Жаңа дәрілік заттардың биологиялық белсенділігін зерттеу әдістері

13-дәріс

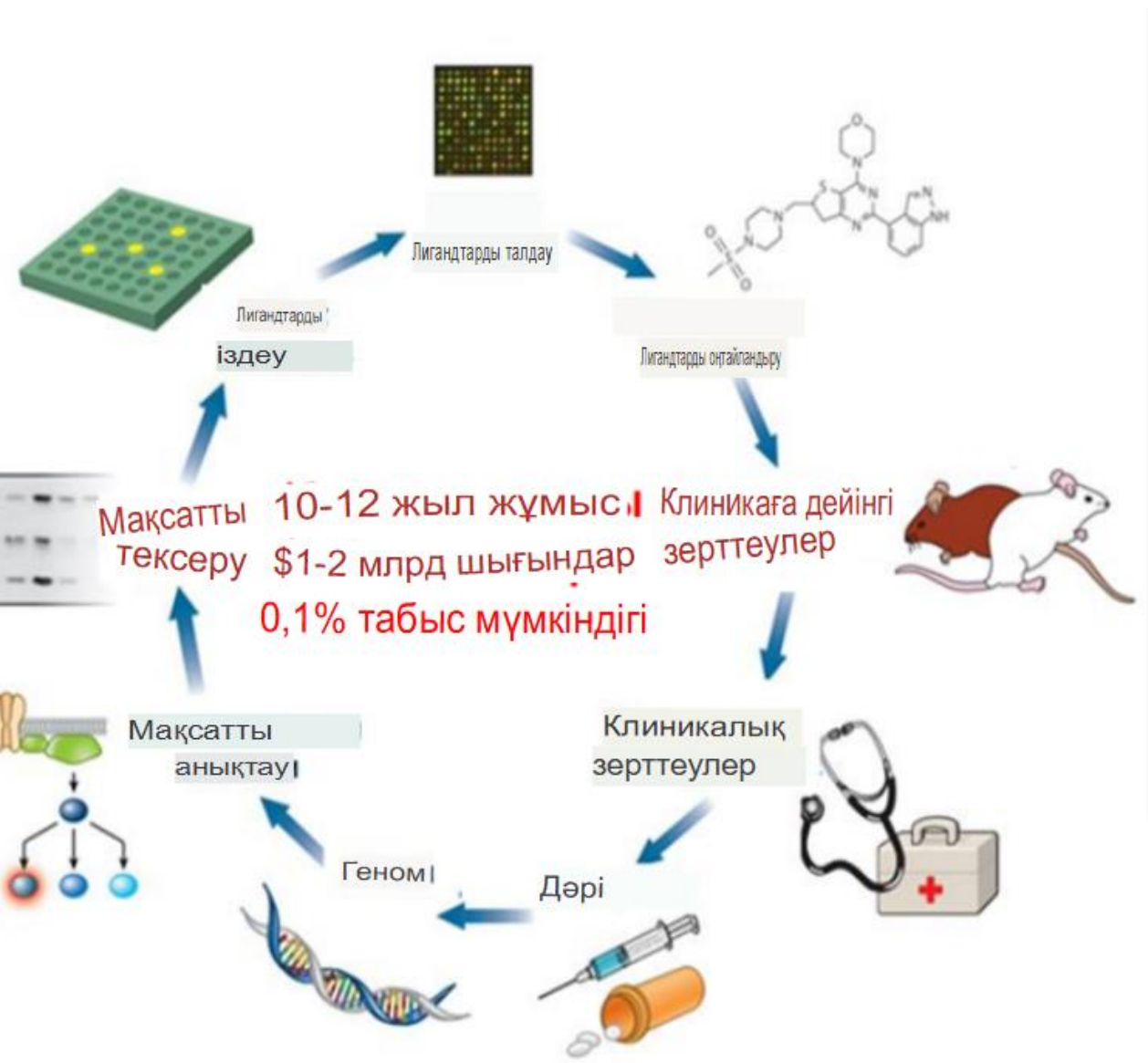
дәріскер: доцент К.Б. Бажықова

