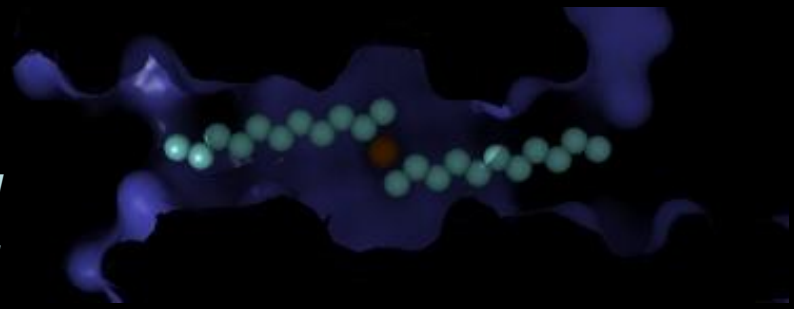
An Overview of FDA Approved Small-Molecule Pharmacopeia

Dominique Douguet

BigChem School – 19-21th of April 2017

Neurosciences
&
Pharmacology

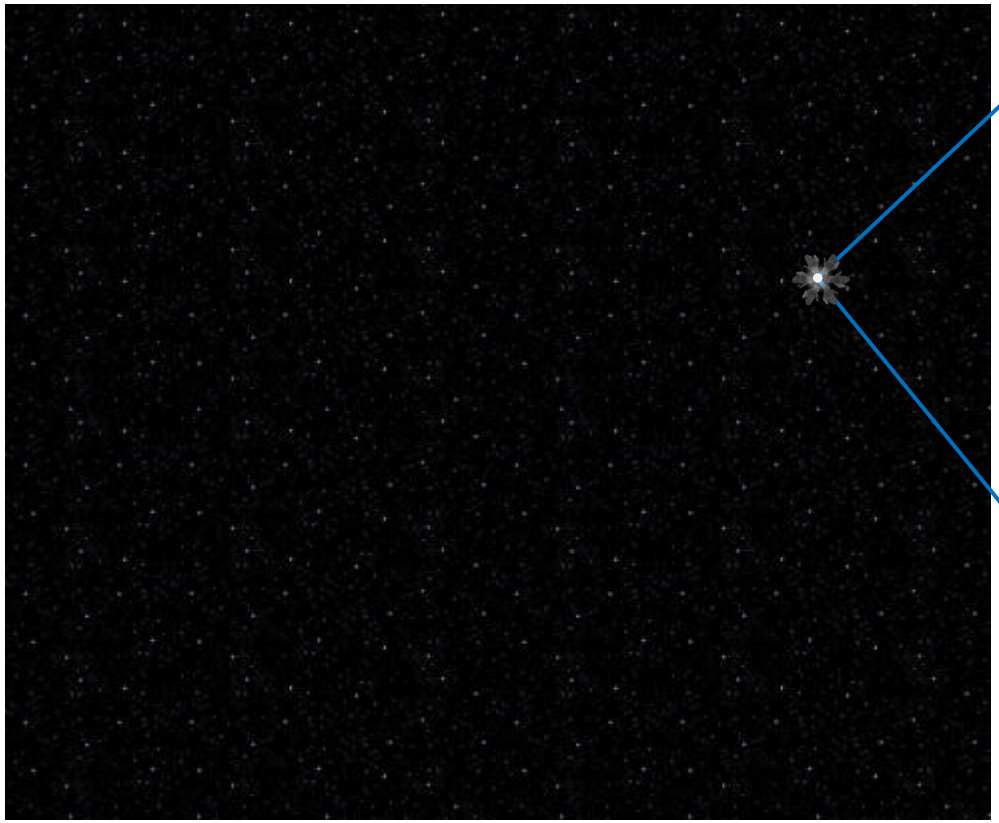
Genomic platform,, small G proteins, vesicular transport, immunology…



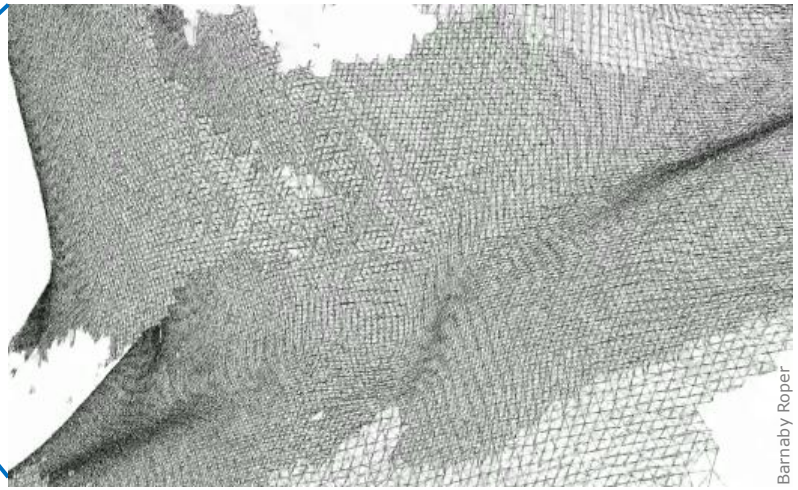
Institut de Pharmacologie Moléculaire et Cellulaire, UMR 7275 CNRS - Université Nice Sophia Antipolis, France

Chemical Space

Chemical universe



10^{60} 'druglike' molecules



« **The chemist as astronaut**: Searching for biologically useful space in the chemical universe »
D. Triggle, *Biochem.Pharmacol.*, 2009.

'Druglike': C, N, O, S, P, H, Cl, Br, F, I and MW ≤ 500 (Dobson C.M., *Nature*, 2004)

Chemical Space & Screening

10^{80}
atoms
in the Universe *

10^{60}
'druglike' molecules
(theoretically **)

10^{20}
sand grains
in the dune

10^{17}
seconds
age of the Earth

10^{7}
isolated molecules

Dune of Pilat

« The chemist as astronaut »

- **CAS: ~70.10^6**
  (organics/inorganics)

- **Pharmacology:**

Commercial: 10^6 (screening libraries)

Naturals: 10^6 (theoretically)
$< 0.1.10^6$ (isolated (**10%**))

Toxins: 20.10^6 (theoretically)
$\sim 0.2.10^6$ (UniProtKB (**1%**))

FDA approved small-molecule drugs ≈1800 structures (with MW ≤ 2000)

** 'Druglike': C, N, O, S, P, H, Cl, Br, F, I and MW ≤ 500 (Dobson C.M., *Nature*, 2004)
* Source: C. Magnan, Collège de France, http://www.lacosmo.com/dixpuissance80.html

Pharmacology

Pharmacopeia

Approved drugs are the most studied small molecules for their function and effects on Humans

What we know:

- **Chemical Structures**
  - **Physico-chemical properties**
  - **Privileged structures**
- **Registration Data**
  - **History**
- **Pharmacodynamics**
  - **What the drug does to the body**
- **Pharmacokinetics**
  - **What the body does to the drug**

Source: Drugs@FDA Data File; drug label; SciFINDER/CAS; WHO/ATC; PubMed; DailyMed (U.S. National Library of Medicine); Drugs.com; VIDAL

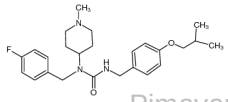
e-Drug$_{3D}$

What we know:

Mirror of the FDA content

1557 princeps / 1822 different structures with MW ≤ 2000 [1939 – 2016] (last update: July 2016)

❑ Chemical Structures



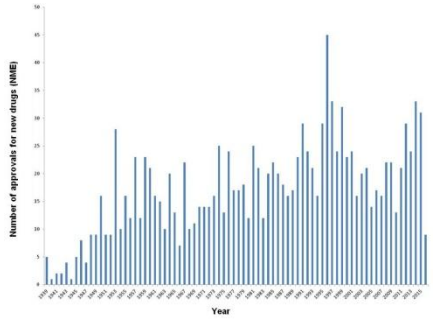
Pimavanserin (2016)

Physico-chemical properties (calculated)
1D/2D (MW, LogP, PSA, solubility, nbHBD, nbHBA, nbRot, charge…)
3D (conformations, shape …)

Privileged structures (fragments, scaffolds, frameworks, peptide, natural compounds…)

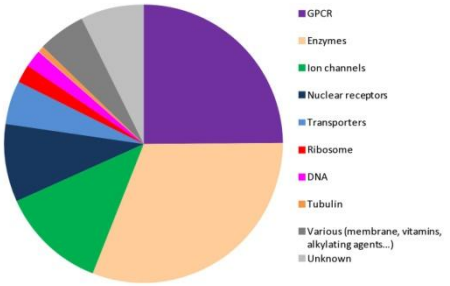
❑ FDA Registration Data

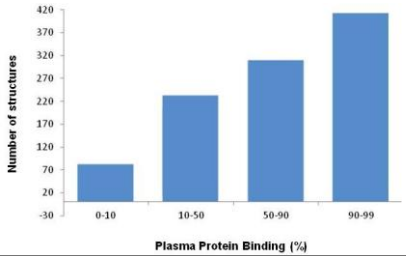
(Year, Company, label…)



❑ Pharmacodynamics

(Class, Target)





❑ Pharmacokinetics

(active metabolites, routes, VD, Cl, HT, PPB, F, Cmax…)

* e-Drug3D: release of July 2016

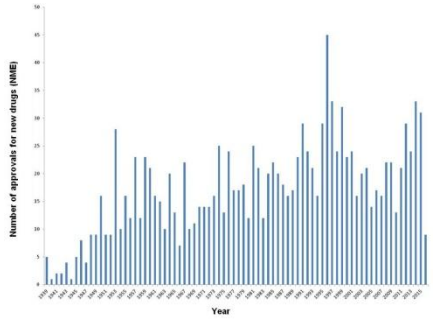
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

e-Drug$_{3D}$

What we know:

1557 princeps / 1822 different structures with MW ≤ 2000 [1939 – 2016] (last update: July 2016)

- **Chemical Structures**
  - **Physico-chemical properties**
  - **Privileged structures**
- **FDA Registration Data**
  (Year, Company, label…)



- **Pharmacodynamics**
  (Class, Target)
- **Pharmacokinetics**
  (metabolites, routes, VD, Cl, HT, PPB, F…)

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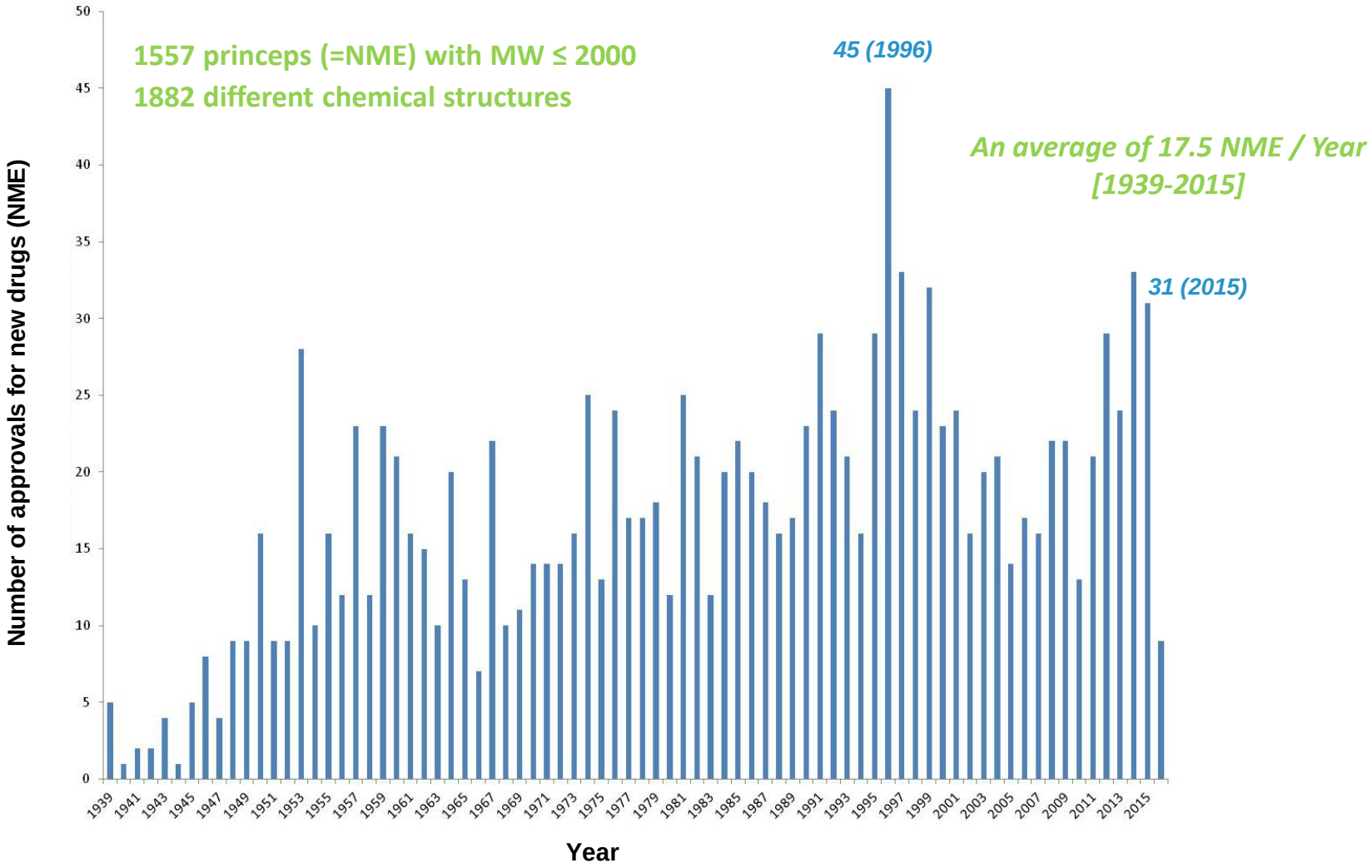
Statistics on Approvals

➢ **Statistics on approved drugs*: How many NME (new drugs) ?**



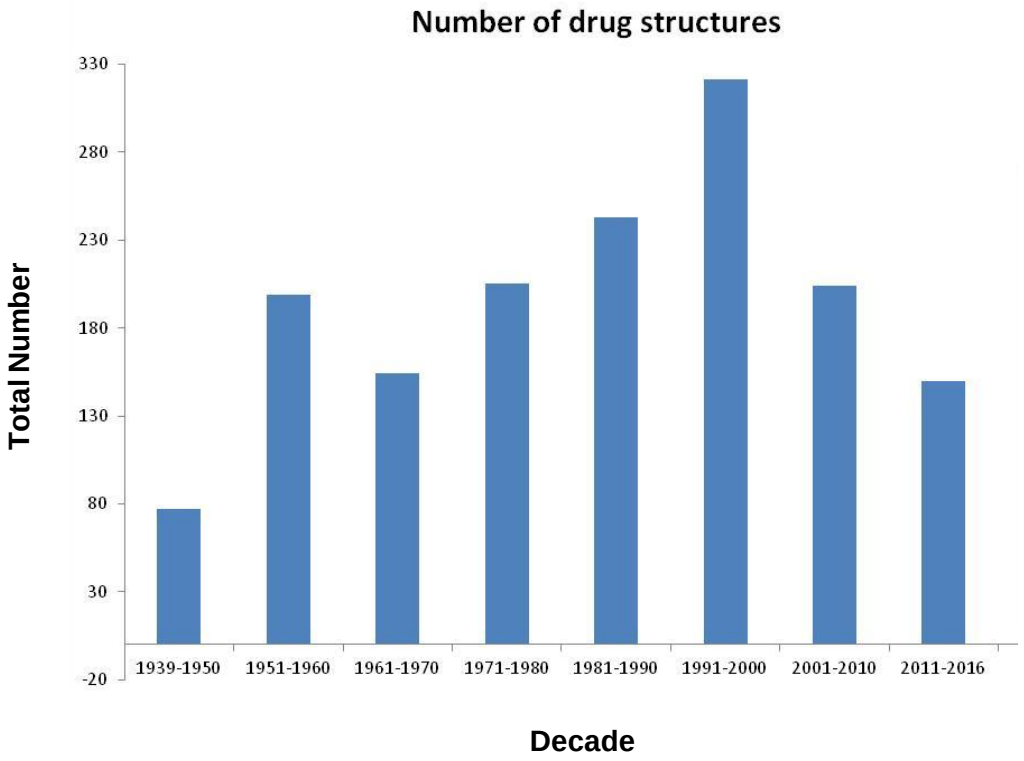
* e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures) - 372 discontinued structures - 218 without identified year of first approval
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

Statistics on Approvals

- **Statistics on approved drugs*: How many NME (new drugs) ?**

1557 princeps (=NME) with MW ≤ 2000

1882 different chemical structures



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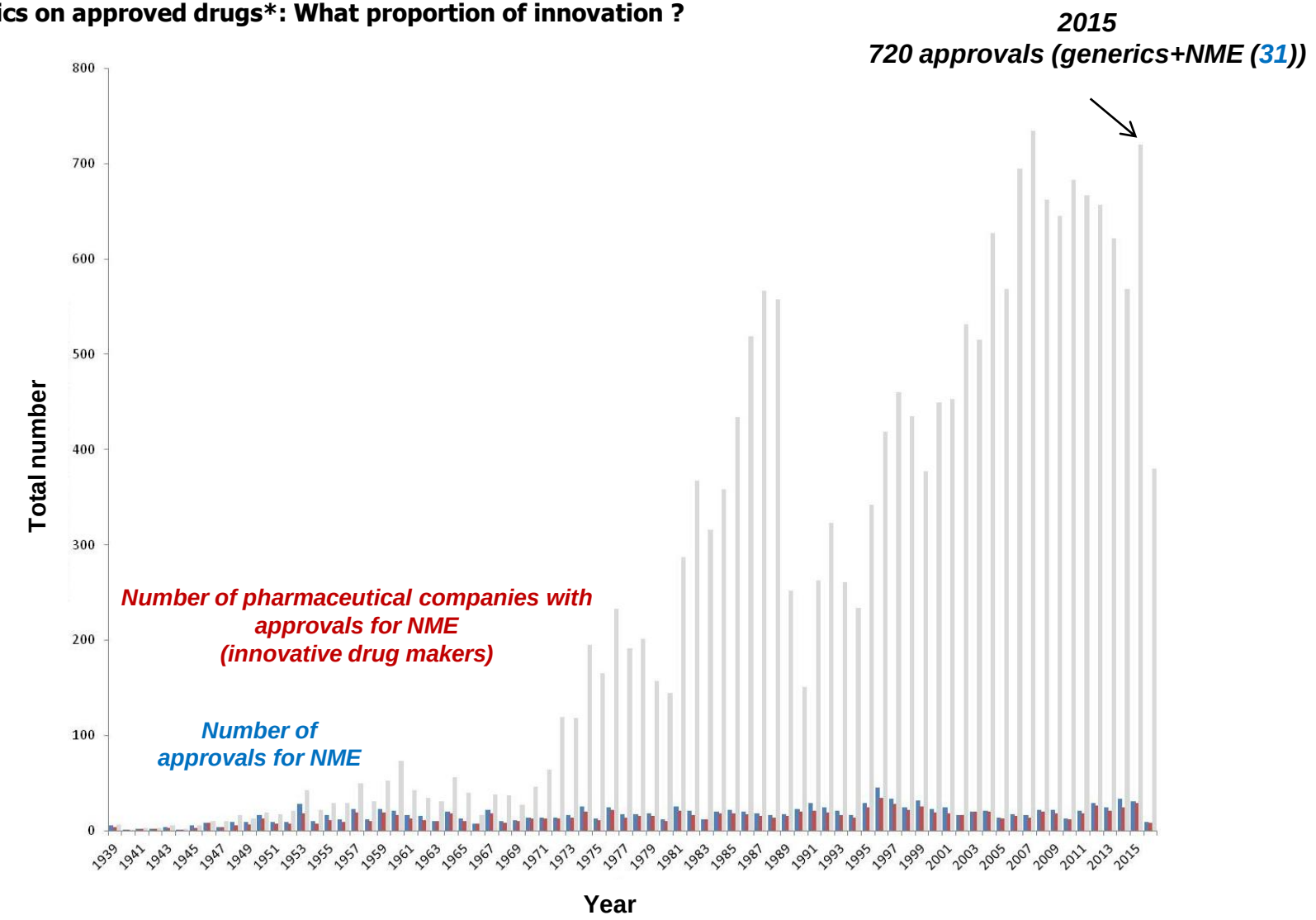
Statistics on Approvals

➢ **Statistics on approved drugs*: What proportion of innovation ?**



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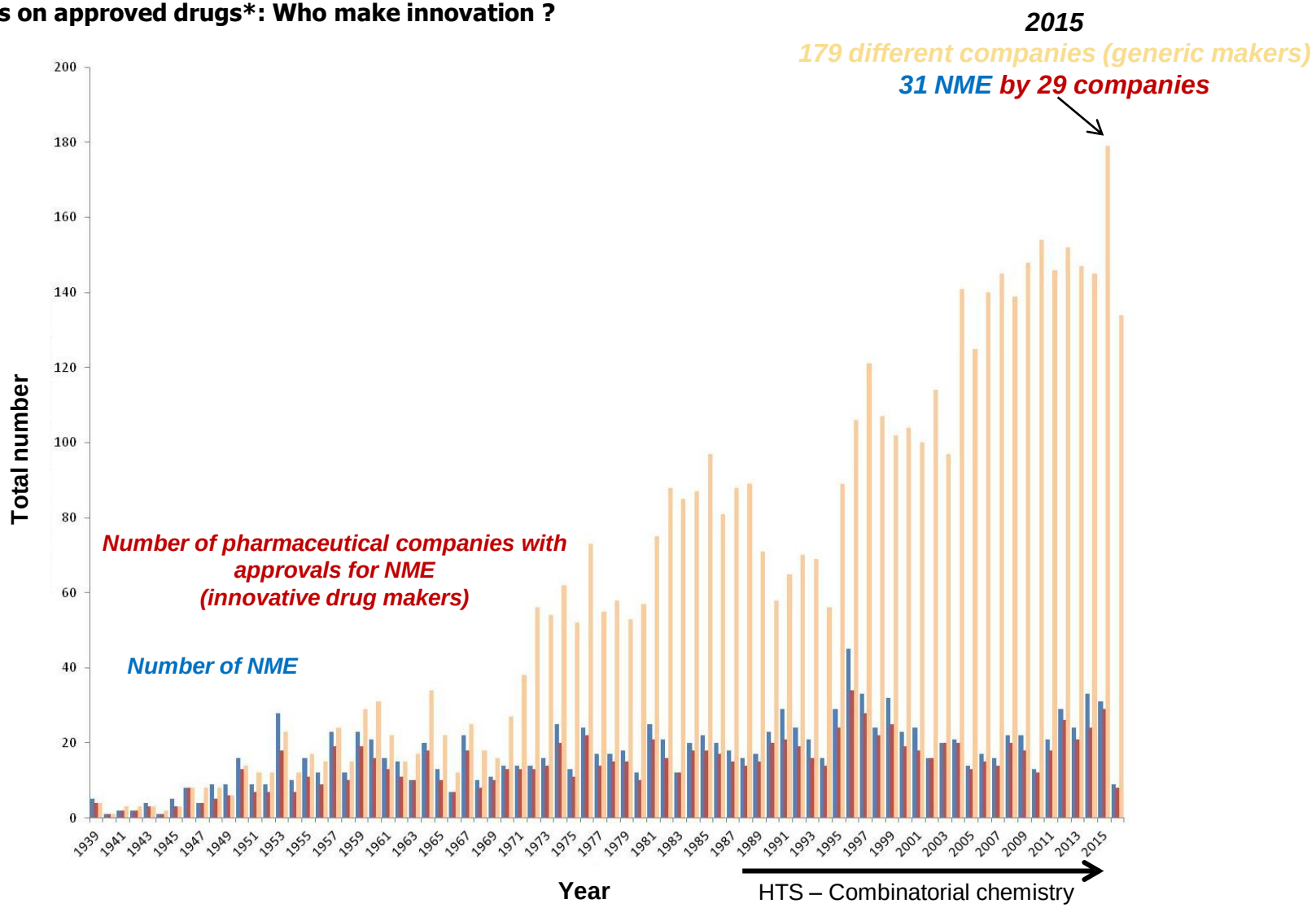
Statistics on Approvals

➢ **Statistics on approved drugs*: Who make innovation ?**



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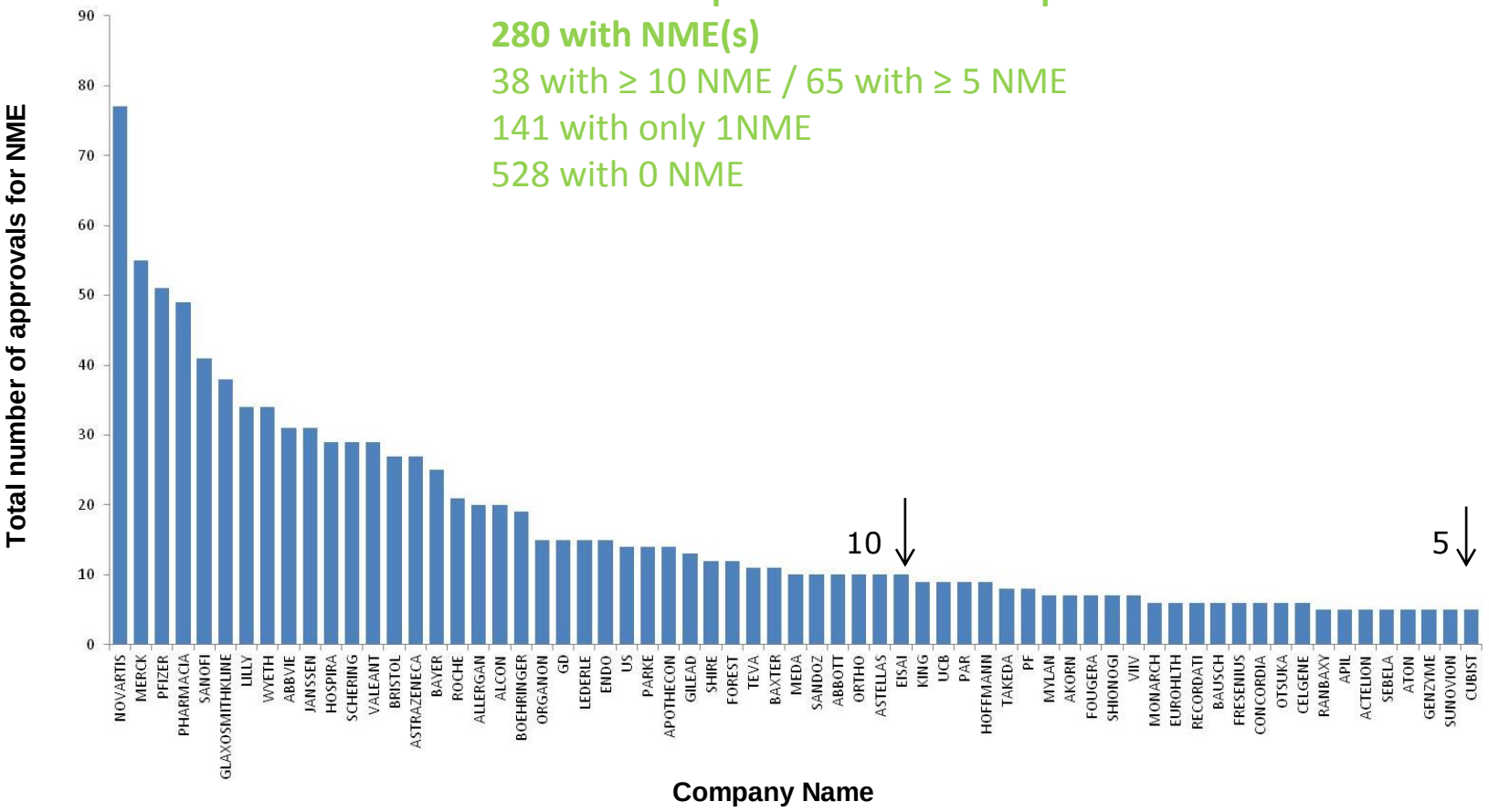
Statistics on Approvals

