1 Chemogenomics in Drug Discovery

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Abstract. Chemogenomics is a new strategy in drug discovery which, in principle, searches for all molecules that are capable of interacting with any biological target. Because of the almost infinite number of drug-like organic molecules, this is an impossible task. Therefore chemogenomics has been defined as the investigation of classes of compounds (libraries) against families of functionally related proteins. In this definition, chemogenomics deals with the systematic analysis of chemical–biological interactions. Congeneric series of chemical analogs are probes to investigate their action on specific target classes, e.g., GPCRs, kinases, phosphodiesterases, ion channels, serine proteases, and others. Whereas such a strategy developed in pharmaceutical industry almost 20 years ago, it is now more systematically applied in the search for target- and subtype-specific ligands. The term "privileged structures" has been defined for scaffolds, such as the

benzodiazepines, which very often produce biologically active analogs in a target family, in this case in the class of G-protein-coupled receptors. The SOSA approach is a strategy to modify the selectivity of biologically active compounds, generating new drug candidates from the side activities of therapeutically used drugs.

1.1 Introduction

Chemical biology, chemical genetics, and chemogenomics are recent strategies in drug discovery. Although definitions in the literature are somehow diffuse and inconsistent, a differentiation of the terms will be attempted here:

Chemical biology may be defined as the study of biological systems, e.g., whole cells, under the influence of chemical libraries. If a new phenotype is discovered by the action of a certain substance, the next step is the identification of the responsible target.

Chemical genetics is the dedicated study of protein function, e.g., signaling chains, under the influence of ligands which bind to certain proteins or interfere with protein–protein interaction; sometimes orthogonal ligand–protein pairs are generated to achieve selectivity for a certain protein.

Chemogenomics defines, in principle, the screening of the chemical universe, i.e., all possible chemical compounds, against the target universe, i.e., all proteins and other potential drug targets. Whereas this task can never be achieved, due to the almost infinite size of the chemical universe, the systematic screening of libraries of congeneric compounds against members of a target family offers unprecedented chances in the search for compounds with significant target or subtype specificity.

1.2 Chemical Biology

In classical drug discovery, research was often based on vague hypotheses on structure–activity relationships. Compounds were synthesized and tested in whole animals. If a biological effect was observed, a medicinal chemistry project started to optimize chemical structures

with respect to activity, pharmacokinetic properties, and lack of toxic side effects. Later on, this approach was replaced by in vitro screening on defined targets, most often human proteins. Only in recent years have we experienced a more systematic investigation of drug-like compounds in biological systems, called chemical biology.

One illustrative example of the chemical biology approach is the discovery of monastrol, a molecule that prevents spindle formation in mitotic cells by inhibiting the kinesin Eg5, a motor protein required for spindle bipolarity (Mayer et al. 1999). In this manner, monastrol stops cell division by mitotic arrest.

Another example of the concept of chemical biology is the discovery of synthetic small molecules that influence embryonic stem (ES) cell fate (Ding et al. 2003). A high-throughput phenotypic cell-based screen identified a 4,6-disubstitued pyrrolo-pyrimidine, which induces the differentiation of ES cells to neurons. Glycogen synthase kinase-3β (GSK-3β) has been identified as the target of this compound.

On the other hand, screening of any compounds may not result in the desired output of results. The production of a 2.18 million-compound natural product library by diversity-oriented synthesis (Tan et al. 1998; Schreiber 2000) generated much hype but, so far, not the anticipated results with respect to biological activities. In a later comment, the author Stu Schreiber had to admit that the chemical diversity of his library was seemingly too narrow – "disappointingly similar" by molecular descriptors; the compounds "tend to cluster in discrete regions of multidimensional descriptor space" (Schreiber 2003). This goes hand in hand with another problem: biologically active compounds seem to be distributed only in certain areas of chemical space, by their physicochemical properties and their structural features (Lipinski and Hopkins 2004). If we consider the chemical universe as a huge ocean, with small islands or groups of islands of biologically active compounds (e.g., the so-called privileged compounds, cf. Sect. 1.4.1), we have to understand and accept that most chemistry-driven approaches will end up in water, instead of discovering new islands. For the broad exploration of biology with small organic molecules (Stockwell 2004), the National Institutes of Health (NIH) has started an initiative to provide a repository of chemically diverse molecules for the public and private sector (Austin et al. 2004).

1.3 Chemical Genetics

Classical genetics sets a (random) mutation, e.g., by irradiation, and tries to conclude from a new phenotype to the genotype. "Chemical genetics" is another new term for a strategy that has also been used since long ago, in a less systematic manner; it describes the purposeful investigation of proteins by small molecules or libraries, for target identification (forward chemical genetics) or target validation (reverse chemical genetics) (Russell and Michne 2004). Sometimes, orthogonal ligand-receptor pairs are constructed if selective ligands are not available. Selective kinase inhibition has been achieved by specifically converting nonspecific, low-affinity inhibitors into larger analogs and to construct certain kinase mutants (e.g., v-Src I338G or Cdk II F80G) that specifically accommodate these originally less well-fitting ligands by their larger binding pocket (Bishop et al. 2000). In this manner, the specific inhibition of a certain kinase can be studied without having developed an inhibitor of comparable specificity against the wild-type kinase.