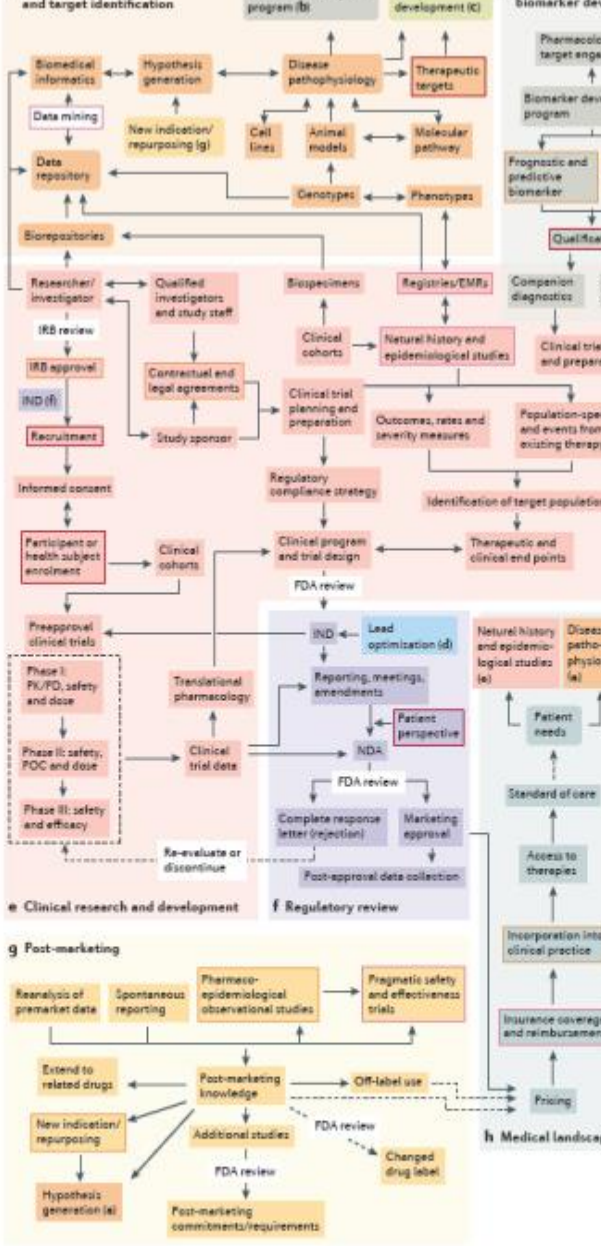


Тіркелген дәрі-дәрмектердің саны (1899-2018)

Орташа: жыл сайын ~80 дәрі (1999-2018)