➢ **Statistics on approved drugs*: Who make innovation ?**

~800 different pharmaceutical companies names
280 with NME(s)
38 with ≥ 10 NME / 65 with ≥ 5 NME
141 with only 1NME
528 with 0 NME



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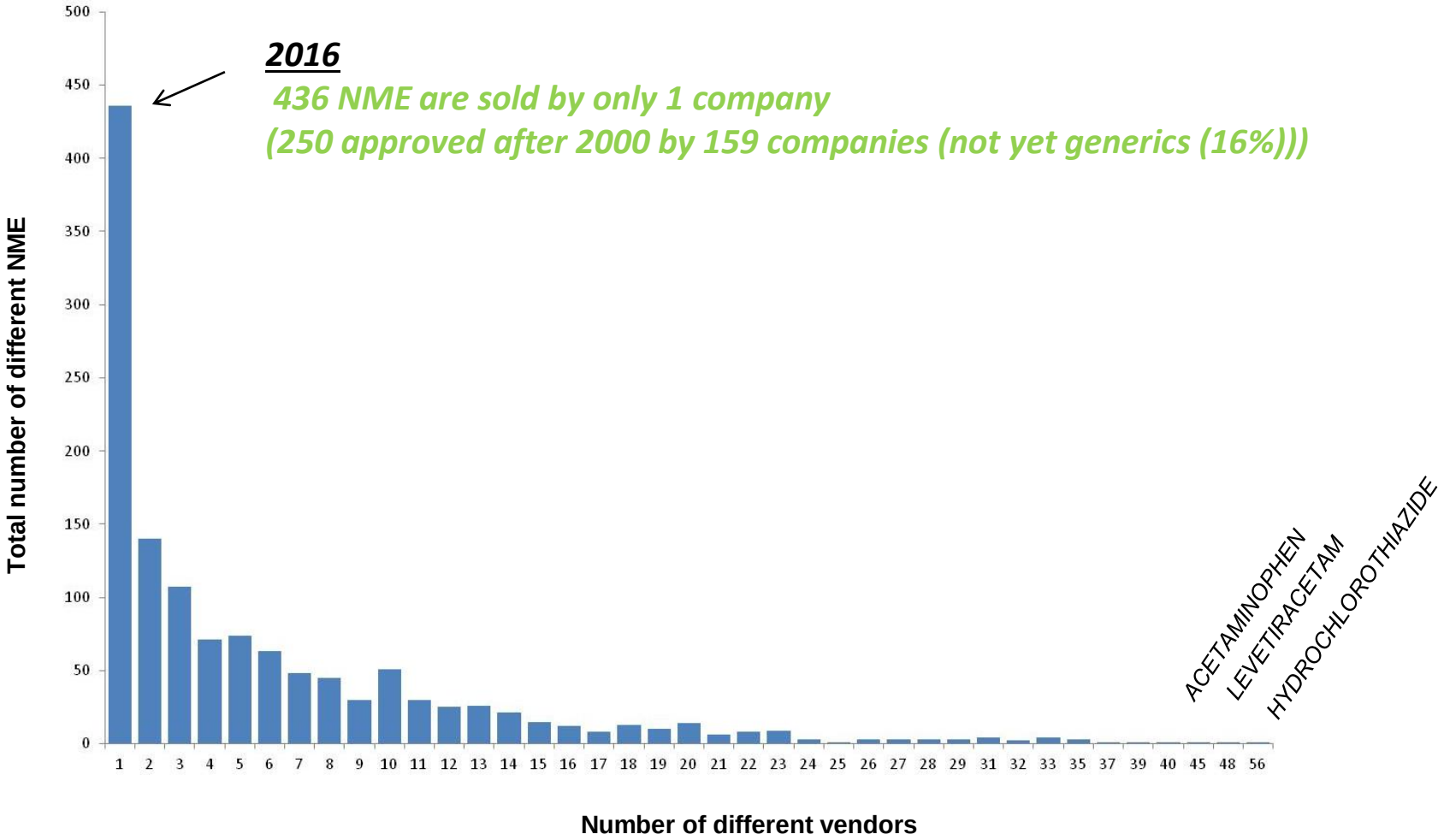
Statistics on Approvals

➢ **Statistics on approved drugs*: How many vendors / drug ?**



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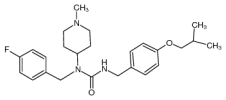
e-Drug$_{3D}$

What we know:

1557 princeps / 1822 different structures (July 2016)

❑ Chemical Structures



Pimavanserin (2016)

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  3D (conformations, shape …)
- **Privileged structures** (fragments, scaffolds, frameworks, peptide, natural compounds…)

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(Year, Company, label…)

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(Class, Target)

❑ Pharmacokinetics

(metabolites, routes, VD, Cl, HT, PPB, F…)

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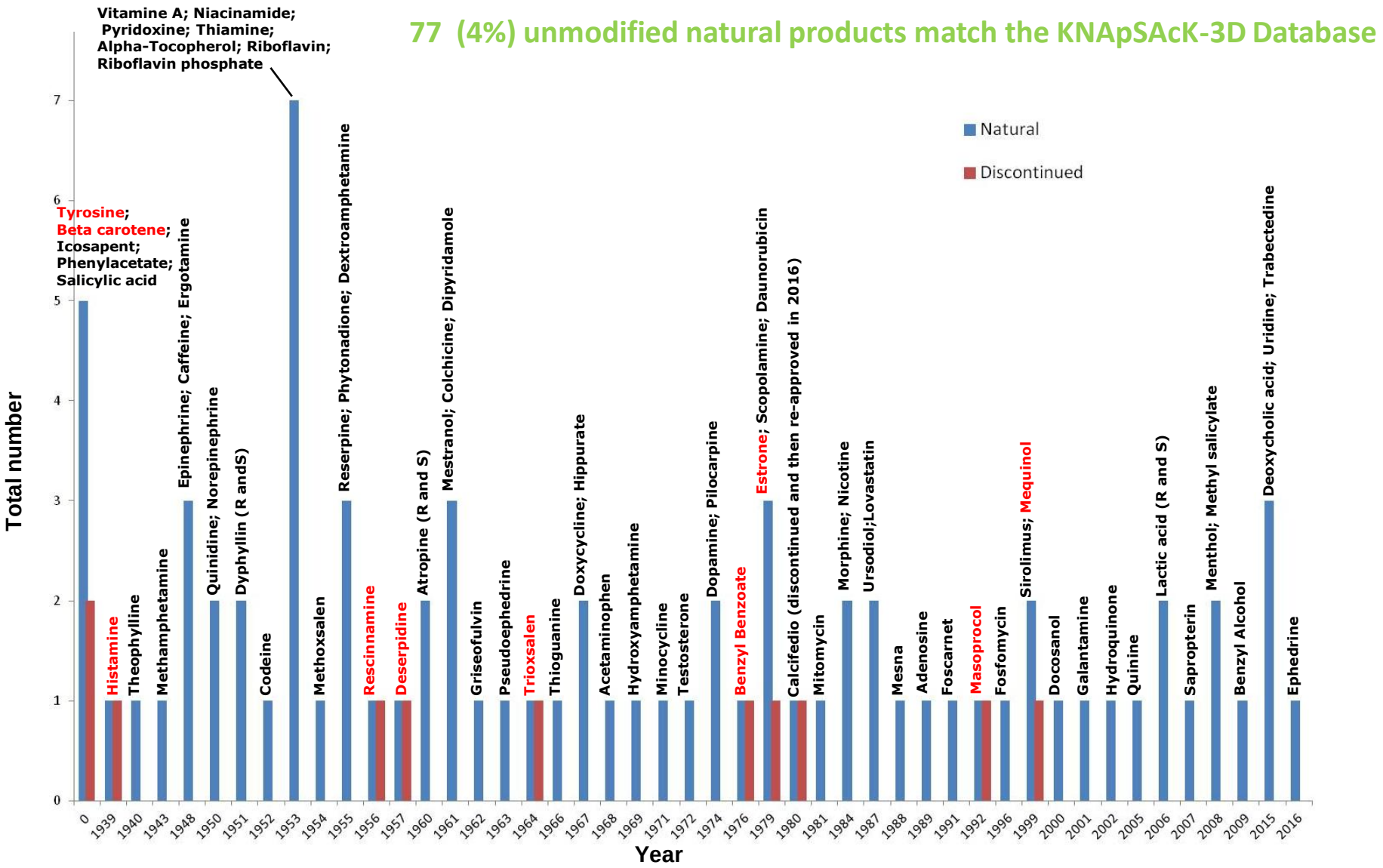
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

Diversity of Approved Drugs

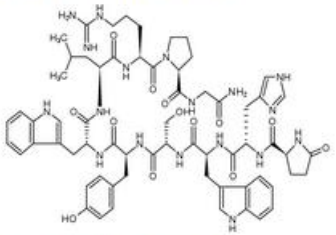
- **Statistics on approved drugs: origins of structures ?**



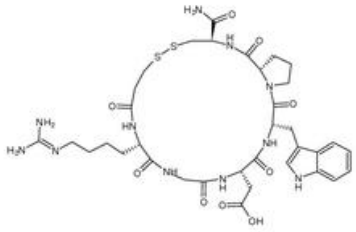
Diversity of Approved Drugs

18 modified peptides

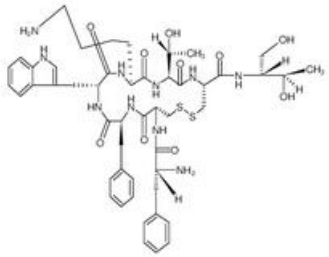
TRIPTORELIN Approved in 2000 (PDB entries)



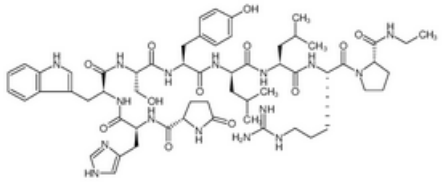
EPTIFIBATIDE Approved in 1998 (PDB entries)



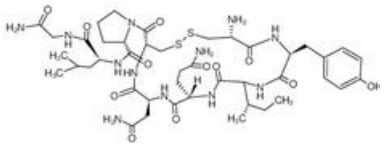
OCTREOTIDE Approved in 1988 (PDB entries)



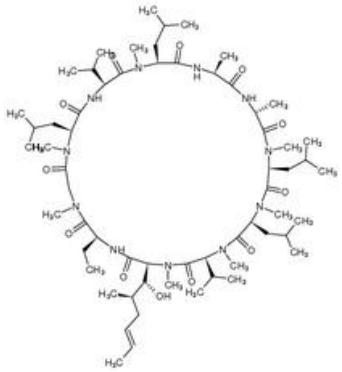
LEUPROLIDE Approved in 1985 (PDB entries)



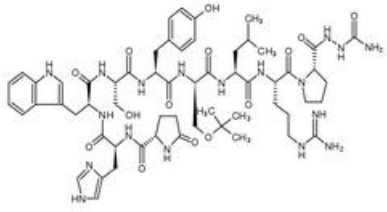
OXYTOCIN Approved in 1980 (PDB entries)



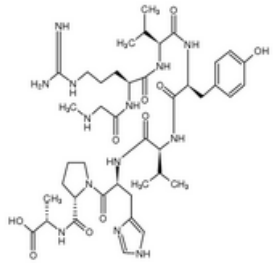
CYCLOSPORINE Approved in 1983 (PDB entries)



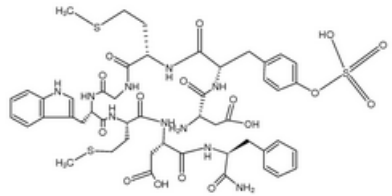
GOSERELIN Approved in 1989 (PDB entries)



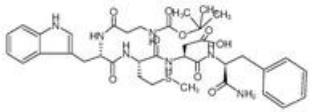
SARALASIN DISCONTINUED (PDB entries)



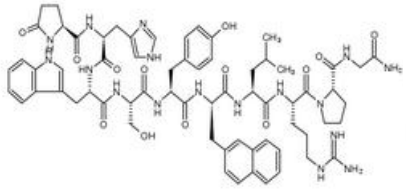
BINCALIDE Approved in 1976 (PDB entries)



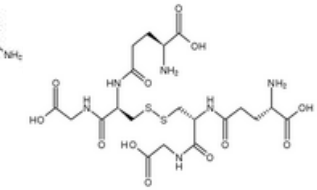
PENTAGASTRIN DISCONTINUED (Approved in 1974) (PDB entries)



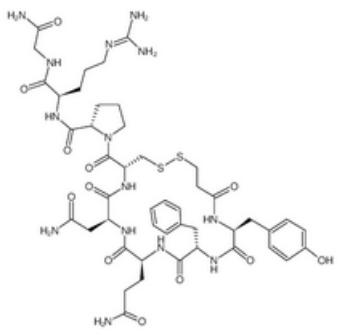
NAFARELIN Approved in 1990 (PDB entries)



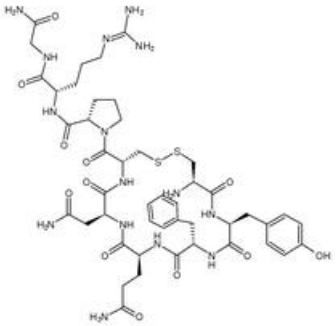
GLUTATHIONE DISULFIDE Approved in 1961 (PDB entry 1YKC)



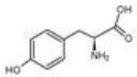
DESMOPRESSIN Approved in 1978 (PDB entries)



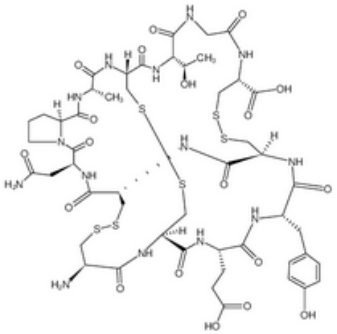
VASOPRESSIN (Re)approved in 2014 (PDB entries)



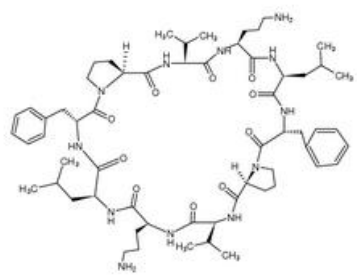
TYROSINE DISCONTINUED (PDB entry 4QBT)



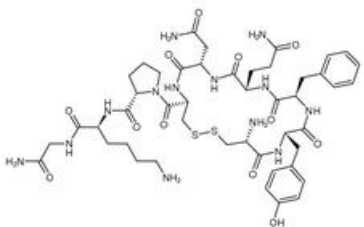
LINACLOTIDE Approved in 2012 (PDB entries)



GRAMICIDIN Approved in 1968 (PDB entries)

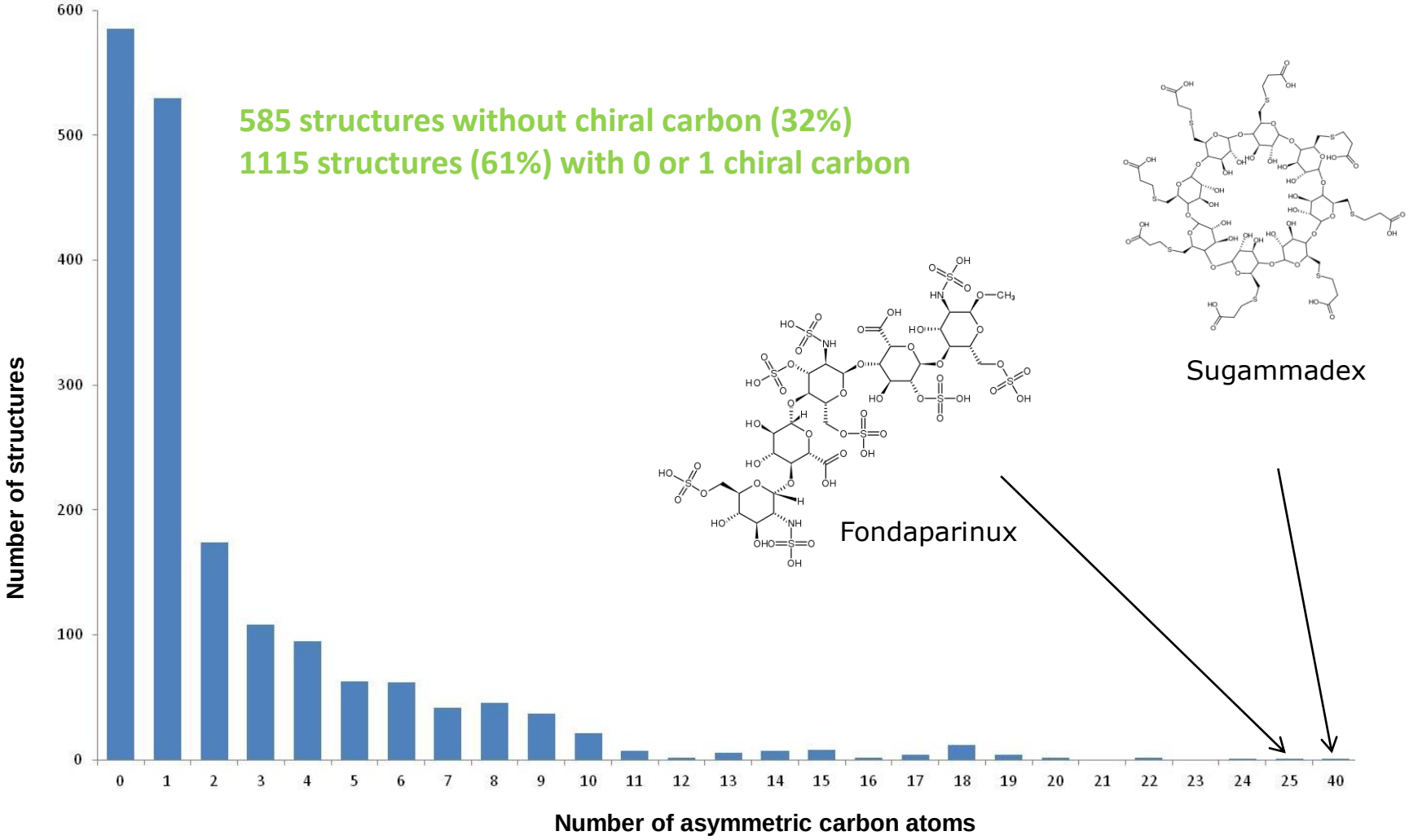


LYPRESSIN DISCONTINUED (PDB entries)



Structural Diversity of Approved Drugs

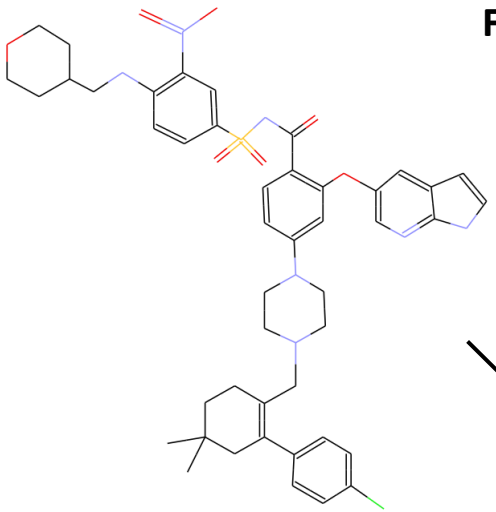
➢ **Statistics on approved drugs*: How many chiral carbons ?**



* e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures)
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

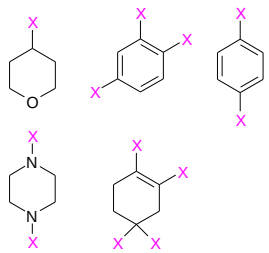
Drug-like Fragments

Venetoclax
BCL-2 Inhibitor

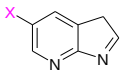


Fragments (legos)

rings

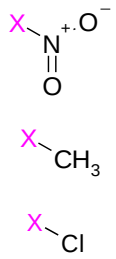


fused rings

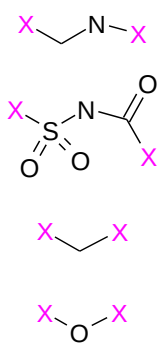


acyclics

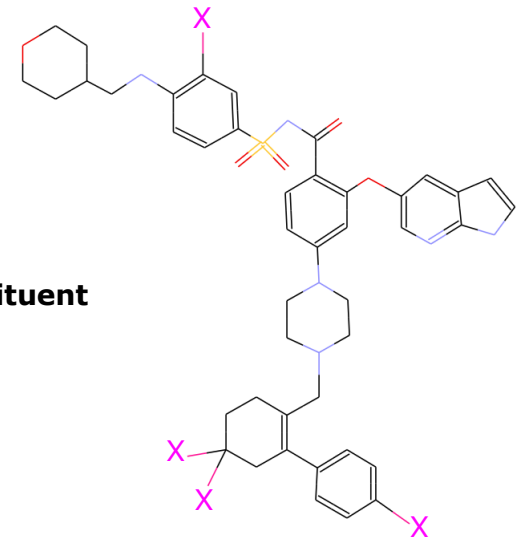
Substituents



linkers

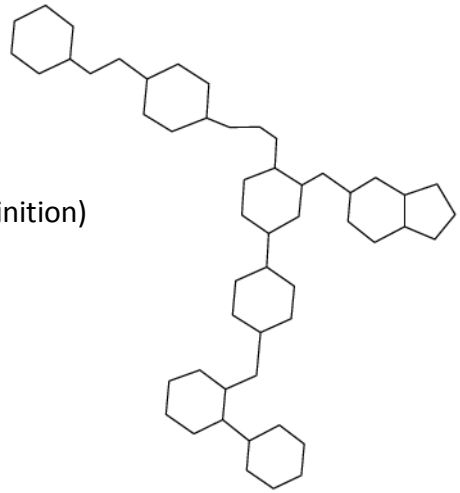


Scaffold



X : anchoring point for a substituent

Framework
(Bemis & Murcko definition)



e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures) - 1779 different legos - 1189 different scaffolds - 512 different frameworks
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

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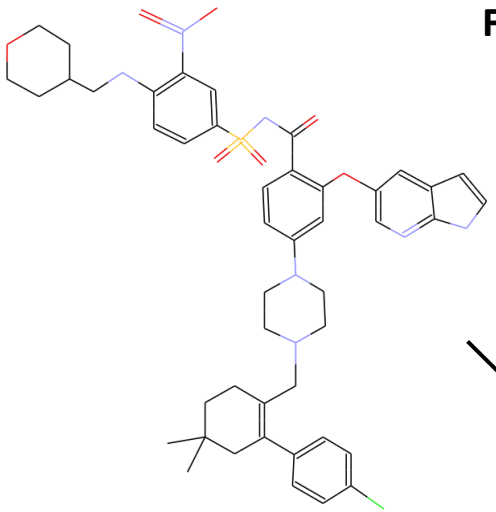
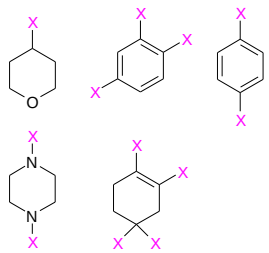
Venetoclax
BCL-2 Inhibitor

