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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 2,2'-(5-FLUORO-2,4-DIOXOPYRIMIDINE-1,3(2H,4H)-DIYL)BIS(N-(3-(TRIFLUOROMETHYL)PHENYL)ACETAMIDE

Annotation

In this study, a new compound was synthesized by the reaction of the chloroacetylation product of 3-trifluoromethyl aniline with 5-fluorouracil (5-Fu). The process was carried out in 2 stages, firstly, the chloroacetylation reaction of 3-trifluoromethyl aniline was carried out, and in the second stage, the new product 2,2'-(5-fluoro-2,4-dioxopyrimidine-1,3(2H,4H)-diyl)bis(N-(3-(trifluoromethyl)phenyl) acetamide was synthesized based on the reaction of the obtained compound with 5-Fu. The structure of the product was confirmed using 1H, 13C NMR, IR and Mass spectrometry methods. The liquefaction temperature, reaction yield, solubility of the obtained product were determined, and 3 cancer cells were selected to test the biological activity: Hela (cervical cancer), HT-29 (colon cancer cell) and MCF-7 (breast cancer cell).

Key words: 5-Fluorouracil (5-Fu), chloracetyl chloride, 3-trifluoromethyl aniline, 2-chloro-N-(3-(trifluoromethyl) phenyl)acetamide.

СИНТЕЗ И БИОЛОГИЧЕСКАЯ АКТИВНОСТЬ 2,2'-(5-ФТОР-2,4-ДИОКСОПИРИМИДИН-1,3(2H,4H)-ДИИЛ)БИС(N-(3-(ТРИФТОРМЕТИЛ)ФЕНИЛ)АЦЕТАМИДА

Аннотация

В данной исследован синтез хлорацетилирования 3-трифторметил анилина с 5-фторурацилом (5-Фу). Синтез осуществлен в 2 стадии, сначала была проведена реакция хлорацетилирования 3-трифторметиланилина, после этого проведена реакция с 5-Фу и синтезирован 2,2'-(5-фтор-2,4-диоксопиримидин-1,3(2H,4H)-диил)бис(N-(3 (трифторметил) фенил) ацетамид. Химическая структура конечного продукта была подтверждена с использованием методов ^{1}H, ^{13}C ЯМР и ИК спектроскопия, а также метод масс-спектрометрии. Были определены некоторые физико-химические показатели и биологическая активность на клетках: Hela (рак шейки матки), HT-29 (клетка рака толстой кишки) и MCF-7 (клетка рака молочной железы).

Ключевые слова: 5-Фторурацил (5-Фу), хлорацетилхлорид, 3-трифторметил анилин, 2-хлор-N-(3-(трифторметил) фенил)ацетамид.

2,2'-(5-FTOR-2,4-DIOKSOPIRIMIDIN-1,3(2H,4H)-DIIL)BIS (N-(3-(TRIFTORMETIL) FENIL) ASETAMIDNING SINTEZI VA BIOLOGIK FAOLLIGI

Annotatsiya

Ushbu tadqiqotda 3-triftormetil anilinning xloratsetillash mahsulotining 5-ftoruratsil (5-Fu) bilan reaksiyasi yordamida yangi birikma sintez qilingan. Jarayon 2-bosqichda amalga oshirilgan bo’lib, dastlab 3-triftormetil anilinning xloratsetillash reaksiyasi amalga oshirilgan va ikkinchi bosqichda olingan birikmaning 5-Fu bilan reaksiyasi asosida yangi 2,2'-(5-ftor-2,4-dioksopirimidin-1,3(2H,4H)-diil)bis(N-(3-(triftormetil)fenil) asetamid mahsuloti sintez qilingan. Mahsulotning tuzilishi ^{1}H, ^{13}C YaMR , IQ spektoskopiya va mass spektrometriya usullari yordamida tasdiqlangan. Olingan mahsulotning ayrim fizik-kimyoviy xarakteristikalari va biologik faolligini 3 ta saraton hujayralarida: Hela (bachadon bo’yni saratoni), HT-29 (yo'g'on ichak saraton hujayrasi) va MCF-7 (ko'krak saratoni hujayrasi) o’rganilgan.

