Topics in Organic Chemistry: Medicinal Chemistry (CHEM 515)

I. Introductory lecture

A. Three drug examples to illustrate drug development

1. Ephedrine

		**a) Folk medicine (traditional medicine)=natural product** 3000 BCE Emperor Shen Nung -from the plant ma huang -suppresses coughing **b) Acts at a receptor** -The principal mechanism of action relies on its indirect stimulation of the adrenergic receptor system by increasing the activity of noradrenaline at the postsynaptic α- and β-receptors.

<u>Ephedrine use (from Wikipedia and internet):</u>
- _____ stimulant often used to prevent low blood pressure during anesthesia.

-treatment of _____

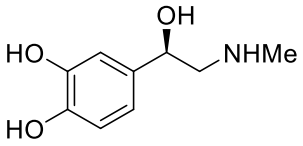
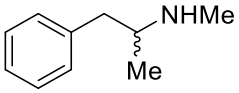
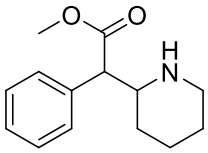
-_____ but is not the preferred treatment.

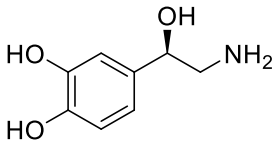
Related structrues:
Pseudoephedrine

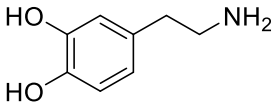
-active ingredient in _____ medications Sudafed (McNeil, J&J), Actifed (GSK), Claritin-D (Bayer), Allegra-D (Sanofi-Aventis)

-now _____

-nasal/sinus decongestant without drowsiness; has stimulant effects

 epinephrine (adrenalin)	 methamphetamine	 Ritalin (methylphenidate)


norepinephrine (noradrenaline)


dopamine

Common structural element: _____

Pharmacophore=_____

2. cimetidine (_____), an _____

(Smith, Kline & French→ _____)

-mid 1970's

-<u>note:</u> cimetidine= _____; Tagamet= _____ (_____ name);

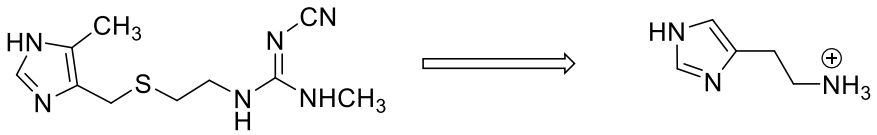
pre-clinical = e.g. _____

a) blocks H2 <u>histamine</u> <u>receptors =</u> _____

_____ : _____ :: _____ : _____

_____ : _____ :: _____ : _____

-no H2 histamine receptor X-ray structure or related receptor structural information!



Key development: _____!

b) _____ →evolved from modifications of natural agonist, histamine

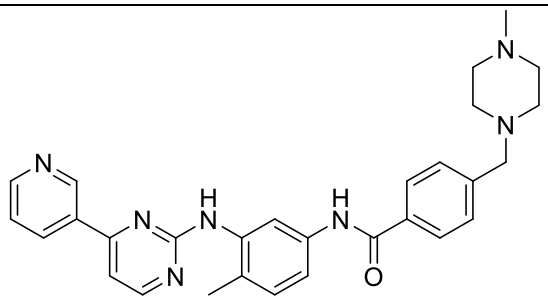
-1988 Sir James Black, Nobel Prize in Physiology or Medicine (also for propranolol)

Zantac (ranitidine—_____, GSK also)

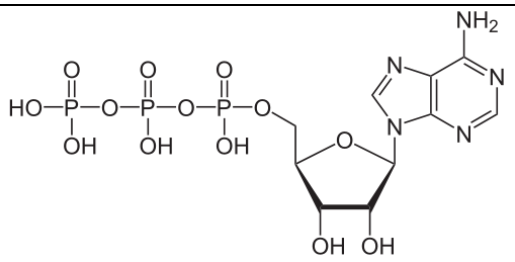
[Eventually replaced by _____ like Prilosec, generic name: omeprazole.]