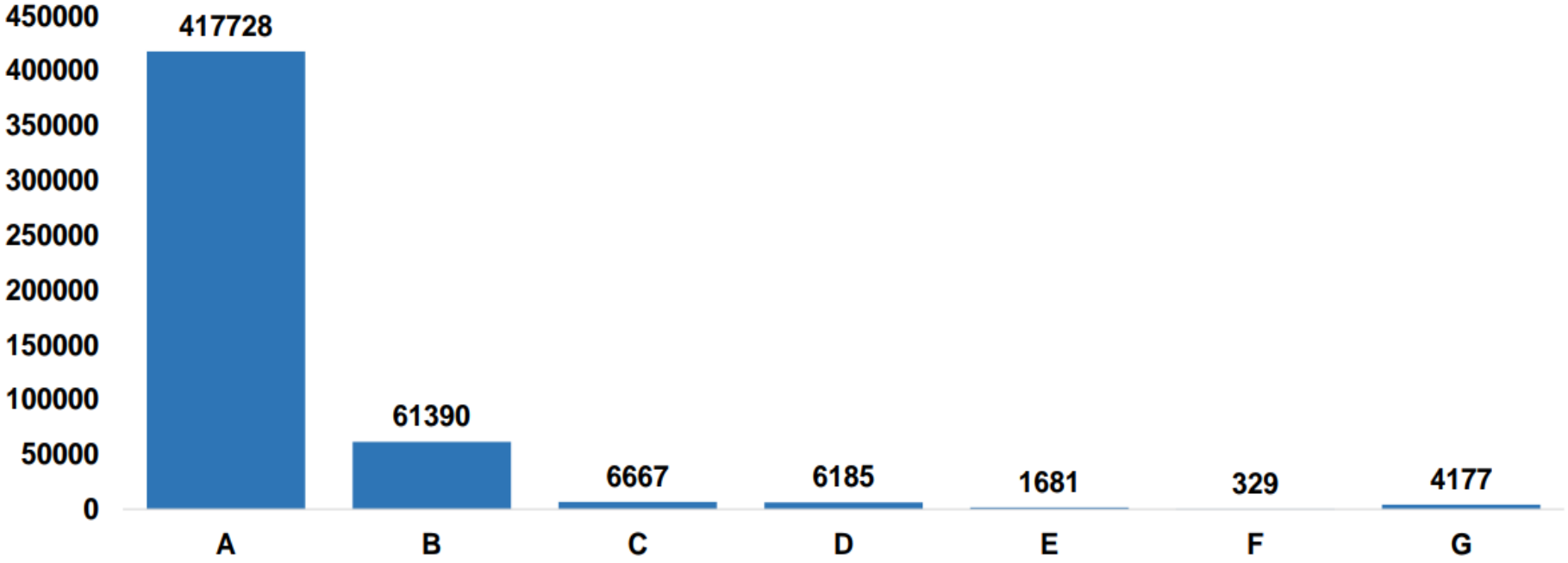
Дереккөз: Clarivate Analytics Integrity





Yap и Workman, Annu.Rev.Pharmacol.Toxicol., 2012
Wagner J. et al. Nature Reviews Drug Discovery, 2017. doi: 10.1038/nrd.2017.217
Poroikov V., Druzhilovskiy D. In: *In Silico Drug Design*, Ed. Runal Roy, Academic Pr

Химия-биологиялық әрекеттесу мәліметтері



Тестілеудің әртүрлі кезеңдеріндегі хим. қосылыс саны ДП жасау мақсатында:
A-биологиялық сынақтар;
B- клиникаға дейінгі зерттеулер;
C, D және **E** - клиникалық зерттеулер (сәйкесінше I, II және III фазалар);
F- тіркеу;
G - медициналық қолдануға рұқсат алынды

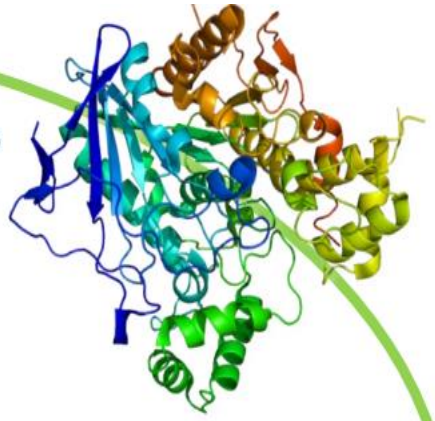
Дружиловский Д.С. Известия Академии наук. Серия химическая, 2017, (10), 1832-1841

Химиялық-биологиялық өзара әрекеттесу деректері



Ауыру

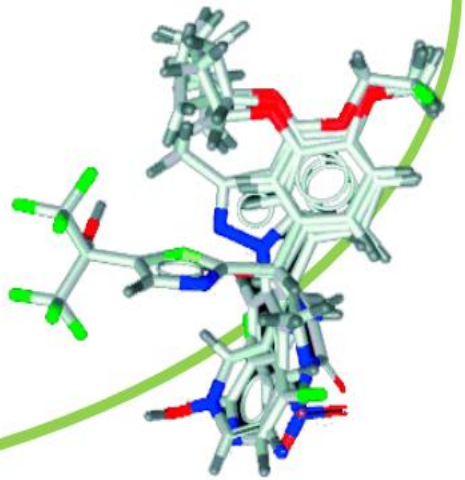
Мишень

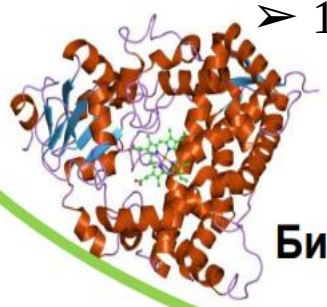


Дәріге ұқсас органикалық қосылыстар

- ➢ 100 млн синтезделген
- ➢ 1.75 млрд SAVI-2020
- ➢ 166 млрд GDB-17
- ➢ 1030 – 1060 мүмкін