Kalit so‘zlar: 5-Ftoruratsil (5-Fu), xloratsetilxlorid, 3-triftor metil anilin, 2-xlor-N-(3-(triftormetil) fenil)asetamid.

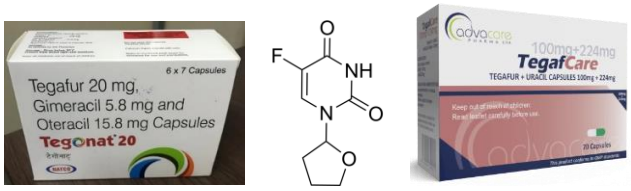
Kirish. Saraton hujayralarining sog‘lom hujayradan farqli o‘laroq, bunday hujayralarda tabiiy o‘lim holati o‘chirilgan, ya’ni ular to‘xtovsiz bo‘linish jarayonida bo‘ladi. Saraton butun dunyo bo'ylab o'limning asosiy sababi bo'lib, 2020-yilda 10 millionga yaqin o'limni yoki har oltita o'limdan bittasini tashkil qiladi. Eng keng tarqalgan saraton turlari ko'krak, o'pka, yo'g'on, to'g'ri ichak va prostata saratonlaridir. Tamaki iste'moli saraton kasalligida o‘limning taxminan 22% sababchisi hisoblanadi.

Shuningdek 10% semizlik, noto‘g‘ri ovqatlanish, jismoniy harakatning etishmasligi yoki spirtli ichimliklarni haddan tashqari ko’p iste’mol qilish ham saraton kasalligiga olib keladi. O‘ziga xos viruslar, bakteriyalar, havo ifloslanishi va parazitlar bilan infeksiya butun dunyo bo‘ylab saraton kasalliklarining taxminan 16-18% ni keltirib chiqaradigan ekologik omil hisoblanadi. Saraton kasalliklarini davolashda ko’plab dorilar ishlab chiqilgan bo’lib ular tibbiyotda keng miqyosda foydalaniladi. Ular bilan birgalikda 5-Fu va unga asoslangan dorilar ham bir qancha saraton kasalliklari: yo’g’on ichak, qizilo'ngach, oshqozon, oshqozon osti bezi, ko'krak va bachadon bo'yni saratoni kabi kasalliklarni davolashda foydalanilmoqda.

Adabiyotlar tahlili. Saraton kasalliklarini davolashda turli xil usullardan foydalaniladi, xususan jarrohlik, radioterapiya, kimyoviy dori-darmonlar, biologik immunizatsiya terapiyalari asosiy davolash strategiyalari bo'lib, ular orasida kimyoterapiya saraton kasalligini davolashda muhim rol o'ynaydi [1–5]. 5-Ftoruratsil (5-Fu) ilk bor 70-yil avval sintez qilingan bo’lib u geterosiklik aromatik organik birikma bo'lib, beshinchi ugleroddagi vodorod atomi fторga almashinishidan hosil bo’lgan uratsilning analogidir [6]. 5-Fu 282-283º C da suyuqlanuvchan oq rangli, hidsiz kukunsimon kristal modda bo’lib u asosan DMFA, DMSO, atsetonitril-metanol(1:1) kabi erituvchilarda yaxshi eriydi, etanol, suvda yomon, efir, xloroform va benzolda deyarli erimaydi[7]. 5-Fu ning bir qancha salbiy ta’sirlariga qaramay u asosida turli xil dori vositalar ishlab chiqilgan va terapiyada o’sma kasalliklarni keng turini davolashda ishlatilib kelinmoqda. 5-Fu asosidagi dorilarning aksariyati Adrucil nomi ostida sotiladi.