3. Gleevec, an anti-cancer drug (Novartis)

-generic name= _____



imatinib



ATP

- _____ inhibitor

- binds in _____ pocket → _____

-**genetic research**→ provided target

- _____ (HTS) to find _____ that was selective

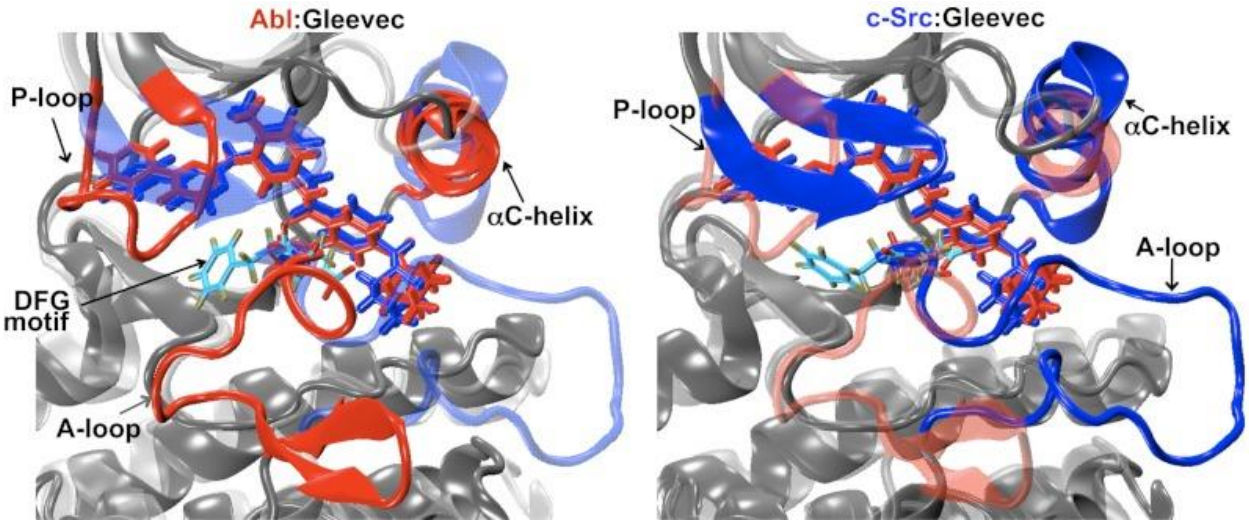
- _____ studies optimized the lead

_____

-genetic defect (chromosome translocation) discovered in chronic myelogenous leukemia (CML) leads to aberrant protein (Abl, a tyrosine kinase—attaches phosphate groups to proteins) that is overactive.

No crystal structure known while development occurred.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3562763/figure/fig01/



Details of intermolecular interactions with target are critical to bioactivity and therapeutic optimization → X-ray information is critical

B. Drug Development: the task

1. Medicinal Chemistry=the study of _____ to develop and

optimize the _____ of the chemicals.

Who's involved? _____.

Organic chemists (called _____ and _____ chemists),

_____

2. All bioactive chemicals have both _____ and

_____ on humans.

a) Quantifying positive vs. negative effects….

therapeutic index= _____

=_____ or LD_{50}/ED_{50}

(1) effective dose= _____

-ED_{50}= _____

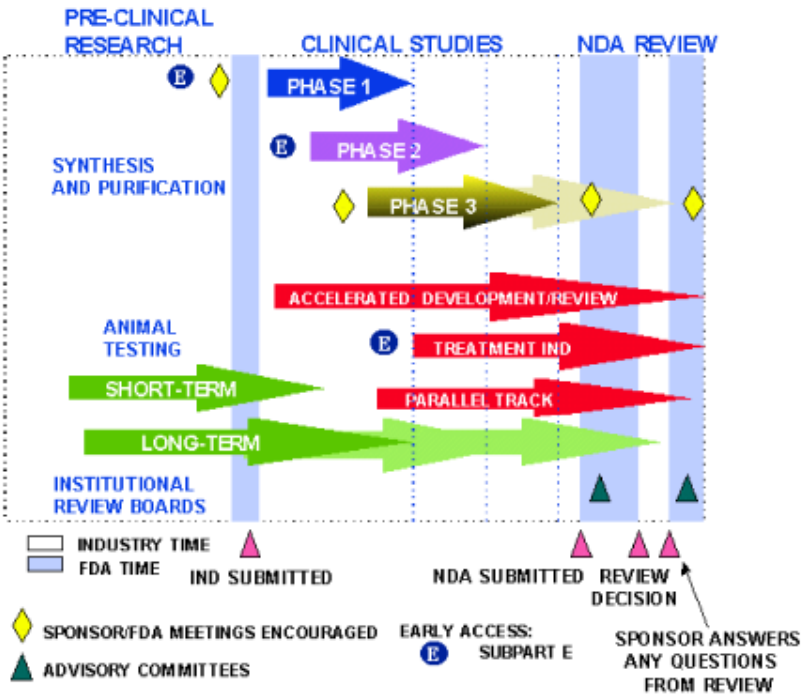
(2) LD_{50}= _____

b) Goal=find a _____ concentration to achieve ED_{50} and a _____

concentration to obtain LD_{50}.