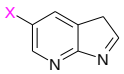


Fragments (legos)

rings

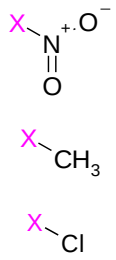


fused rings

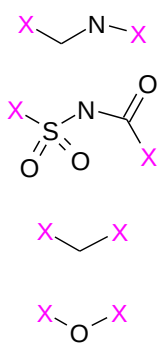


acyclics

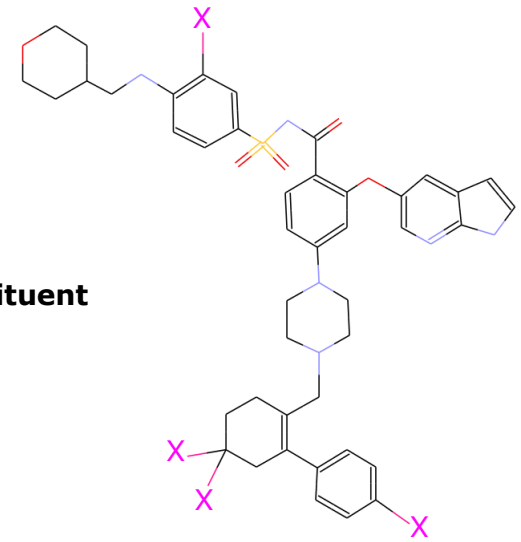
Substituents



linkers

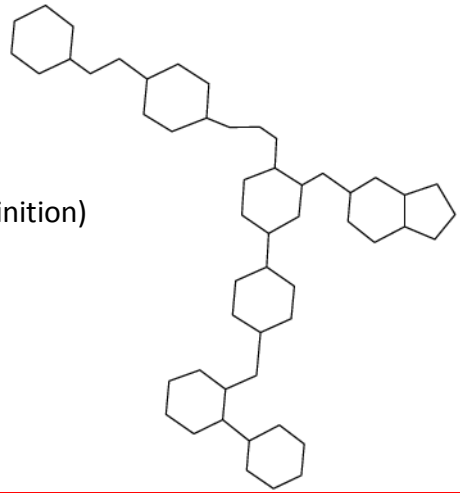


Scaffold



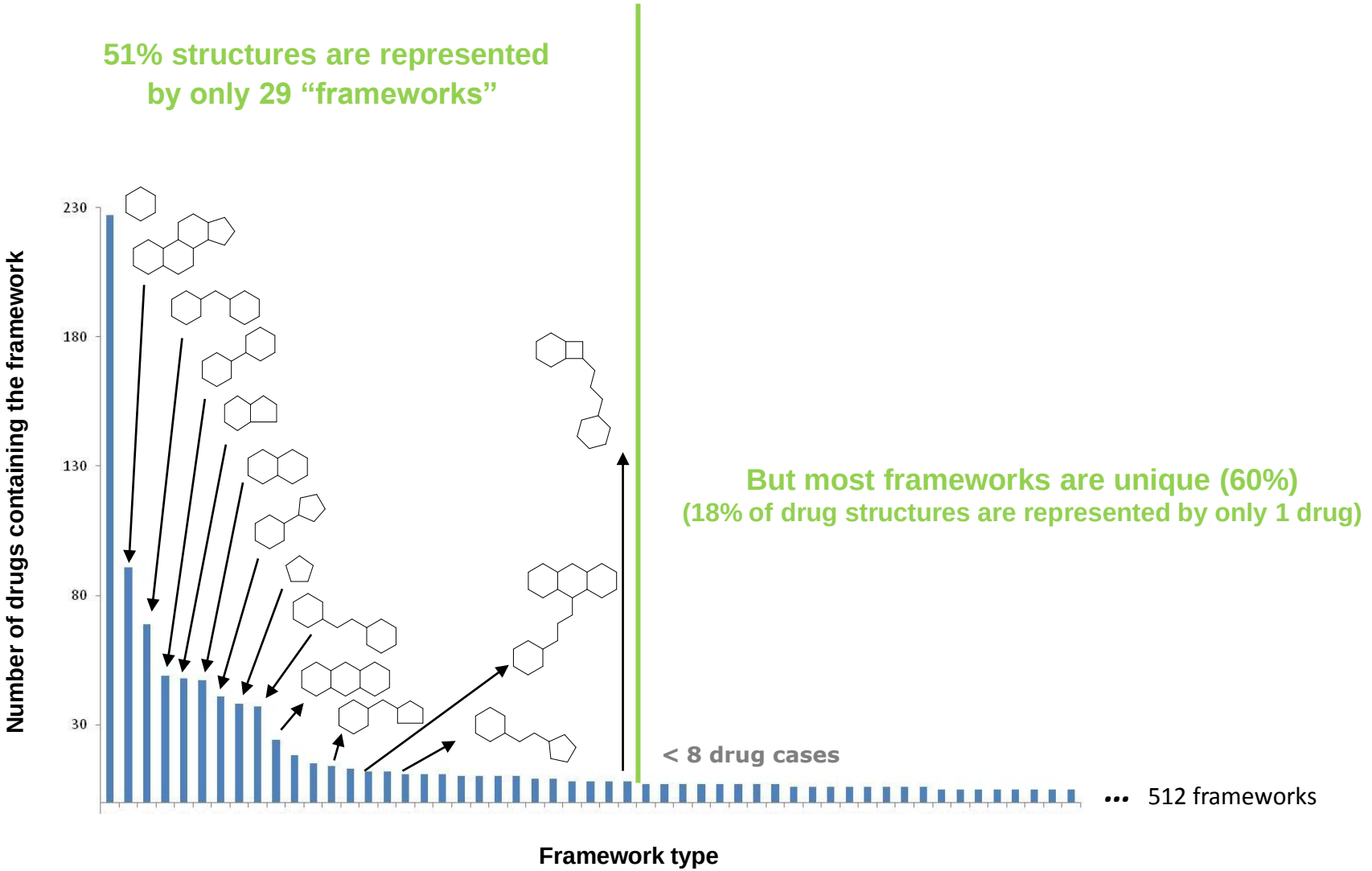
X : **anchoring point for a substituent**

Framework
(Bemis & Murcko definition)



e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures) - 1779 different legos - 1189 different scaffolds - 512 different frameworks
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

Drug Frameworks Diversity



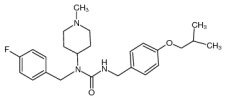
e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures) - 1189 different scaffolds (out of 1697) - 512 different frameworks
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

e-Drug$_{3D}$

What we want to know:

Structure-Activity Relationships

❑ Chemical Structures

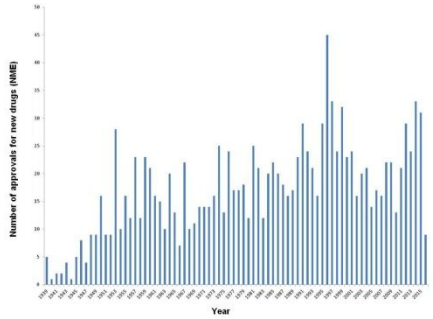


Pimavanserin (2016)

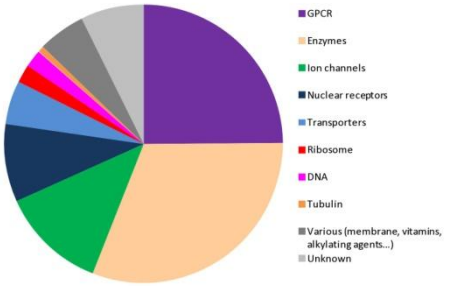
Physico-chemical properties
1D/2D (MW, LogP, PSA, solubility, nbHBD, nbHBA, nbRot, charge …)
3D (conformations, shape …)

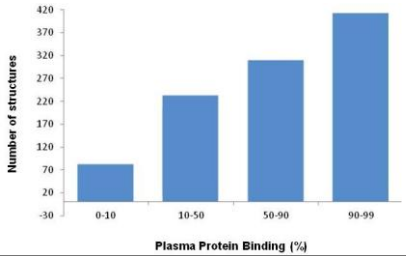
Privileged structures (fragments, scaffolds, frameworks, peptide, natural compounds…)

❑ FDA Registration Data
(Year, Company, label…)



❑ Pharmacodynamics
(Class, Target)

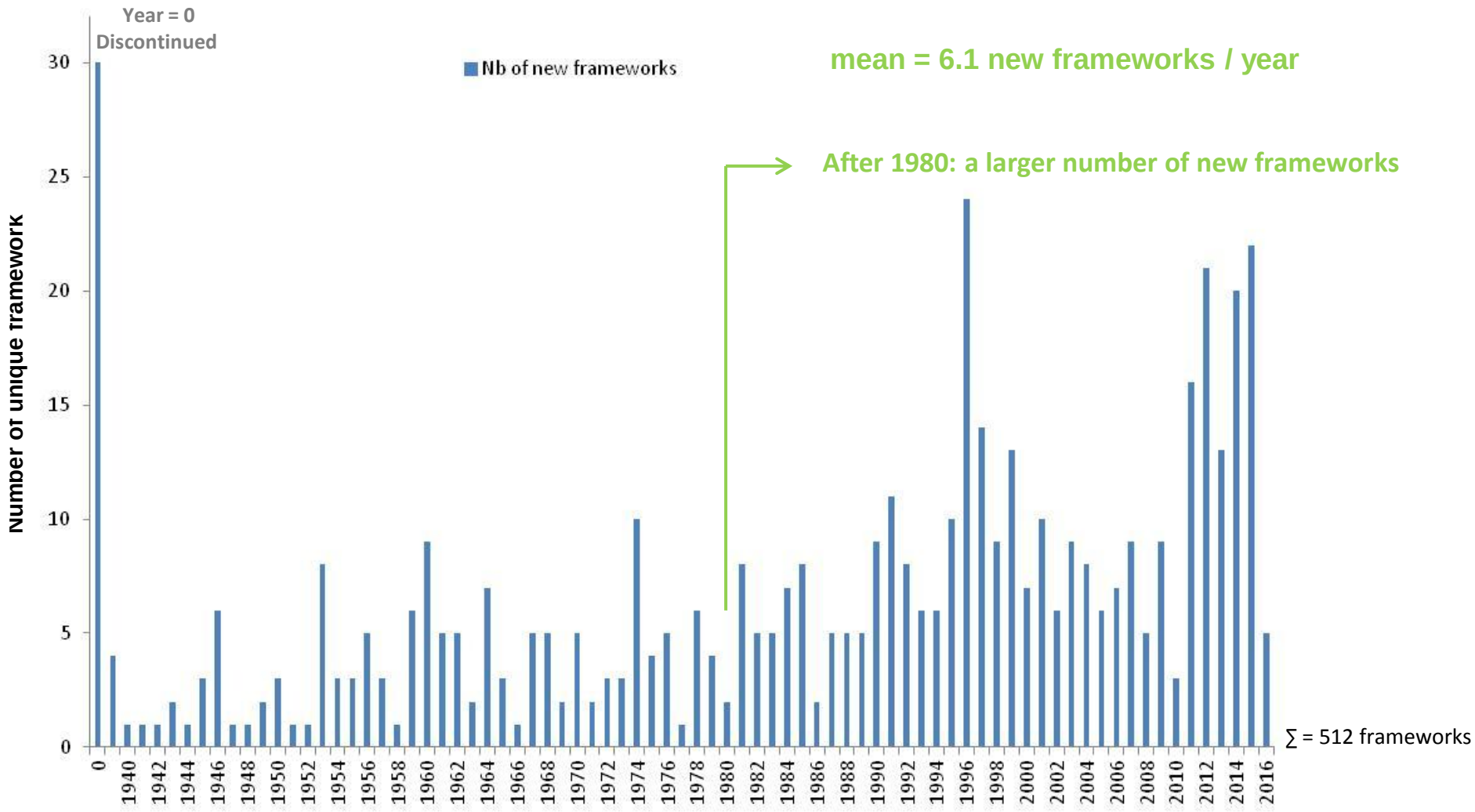




❑ Pharmacokinetics
(metabolites, routes, VD, Cl, HT, PPB, F…)

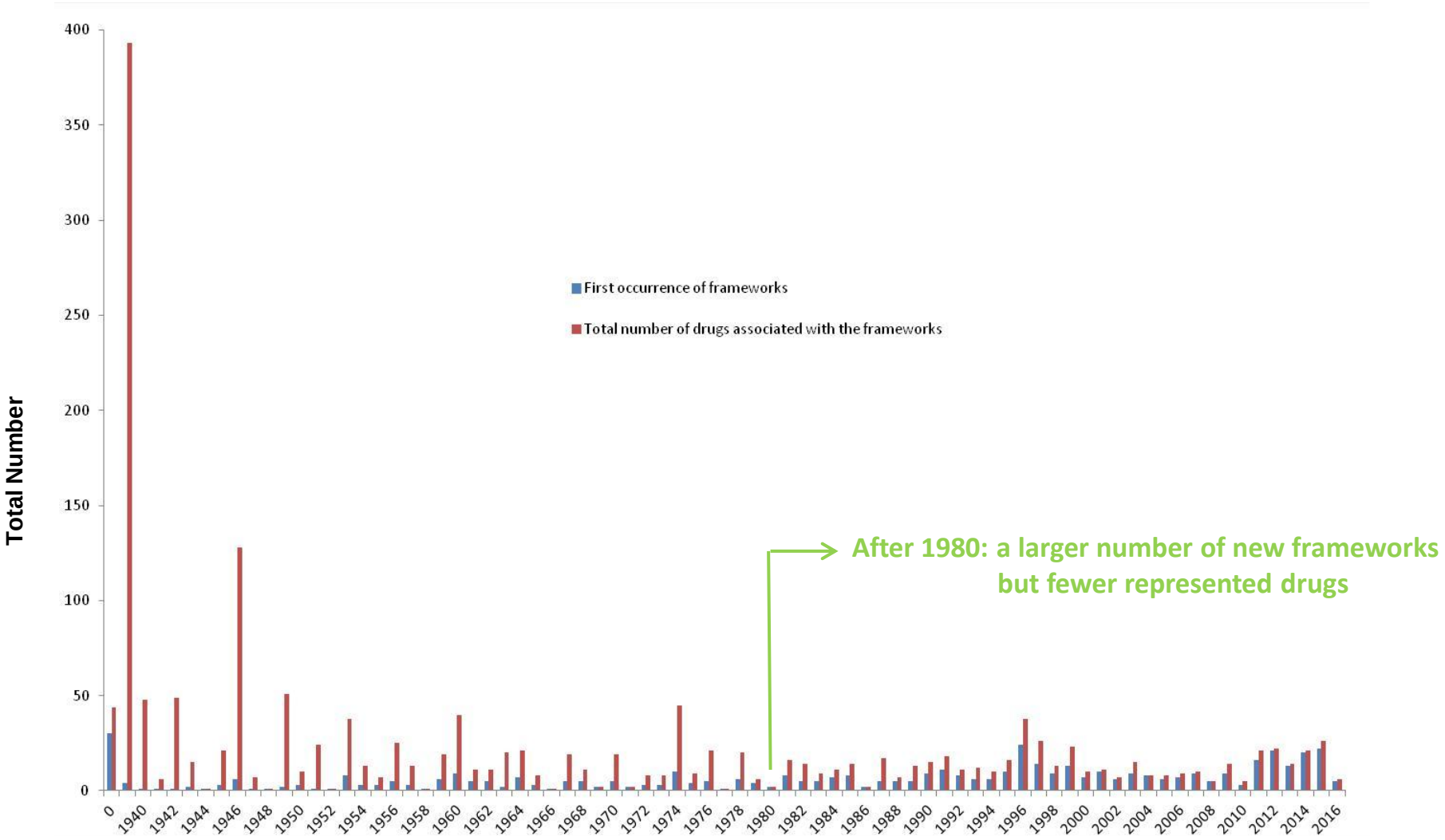
* e-Drug3D: release of July 2016
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

Drug Frameworks over years



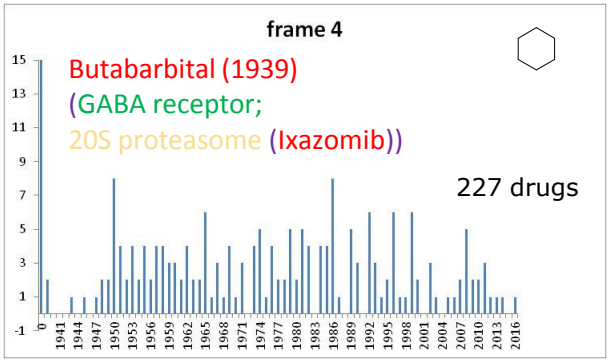
e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures) - 1189 different scaffolds (out of 1697) - 512 different frameworks
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

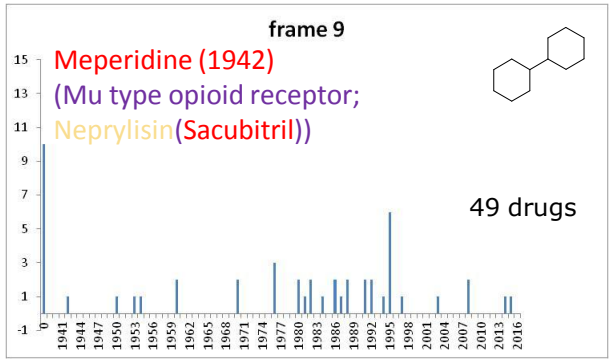
Examplification of drug Frameworks over years

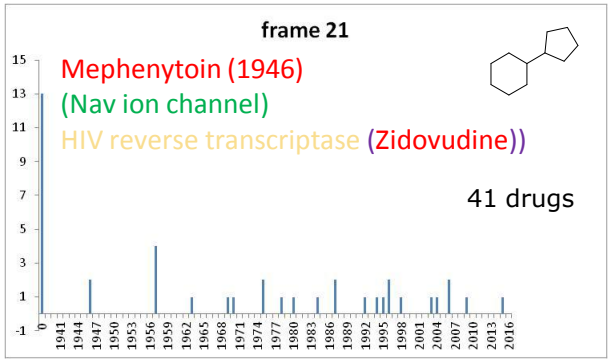


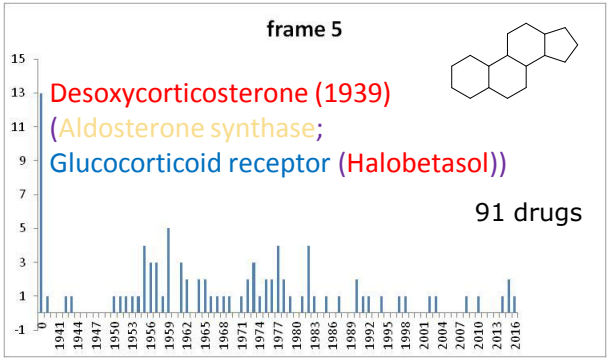
e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures) - 1189 different scaffolds (out of 1697) - 512 different frameworks
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

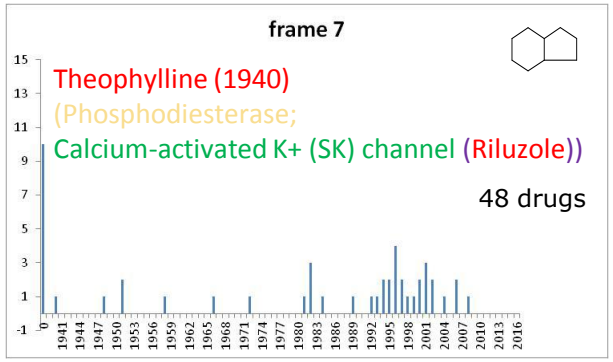
Drug Frameworks

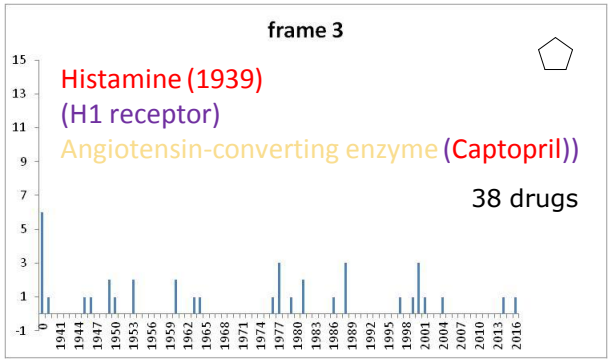


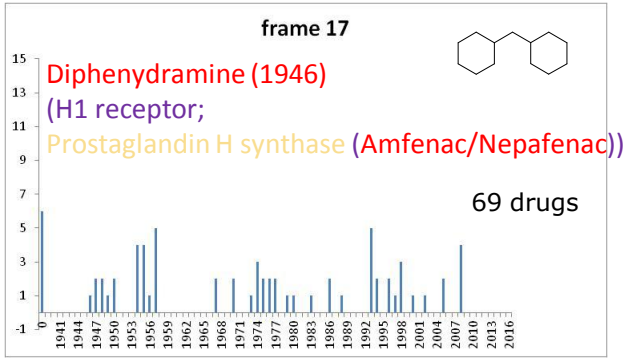


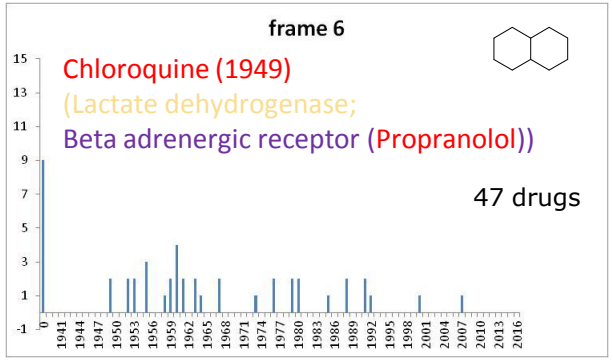


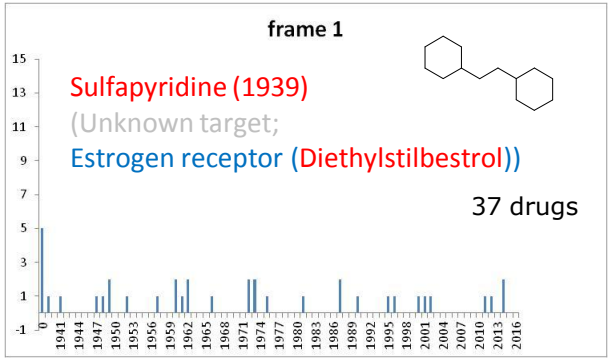






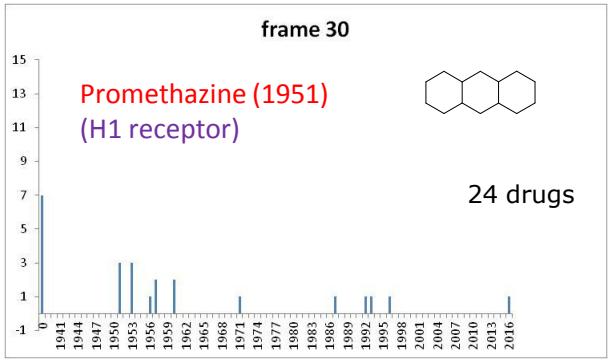


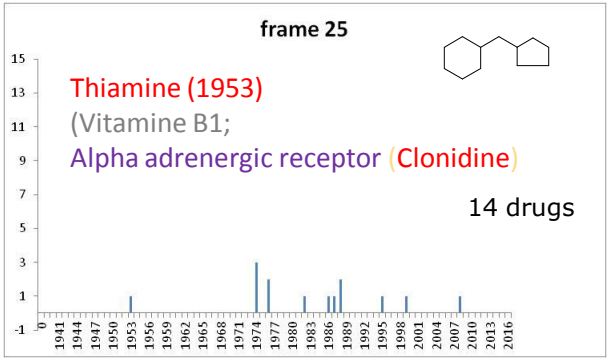


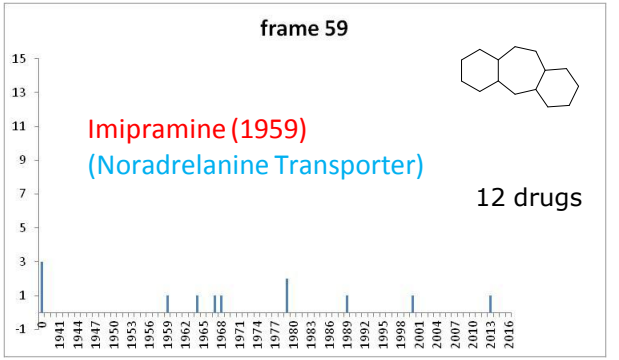


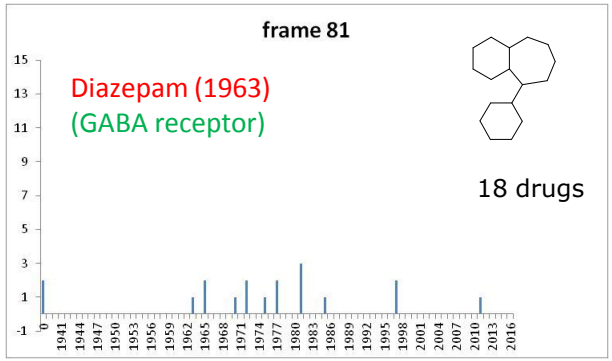
e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures) - 1189 different scaffolds (out of 1697) - 512 different frameworks
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

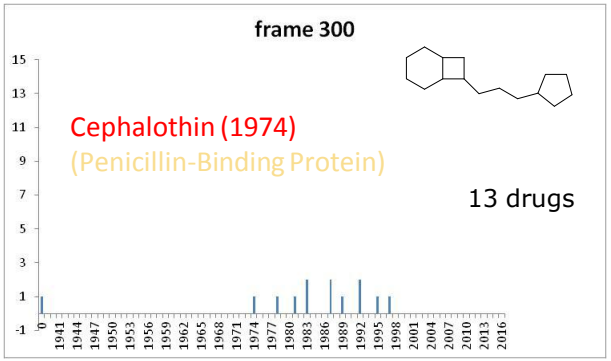
Drug Frameworks

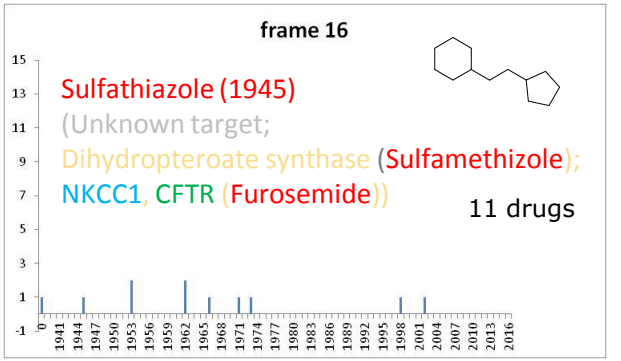


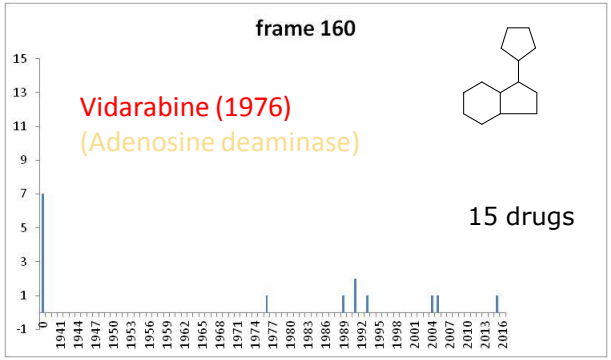


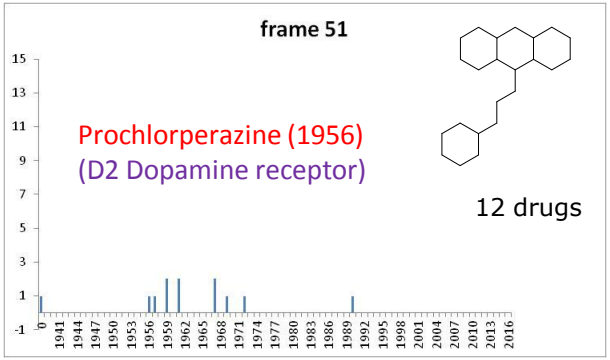


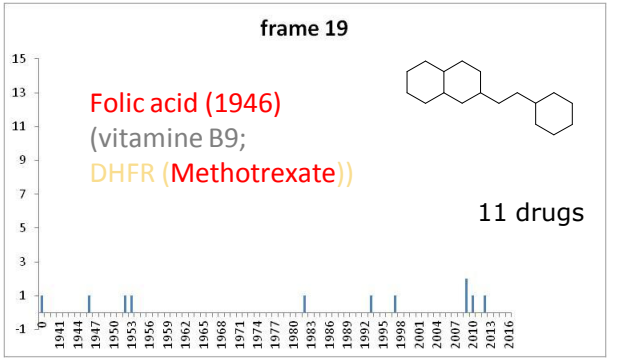






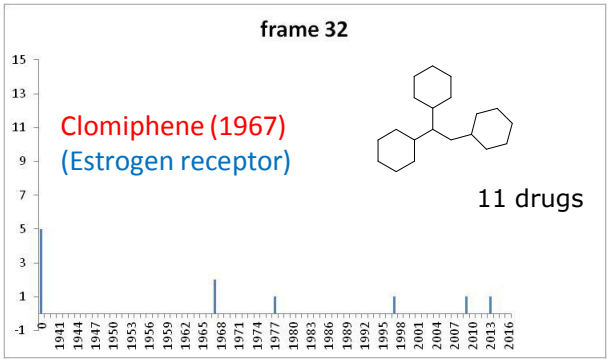


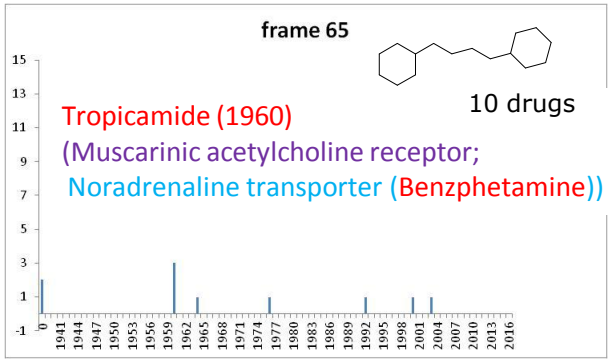


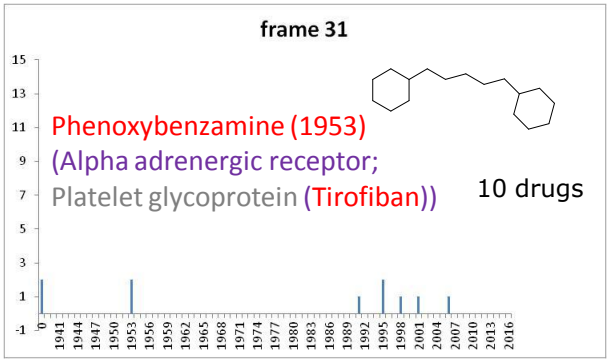


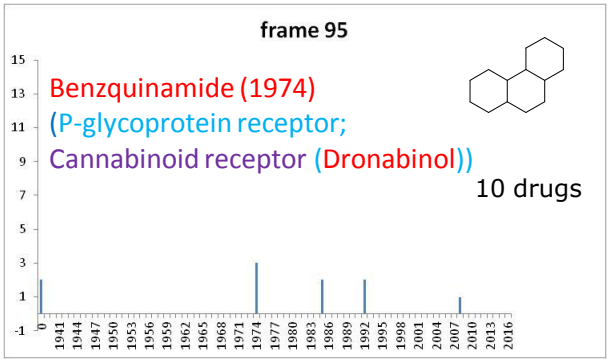
e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures) - 1189 different scaffolds (out of 1697) - 512 different frameworks
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

