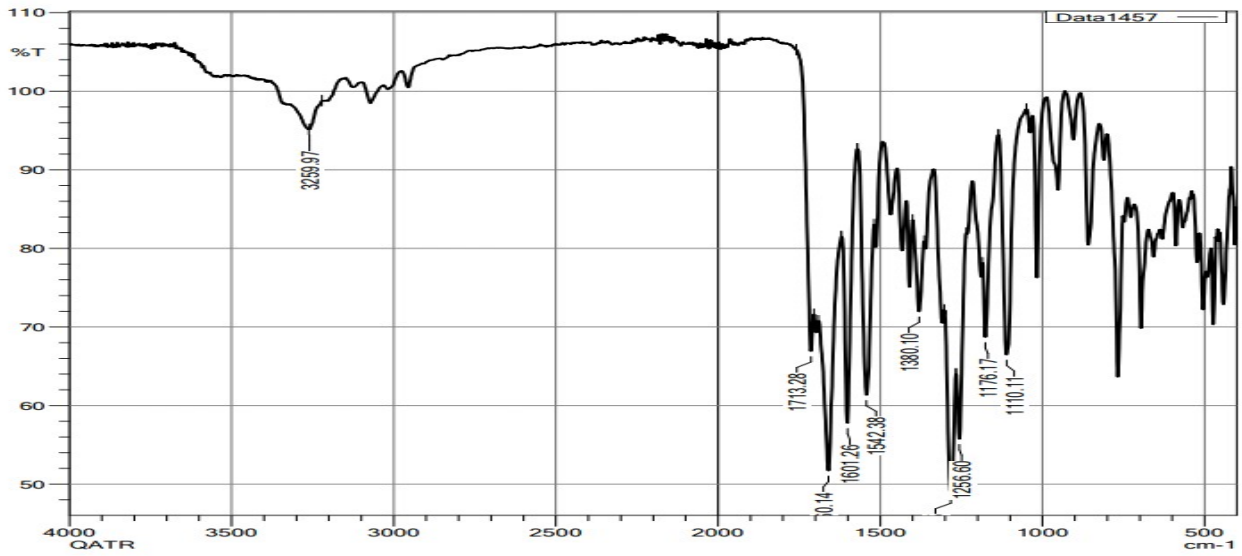
Reaksiyaning ikkinchi bosqichida 5-Fu (0.625 mmol, 0.081 gr) 2 ml DMFA da xona haroratida eritilgan va K_2CO_3 (1.25 mmol, 0.1725 gr) qo'shilgan. So'ngra aralashtirilgan holatda 4-aminobenzoatning N-xloratsetil hosilasi (1.25 mmol) ta'sir ettirilgan va reaksiya 7-9 soat davomida 40-50 ^oC haroratida olib borilgan. Reaksiya aralashmasi YuQX yordamida (geksan:atseton,1:1.5) har ikki soatda tekshirilgan va tozalangan.

Sxema-2. Reaksiya tenglamasining ikkinchi bosqichi



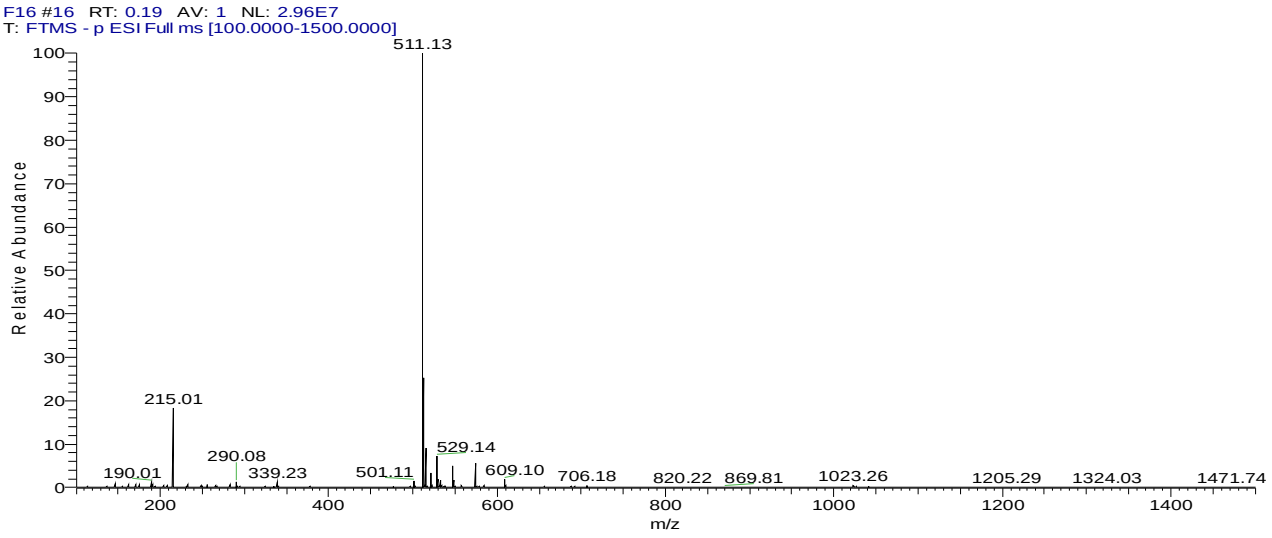
Mahsulotning nomi: **Dimetil 4,4'-((2,2'-(5-ftor-2,4-dioksopirimidin-1,3(2H,4H)-diil)bis(asetil))bis(azanedil))dibenzoat.**