c) The larger the therapeutic index,…

C. Drug Development process: an overview



from:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm053131.htm

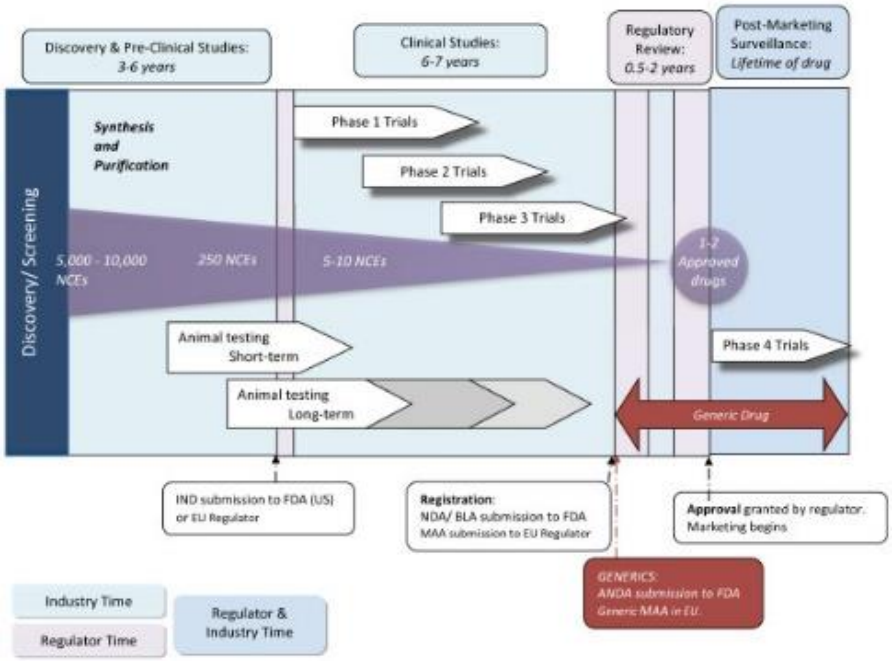


Figure from https://www.researchgate.net

1. Pre-clinical research

**our primary focus!!

a) Discovery of a _____

-drive by _____

-develop an _____ to screen compounds; preferably amenable to _____

-in vitro assays = _____

-in vivo= _____

b) Discovery of a bioactive molecule or lead discovery

***start of med chem**

-random screening: _____

-e.g. Gleevec

-most common today!

-non-random screening: _____

-e.g. cimetidine

-other serendipitous starting points:

-_____

-_____ that reveal the true active component

-e.g. sulfa drugs from _____

-clinical observation: _____

-e.g. rogaine, an anti-hypertensive that lead to _____

-e.g. Viagra, an anti-hypertensive that leads to _____

c). Analyzing and modifying chemical structures

(1) It's all about the _____!

- _____ =everything not C and H; _____

Why? They form most important _____!--> more next week

(2) SAR studies

-changes to structure are analyzed for impact on bioactivity

(i) two basic changes

-keep it the same: use isosteres/bioisosteres

Bioisosteres/Isosteres

Bioisosteres=

Isosteres=

Isosteres:

1. Univalent atoms

a) $-CH_3$ = $-NH_2$ = -OH = -F = -Cl = -SH

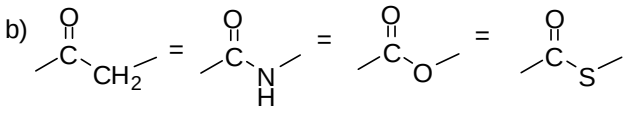
b) -Cl = -SH

c) -Br = i-Pr

d) -I = t-Bu

2. Bivalent atoms

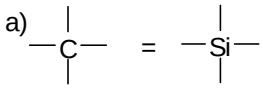
a) $-CH_2-$ = -NH- = -O- =-S- = -Se-

b) 