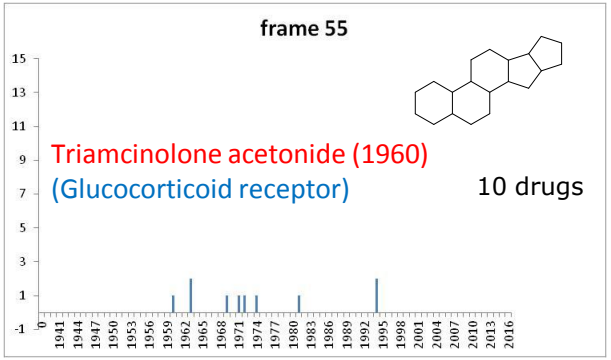
Drug Frameworks











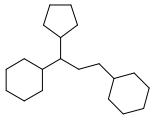
∑ (represented drugs) = 828/1822 = 45.4%
of drug structures are represented by 23 frameworks

The simplest frameworks appeared first and are the most populated

e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures) - 1189 different scaffolds (out of 1697) - 512 different frameworks
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

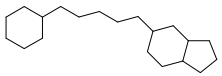
Drug Frameworks

Discontinued



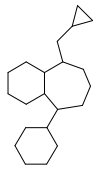
Cycrimine ()
(Muscarinic acetylcholine receptor M1)

2 drugs



Protokylol ()
(Beta 1/Beta 2 adrenergic receptor)

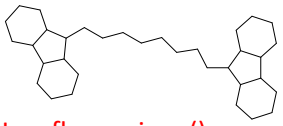
2 drugs



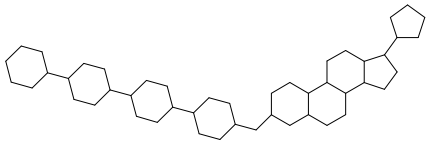
Prazepam ()
(GABA receptor)

Candicidin () large polyene structure
(membrane)

Ceruleptide () large structure
(Cholecystokinin type A)

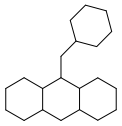


Hexafluorenium ()
(Cholinesterase)



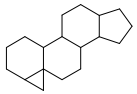
Deslanoside ()
(Sodium/potassium ATPase)

1 drug



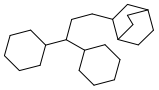
Methixene ()
(Muscarinic acetylcholine receptor)

2 drugs



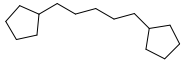
Trilostane ()
(Estrogen receptor)

Viomycin () large ring
(70S ribosome)



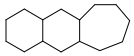
Clidinium ()
(Muscarinic acetylcholine receptor)

2 drugs

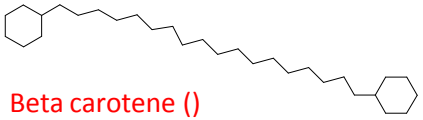


Pentolinium ()
(antihypertensive)

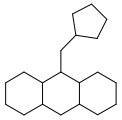
1 drug



Dezocine ()
(Kappa/Mu opioid receptor)

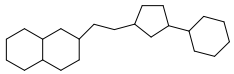


Beta carotene ()
(Beta carotene monooxygenase)

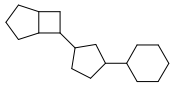


Clidinium ()
(Muscarinic acetylcholine receptor)

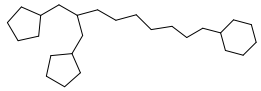
2 drugs



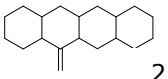
Pyrvinium ()
(anthelmintic)



Hetacillin ()
(Penicillin-Binding Proetins 1A/1B)

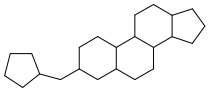


Saralasin ()
(Angiotensin II receptor)

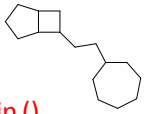


Meclocycline () & Methacycline ()
(Ribosome)

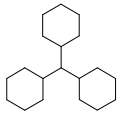
2 drugs



Quinestrol ()
(Estrogen receptor)



Amdinocillin ()
(Penicillin-Binding Proetins 2B)

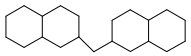


Gentian violet ()
(NADPH oxidase)

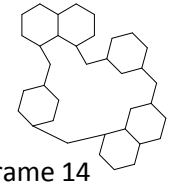
e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures) - 1189 different scaffolds (out of 1697) - 512 different frameworks
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

Drug Frameworks

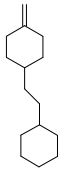
Discontinued



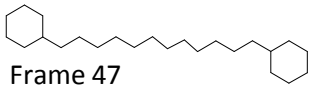
Frame 13
Dicumarol (1944)
(Xanthine oxidase)



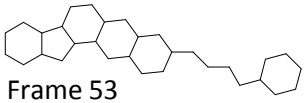
Frame 14
Metocurine/Tubocarine (1945)
(5-HT3 receptor)



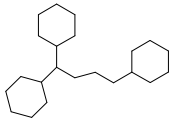
Frame 41
Très proche de frame 1 (sulfapyridine)
Hydroxystilbamidine (1953)
antiparasitic
(Unknown target)



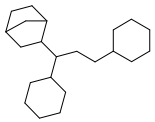
Frame 47
Ambenonium (1956)
(Cholinesterase)



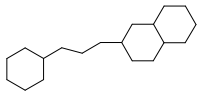
Frame 53
Rescinnamine (1956)
(Angiotensin-converting enzyme)



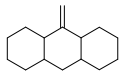
Frame 56
Diphenidol (1967)/Oxyphencyclimine
(Muscarinic acetylcholine receptor)



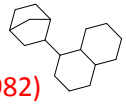
Frame 64
Biperiden (1959)
(Muscarinic acetylcholine receptor)



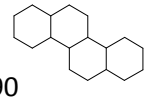
Frame 66
Benzthiazide (1960)
(Antihypertensive)



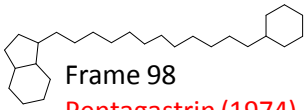
Frame74
Chlorprothixene (1967)
(D2 Dopamine receptor)



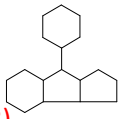
Frame 79
Cyclothiazide (1982)
(Glutamate receptor 2)



Frame 90
Testolactone (1969)
(CYP450 19-aromatase)

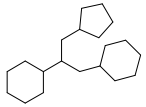


Frame 98
Pentagastrin (1974)
(Cholecystokinin type B receptor)

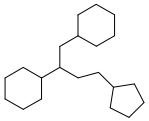


Frame 100
Mazindol (1973)
(Noradrenaline & Dopamine transporter)

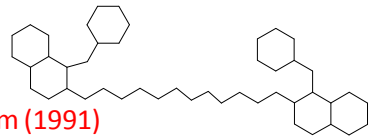
Frame 119
Guanadrel (1982)
(Antihypertensive)



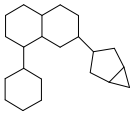
Frame 131
Antazoline (1990)
(Cav channel)



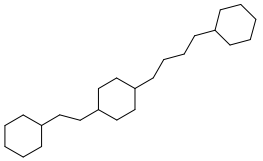
Frame 136
Bepridil (1990)
(Ca channel)



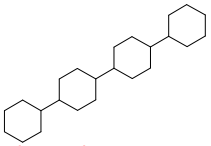
Frame 161
Doxacurium (1991)
(Muscarinic acetylcholine receptor M1)



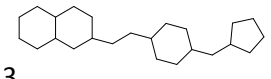
Frame 173
Trovafloxacin/Alatrofloxacin (1997)
(DNA gyrase)



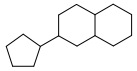
Frame 174
Cisapride (1993)
(5-HT4 receptor)



Frame 175
Levocabastine (1993)
(Histamine H1 receptor)



Frame 213
Troglitazone (1997)
(PPAR gamma)



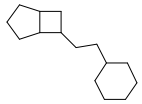
Frame 239
Pemirolast (1999)
(antiinflammatory)

Frame 245
Telithromycin (2004) large ring
(50S ribosome)

e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures) - 1189 different scaffolds (out of 1697) - 512 different frameworks
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

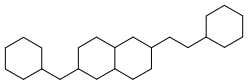
Drug Frameworks

Discontinued

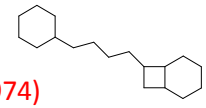


Frame 297
Cyclacillin / Methicillin (1979)
(Penicillin-Binding Proetins 1A/1B)

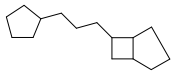
Frame 303
Troleandomycin (1969) large ring
(ribosome)



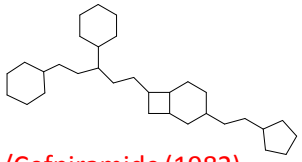
Frame 304
Novobiocin (1964)
(DNA gyrase)



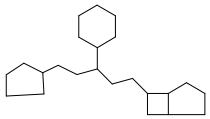
Frame 306
Cephapirin (1974)
(Penicillin-Binding Proetins 1A/1B)



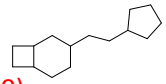
Frame 309
Ticarcillin (1976)
(Penicillin-Binding Proetins 1A/1B)



Frame 314
Cefoperazone/Cefpiramide (1982)
(Penicillin-Binding Proetins 1A/1B)



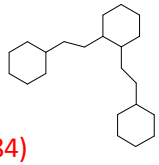
Frame 315
Azlocillin/Mezlocillin (1981)
(Penicillin-Binding Proetins 1A/1B)



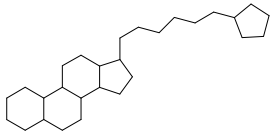
Frame 325
Cefmetazole (1989)
(Penicillin-Binding Proetins 1A/1B)

Frame 327
Dirithromycin (1995) large ring
(ribosome)

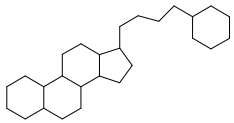
Frame 343
Guanethidine (1960)
(Nitric oxide synthase)



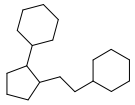
Frame 346
Bitolterol (1984)
(Beta 2 adrenergic receptor)



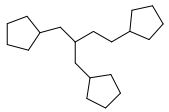
Frame 377
Hydrocortisone cypionate (1955)
(Glucocorticoid receptor)



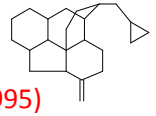
Frame 380
Nandrolone phenpropionate (1959)
(Androgen receptor)



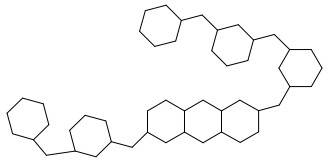
Frame 381
Sulfaphenazole (1974)
(CYP450)



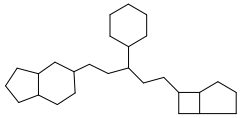
Frame 386
Protirelin (1976)
(Hormone analog)



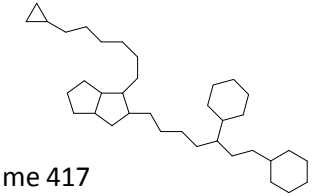
Frame 392
Nalmefene (1995)
(Opioid receptor)



Frame 396
Plicamycin (1970)
(Unknown target)

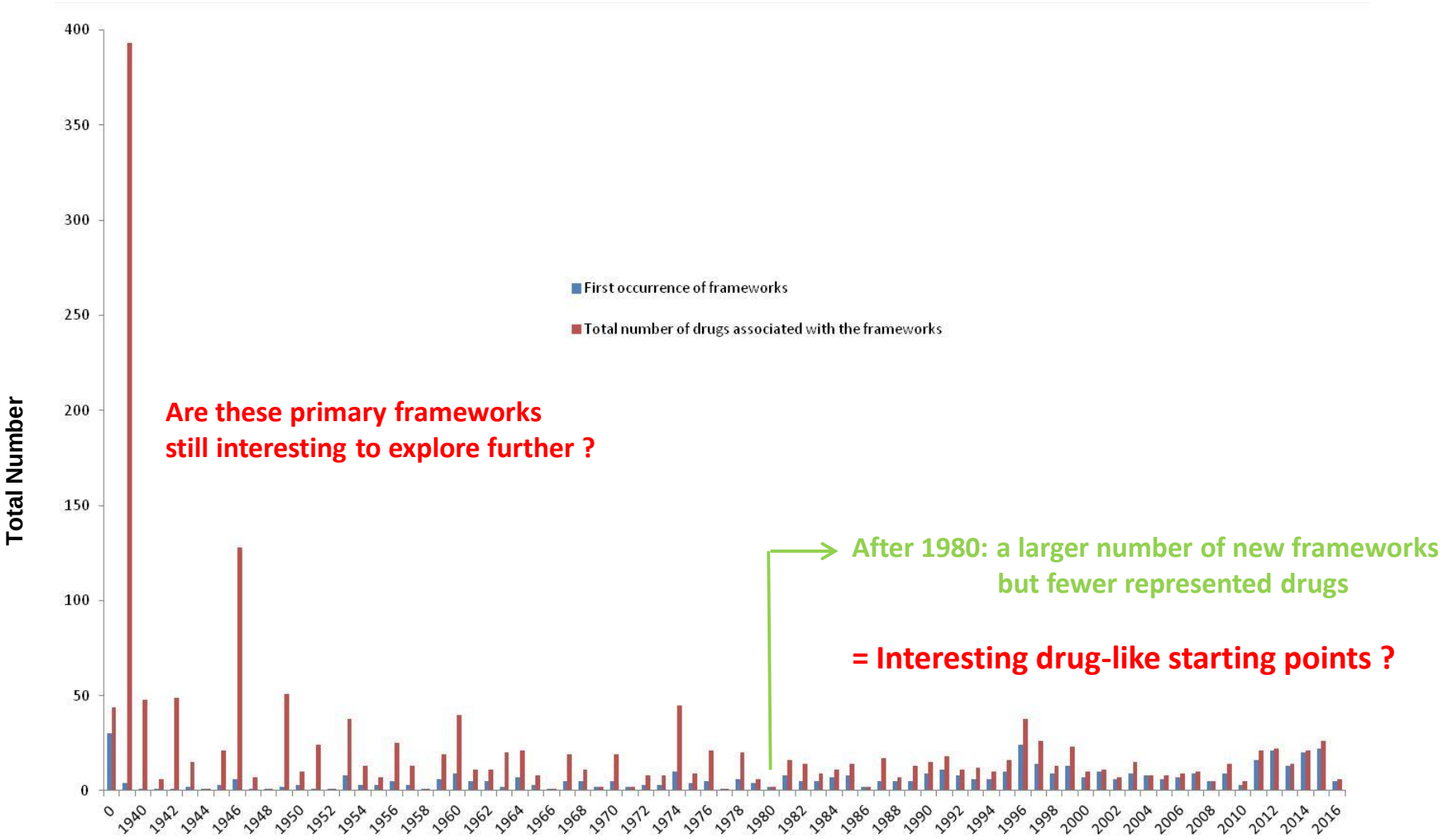


Frame 397
Carbenicillin indanyl (1972)
(Penicillin-Binding Proetins)



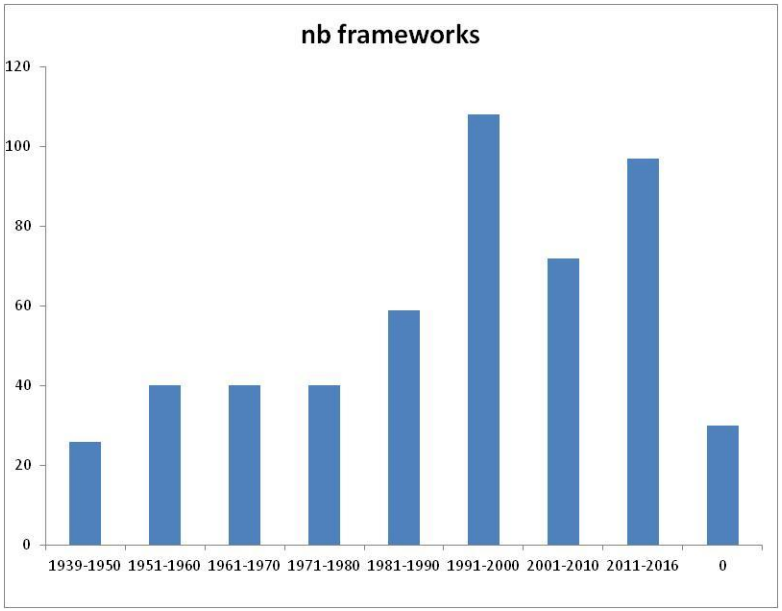
Frame 417
Telaprevir (2011)
(NS3/4A protease)

Examplification of drug Frameworks over years



e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures) - 1189 different scaffolds (out of 1697) - 512 different frameworks
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

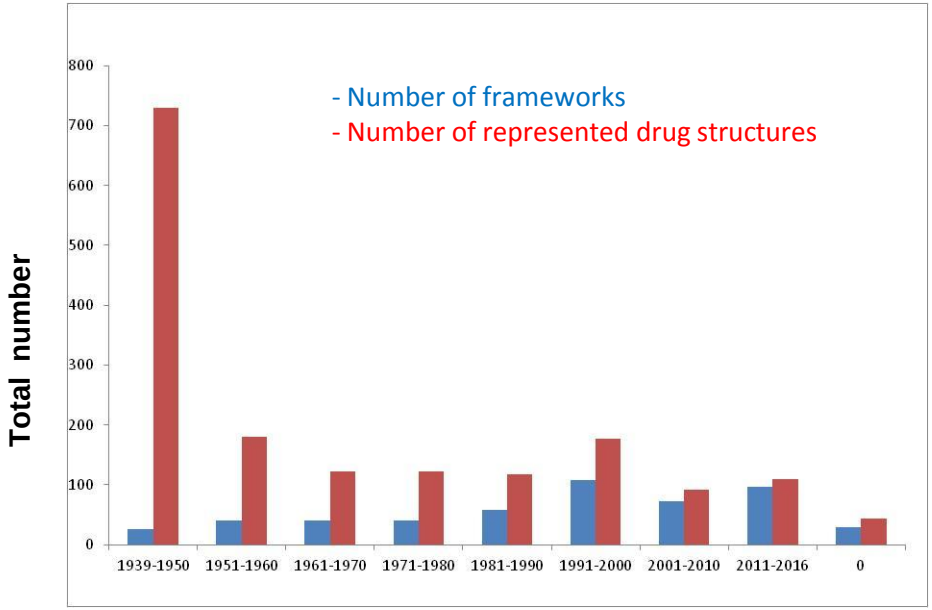
Drug Frameworks



A continuous increase in the number of new frameworks

mean = 6.1 new frameworks / year

mean = 3.5 drugs / framework

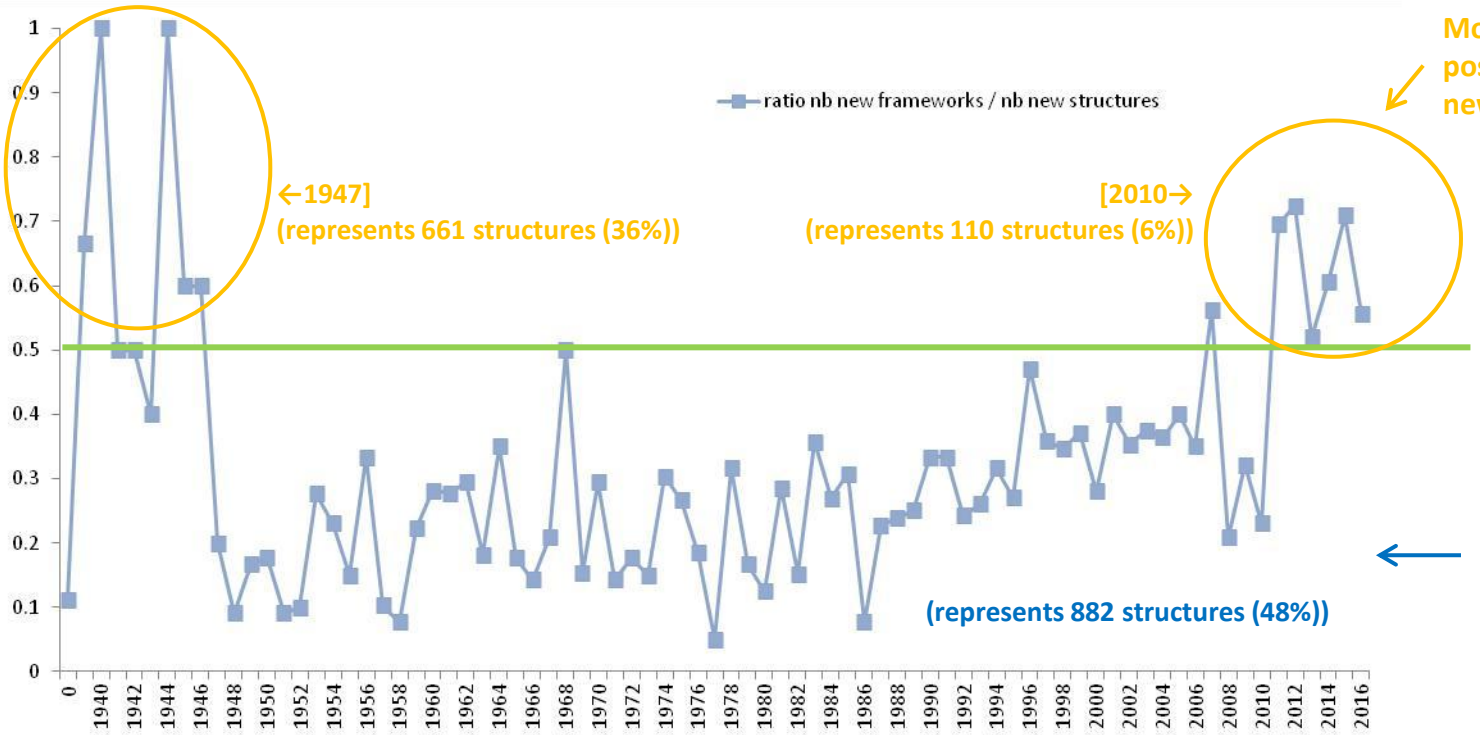


First and simplest frameworks represent most of the drug structures

e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures) - 1189 different scaffolds (out of 1697) - 512 different frameworks
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

Drug Frameworks

ratio = 1
Same number of new frameworks and new drugs



←1947]
(represents 661 structures (36%))

[2010→
(represents 110 structures (6%))

Most of new drugs
possess a
new framework

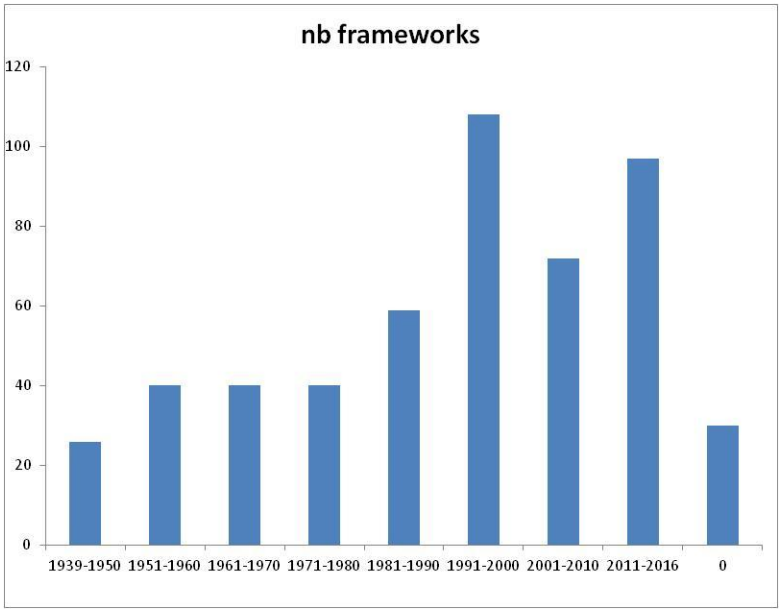
ratio = 0.5
half of the new drugs
has a new framework