1.4 Chemogenomics

As well as in the other two cases, chemogenomics defines an approach that has also been used earlier, but less systematically. Since a screening of the chemical universe against the target universe is practically impossible, due to the almost infinite number of potential drug-like compounds, the method defines the screening of congeneric chemical libraries against certain target families, e.g., the G protein-coupled receptors, nuclear receptors, different protease families, kinases, phosphodiesterases, ion channels, transporters, etc. (Caron et al. 2001; Bleicher 2002; Jacoby et al. 2003; Miller 2003; Kubinyi and Müller 2004); this systematic strategy aims to discover highly potent, selective ligands against functionally and evolutionarily related targets, with the least effort.

1.4.1 Privileged Structures

Many drugs have been derived from certain chemotypes, e.g., phenethylamines, tricyclics, steroids, or benzodiazepines, whereas others have

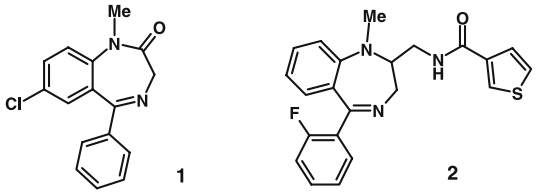


Fig. 1. Diazepam **1** (Valium) was one of the first tranquilizers and the prototype of a series of other GABA receptor agonists, antagonists, and inverse agonists. The chemically closely related benzodiazepine Tifluadom **2** is a κ-opiate receptor agonist and a nanomolar cholecystokinin receptor antagonist

certain structural features in common, e.g., diphenylmethane, diphenylamine, or arylpiperazine groups. The systematic chemical variation of benzodiazepines, e.g., the GABA-agonist diazepam **1** produced not only tranquilizers but also GABA antagonists, inverse agonists, and the strong κ-opiate receptor agonist tifluadom **2** (Fig. 1) (Römer et al. 2002).

When Evans discovered that tifluadom is also a nanomolar cholecystokinin receptor antagonist, he concluded that "these structures appear to contain common features which facilitate binding to various . . . receptor surfaces, perhaps through binding elements different from those employed for binding of the natural ligands . . . " and formulated ". . . what is clear is that certain 'privileged structures' are capable of providing useful ligands for more than one receptor and that judicious modification of such structures could be a viable alternative in the search for new receptor agonists and antagonists" (Evans et al. 1988). Minor chemical modifications of such privileged structures (Fig. 2) (Patchett and Nargund 2000) may result in highly selective ligands or drugs, e.g., the estrogenic, gestagenic, androgenic, glucocorticoid, and mineralocorticoid steroids, or the α-adrenergic, β-adrenergic, and β-antiadrenergic phenethylamines. Others lack such target selectivity: the atypical neuroleptic olanzapine is a highly promiscuous tricyclic ligand, with nanomolar affinities at various GPCRs, including 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, dopaminergic D_1, D_2, D_4, muscarinic M_1, M_2, M_3, M_4, M_5, adrenergic α_1, and histaminic H_1 receptors, as well as the 5-HT_3 ion channel (Bymaster et al. 1996, 1999).

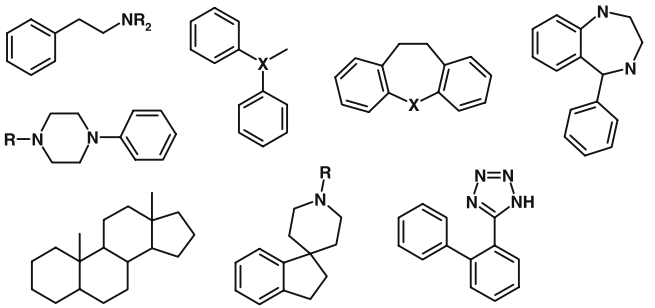


Fig. 2. Privileged structures are scaffolds or substituents that often produce biologically active compounds, e.g., phenethylamines, diphenylmethyl and diphenylamine compounds (X = C or N, respectively), tricyclic compounds (X = C or N), benzodiazepines, arylpiperidines, steroids, spiropiperidines, and tetrazolobiphenyls (from the *upper left* to the *lower right*)

Privileged structures, even if they are promiscuous ligands, should not be confused with some structural classes, which seemingly bind with micromolar affinity to various enzymes. This unspecific binding behavior is caused by an aggregation of the ligands and clumping of these aggregates to the protein (McGovern et al. 2002, 2003; McGovern and Shoichet BK 2003; Seidler et al. 2003).