Лиганд

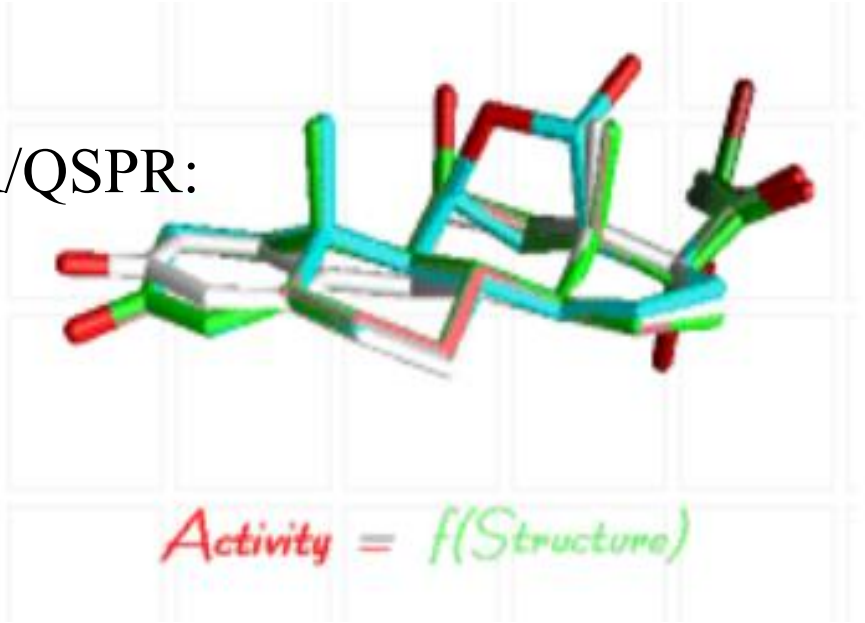




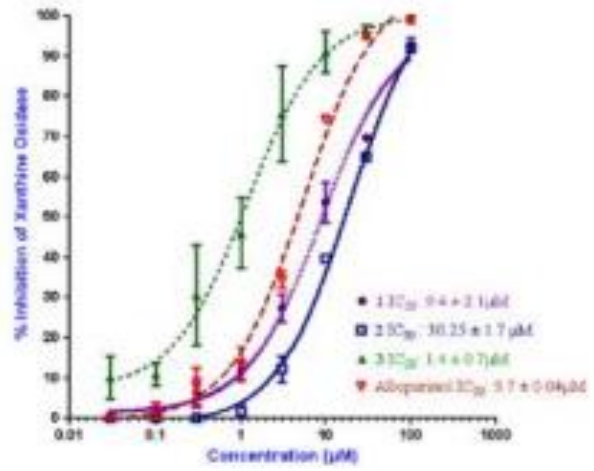
Биотрансформация

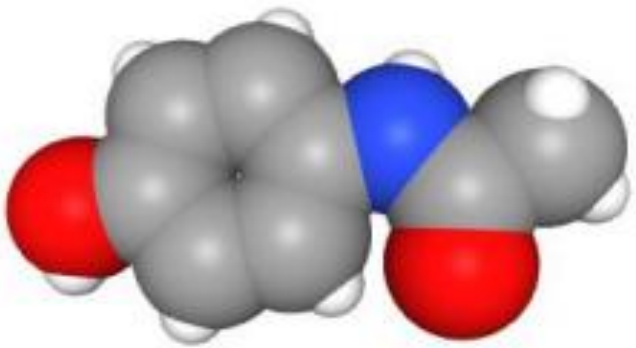
В. В. Поройков, Биомедицинская химия, 2020 том 66, вып. 1, с. 30-41.

Негізгі догма SAR/QSAR/QSPR:

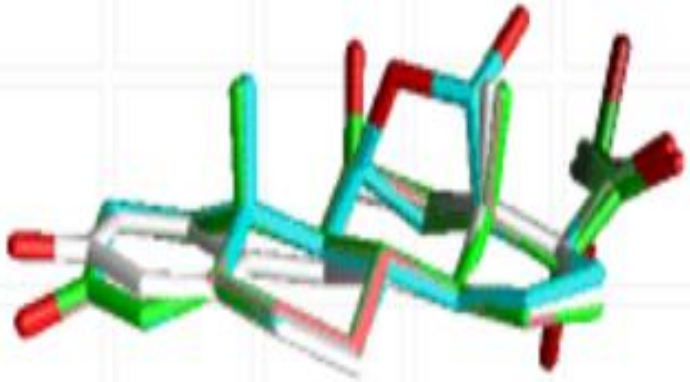


Белсенділік = Функция (Құрылымы)





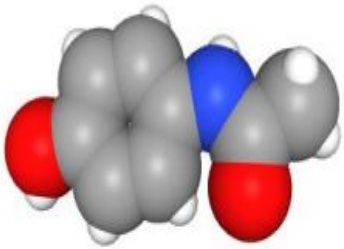
Негізгі догма SAR/QSAR/QSPR:

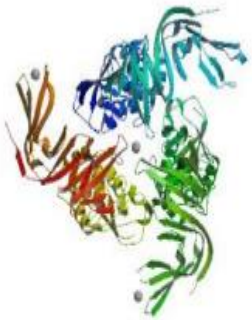


Activity = f(Structure)