Old frameworks prevail
in new drugs

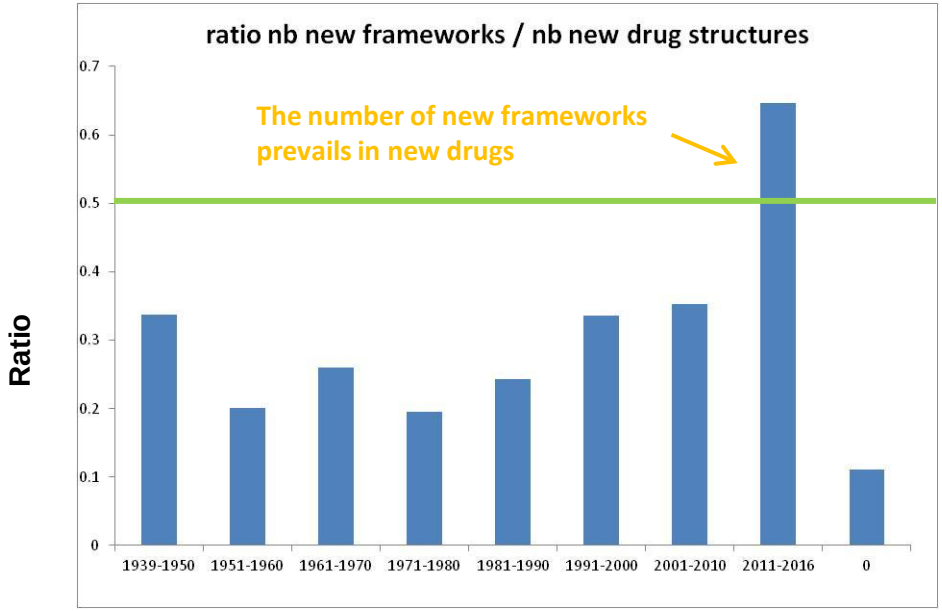
(represents 882 structures (48%))

e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures) - 1189 different scaffolds (out of 1697) - 512 different frameworks
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

Drug Frameworks

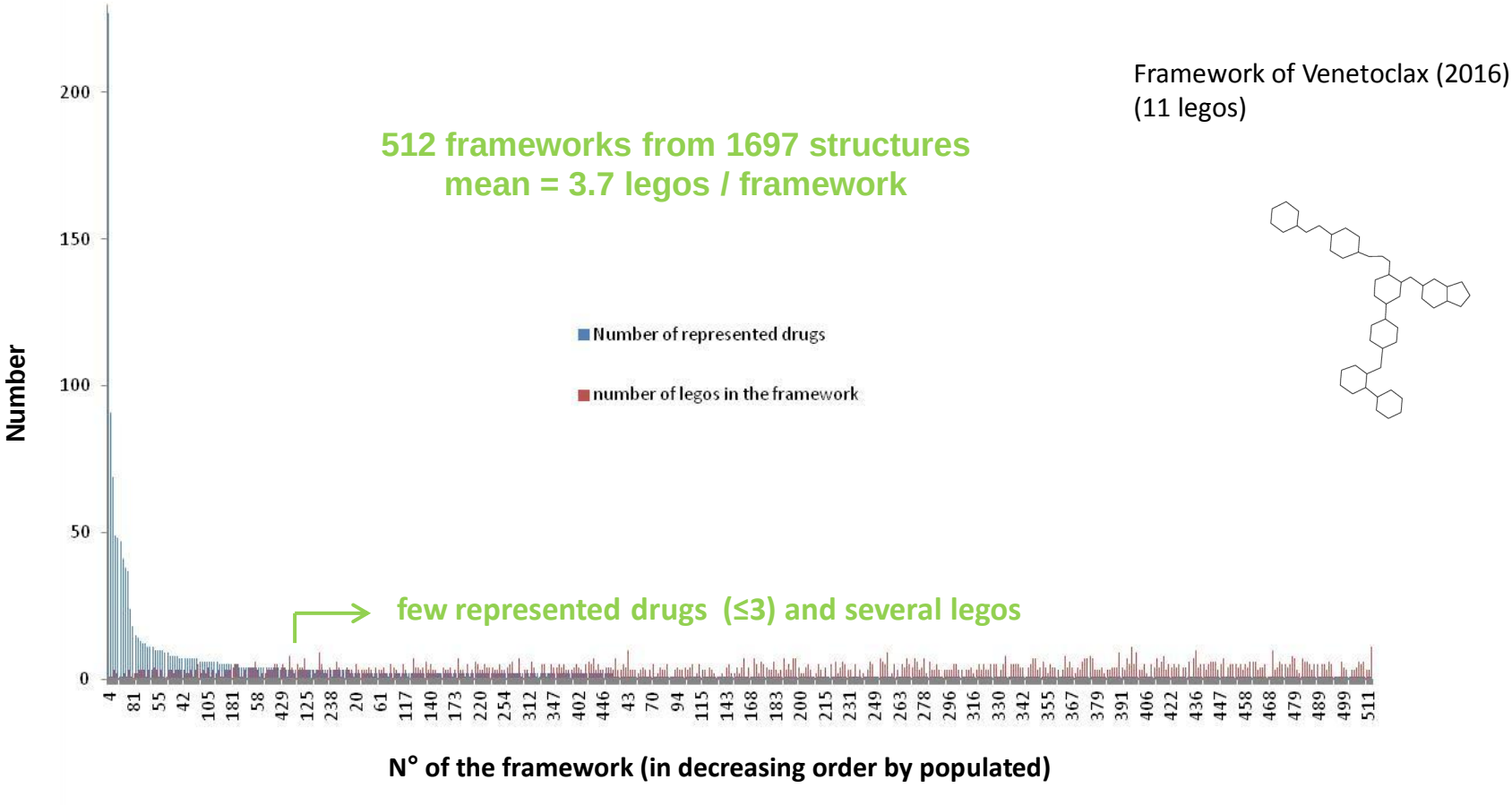


An increase of the ratio of new frameworks to the new structures



e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures) - 1189 different scaffolds (out of 1697) - 512 different frameworks
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

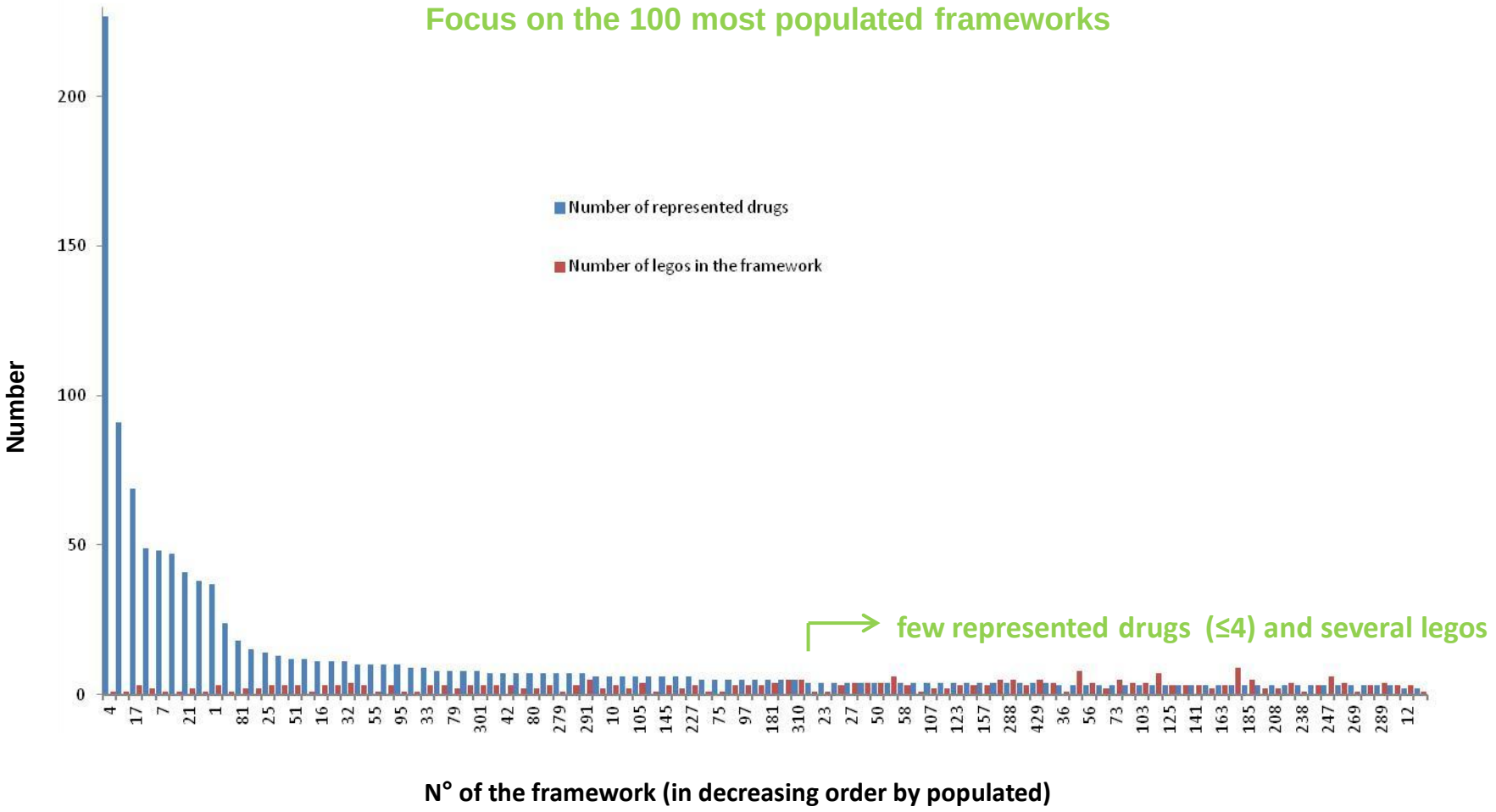
Drug Frameworks/Legos



Framework of Venetoclax (2016)
(11 legos)

e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures) - 1189 different scaffolds (out of 1697) - 512 different frameworks
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

Drug Frameworks/Legos



e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures) - 1189 different scaffolds (out of 1697) - 512 different frameworks
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

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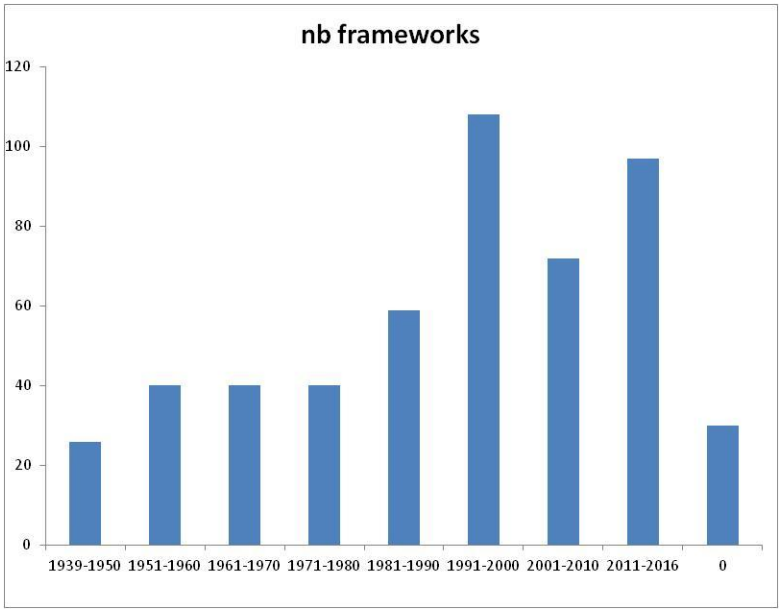
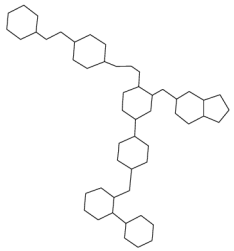
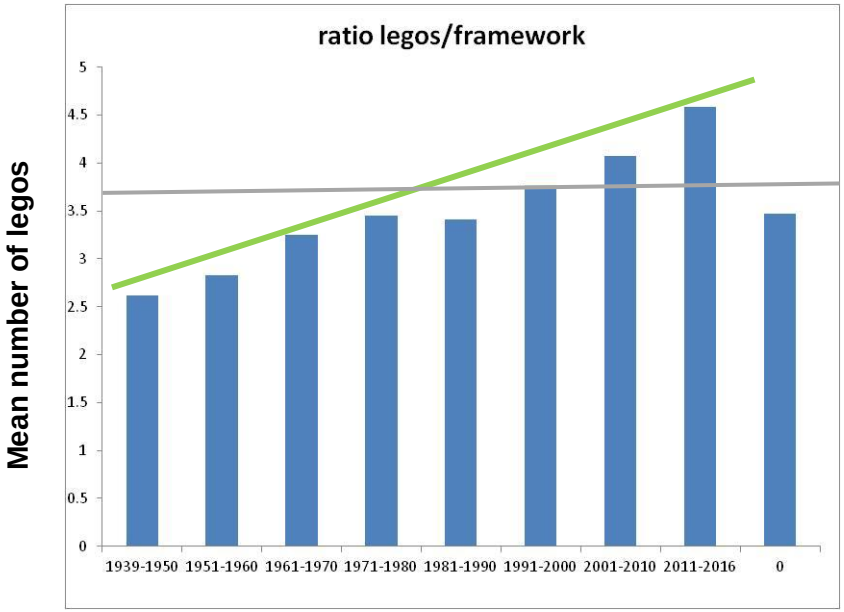


A continuous increase in the complexity of new frameworks (highly branched structures)

Framework of Venetoclax (2016)
(11 legos)



mean = 3.7 legos / framework



New frameworks are topologically more complex

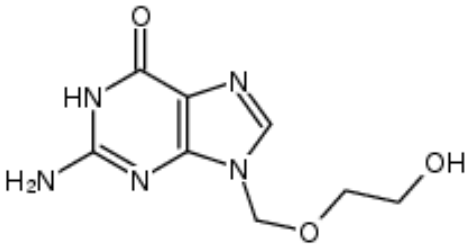
e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures) - 1189 different scaffolds (out of 1697) - 512 different frameworks
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

Structural Diversity of Approved Drugs

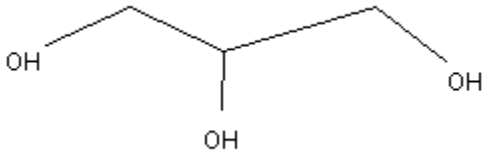
➢ **Siegel M.G. and Vieth M., *DDT*, 2007.**

Study on 1386 drugs

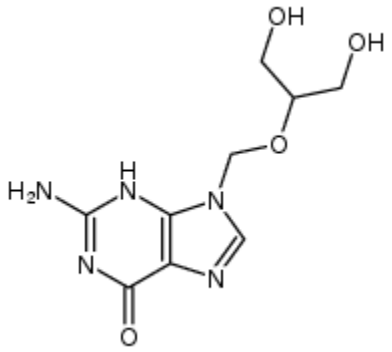
- **41 %** of drugs:
  - are substructures of another drug (e.g. acyclovir is a substructure of ganciclovir)
  - are structures containing another drug



acyclovir



glycerine



ganciclovir

(1) Siegel M.G. and Vieth M., *Drug Discovery Today.*, 2007.

Structural Diversity of Approved Drugs

- **In 2000**

29 FDA approved molecules (1)

19/29

- 1 structure is a prodrug of a known approved drug (ester)
- 3 structures are isolated enantiomers of known approved drugs
- 11 structures are derived from known approved drugs
- 4 structures are derived from natural molecules
- 4 structures are derived from literature
- 5 structures without identified starting point
- 1 structure mentioned as identified from HTS campaign

- **1981-2006** – 25 years (2):

4% are natural compounds **(e-Drug3D: 77 structures (4%) match Knapsack DB)**
30% from organic synthesis
49% derived from natural products

(1) Proudfoot J.R., *Bioorg. Med. Chem.*, 2002.
(2) Newman and Cragg, *J.Nat.Prod.*, 70,461-411, 2007.

The classical paradigm of drug design

- "The most fruitful basis for the discovery of a new drug is to start with an old drug"

Nobel Prize laureate (1988) Sir James Black (1)

- *Clinical observations + Reliable animal models + Medicinal chemistry (incremental modification)*

(conservatism in the exploration of the chemical space)

Paul Janssen (2)

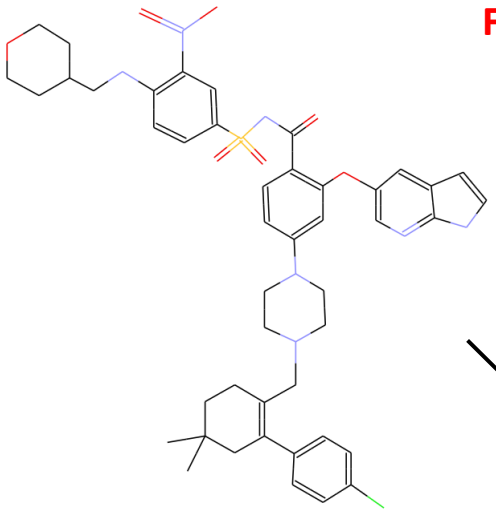
- SOSA approach: Selective Optimization of Side Activities

Camille Georges Wermuth

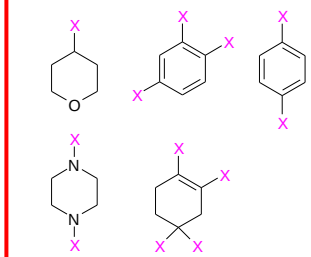
(1) Raju, T. N. Lancet, 2000, 355, 1022.
(2) Vangestel, S.; Schuermans, V. Drug Dev Res, 1986, 8, 1-13

Drug-like Fragments

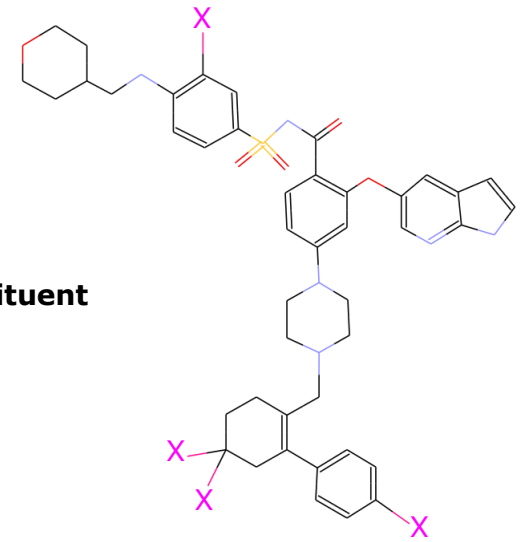
Venetoclax
BCL-2 Inhibitor



Fragments (legos)

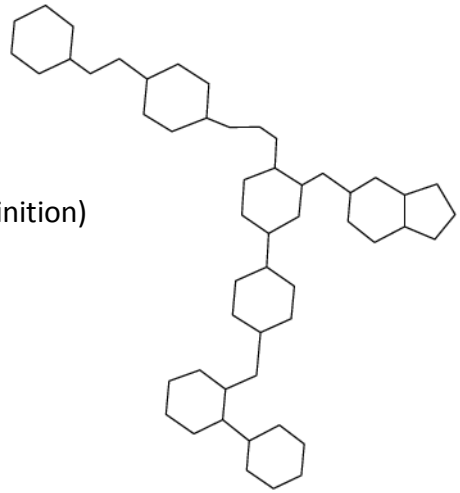


Scaffold



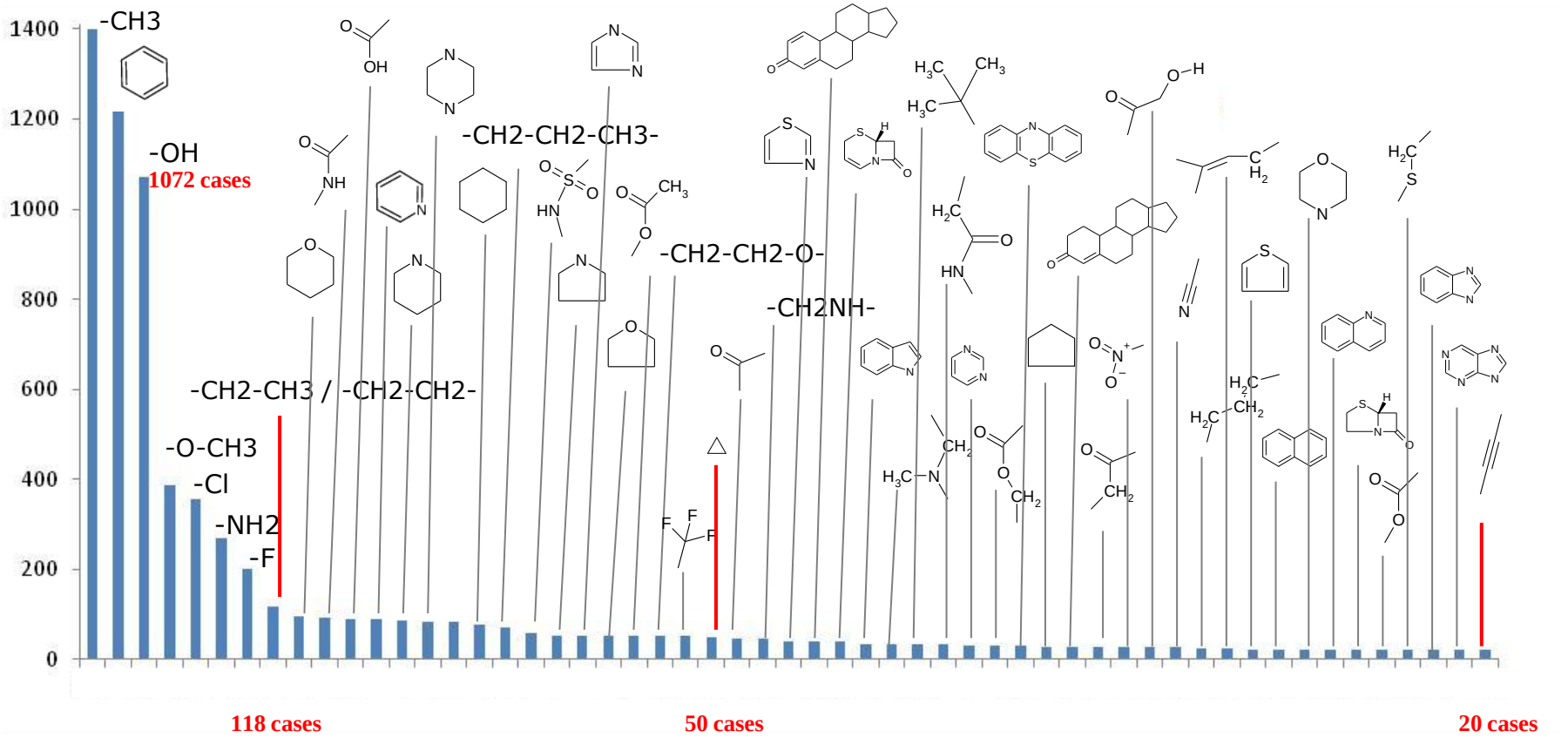
X : anchoring point for a substituent

Framework
(Bemis & Murcko definition)



Drug-like Legos

❑ **Lego extracted from drugs (∑ $_{1822}$ legos = 1779** (out of which **1144** are unique (when 'X' anchor points are excluded))**)**



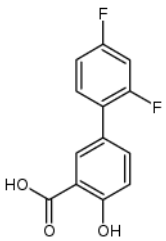
Legos in decreasing order by populated

Drug-like Substructures that are commercially available

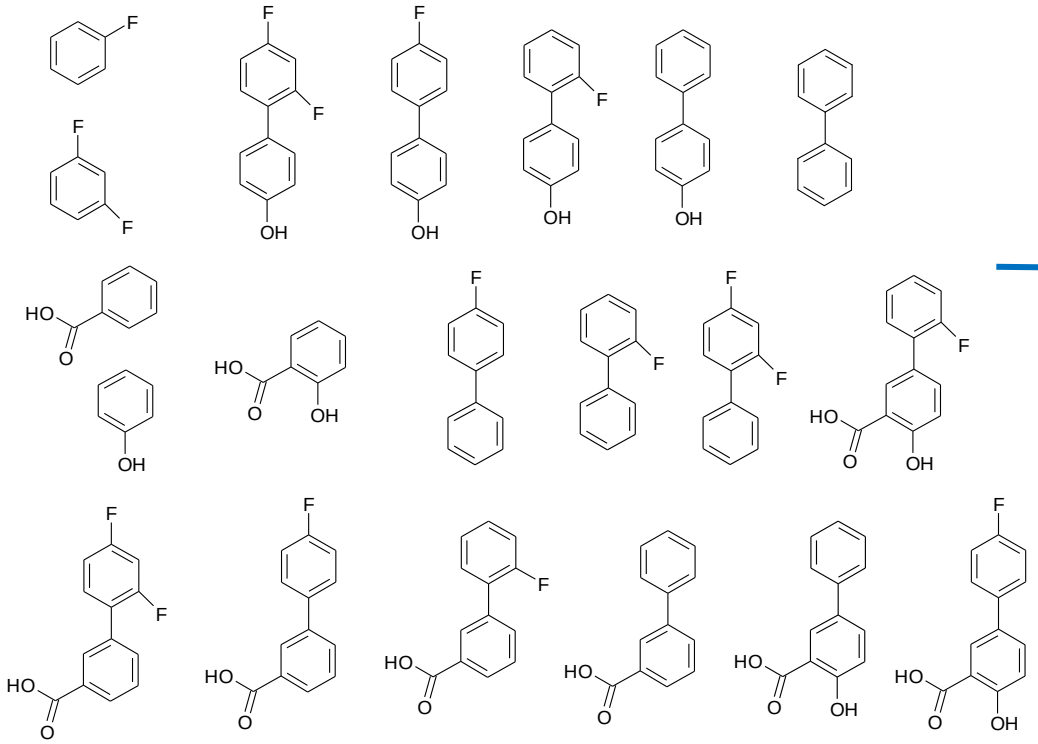
- **Lego extracted from drugs ($\sum_{1822}$ legos = 1779)**
- **If combining legos for each drug = { substructures of drugs (21 064 structures) }**
  mean = 5.3 legos/drug

1629 structures
FBDD / FBLD strategies

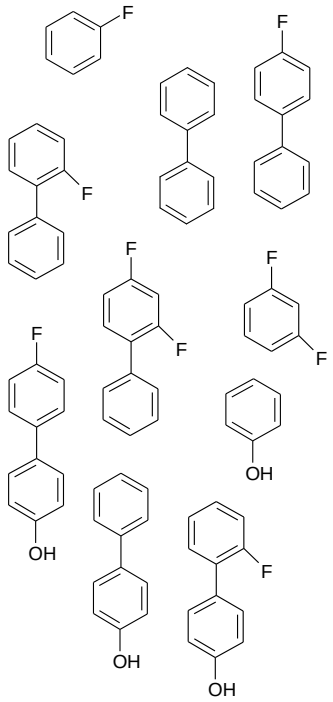
Diflunisal (1982)
(6 legos)



Substructures of Diflunisal (20)



Commercials (10)



e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures) - 1779 different legos - 1189 different scaffolds - 512 different frameworks
Link: http://chemoinfo.ipmc.cnrs.fr/MOLDB/fragment.html ; Pihan *et al.*, *Bioinformatics*, 2012.