Och pushti rangli kukunsimon mahsulot bo'lib, reaksiya unumi 72%, suyuqlanish harorati 242-244^oC, Rf=0.69 (sistema atseton-geksan 2-3 nisbat). Tuzulishi IQ, ^1H, ^{13}C YaMR spektroskopiya va mass spektrometriya usullaridan foydalanib aniqlangan.



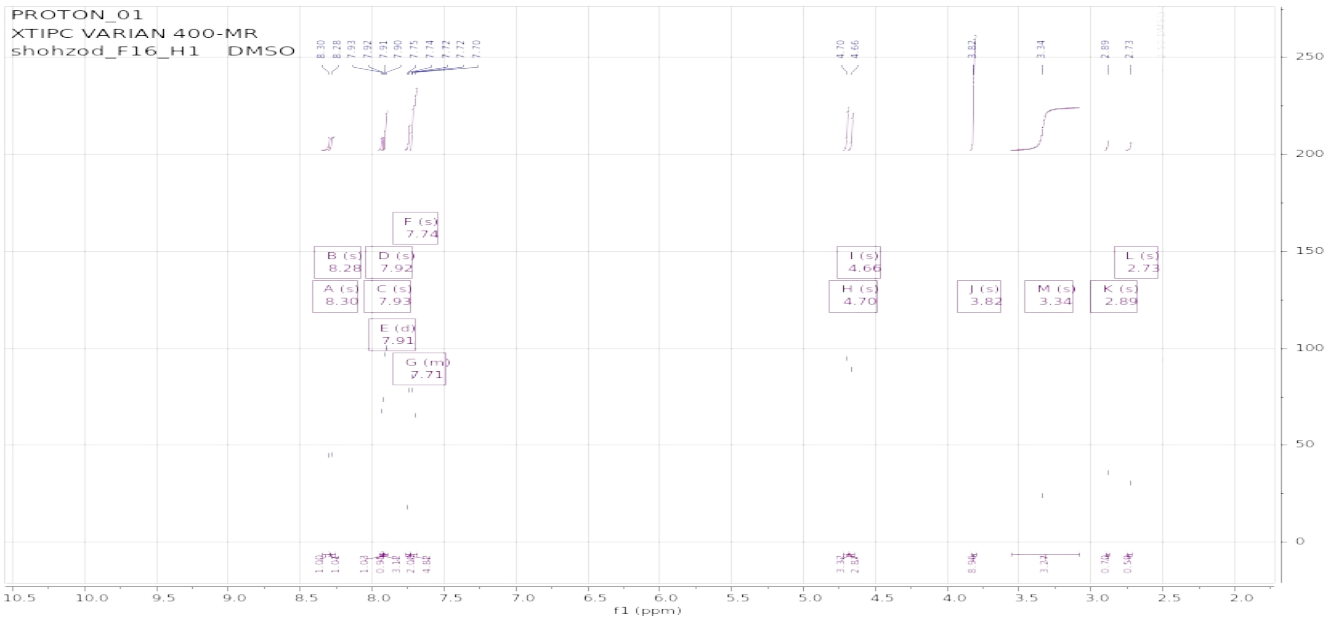
1-rasm. **Dimetil 4,4'-((2,2'-(5-ftor-2,4-dioksopirimidin-1,3(2H,4H)-diil)bis(asetil)) bis(azanedil))dibenzoatning IQ spektri**