26 of 550 Possible Pharmacological Effects a

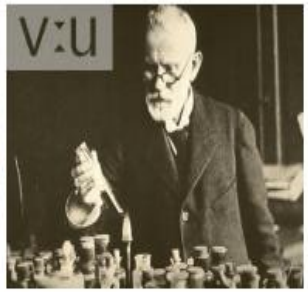
0.879	0.008	Immunostimulant (HIV)
0.860	0.003	Antidote, cyanide
0.852	0.004	Alopecia treatment
0.788	0.014	Antiseborrheic
0.702	0.006	Anterior pituitary suppressant
0.683	0.022	Fibrinolytic
0.687	0.027	Sialagogue
0.662	0.004	Leukopoiesis inhibitor
0.693	0.049	Ionotropic
0.656	0.019	Mucositis treatment
0.652	0.025	Antiviral (Arbovirus)
0.625	0.007	Antipyretic
0.609	0.016	Gastroprotector
0.606	0.014	Immunomodulator (HIV)
0.592	0.008	Erythropoiesis stimulant
0.593	0.012	Leukopoiesis stimulant
0.579	0.029	Gastric secretion stimulant
0.565	0.018	Vasodilator, renal
0.546	0.004	Antiuremic
0.539	0.005	Allergic conjunctivitis treatment
0.545	0.023	Respiratory analeptic
0.529	0.026	Skin diseases treatment
0.517	0.016	Natural killer cell stimulant
0.516	0.018	Cardiovascular analeptic
0.512	0.026	Antiinflammatory, intestinal
0.515	0.030	Potassium sparing diuretic



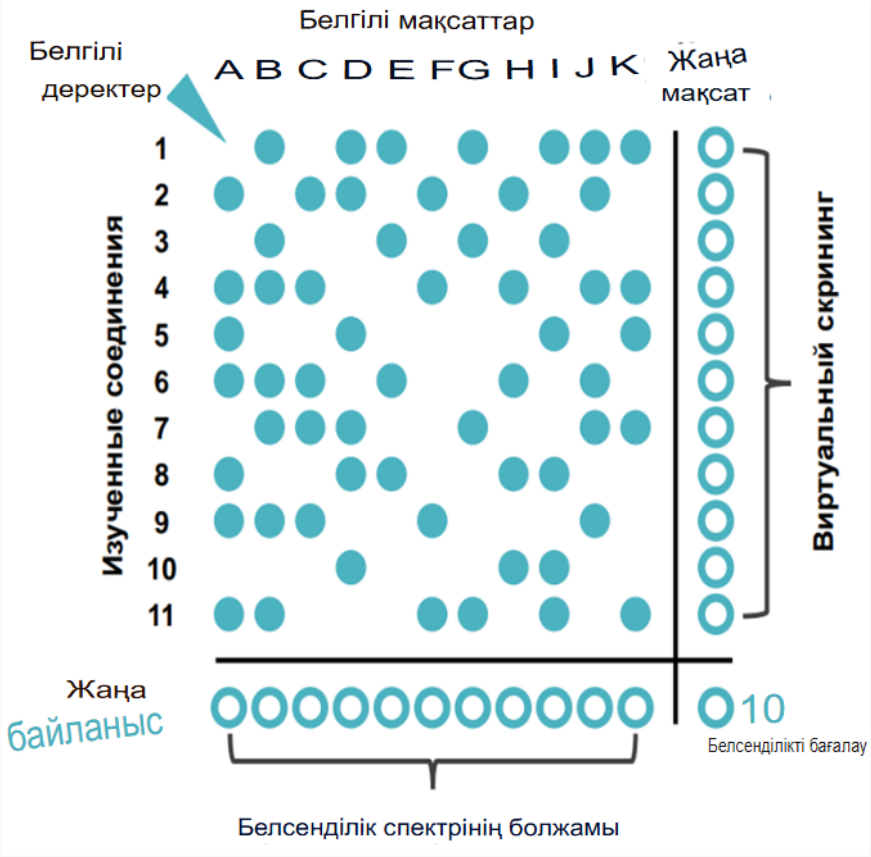








Tarasova O.A. et al., J. Chem. Inform. Model., 2015, 55(7), 1388-99. doi: 10.1021/acs.jcim.5b00019.



Виртуалды скрининг міндеті - тұжырымдалған талаптарға сәйкес келетін көптеген мүмкін органикалық қосылыстардың ішінен таңдау.