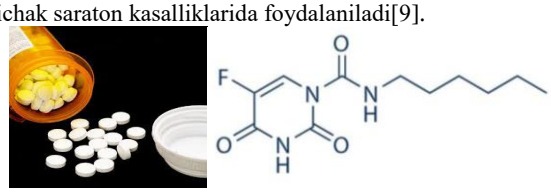
5-Ftoruratsil asosidagi dori vositalar

5-Fu ning ko’plab N-almashingan hosilalari sintez qilingan va ular yo’g’on ichak, oshqozon, jigar, o’pka, bachadon bo’yni va ko’krak saratoni kabi kasalliklarini davolashda foydalanib kelinmoqda. Ularga misol qilib kimyoterapiyada keng qo’llaniladigan Tegafurni keltirishimiz mumkin. 5-Fu ning 2-asetoksitetragidrofuran bilan DMFA erituvchisida 90°C da alkillanishidan 72 % unum bilan Tegafur olingan[8].



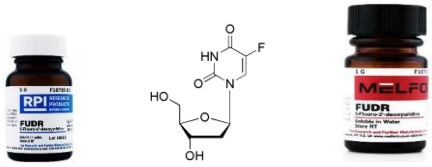
Tegafurning kimyoviy tuzilishi va dori shakli

5-Fu asosida olingan yana bir dori vositasi Carmofur (1-geksilkarbamoil-5-ftorurasil) bo’lib u tabletka ko’rinishda ishlab chiqariladi va yo’g’on, ingichka ichak saraton kasalliklarida foydalaniladi[9].



Carmofurning kimyoviy tuzilishi va dori shakli

5-Fu asosida sintez qilingan navbatdagi suvda eruvchan dori vositasi 5-ftor-2'-deoksiuridin (FdUrd, floksiuridin). U ham saraton kasalliklarini davolashda keng foydalanilib kelinmoqda.



Floksiuridinning kimyoviy tuzilishi va dori shakli

Floksiuridin - 5-Fu dan olinadigan ftordeoksiuridilat (FdUMP) hosilaning faol metabolitidir. U 5-Fu dan timidin fosforilaza tomonidan hosil bo'ladi, so'ngra FdUMP hosil qilish uchun timidin kinaza bilan fosforlanadi. Floksiuridin vositasi (1 mkM), timidilat sintaza etishmaydigan FM3A sichqon ko'krak saratoni hujayralarida DNKning ikki zanjirli uzilishlarini keltirib chiqaradi, shuningdek, dATP darajasini oshiradi va notanish tipdagi timidilatni hosil qiluvchi FM3A F28-7 sichqon ko'krak saratoni hujayralarida dTTP va dGTP darajasini pasaytiradi. L1210 leykemiya va HeLa saraton hujayralarining ko'payishiga kuchli qarshilik qiladi

(IC_{50} = 1,1 va 9,4 nM mos ravishda)[10]. Floksiuridin (200 mg/kg) S180 sichqon sarkomasi modelida o'simta o'sishini 86,3% ga kamaytiradi[11]. 5-Fu ning nojo’ya ta’sirlarini kamaytirib, biologik faolligini yaxshilash maqsadida uning yangi hosilalari sintez qilingan. Bu tadqiqot ishida ham 3-triftor metil anilinning xloratsetillash mahsulotini 5-Fu bilan reaksiyalari o’rganilgan va tuzilishi ^{1}H, ^{13}C YaMR ,IQ va Mass spektrometriya usullari yordamida tasdiqlangan va biologik faolligini o’rganish uchun 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)tanlab olingan.

Tajriba qismi. Olingan mahsulotning suyuqlanish haroratini o’lchash uchun M-560 jihozdan foydalanilgan. 1H va 13C YaMR spektrlari DMSO erituvchisida VARIAN MR 400 MHz spektrometrlarida olingan. Yuqori aniqlikdagi massa 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 KBr tabletkalari yordamida o’lchangan.