3. Trivalent atoms

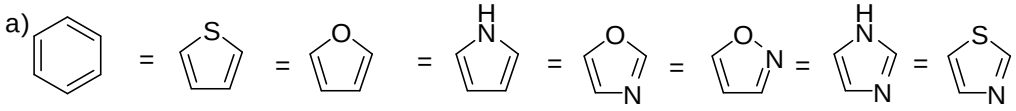
-CH= = -N=

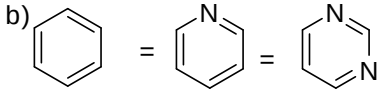
4. Tetravalent atoms

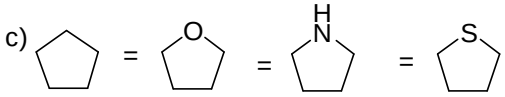
a) 

b) =C= = $=\overset{\oplus}{N}=$

5. Ring equivalents

a) 

b) 

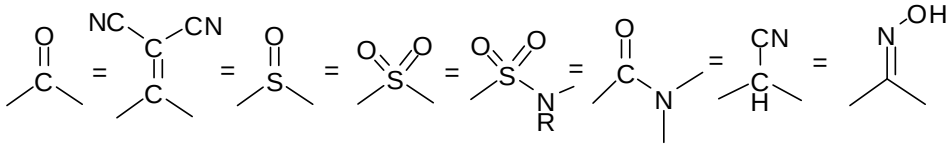
c) 

<u>Bioisosteres</u> (less similar structurally)

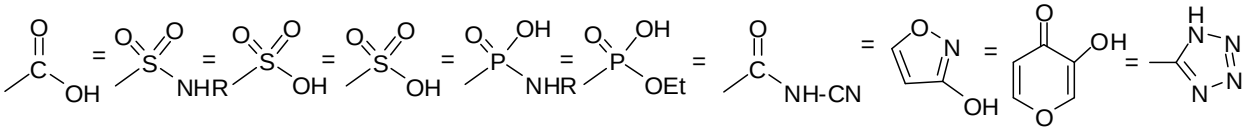
1. Hydrogen

-H = -F

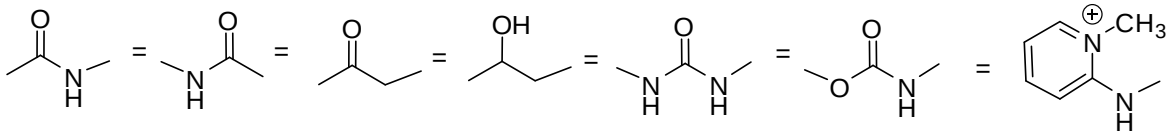
2. Carbonyl group



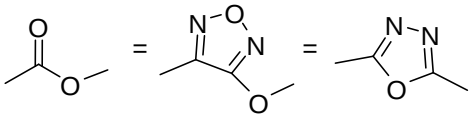
3. Carboxylic acid group



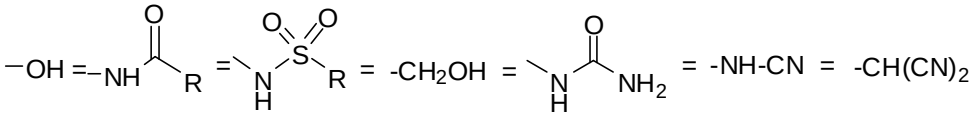
4. Amide group



5. Ester group

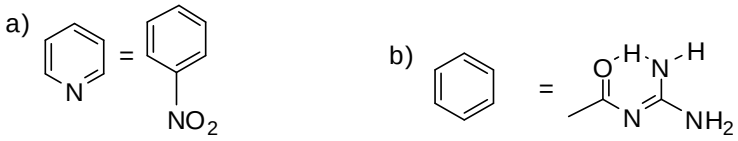


6. Hydroxy group

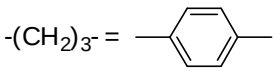


7. Halogen

8. Ring equivalents



9. Spacer group



Key reference: **Bioisosterism: A Rational Approach in Drug Design** , George A. Patani and Edmond J. LaVoie*, *Chem. Rev.*, 1996, 96 (8), pp 3147–3176. Abstract (found 1.10.14)

More updated reference on bioisosteres: **Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design,** Nicholas A. Meanwell, *J. Med. Chem.*, 2011, 54 (8), pp 2529–2591. Abstract (found 10.16.14)

-change it up: ______________________________ structure

impact of additions/deletions:

(1) change _______________________________________

(2) change _______________________________________

(3) change __________________________________

(4) change __________________________________

-these will impact both __________________________ and

____ properties

THIS IS AN _________________________ PROCESS!