Биологиялық белсенділік спектрін болжау міндеті - көптеген ықтимал биологиялық белсенділіктің ішінен тұжырымдалған талаптарға сәйкес келетінін таңдау.

Екі жағдайда да көптеген мүмкіндіктердің ішінен *ең жақсы жиынтықты* таңдау қажет.

= Функция (Құрылым, Мақсат)

Poroikov, Filimonov. «Multitarget profiling» in: Muratov E.N. et al. QSAR without borders. Chemical Society Reviews, 2020, 49, 3525-3564. DOI: 10.1039/d0cs00098a.



1992
PASS бірінші нұсқасы:
9 314 BAV, 114 АК, 0.85 ТР

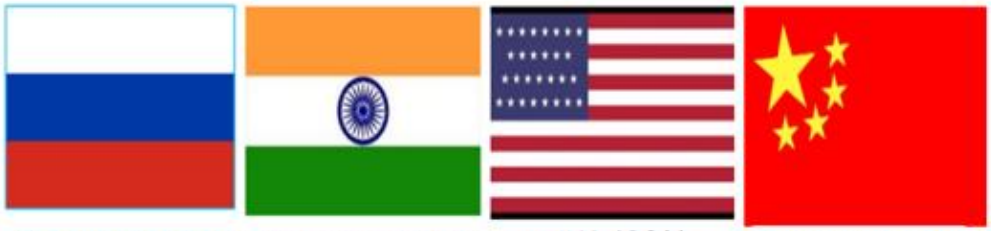
1998
PASS жаңа нұсқасы:
31 000 БАВ, 435 АК, 0.94 ТП

1999
Интернеттегі алғашқы pass программaline бағдарламасы

2009
PASS жаңа нұсқасы:
206 000 БАВ, 3 750 АК, 0.95 ТП

2021
PASS жаңа нұсқасы:
1 370 000 БАВ, 7 500 АК, 0.95 ТП

2021: 20 веб-қызмет
PASS Статистline статистикасы:
1 137 046 болжам;
> 1 200 жарияланым;
әлемнің 104 елінен 30 758 пайдаланушы
> 1 200 жарияланым;



Ресей (27,6%) Үндістан (12,4%) АҚШ (8%) Қытай (5,3%)

1990 2000 2010 2021

Оқыту үлгісіндегі БАВ-К-в қосылыстары; АК-К-в белсенділіктің болжамды түрлері;
ТП-болжамның орташа инвариантты дәлдігі

C:\4444\Chemistry\World Wide Approved Drugs\WWAD2020.sdf

5x5 | 4x4 | 3x3 | 2x2 | Molecular Structure | MNA

Known | Effects | Mechanisms | Toxicity | Antitargets | Metabolism | Gene Expression

369

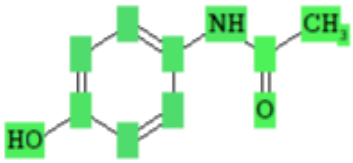
370

371

372

373

374



27 of 561 Possible Pharmacological Effects at Pa > 0.500

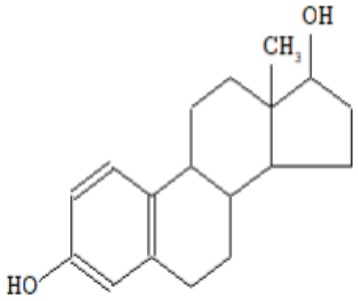
0.882	0.008	Immunostimulant (HIV)
0.853	0.004	Alopecia treatment
0.789	0.015	Antiseborrheic
0.714	0.012	Kidney function stimulant
0.688	0.013	Antineoplastic (basal cell carcinoma)
0.674	0.004	Leukopoiesis inhibitor
0.682	0.023	Fibrinolytic
0.694	0.050	Ionotropic
0.654	0.026	Antiviral (Arbovirus)
0.627	0.015	Immunomodulator (HIV)
0.619	0.018	Mucositis treatment
0.603	0.008	Antipyretic
0.611	0.016	Gastroprotector
0.592	0.008	Erythropoiesis stimulant
0.594	0.012	Leukopoiesis stimulant
0.557	0.005	Allergic conjunctivitis treatment
0.565	0.017	Vasodilator, renal
0.547	0.004	Antiuremic
0.528	0.017	Hepatitis alcoholic treatment
0.535	0.025	Respiratory analeptic
0.531	0.026	Skin diseases treatment
0.519	0.017	Natural killer cell stimulant
0.518	0.018	Cardiovascular analeptic
0.542	0.052	Hepatitis treatment
0.515	0.026	Antiinflammatory, intestinal
0.515	0.031	Potassium sparing diuretic
0.560	0.107	Antineoplastic (Kaposi's sarcoma)