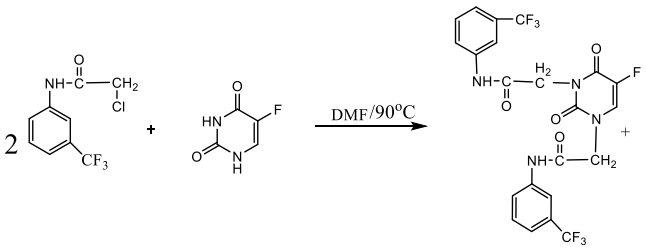
Tadqiqot natijalari va muhokama.

Sintez metodi

3-Triftor metil anilinning N-xloratsil mahsuloti va 5-Fu orasidagi reaksiya natijasidan 5-Fu ning aromatik amin tutgan hosilasi sintez qilingan. Reaksiya ikki bosqichda amalga oshirilgan bo’lib, dastlab 3-triftor metil anilinning N- xloratsil mahsuloti olingan. Bu mahsulotni olishda aromatik aminning (0,01 mol) miqdori tubi yumaloq kolbada eritilgan, ustiga K_2CO_3 tuzi (0,01 mol) qo’shilgan va haroratni - C^o gacha pasaytirib yarim soat davomida magnitli aralashtirgichda xloratsilxlorid (0,01 mol) tomchilatib qo’shilgan. So’ngra 2 soat davomida ultra tovushli suv hammomida qoldirilgan va aralashma YuQX yordamida (geksan:atseton,1-1.5) har soatda tekshirilib borilgan va tozalanib qurutilgan.

Reaksiyaning ikkinchi bosqichida 5-Fu ning 0.625 mmol miqdori 2 ml DMFA da xona haroratida eritilgan va ustiga K_2CO_3 1.25 mmol tuzi qo’shilgan. So’ngra reaksion aralashmaga 2-xlor-N-(3-(triftormetil) fenil)asetamidning 1.25 mmol miqdori ta’sir ettirilgan va reaksiya jarayoni 8-9 soat davomida 90^o C haroratda olib borilgan. Reaksion aralashma YuQX yordamida (geksan:atseton,1-1.5) har soatda tekshirilgan va tozalangan. Quyida ikkinchi bosqich reaksiya tenglamasi keltirilgan.

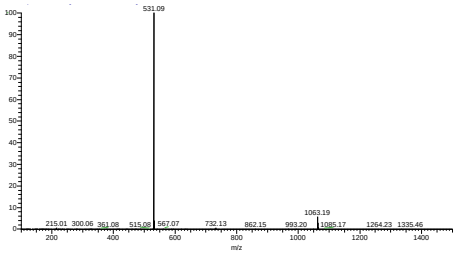
Sxema-1



2,2'-(5-ftor-2,4-dioksopirimidin-1,3(2H,4H)-diil)bis(N-(3-(triftormetil) fenil) asetamidning sintez tenglamasi

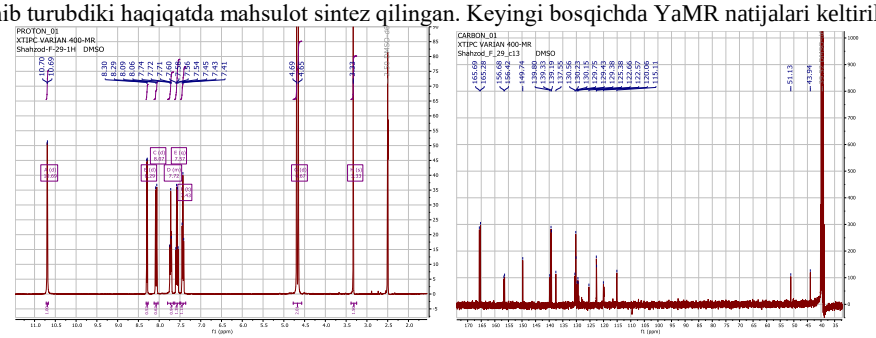
Mahsulot qattiq kukunsimon modda bo’lib, reaksiya unumi 75%, suyuqlanish harorati 195-197°C. Rf=0,70 (geksan:atseton, 2:3). Kimyoviy tuzulishi IQ, H^1,C^{13} YaMR spektroskopiya va mass spektrometriya usullaridan foydalanib tasdiqlangan.