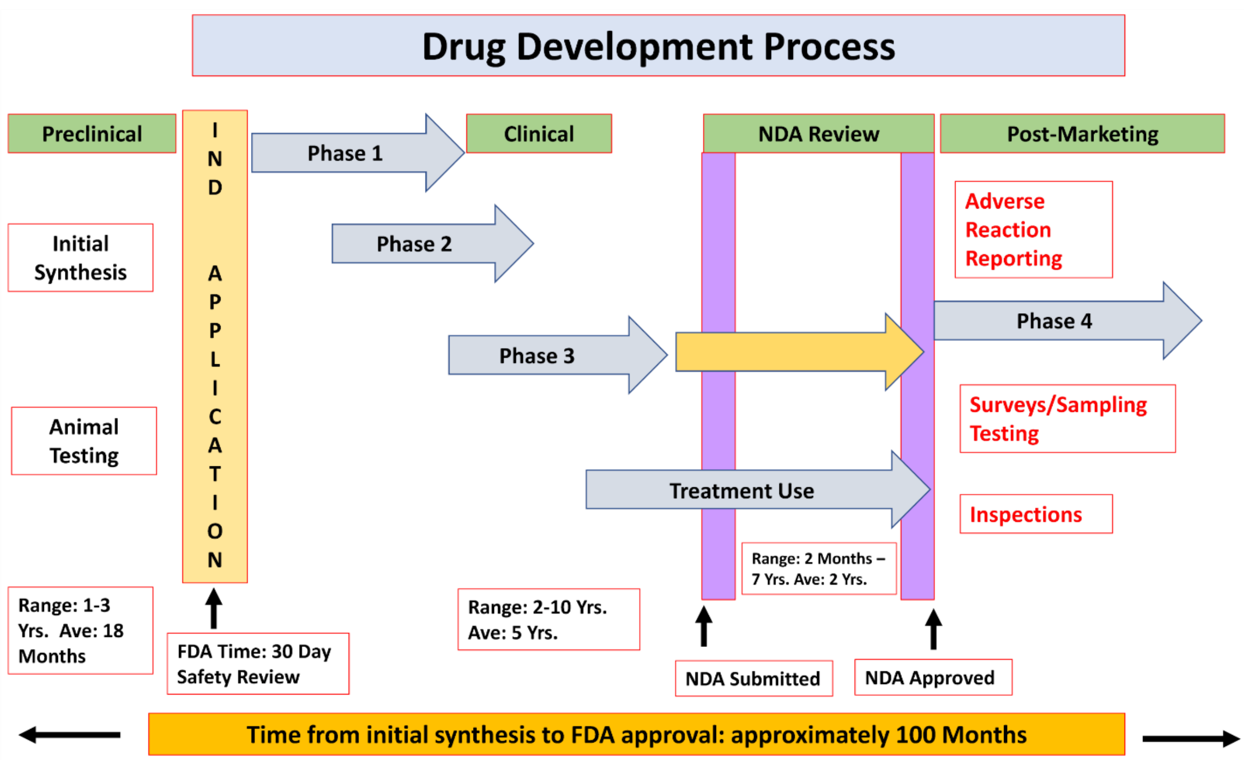
***end of med chem**

>>>

patent filing

-Investigational new drug (_________), a.k.a. new chemical entity (____________)

2. Clinical research: ______________________________



From: Edit image, resize image, crop pictures and appply effect to your images

-phase 1: _____

-phase 2: _____

-phase 3: _____

-phase 4: _____

New drug application (NDA)→ _____

*entire process can take _____ years

-$ _____

D. Other Drug Development Details

1. Reasons for drug failure

- _____ ~40% in UK study 1964-1985

- _____ ~35% in US trials, 1981-1992

- _____ ~30% (market changes) in US trials, 1981-1992

2. types of therapeutics:

a) _____

b) _____

c) _____

3. How many drug targets are there?

From J. P. Overington et al. Nature Reviews Drug Discovery 2017, 16, 19-34

-893 human and pathogen-derived biomolecules

-acted upon by 1,578 US FDA-approved drugs

>>

Therapeutic drug use statistics

see: http://www.cdc.gov/nchs/fastats/drug-use-therapeutic.htm

also: http://www.drugbank.ca/stats

Table 1.1 Important milestones in drug research
Year Substance Indication/Mode of action
1806 Morphine Hypnotic
1875 Salicylic acid Anti-inflammatory
1884 Cocaine Stimulant, local anesthetic
1888 Phenacetin Analgetic and antipyretic
1889 Acetylsalicylic acid Analgetic and antipyretic
1903 Barbiturate Sedative
1909 Arsphenamin Anti-syphilitic
1921 Procaine Local anesthetic
1922 Insulin Antidiabetic
1928 Estrone Female sex hormone
1928 Penicillin Antibiotic
1935 Sulfamidochrysoidine Bacteriostatic
1944 Streptomycin Antibiotic
1945 Chloroquine Antimalarial
1952 Chlorpromazine Neuroleptic
1956 Tolbutamide Oral antidiabetic
1960 Chlordiazepoxide Tranquilizer
1962 Verapamil Calcium channel blocker
1963 Propranolol Antihypertensive (b-blocker)
1964 Furosemide Diuretic
1971 L-DOPA Parkinson's disease
1973 Tamoxifen Breast cancer (estrogen receptor antagonist)
1975 Nifedipine Calcium channel blocker
1976 Cimetidine Gastrointestinal ulcer (H_2 blocker)
1981 Captopril Antihypertensive (ACE inhibitor)
1981 Ranitidine Gastrointestinal ulcer (H_2 blocker)
1983 Ciclosporin A Immunosuppressant
1984 Enalapril Antihypertensive (ACE inhibitor)
1985 Mefloquine Antimalarial
1986 Fluoxetine Antidepressant (5-HT-transport inhibitor)
1987 Artemisinin Antimalarial
1987 Lovastatin Cholesterol biosynthesis inhibitor
1988 Omeprazole Gastrointestinal ulcer (H^+/K^+-ATPase inhibitor)
1990 Ondansetron Antiemetic (5-HT_3 blocker)
1991 Sumatriptan Migraine (5-$HT_{1B,D}$ agonist)
1993 Risperidone Antipsychotic (D_2/5-HT_2-blocker)
1994 Famciclovir Antiviral/herpes (DNA polymerase inhibitor)
1995 Losartan Arterial hypertension (ATII antagonist)
1995 Dorzolamide Glaucoma (carboanhydrase inhibitor)
1996 Saquinavir HIV protease inhibitor
1996 Ritonavir HIV protease inhibitor
1996 Indinavir HIV Protease inhibitor
1996 Nevirapine HIV reverse transcriptase inhibitor

Table 1.1 (continued)
Year Substance Indication/Mode of action
1997 Sibutramine Obesity (uptake inhibitor)

1997 Orlistat Obesity (lipase inhibitor)
1997 Tolcapon Parkinson's disease (COMT inhibitor)
1998 Sildenafil Erectile dysfunction (PDE5 inhibitor)
1998 Montelukast Broncholytic (leukotriene receptor antagonist)
1999 Infliximab Antirheumatic (TNFa antagonist)
2000 Celecoxib Analgesic (COX-2 inhibitor)
2000 Verteporfin Macular degeneration (photodynamic therapy)
2001 Imatinib Acute myeloid leukemia (kinase inhibitor)
2002 Boscutan Arterial hypertension (endothelin-1 receptor antagonist)
2002 Aprepitant Antiemetic (neurokinin receptor antagonist)
2003 Enfuvirtid HIV fusion inhibitor (oligopeptide)
2004 Ximelagatran Coagulation inhibitor (thrombin inhibitor)
2004 Bortezomib Multiple myeloma (proteasome inhibitor)
2005 Bevacizumab Cytostatic (angiogenese inhibitor)
2006 Natalizumab Multiple sclerosis (monoclonal antibody; integrin inhibitor)
2006 Aliskiren Antihypertensive (renin inhibitor)
2007 Maraviroc HIV fusion inhibitor (CCR5 antagonist)
2007 Sitagliptin Type-II diabetes (DPPVI inhibitor)
2008 Raltegravir HIV integrase inhibitor
2009 Rivaroxaban Oral Anticoagulant (FXa inhibitor)
2010 Mifamurtide Drug against Osteosarcoma (bone cancer)
2011 Fingolimod Immunomodulating drug (multiple sclerosis treatment)

(from Drug Design: Methodology, Concepts, and Mode of Action by Gerhard Klebe, 2013)