> <Name>
paracetamol

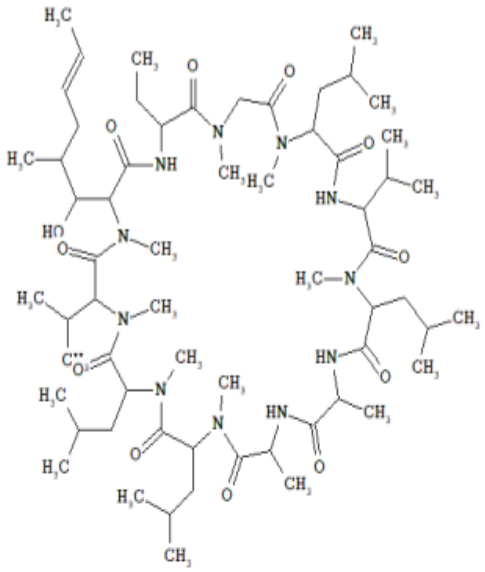
24 Substructure Descriptors; 0 new. Mol.Mass: 151.16.
There are 775 known activities.
2348 of 8438 Possible Activities
27 of 561 Possible Pharmacological Effects
245 of 4617 Possible Mechanisms of Action
344 of 692 Possible Toxic and Adverse Effects
2 of 161 Possible Antitargets
24 of 225 Possible Metabolism-Related Actions
1719 of 2414 Possible Gene Expression Regulation
0 of 86 Possible Transporters-Related Actions

371/4223 | 0.882 0.008 Immunostimulant (HIV)

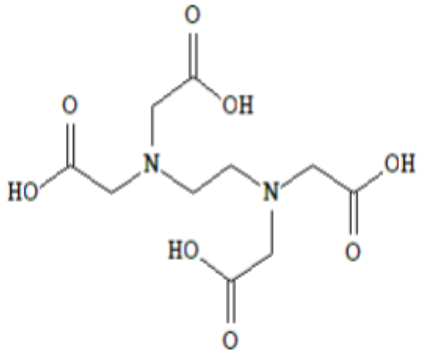
Филимонов Д.А. и др., Biomedical Chemistry: R&M, 2018, 1(1), e00004. DOI: 10.18097/BMCRM00004