1-rasmda keltirilgan dimetil 4,4'-((2,2'-(5-ftor-2,4-dioksopirimidin-1,3(2H,4H)-diil)bis(asetil)) bis(azanedil))dibenzoatning IQ spektriga asosan, ν=3259 $см^{-1}$ sohada amid guruxiga tegishli NH- tebranish chastotalari kuzatiladi, 1713 $см^{-1}$ sohada murakkab efir bog'idagi –C=O ning valent tebranishlari namoyon bo'lsa, amid guruhidagi C=O valent tebranishlari ν=1660 $см^{-1}$ sohada kuzatiladi. 5-Ftoruratsil xalqadagi C=O valent tebranishlari esa 1601 $см^{-1}$ sohada namoyon bo'ladi. ν=1542 $см^{-1}$ sohada murakkab efir bog'idagi –C-O-C- bog'ining valent tebranishlari kuzatiladi, 5-Ftoruratsil xalqadagi (C-F) valent tebranishlari esa 1176 $см^{-1}$ sohada namoyon bo'ladi.



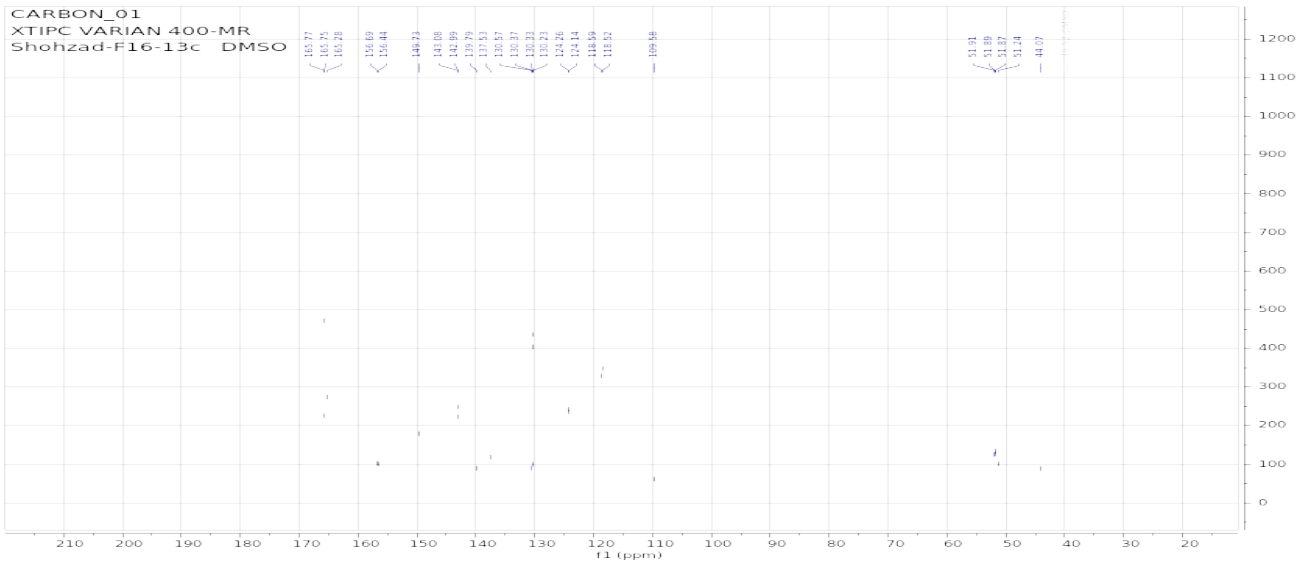
2-rasm. **Dimetil 4,4'-((2,2'-(5-ftor-2,4-dioksopirimidin-1,3(2H,4H)-diil)bis(asetil)) bis(azanedil))dibenzoatning mass spektri**

2-rasmda keltirilgan dimetil 4,4'-((2,2'-(5-ftor-2,4-dioksopirimidin-1,3(2H,4H)-diil)bis(asetil)) bis(azanedil))dibenzoat ($C_{24}H_{21}FN_4O_8$, 512.15) ning mass-spektridan ko'rish mumkinki m/z 511,13 asosiy molekulyar ionga tegishli bo'lib, uning parchalanishidan kichik massadagi: m/z 290,08, m/z 501,11, m/z 339,23, m/z 215.01 molekulyar ionlar hosil bo'lgan.