Drug-like substructures that are commercially available

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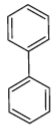
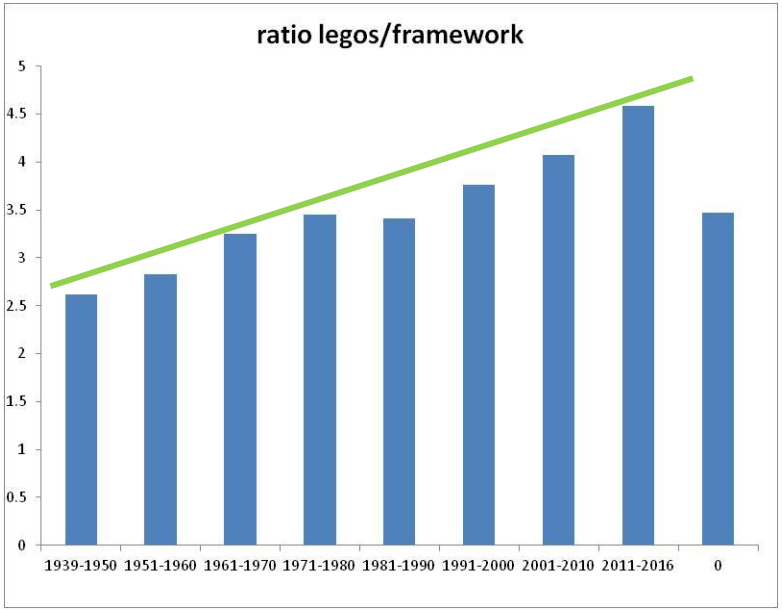
26	264	 MFCD00003054	20 drugs (1.098 %)	AZILSARTAN_KAMEDOXOMIL ; CANDESARTAN ; CANDESARTAN_CILEXETIL ; CANDESARTAN_CILEXETIL ; CONIVAPTAN ; DACLATASVIR ; DIFLUNISAL ; FLURBIPROFEN ; FLURBIPROFEN ; IRBESARTAN ; LOMITAPIDE ; LOSARTAN ; M_AZILSARTAN_KAMEDOXOMIL ; M_LOSARTAN ; M_SACUBITRIL ; OLMESARTAN ; SACUBITRIL ; SONIDEGIB ; TELMISARTAN ; VALSARTAN
27	161	 MFCD00005325	18 drugs (0.988 %)	AZTREONAM ; CEFDINIR ; CEFDITOREN ; CEFDITOREN_PIVOXIL ; CEFEPIME ; CEFIXIME ; CEFMENOXIME ; CEFOTAXIME ; CEFOTIAM ; CEFPODOXIME ; CEFPODOXIME_PROXETIL ; CEFPODOXIME_PROXETIL ; CEFTAZIDIME ; CEFTIBUTEN ; CEFTIZOXIME ; CEFTRIAXONE ; MIRABEGRON ; MELOXICAM
28	131	 MFCD00003276	17 drugs (0.933 %)	ARFORMOTEROL ; ATORVASTATIN ; BUPIVACAINE ; CONIVAPTAN ; DUTASTERIDE ; ERTAPENEM ; FORMOTEROL ; IVACAFTOR ; LEFLUNOMIDE ; LEVOBUPIVACAINE ; MEPIVACAINE ; MEPIVACAINE ; NICLOSAMIDE ; ROPIVACAINE ; TOLVAPTAN ; TOLVAPTAN ; VISMODEGIB
29	298	 MFCD00007043	17 drugs (0.933 %)	CHLORAMPHENICOL ; CHLORAMPHENICOL_PALMITATE ; DANTROLENE ; ENTACAPONE ; FLUTAMIDE ; NICARDIPINE ; NIFEDIPINE ; NIMODIPINE ; NIMODIPINE ; NISOLDIPINE ; NISOLDIPINE ; VENETOCLAX ; M_FLUTAMIDE ; NICLOSAMIDE ; NILUTAMIDE ; NITISINONE ; TOLCAPONE
30	1172	 MFCD00005607	17 drugs (0.933 %)	CERULETIDE ; DAPTOMYCIN ; DOLASETRON ; ELETRIPTAN ; EPTIFIBATIDE ; GOSERELIN ; HISTRELIN ; LANREOTIDE ; LEUPROLIDE ; M_DOLASETRON ; M_DOLASETRON ; NAFARELIN ; OCTREOTIDE ; PASIREOTIDE ; PENTAGASTRIN ; SINCALIDE ; TRIPTORELIN

Drug Frameworks/Legos

➢ **Statistics on approved drugs*: How many NME (new drugs) and how is their complexity ?**

mean = 3.7 legos / framework

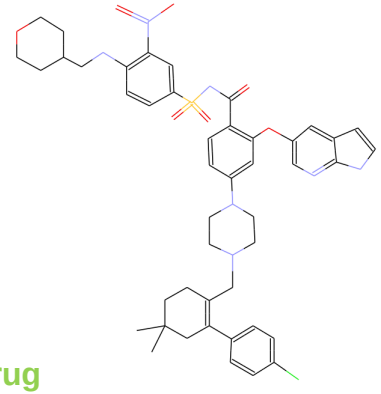


In a framework, a lego is either a ring, a fused ring or a linker

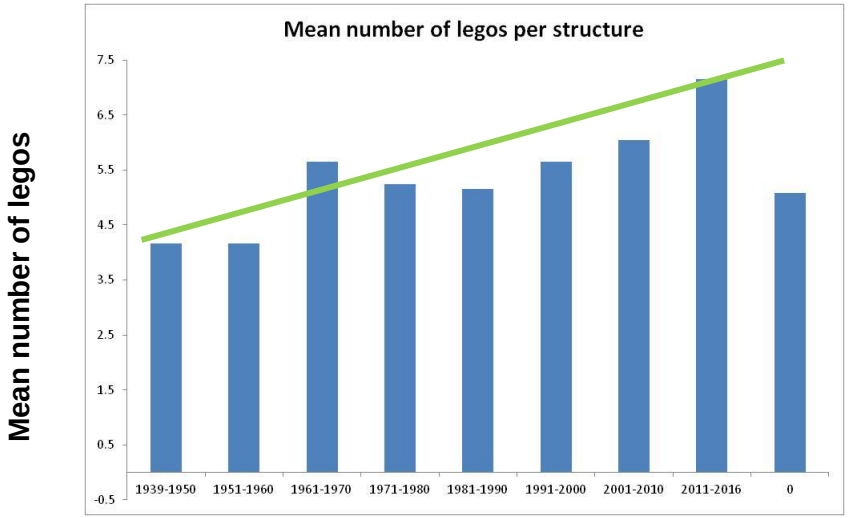
The mean number of legos in a drug = 5.4
- **3.7 legos in the framework (rings + linkers)**
- **1.7 legos in 'decoration' (substituants)**

A continuous increase in the topological complexity of new drugs

Structure of Venetoclax (2016)
(15 legos)



mean = 5.4 legos / drug



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Drug-like Fragments

Venetoclax
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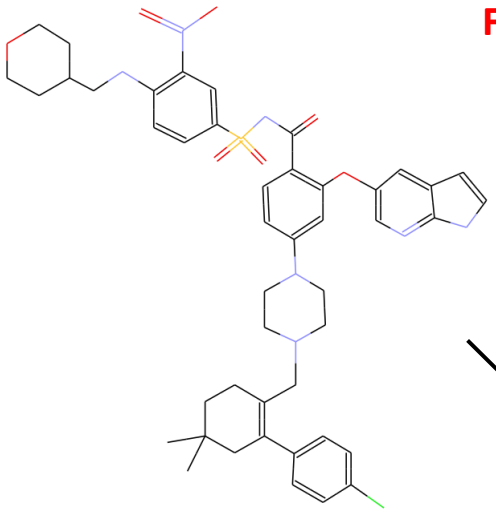
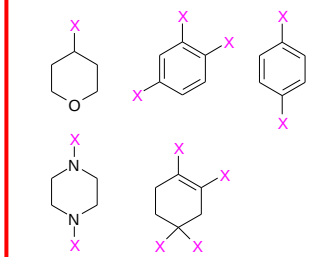
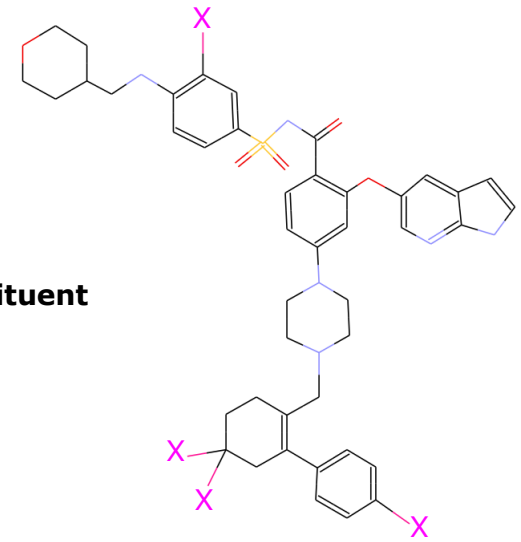


Fragments (legos)



Scaffold



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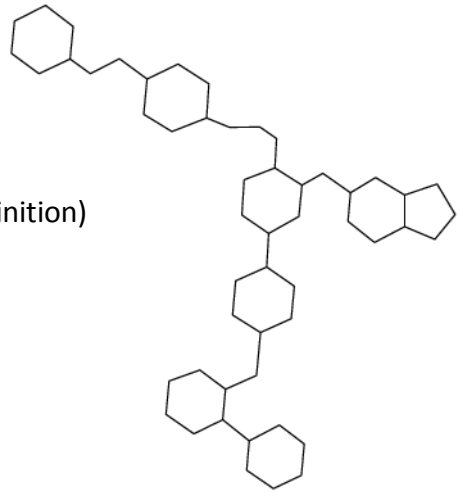
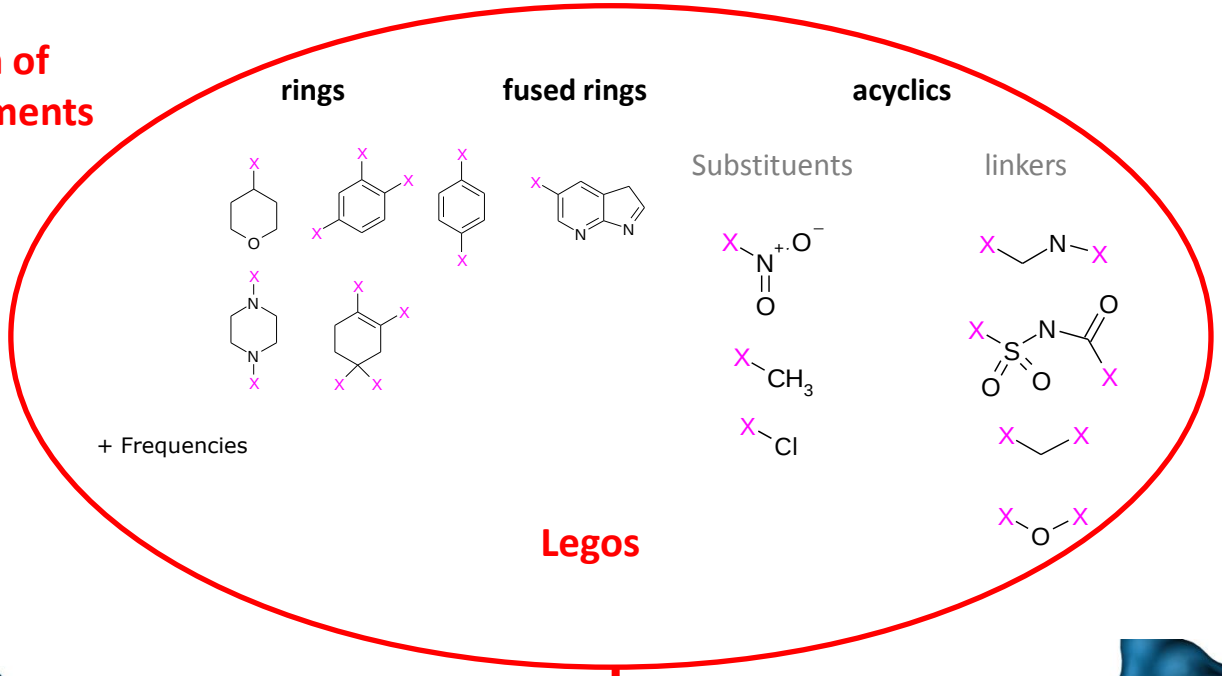
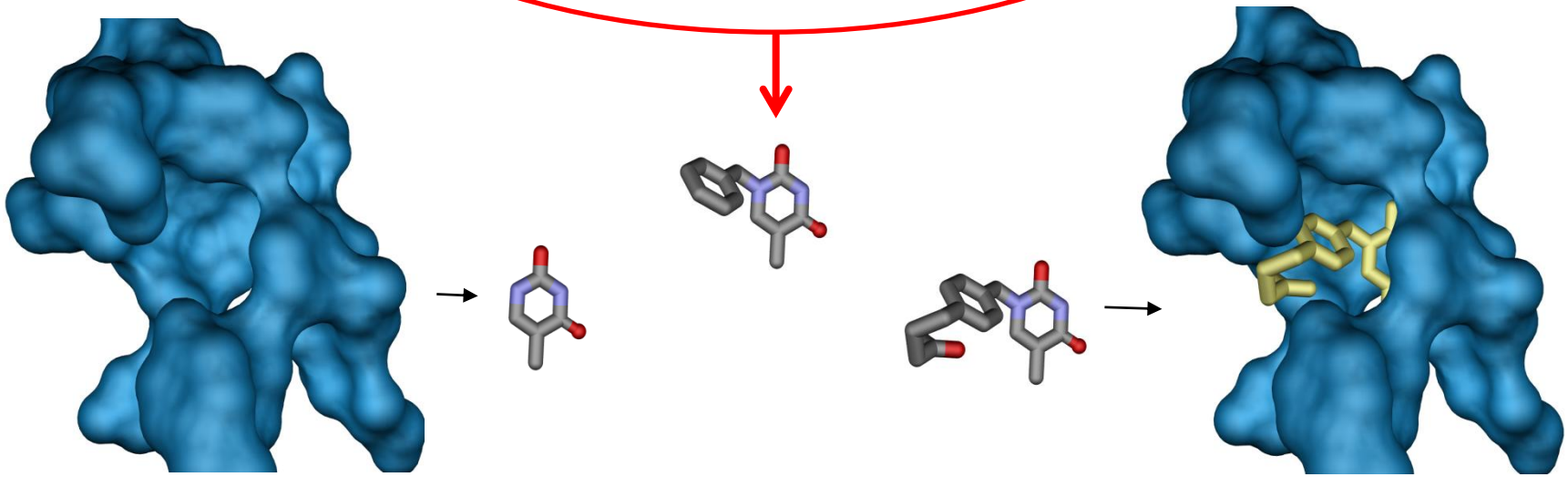


Exploring the Structural Diversity

Combination of privileged fragments

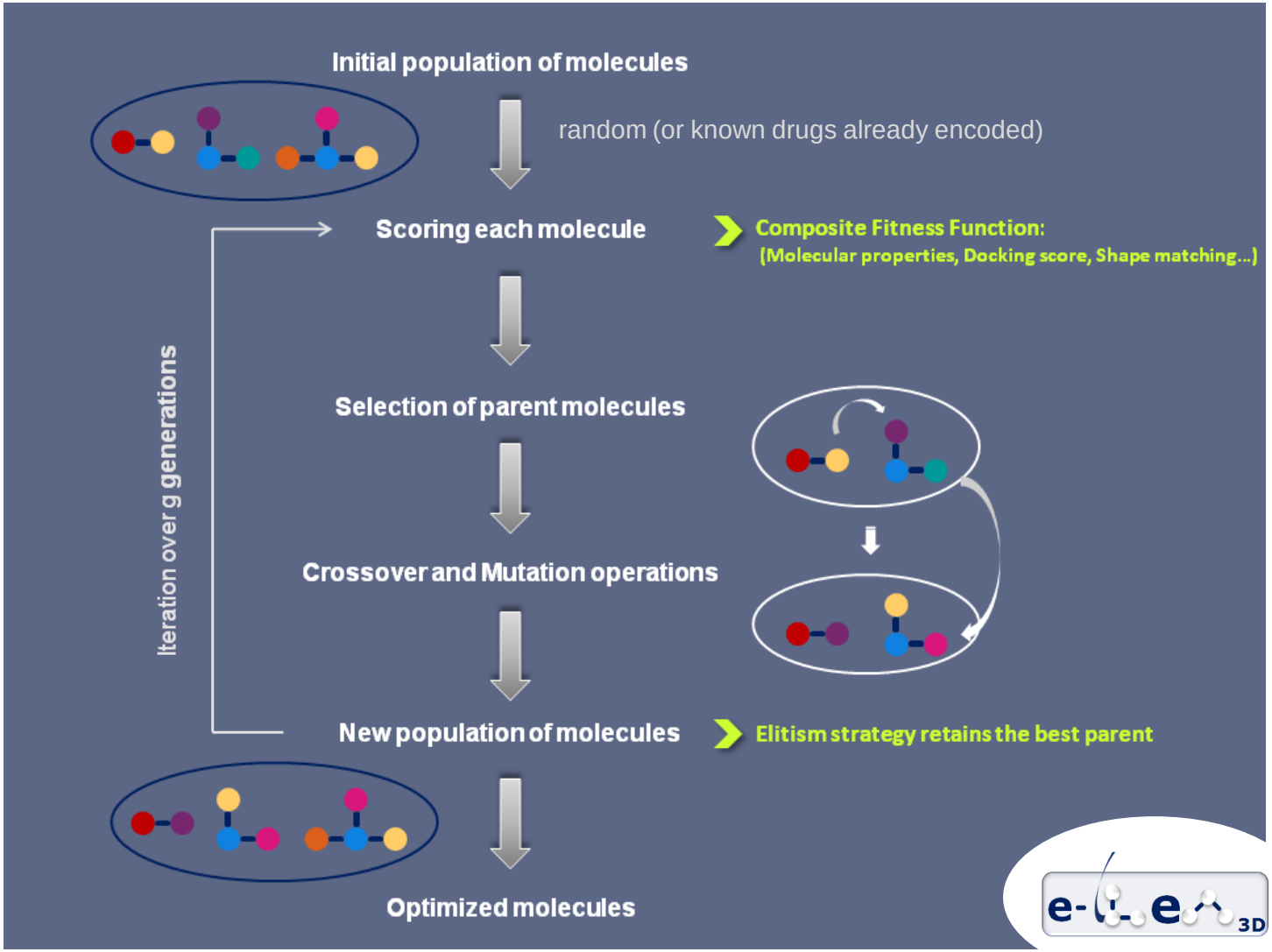




For example: optimizing a ligand- and/or a structure-based scoring function

de novo drug design program

An artificial intelligence program based on a Genetic Algorithm using the Darwinian evolution concept
An heuristic to explore the chemical space



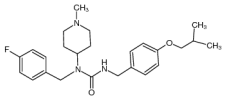
Douguet *et al*., *J. Med. Chem.*, 2005. http://chemoinfo.ipmc.cnrs.fr

e-Drug$_{3D}$

What we know:

1557 princeps / 1822 different structures (July 2016)

❑ Chemical Structures



Pimavanserin (2016)

Physico-chemical properties (calculated)
1D/2D (MW, LogP, PSA, solubility, nbHBD, nbHBA, nbRot, charge…)
3D (conformations, shape …)

Privileged structures (fragments, scaffolds, frameworks, peptide, natural compounds…)

❑ FDA Registration Data
(Year, Company, label…)

❑ Pharmacodynamics
(Class, Target)

❑ Pharmacokinetics
(metabolites, routes, VD, Cl, HT, PPB, F…)

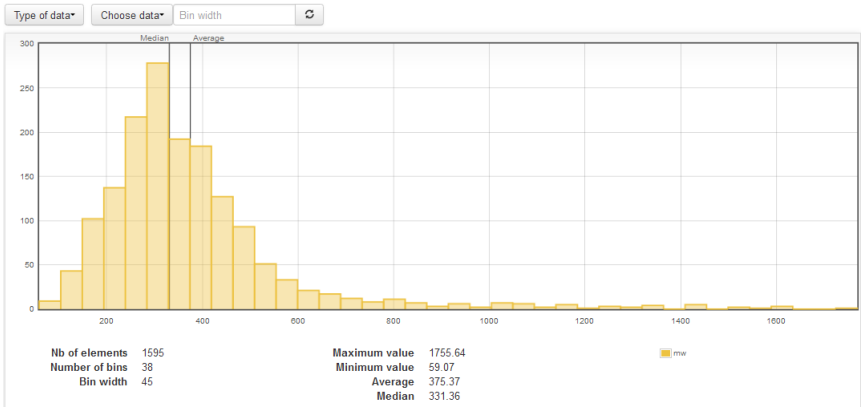
* e-Drug3D: release of July 2016
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

Physico-Chemical Properties

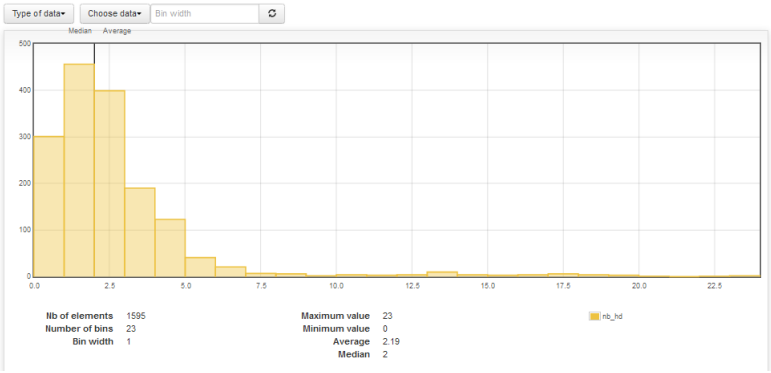
➢ **Lipinski's rule of 5 *: 'druglike'**

- Molecular weight (MW) < 500
- Number of hydrogen bond donors < 5
- Number of hydrogen bond acceptors < 10
- LogP < 5

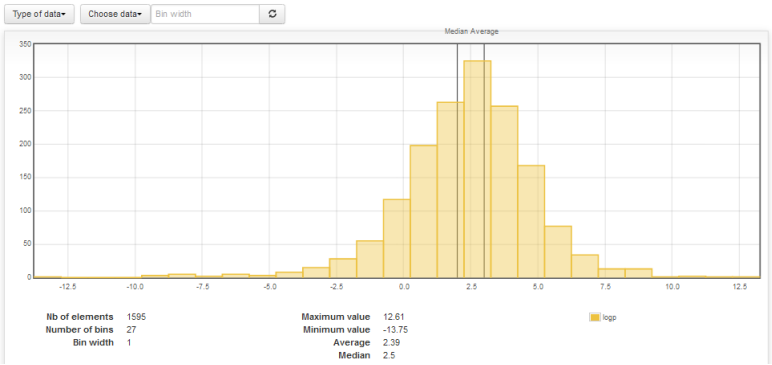
MW



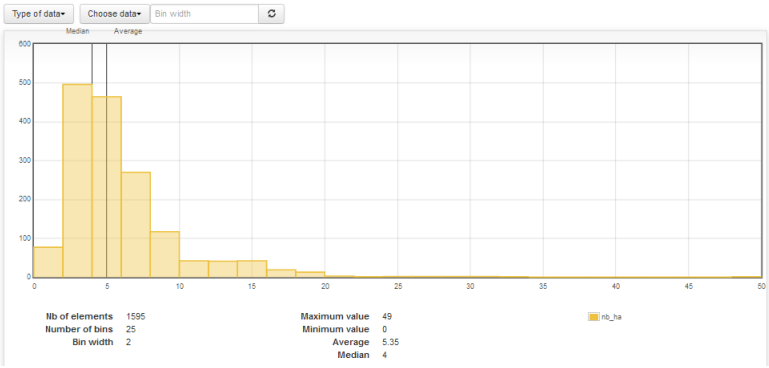
NbHD



LogP (XLogP)



NbHA

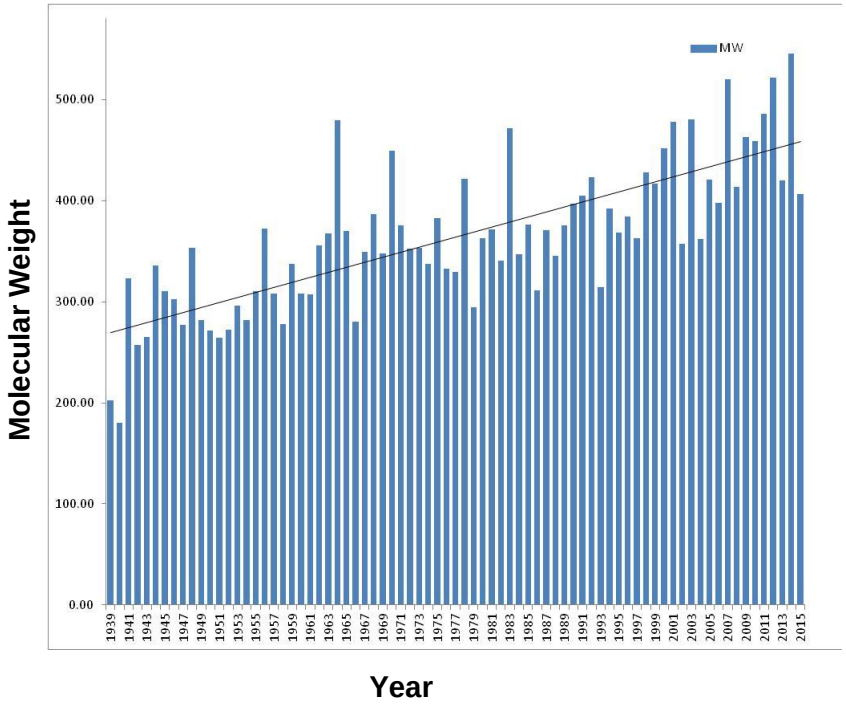


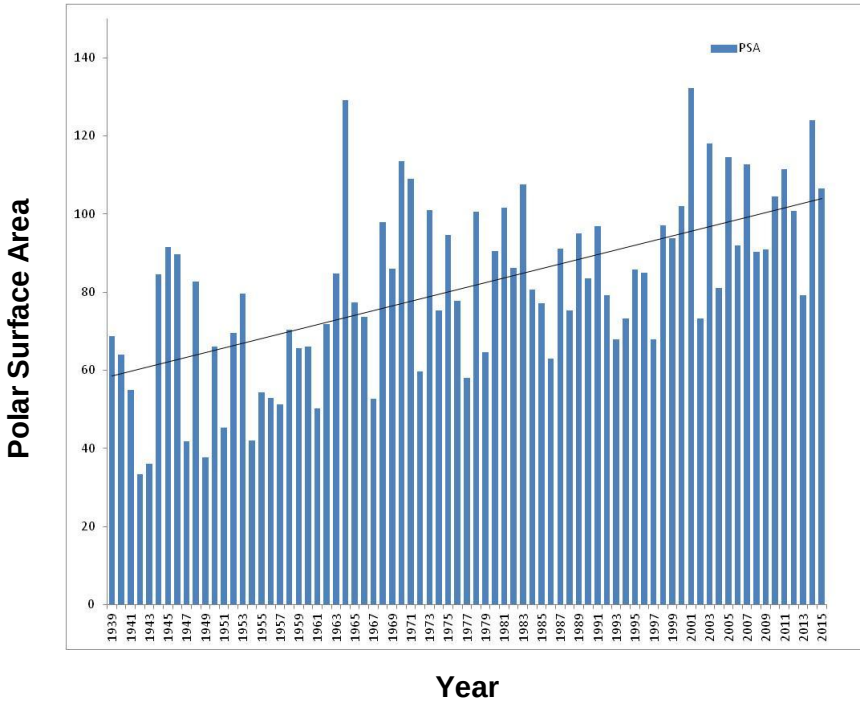
e-Drug3D: release of January 2013 (1595 different structures)

* Lipinski C.A. *et al.*, *Advanced Drug Delivery Reviews*, 2001, 46, 3-26.