2,2'-(5-ftor-2,4-dioksopirimidin-1,3(2H,4H)-diil)bis(N-(3-(triftormetil) fenil) asetamidning IQ spektri KBr granulalari yordamida olingan bunda : ν=3275.92 (NH), 3081.84 (Ar-H), 1687.41 (-C=O, amid), 1662.82 (-C=O, 5-Fu), 1548.49 aromatik (C=C), 1329.04 (Ar-CF_3), 1113.63 (C-F) $см^{-1}$. Mahsulotning spektr natijalaridan ko’rish mumkinki 5-Fu ning spektridan tubdan farq qiladi va yangi spektrlar kuzatilgan.



2-rasm. Mahsulotning mass spektri.

HR-ESI-MS m/z 531.09. [M-H]$^-$, formula bo’yicha nazariy ($C_{22}H_{15}N_4O_4F_7$)=532.05. 5-Fu ning massa 130.08 ga teng. Natijalardan ko’rinib turubdiki haqiqatda mahsulot sintez qilingan. Keyingi bosqichda YaMR natijalari keltirilgan.



3-rasm. Mahsulotning 1H va 13C YaMR spektrlari.

Mahsulotning 1H YaMR analizi (400 MHz, DMSO-D_6) δ 10.69 (d, J = 3.2 Hz, 2H), 8.29 (d, J = 6.5 Hz, 2H), 8.07 (d, J = 11.6 Hz, 2H), 7.80 – 7.66 (m, 2H), 7.57 (q, J = 7.5 Hz, 2H), 7.43 (t, J = 7.7 Hz, 2H), 4.67 (d, J = 17.1 Hz, 2H), 3.33 (s, 1H). 13C YaMR (101 MHz, DMSO-D_6) spektr natijalari δ 165.69, 165.28, 156.68, 156.42, 149.74, 139.80, 139.33, 139.19, 137.55, 130.56, 130.23, 130.15, 129.75, 129.43, 129.38, 125.38, 122.66, 122.57, 120.06, 115.11, 51.13, 43.94. Mahsulotning amaliy olingan YaMR va nazariy Chem Draw dasturi natijalari bir biriga juda ham yaqin ekanligi o’rganilgan.

Biologik faolligi

2,2'-(5-ftor-2,4-dioksopirimidin-1,3(2H,4H)-diil)bis(N-(3-(triftormetil)fenil) asetamidning 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 **87. 17%** (5-Fu=27.08%), HT-29 (yo'g'on ichak saraton hujayrasi)ni ingibirlash ko’rsatgichi **83.17%** (5-Fu=40.75%) va MCF-7 (ko'krak saratoni hujayrasi)ni ingibirlash ko’rsatkichi **83.31%,** 5-Fu uchun esa 41.49% ni tashkil etishi aniqlangan.

Xulosa Ilk bor 2,2'-(5-ftor-2,4-dioksopirimidin-1,3(2H,4H)-diil)bis(N-(3-(triftormetil)fenil) asetamid sintez qilib olingan va uning kimyoviy tuzilishi IQ, 1H, 13C YaMR va mass spektrometriya usullari yordamida tasdiqlangan. 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 3 marta kuchliroq ekanligi, HT-29 va MCF-7 hujayralariga nisbatan 5-Fu dan 2 marta faolroq ekanligini namoyon qilgan.

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