3-rasm. **Dimetil 4,4'-((2,2'-(5-ftor-2,4-dioksopirimidin-1,3(2H,4H)-diil)bis(asetil)) bis(azanedil))dibenzoatning ^{1}H YaMR spektri**

3-rasmda dimetil 4,4'-((2,2'-(5-ftor-2,4-dioksopirimidin-1,3(2H,4H)-diil)bis(asetil)) bis(azanedil))dibenzoatning ^{1}H YaMR spektri keltirilgan bo'lib unda quyidagi ketma-ketlikdagi molekula tarkibidagi proton signallarining m.u. kimyoviy siljish qiymatlarini kuzatish mumkin bo'ladi: δ 8.30 (s, 1H), 8.28 (s, 1H), 7.93 (s, 1H), 7.92 (s, 1H), 7.91 (d, J = 4.8 Hz, 2H), 7.74 (s, 2H), 7.73 – 7.69 (m, 2H), 4.70 (s, 2H), 4.66 (s, 2H), 3.82 (s, 4H), 3.34 (s, 2H), 2.89 (s, 1H).



4-rasm. Dimetil 4,4'-((2,2'-(5-ftor-2,4-dioksopirimidin-1,3(2H,4H)-diil)bis(asetil)) bis(azanedil))dibenzoatning ^{13}C YaMR spektri

4-rasmda dimetil 4,4'-((2,2'-(5-ftor-2,4-dioksopirimidin-1,3(2H,4H)-diil)bis(asetil)) bis(azanedil))dibenzoatning ^{13}C YaMR spektri keltirilgan bo'lib, bu yerda uglerod atomlarining kimyoviy siljishi kiymatlari m.u. quyidagi sohalarda namoyon bo'lishini kuzatish mumkin. δ 165.77, 165.75, 165.28, 156.69, 156.44, 149.73, 143.08, 142.99, 139.79, 137.53, 130.57, 130.37, 130.33, 130.23, 124.26, 124.14, 118.59, 118.52, 109.58, 51.91, 51.89, 51.87, 51.24, 44.07.

Biologik faolligi

Dimetil 4,4'-((2,2'-(5-ftor-2,4-dioksopirimidin-1,3(2H,4H)-diil)bis(asetil)) bis(azanedil))dibenzoatning biologik faolligi 3 xil turdagi saraton hujayralarida ta'siri o'rganilganda (50 mmol/l) asosan Hela (bachadon bo'yni saraton hujayrasi)ni o'sishini ingibirlash ko'rsatgichi 65.91% (5-Fu=27.08%), HT-29 (yo'g'on ichak saraton hujayrasi)ni ingibirlash ko'rsatgichi 54.15% (5-Fu=40.75%) va MCF-7 (ko'krak saratoni hujayrasi)ni ingibirlash ko'rsatkichi 45.05%, 5-Fu uchun esa 41.49% ni tashkil etishi aniqlandi.

Xulosa

Birinchi marta 4,4'-((2,2'-(5-ftor-2,4-dioksopirimidin-1,3(2H,4H)-diil)bis(asetil)) bis(azanedil))dibenzoat sintez qilib olindi va uning kimyoviy tuzilishi IQ, ^{1}H, ^{13}C YaMR va mass-spektrometriya usullari yordamida tasdiqlandi. Olingan birikmaning biologik faolligi Hela (bachadon bo'yni saraton hujayrasi), HT-29 (yo'g'on ichak saraton hujayrasi)

va MCF-7 (ko'krak saratoni hujayrasi)ga nisbatan ingibirlash xususiyati o’rganilganda, olingan moddaning Hela hujayrasiga ingibirlashi 5-Fu ga nisbatan 2.5 marta kuchliroq ekanligi, HT-29 ga nisbatan qisman 5-Fu dan faolroq ва MCF-7 hujayrasiga nisbatan esa 5-Fu bilan deyarli bir xil faollikni namoyon qilishi kuzatildi.

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