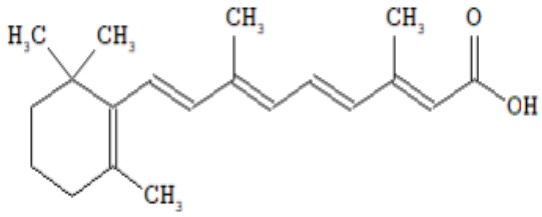
Estradiol 35 MNA 1289 AK



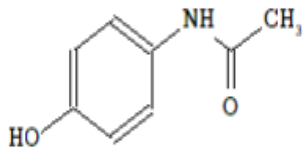
Ciclosporin 59 MNA 1134 AK



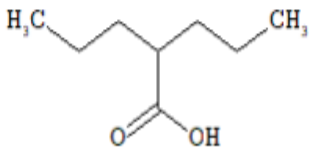
Edetic Acid 15 MNA 864 AK



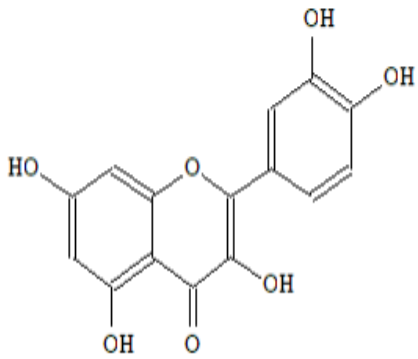
Tretinoin 34 MNA 1282 AK



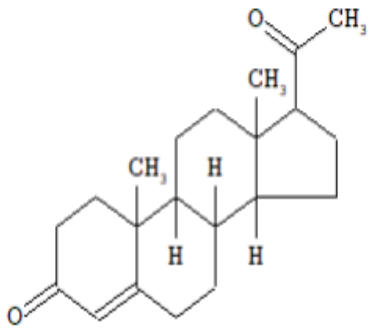
Paracetamol 24 MNA 775 AK



Valproic Acid 19 MNA 1251 AK

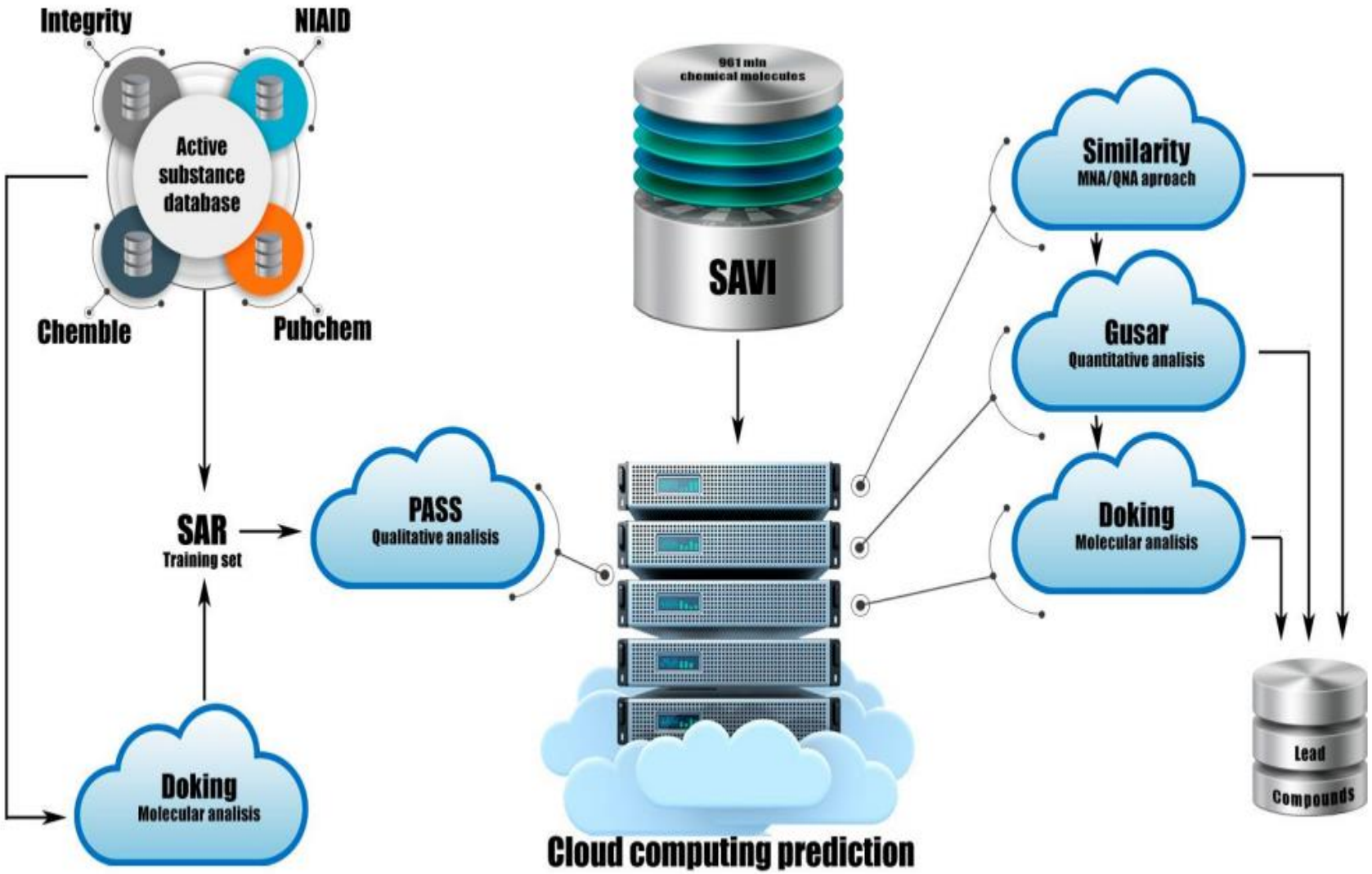


Quercetin 27 MNA 952 AK



Progesterone 33 MNA 656 AK

Кезеңді стратегия: Big Data химиялық скрининг



Druzhilovskiy D.S. et al. Supercomputing Frontiers and Innovations, 2020, 7 (3), 57-76.
DOI: 10.14529/jsfi200306

PASS болжамы көптеген жағдайларда синтез үшін ең перспективті қосылыстарды таңдауға және олардың биологиялық белсенділігін тексерудің басым бағыттарын анықтауға мүмкіндік берді



>1000 публикаций