Physico-Chemical Properties

- **Statistics on approved drugs*: Evolution of drug properties**

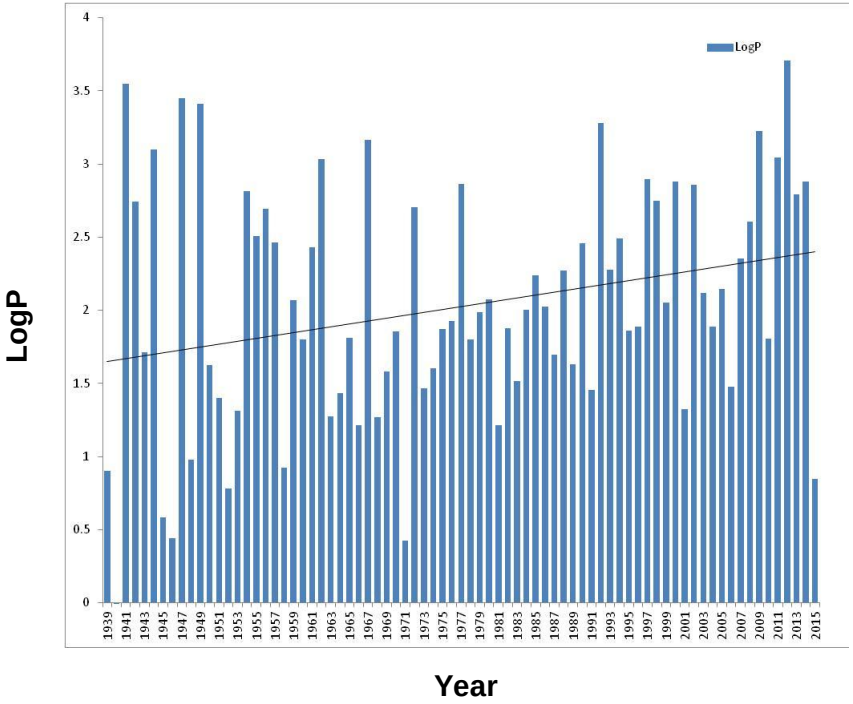


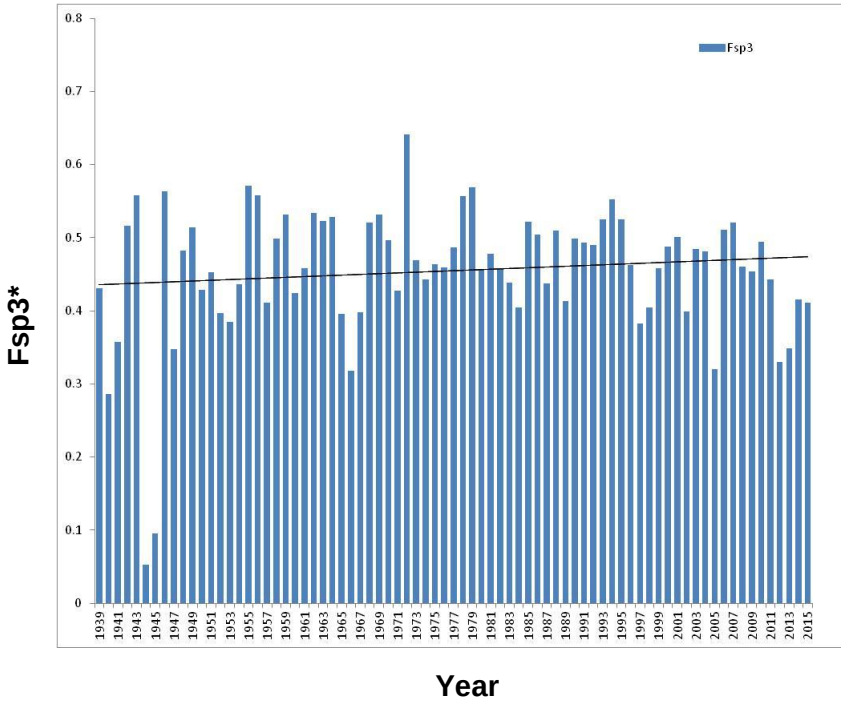


*e-Drug3D: release of March 2015 (1746 different structures)

Physico-Chemical Properties

➢ **Statistics on approved drugs*: Evolution of drug properties**





*e-Drug3D: release of March 2015 (1746 different structures)
** Fsp3 = Number of C(sp3) / Number of C

➢ Formal charges ?

- 1372 **(75%) neutral structures**
- 72 (**4%**) with positive charge(s)
- 356 (**20%**) with negative charge(s)
- 22 zwitterions

- If corrected by putative protonated terciary amine (681 identified cases):
  - **46% neutral structures**
  - **33% with positive charge(s)**
  - **12%** with negative charge(s)
  - 6 zwitterions

The prediction of protonation states is by no means satisfactorily solved

* e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures)
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

➢ **Solubility**

- 940 structures with **experimental** solubility information

~ 456 (48%) are soluble (77% possess are an oral route of administration)

~ **484 (52%) are insoluble, not soluble, slightly, sparingly or poorly soluble (or low water solubility)**
(77% possess are an oral route of administration)

A quarter to half the 1822 approved drugs have low solubility in water

Are these drugs suitable for testing in biochemical assays ?

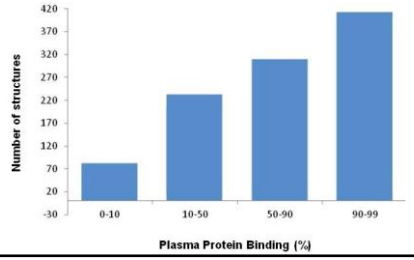
* e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures)
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

e-Drug3D

What we know:

1557 princeps / 1822 different structures (July 2016)

- **Chemical Structures**
  - **Physico-chemical properties (calculated)**
  - **Privileged structures**
- **FDA Registration Data**
  (Year, Company, label…)
- **Pharmacodynamics**
  (Class, Target)



- **Pharmacokinetics**
  (active metabolites, routes, VD, Cl, HT, PPB, F…)

* e-Drug3D: release of July 2016
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

Pharmacokinetic Parameters

➢ **Active Metabolites:** **481/1822 (26%) structures are or have active metabolite(s)**
183 groups of drugs and active metabolites belonging to the same family
(a structure is either a mother or an offspring of another one)
http://chemoinfo.ipmc.cnrs.fr/MOLDB/metabolite_groups.html

#Group number | e-Drug3D IDs | Names | Html link

Group 1 | 1 81 1399 625 1266 | - SULFAPYRIDINE - SULFASALAZINE - MESALAMINE - OLSALAZINE - BALSALAZIDE | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=1_81_1399_625_1266

Group 2 | 5 1791 6 | - DESOXYCORTICOSTERONE ACETATE - DESOXYCORTICOSTERONE - DESOXYCORTICOSTERONE PIVALATE | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=5_1791_6

Group 3 | 11 17 961 19 20 21 | - ESTRONE - ESTRADIOL - ESTROPIPATE - ESTRADIOL VALERATE - ESTRADIOL CYPIONATE - ESTRADIOL ACETATE | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=11_17_961_19_20_21

Group 4 | 16 568 | - HYDROCODONE - HYDROMORPHONE | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=16_568

Group 5 | 18 383 | - ETHINYL ESTRADIOL - QUINESTROL | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=18_383

Group 6 | 22 294 1106 1332 177 1319 249 1306 | - METHAMPHETAMINE - BENZPHETAMINE - AMPHETAMINE - DEXTROAMPHETAMINE - HYDROXYAMPHETAMINE - HYDROXYAMPHETAMINE - PHENYLPROPANOLAMINE - LISDEXAMFETAMINE | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=22_294_1106_1332_177_1319_249_1306

Group 7 | 24 1325 | - VITAMIN A - VITAMIN A PALMITATE | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=24_1325

Group 8 | 32 1773 | - TRIMETHADIONE - M TRIMETHADIONE | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=32_1773

Group 9 | 33 105 | - FOLIC ACID - LEUCOVORIN | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=33_105

Group 10 | 44 605 | - MOMETASONE FUROATE - MOMETASONE | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=44_605

Group 11 | 48 1419 | - ALPHA-TOCOPHEROL - ALPHA-TOCOPHEROL ACETATE | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=48_1419

Group 12 | 61 1772 | - AMODIAQUINE - M AMODIAQUINE | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=61_1772

Group 13 | 64 498 1160 | - EPINEPHRINE - DIPIVEFRIN - DIPIVEFRIN | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=64_498_1160

Group 14 | 65 66 | - SULFISOXAZOLE - SULFISOXAZOLE ACETYL | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=65_66

Group 15 | 76 78 | - AMINOSALICYLIC ACID - PHENYL AMINOSALICYLATE | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=76_78

Group 16 | 82 1771 | - CORTISONE ACETATE - CORTISONE | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=82_1771

Group 17 | 84 1770 1435 | - ASPIRIN - M ASPIRIN - METHYL SALICYLATE | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=84_1770_1435

Group 18 | 108 109 110 111 191 1327 1328 | - HYDROCORTISONE - HYDROCORTISONE ACETATE - HYDROCORTISONE VALERATE - HYDROCORTISONE BUTYRATE - HYDROCORTAMATE - HYDROCORTISONE CYPIONATE - HYDROCORTISONE PROBUTATE | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=108_109_110_111_191_1327_1328

Group 19 | 129 734 | - PHENYTOIN - FOSPHENYTOIN | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=129_734

Group 20 | 139 372 | - MERCAPTOPURINE - AZATHIOPRINE | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=139_372

Group 21 | 143 144 1334 1335 1718 | - TESTOSTERONE - TESTOSTERONE PROPIONATE - TESTOSTERONE ENANTHATE - TESTOSTERONE CYPIONATE - TESTOSTERONE UNDECANOATE | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=143_144_1334_1335_1718

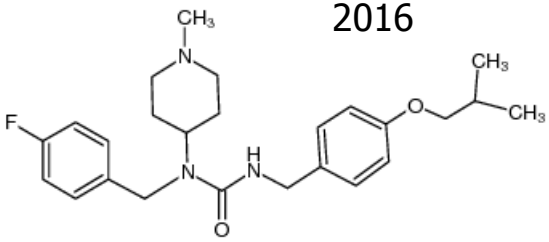
Group 22 | 164 254 255 | - MEPROBAMATE - CARISOPRODOL - CARISOPRODOL | http://chemoinfo.ipmc.cnrs.fr/MOLDB/browse.php?query=164_254_255

* e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures)
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

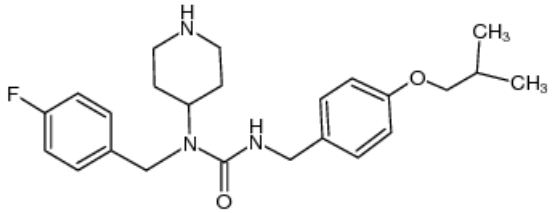
Pharmacokinetic Parameters

➢ **Active Metabolites:** **481/1822 (26%) structures are or have active metabolite(s)**

Pimavanserin
2016

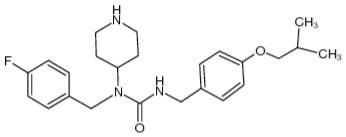


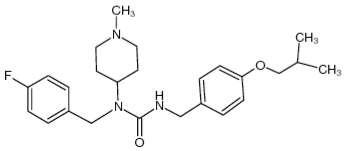
M Pimavanserin
active metabolite



Select all | Unselect all | Subselect

Pharmacology | FDA Registration | Chemistry | Properties | Similarities | Most similar drugs | Fragments

1	INN	Class	Route (list)	PK parameters= Cmax; Tmax; F:bioavailability; HT:half-life; VD:distribution volume; CL:clearance; PP:plasma protein binding; EQN:value calculated using VD=(CL*HT)/0.693	Primary Target	PDB	Links
M PIMAVANSERIN (is an active metabolite) 		ATC - NERVOUS SYSTEM ANTIPSYCHOTIC TREATMENT OF HALLUCINATIONS AND DELUSIONS ASSOCIATED WITH PARKINSON'S DISEASE PSYCHOSIS INVERSE AGONIST / ANTAGONIST SEROTONIN 5-HT2A (KI = 0.087 NANOMOLAR) AND 5-HT2C (KI = 0.44 NANOMOLAR) SIGMA 1 RECEPTOR (KI = 120 NANOMOLAR)	-	HT 200 HOUR	5-HT2A RECEPTOR 5-HT2C RECEPTOR	-	SIDER side effects Dailymed Drugs.com VIDAL (in French) DrugCentral DrugBank:- ChEBI

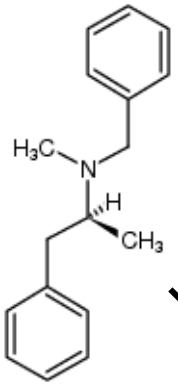
2	INN	Class	Route (list)	PK parameters= Cmax; Tmax; F:bioavailability; HT:half-life; VD:distribution volume; CL:clearance; PP:plasma protein binding; EQN:value calculated using VD=(CL*HT)/0.693	Primary Target	PDB	Links
PIMAVANSERIN (has an active metabolite) 	PIMAVANSERIN TARTRATE	ATC - NERVOUS SYSTEM ANTIPSYCHOTIC TREATMENT OF HALLUCINATIONS AND DELUSIONS ASSOCIATED WITH PARKINSON'S DISEASE PSYCHOSIS INVERSE AGONIST / ANTAGONIST SEROTONIN 5-HT2A (KI = 0.087 NANOMOLAR) AND 5-HT2C (KI = 0.44 NANOMOLAR) SIGMA 1 RECEPTOR (KI = 120 NANOMOLAR)	ORAL	SOLUBILITY SOLUBLE IN WATER HT 57 HOUR TMAX 6 HOUR PP 95 PERCENT VD 2173 LITER	5-HT2A RECEPTOR 5-HT2C RECEPTOR	-	SIDER side effects Dailymed Drugs.com VIDAL (in French) DrugCentral DrugBank:- ChEBI

* e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures)
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

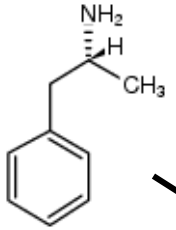
Pharmacokinetic Parameters

➢ **Active Metabolites:** **481/1822 (26%) structures are or have active metabolite(s)**

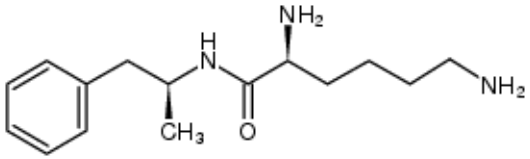
Benzphetamine
1960



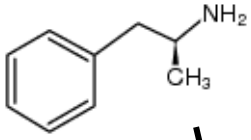
Amphetamine
1955



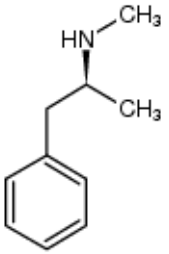
Lisdexamfetamine
2007



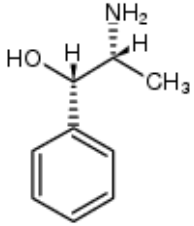
Dextroamphetamine
1955



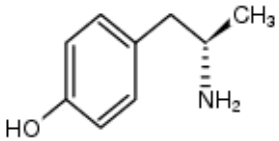
Methamphetamine
1943

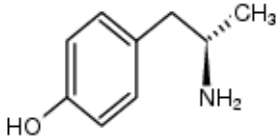


Phenylpropanolamine
1958



Hydroxyamphetamine
1969

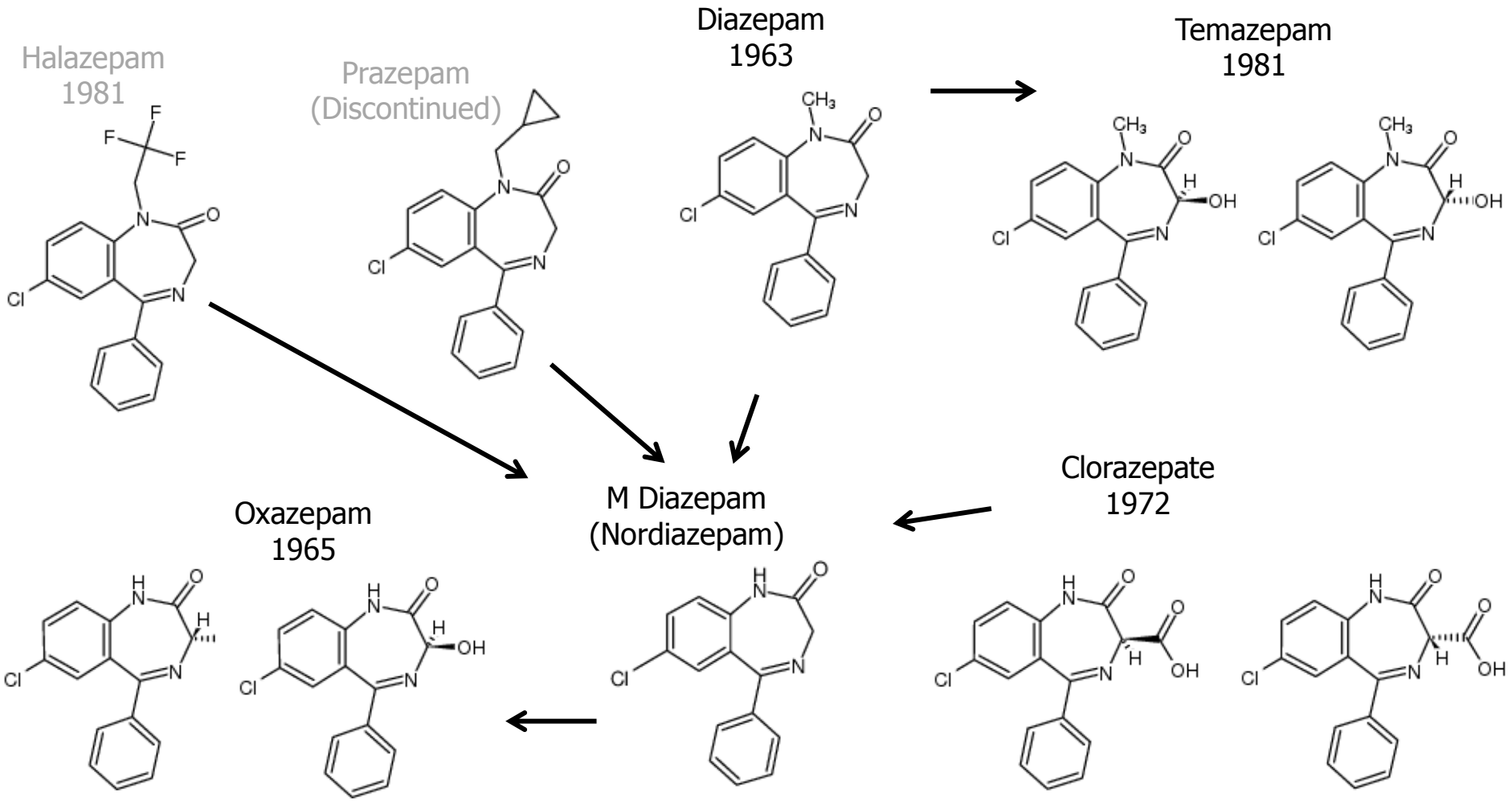




* e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures)
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

Pharmacokinetic Parameters

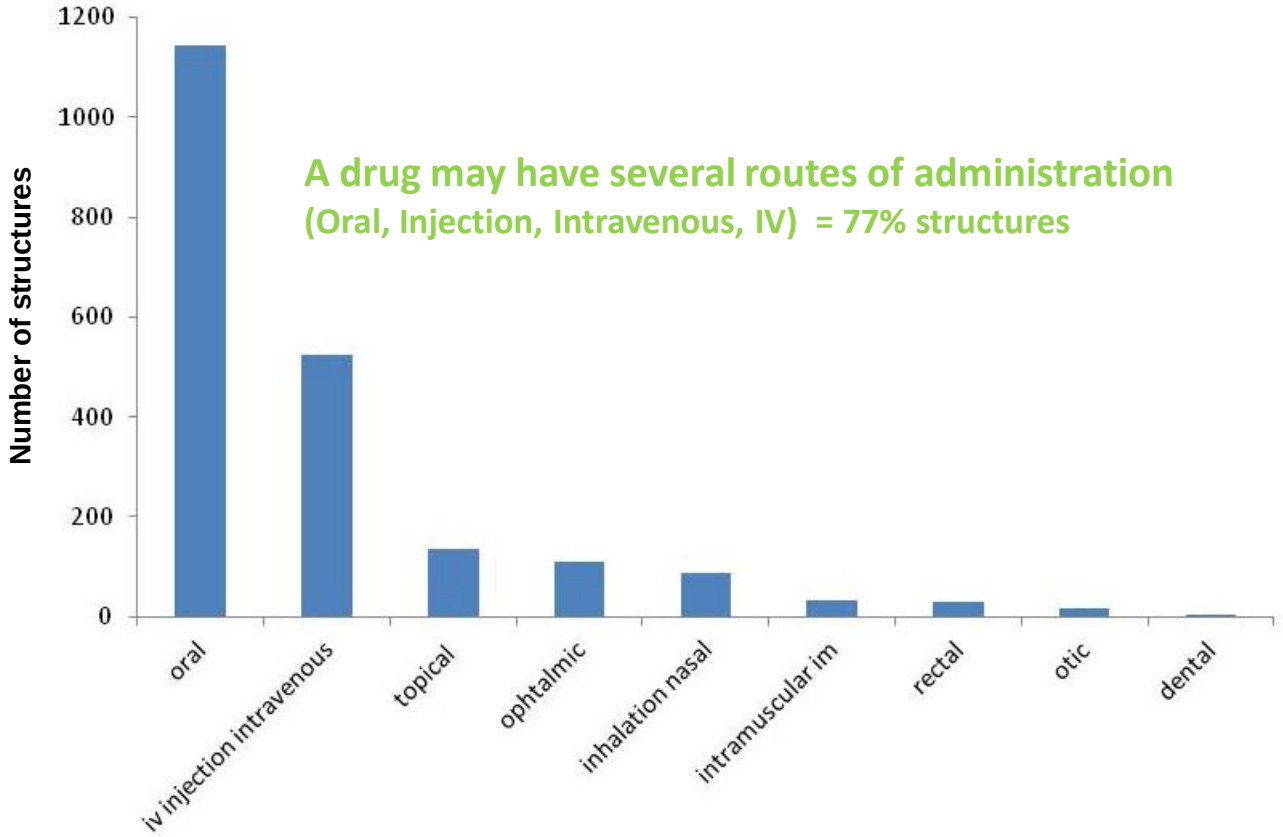
➢ **Active Metabolites:** **481/1822 (26%) structures are or have active metabolite(s)**



* e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures)
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

Pharmacokinetic Parameters

➢ **Route of Administration**



* e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures)
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

Pharmacokinetic Parameters

Title	Property	Number
ID	e-Drug3D ID	1822
Name	INN	1822
CAS	Chemical Abstract number	1820
Year	Year of approval (if identified)	1553(1)
Status	If "Discontinued"	372(2)
Is_a_Metabolite	contains IDs if they exist	235(3)
Has_a_Metabolite	contains IDs if they exist	259(3)
Route	Routes of Administration	1669(4)
VD	Volume of Distribution (liter)	937
Cl	Clearance (liter / hour)	928
*t*1/2	Half-life (hour)	1252
PPB	Plasma Protein Binding (%)	1036
F	Bioavailability (%)	518
Cmax	Maximal concentration in blood	752
Cmax_unit	Cmax unit	752
Tmax	Time taken to reach Cmax (hour)	725
Solubility	Comments on solubility	940

(1) Year = 0 when there is no identified year of approval or when it is an active metabolite; (2) Discontinued structures are not more marketed but still possess a NDA number (FDA approval number); (3) 13 cases are in both categories; (4) The 153 absent structures are active metabolites structures without NDA number; N.F.: Not Found;

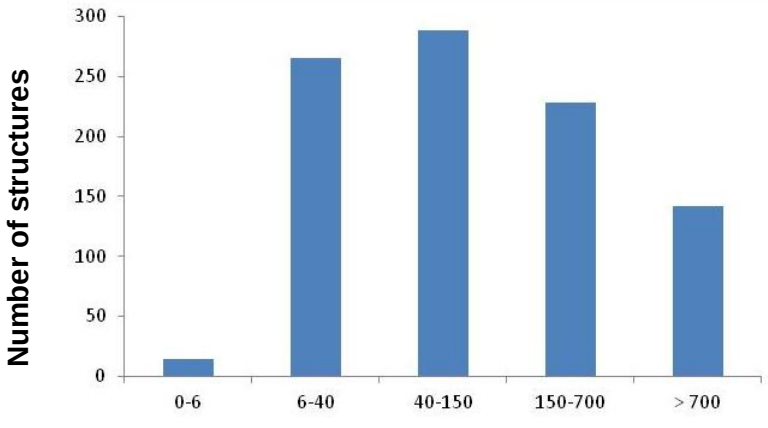
Univariate Statistics

- **VD: Volume of Distribution (liter)**
  N = 937; Range [0.14 – 152620]; Mean = 786 liter
- **Cl: Clearance (liter / hour)**
  N = 928; Range [0.014 - 6900]; Mean = 67.4 liter/hour
- **PPB: Plasma Protein Binding (%)**
  N = 1036; Range [0 - 99.9]; Mean = 68 %
- **HT: Half-life (hour)**
  N = 1252; Range [0.03 – 87600]; Mean = 107 hour
- **F: Bioavailability (%)**
  N = 517; Range [0.6 - 100]; Mean = 59.6 %
- **Cmax: The maximal concentration in blood**
  N = 752; Range [47 picomolar – 1.32 millimolar]
  Mean = 34 μM ** (741 values):
  micromolar {N = 410; Range [0.072 - 932.8]; Mean = 63 μM}
  nanomolar {N = 331; Range [0.01 - 995]; Mean = 177 nM}
- **Tmax: Time to reach the Cmax (hour)**
  N =725; Range [0.03 – 200]; Mean = 3.2 hour

* e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures)
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

**$[\text{alpha1 acid glycoprotein}]_{Blood}$ = 17.5 μM

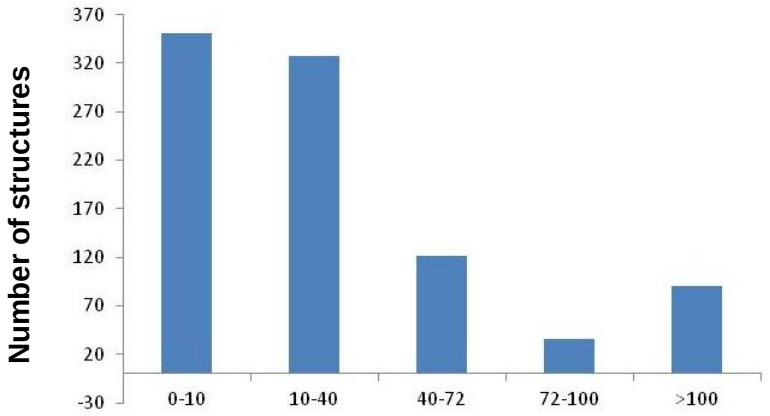
Volume of body fluids ~ 40 liters (intracellular 25L + extracellular 15 L (12 L interstitial + 3 L plasma))



Volume of Distribution (liter)

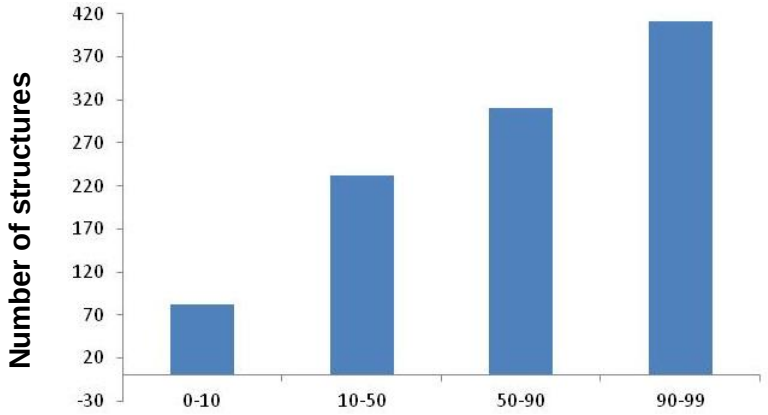
N = 937; Range [0.14 – 152620]; Mean = 786L; Median = 91L

Liver blood flow ~ 1.2 L/min (72 L / hour)



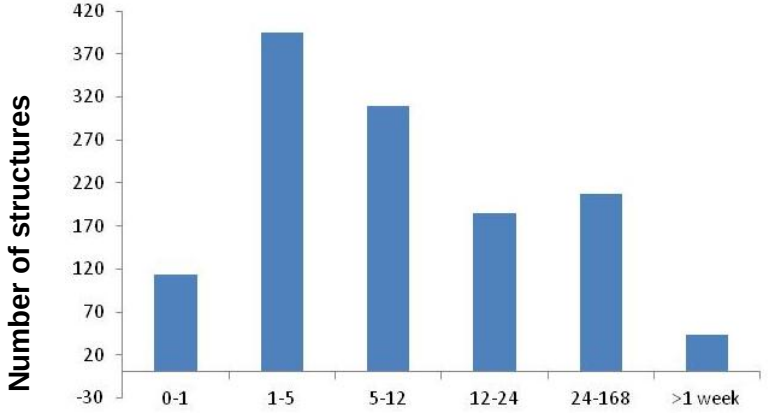
Clearance (liter / hour)

N = 928; Range [0.014 – 6900]; Mean = 67.4 L/h; Median = 17.2 L/h



Plasma Protein Binding (%)

N = 1036; Range [0 – 99.9]; Mean = 68% ; Median = 83%



Half-life $\tau_{1/2}$ (hour)

N = 125; Range [0.03 – 87600]; Mean = 107 h; Median = 7h

830/1252 (66%) with $\tau_{1/2} \leq$ 12 h

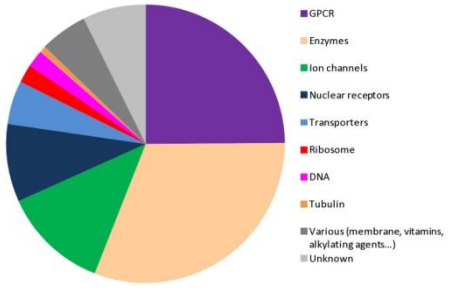
$$\tau_{1/2} = (VD * 0.693) / Cl$$

e-Drug3D

What we know:

1557 princeps / 1822 different structures (July 2016)

- **Chemical Structures**
  - **Physico-chemical properties (calculated)**
  - **Privileged structures**
- **FDA Registration Data**
  (Year, Company, label…)
- **Pharmacodynamics**
  (Class, Target)



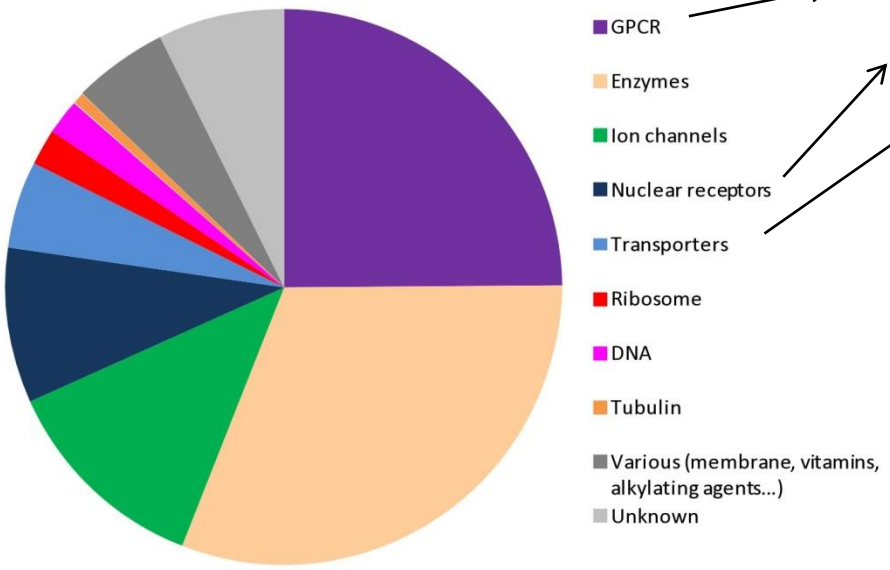
- **Pharmacokinetics**
  (metabolites, routes, VD, Cl, HT, PPB, F…)

* e-Drug3D: release of July 2016
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

Pharmacodynamics: which are Primary Drug Targets ?

➢ **Statistics on approved drugs: How many drug targets * ?**

1690 / 1822 structures with Target information (216 are antiinfectives NMEs)



42% of targets are located at the cell surface
(compared with ~22% of
all proteins in the human genome**)

** **Overington *et al.*, *Nat Rev Drug Disc*, 2006, 1, 727-730.**

* e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures)
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

Drug Targets

➢ **Statistics on approved drugs: How many drug targets ?**

e-Drug3D

1690 structures

- GPCR	455
- Enzymes	564
- Ion channels	225
- Nuclear receptors	164
- Transporters	91
- Ribosome	40
- DNA	37
- Tubulin	12
- Various (membrane, vitamins alkylating agents…)	102
- Unknown	132

Kinch M.S. *et al.*, *Drug Discovery Today*, 2014.

1453 NMEs

(a)

Target class	NME
GPCR Adrenoceptor (78) Acetylcholine receptor (61)	397
Channel Sodium channel (49) GABA (41)	147
Nuclear signaling Glucocorticoid receptor (37) Estrogen receptor (17)	104
Protease Thrombin (14) Acetylcholine esterase (12)	66
Transporter Norepinephrine (15) Serotonin (15)	65
Transpeptidase Penicillin-binding protein (54)	54
Oxygenase Cyclooxygenase (28) Monoamine oxidase (8)	52
Polymerase DNA polymerase (20) RNA polymerase (17)	45
Kinase Tyrosine kinase (35) Serine/threonine kinase (4)	43
Cytokine Interferon (10) Interleukin (7)	37

(b)

Target class	NME
Ribosome	34
Synthase	32
Isomerase	31
Alkylating agent	23
Sterol	20
Esterase	19
Reductase	19
Dehydrogenase	12
Enzyme replacement	11
Tubulin	10
Cell adhesion	7
Anhydrase	6
Carboxylase	6
Chelator	6
Transferase	5
Amidase	5
Other target	102
Unclear mechanism	95

Drug Discovery Today

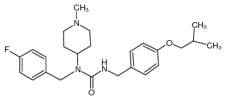
* e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures)
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

e-Drug$_{3D}$

What we want to know:

Structure-Activity Relationships

❑ **Chemical Structures**

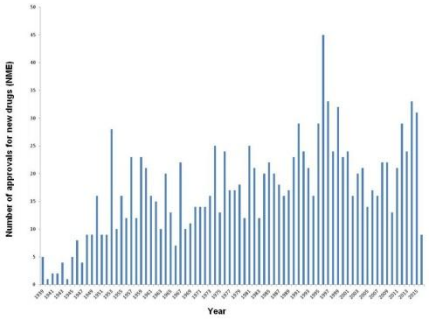


Pimavanserin (2016)

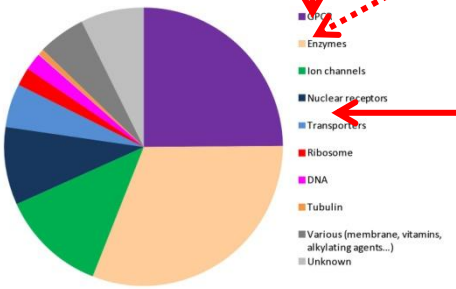
❑ **FDA Registration Data**
(Year, Company, label…)

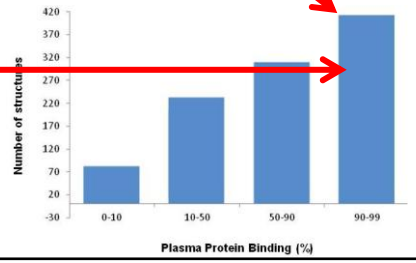
Physico-chemical properties (calculated)
1D/2D (MW, LogP, PSA, solubility, nbHBD, nbHBA, nbRot, charge…)
3D (conformations, shape …)

Privileged structures (fragments, scaffolds, frameworks, peptide, natural compounds…)



❑ **Pharmacodynamics**
(Class, Target)





❑ **Pharmacokinetics**
(metabolites, routes, VD, Cl, HT, PPB, F…)

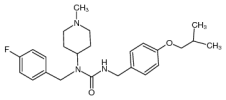
* e-Drug3D: release of July 2016
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

e-Drug$_{3D}$

What we want to know:

Structure-Activity Relationships

❑ Chemical Structures

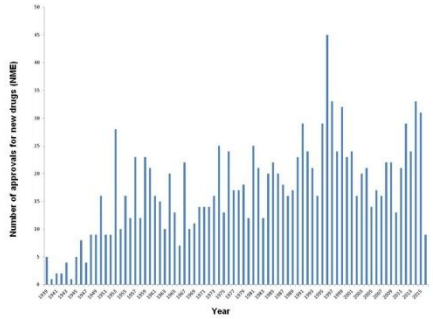


Pimavanserin (2016)

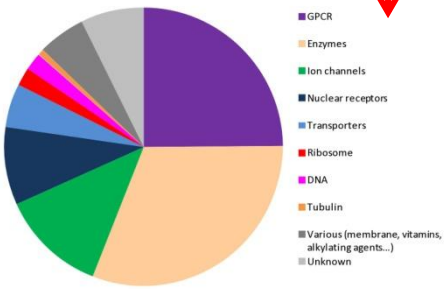
Physico-chemical properties (calculated)
1D/2D (MW, LogP, PSA, solubility, nbHBD, nbHBA, nbRot, charge…)
3D (conformations, shape …)

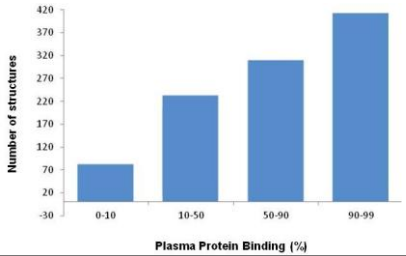
Privileged structures (fragments, scaffolds, frameworks, peptide, natural compounds…)

❑ FDA Registration Data
(Year, Company, label…)



❑ Pharmacodynamics
(Class, Target)





❑ Pharmacokinetics
(metabolites, route, VD, CL, HT, PP, F…)

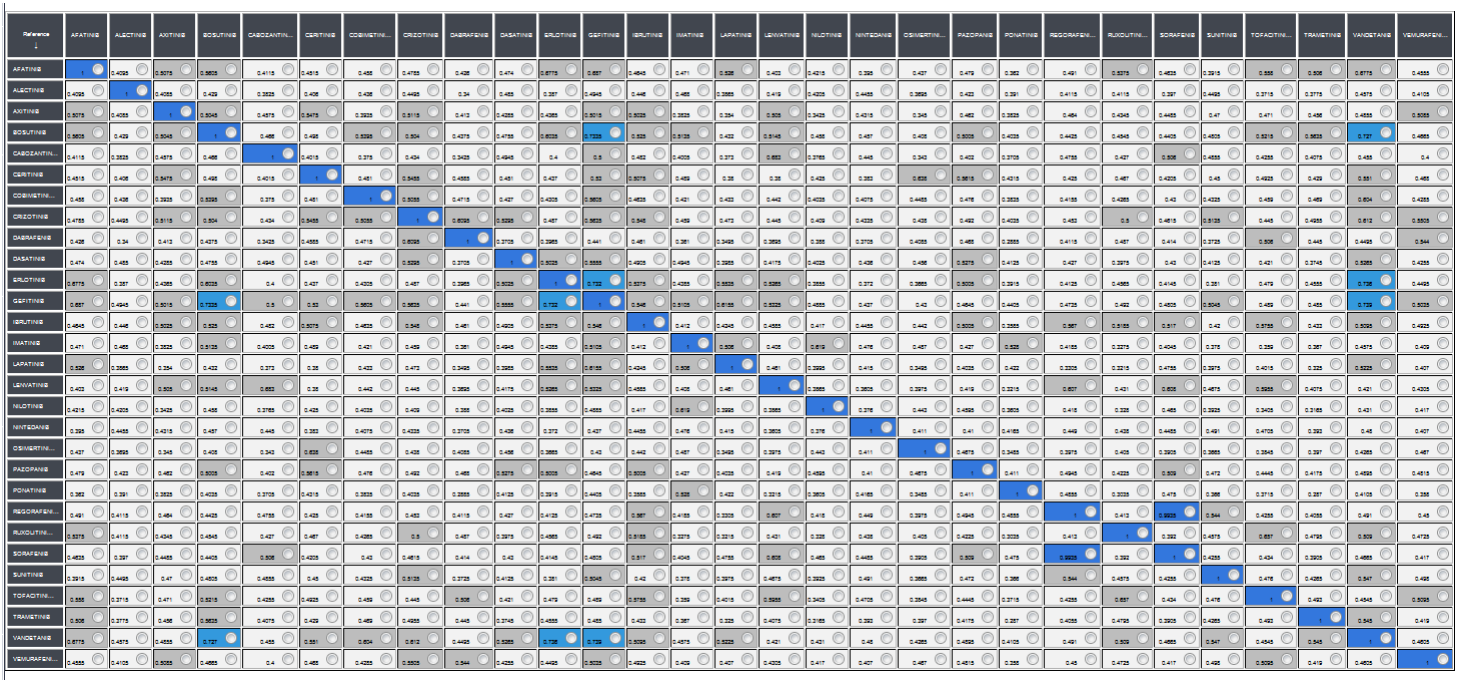
* e-Drug3D: release of July 2016
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

Pharmacology

Structural Similarities

e-Drug3D ⟶ Similarity matrix (drug x drug) by using the shape matching program ROCS (OpenEye Scientific Software Inc.)

1822 structures

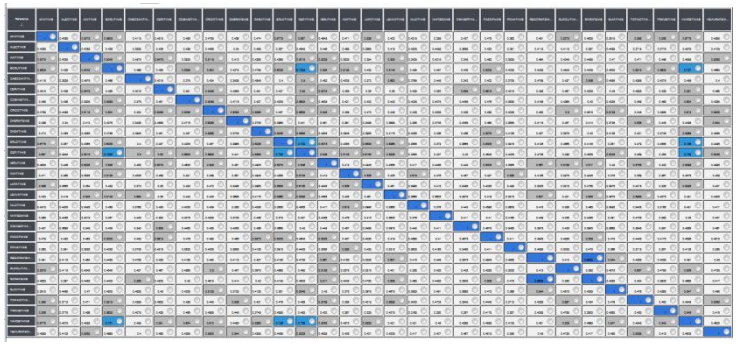


* e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures)
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

Pharmacology

Structural Similarities / Primary Target classes

1822 x 1822

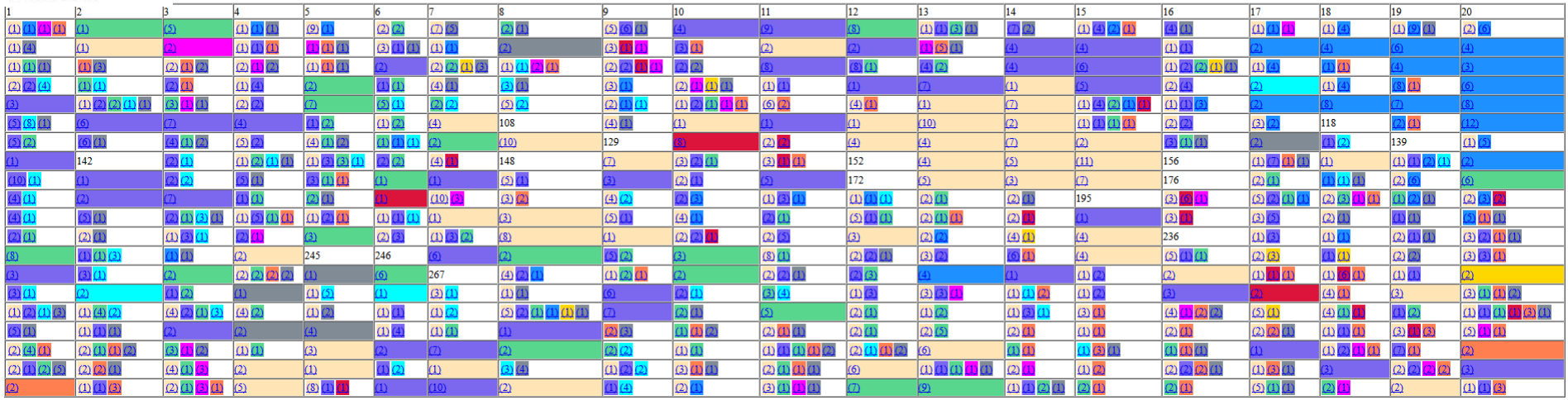


→ Kohonen's Self-Organizing Map (SOM)

↓

Grid 20x20
Colored by Primary
Target Class

- GPCR
- Enzymes
- Ion channels
- Nuclear receptors
- Transporters
- Ribosome
- DNA
- Tubulin
- Various
- Unknown

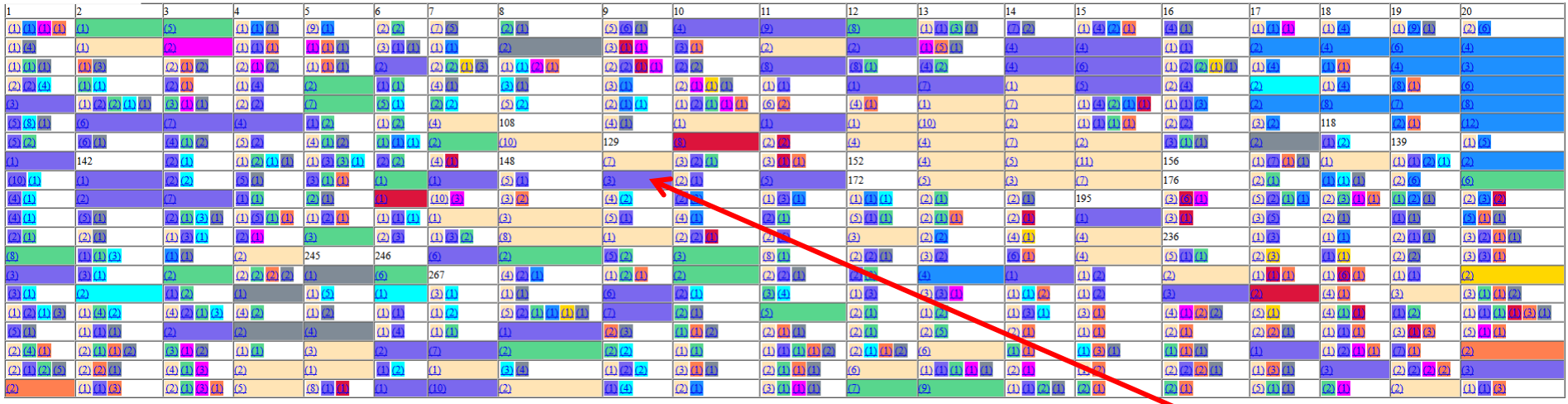


* e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures)
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

Pharmacology

Structural Similarities / Target classes / Compound Profiling

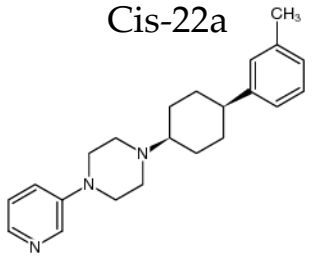
Prediction of the membership in a cell to predict protein target(s)



- **Prediction of potential protein target(s) for new synthesized structures**

e.g.: Optimization of **TRPV6 Calcium Channel Inhibitors** Using a 3D Ligand-Based Virtual Screening Method.
Simonin C. *et al.*, *Angew Chem Int Ed Engl*. **2015**;54(49):14748-52.

Cis-22a



if using ROCS similarity score: 1° Abiraterone/α-hydrolase (0.718)
2° **Paliperidone/5-HT2a, α1, α2, D2, H1** (0.7)
if using SOM1822: **cell no 169 (Doxazosin (R/S) and Terazosin), Predicted Target=Adrenergic α1**

rq: Capsaicin is the only drug associated with TRPV ion channel (TRPV1 agonist); Menthol (TRPM8)

- **Analysis of the poly-pharmacology activity for drugs (structures in cells associated with several target classes)**

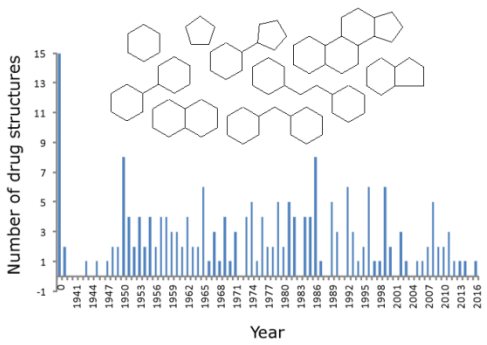
e-Drug$_{3D}$

Restrict access: registration (login & password)

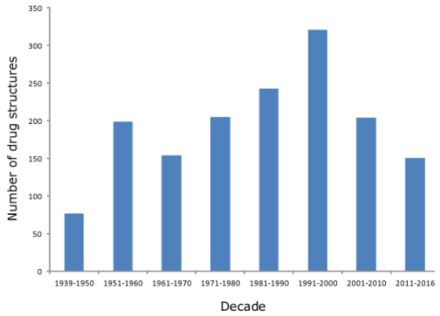
You only need a valid email address and accept the copyright policy

e-Drug3D datasets

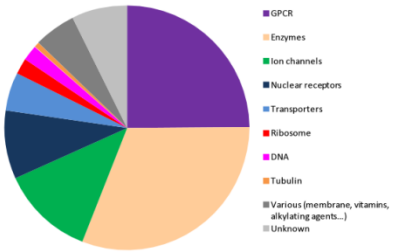
Chemical Structures
(privileged frameworks...)



FDA Registration Data
(year, company, label...)

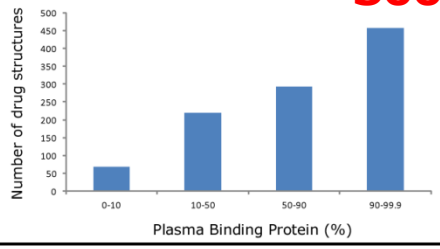


Pharmacodynamics
(class, primary target...)



Pharmacokinetics
(metabolites, routes, VD, Cl, $T_{1/2}$, PPB, F, Cmax, Tmax...)

Soon !



Downloads at http://chemoinfo.ipmc.cnrs.fr/edrug3d.html

e-Drug3D

- **Useful Database for**
  - Computational chemists (cheminformatics, Molecular Modeling and Structural Bioinformatics)
  - Medicinal Chemists
  - Structuralists, biologists
  - Economists…

- **Statistics on Approved Drugs**
  - Evolution of Therapeutics over time
  - Structure–Activity Relationships (PD: pharmacodynamic information: Target(s), ATC Therapeutic Class)
  - Structure–Properties Relationships (PK: pharmacokinetic information: Solubility, F, Cmax/Tmax, VD, PP, CL,T½)
  - ? correlations between calculated Physico-chemical descriptors (MW, LogP, PSA, Volume, Fsp3…) and experimental PK, PD data with the objective of improving predictions (‘druglike’ filters/models and bioactivity profiling)

- **Collection for *in silico* screenings (Drug Repurposing)**
  - Structure-based screening (docking)
  - Ligand-based screening (shape and chemical function similarities)

- **Collection for Fragment-Based Drug Design (FBDD/FBLD)**
  - Commercially available privileged structures (fragments extracted from drugs)

* e-Drug3D: release of July 2016 (1557 princeps / 1822 different structures)
Source: http://chemoinfo.ipmc.cnrs.fr ; Pihan *et al.*, *Bioinformatics*, 2012.

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Thanks for your Attention