1.4.2 Drugs from Side Effects – The SOSA Approach

Many drugs of the past resulted from the experimental or clinical observation of side effects. Diuretic, antihypertonic, antiglaucoma, and antidiabetic drugs were derived from the bacteriostatic sulfonamides; the mood-improving effect of iproniazid was discovered when it was tested as an antituberculous drug; antidepressant inhibitors of neurotransmitter re-uptake, like imipramine and desipramine, stem from the antipsychotic dopamine antagonist chlorpromazine, which itself was derived from H_1 antihistaminics; there are many other stories of this kind (Sneader 1996; Kubinyi 2004). Only recently, Camille Wermuth proposed to investigate the side effects of drugs more systematically, by his "selective optimization of side activities" (SOSA) approach (Wer-

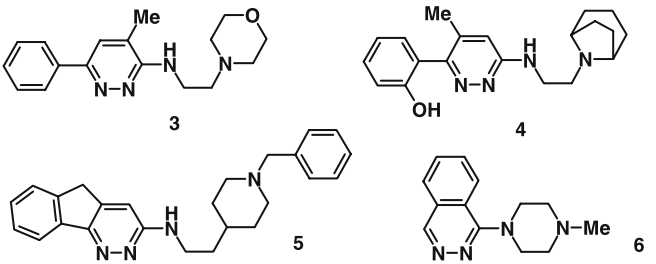


Fig. 3. The antidepressant minaprine **3** is also a weak muscarinic M_1 receptor antagonist ($K_i = 17\ \mu M$) and an acetylcholinesterase inhibitor ($K_i = 600\ \mu M$). By systematic structural variation, these activities could be enhanced to the nanomolar M_1 receptor antagonist **4** ($K_i = 3$ nM) and the acetylcholinesterase inhibitor **5** ($K_i = 10$ nM). A closely related analog of minaprine was optimized to the nanomolar 5-HT_3 receptor antagonist **6** ($IC_{50} = 10$ nM)

muth 2001, 2004). Whenever a side effect of a drug is observed, it might be possible to optimize the candidate to a selective drug with this other biological activity, following a statement by Sir James Black that "the most fruitful basis for discovery of a new drug is to start with an old drug" (Wermuth 2004). Among several other examples, Wermuth demonstrated by his own research the optimization of different weak side effects of the antidepressant minaprine **3** to the nanomolar muscarinic M_1 receptor ligand **4** and the reversible acetylcholinesterase inhibitor **5** (Wermuth 2001, 2004); a closely related analog of minaprine was optimized to the nanomolar 5-HT_3 antagonist **6** (Fig. 3) (Rival et al. 1998). More examples are discussed in refs. (Kubinyi 2004; Wermuth 2001, 2004).

1.4.3 From Target Family-Directed Masterkeys to Selective Drugs

Chemogenomics is mainly based on the masterkey concept of tailor-made privileged structures (Müller 2003, 2004). Starting from such masterkeys, selective ligands can be derived, either by classical medicinal chemistry or by systematic structural variation in combinatorial libraries. The masterkey concept will be illustrated by just one example: selective β_1 and β_2 agonists, as well as β antagonists (β-blockers)

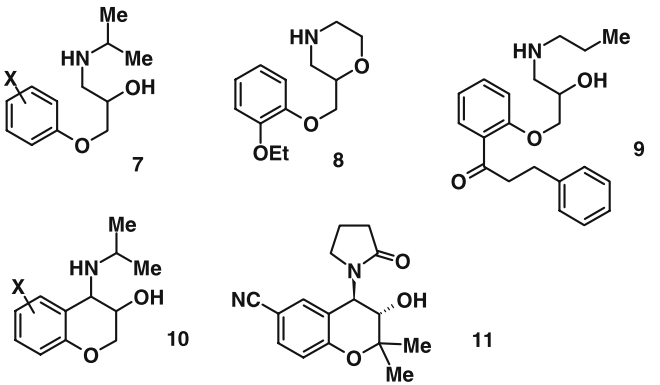


Fig. 4. The β-blocker prototype structure 7, Phenyl-O-CH_2-CH(OR^1)-CH_2NHR^2 is also the key structural element of the antidepressant viloxazine **8** and the class Ic antiarrhythmic propafenone **9**. Structural variation of a cyclic β-blocker analog **10** yielded the potassium channel opener levcromakalim **11**

were derived from the mixed α/β agonist epinephrine. Further chemical variation of the typical β-blocker phenoxypropanolamine structure **7** yielded the antidepressant viloxazine **8** and the class Ic antiarrhythmic propafenone **9**. The optimization of a cyclic β-blocker prototype **10** indeed produced an antihypertensive drug; however, levcromakalim **11** is no longer a β-blocker, it is a vasodilatory potassium channel opener (Fig. 4) (Wermuth 2001, 2004). More examples are discussed in the following sections and in references (Caron et al. 2001; Bleicher 2002; Jacoby et al. 2003; Miller 2003; Kubinyi and Müller 2004; Kubinyi 2004; Wermuth 2001, 2004; Müller 2003, 2004).

Enzyme Inhibitors

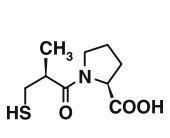
Protease inhibitors are most often derived from the sequence of the amino acids in the positions next to the bond that is cleaved by the enzyme. A simple strategy for a first inhibitor is a conversion of the amide bond of the cleavage site into a noncleavable analog or a group that reacts or coordinates with the catalytic center of the enzyme; the P1, P2, . . . and/or P1′, P2′, . . . amino acids are kept constant.

The structural requirements of the individual protease classes are different:

– For aspartyl protease inhibitors, it is necessary to attach some amino- and carboxy-terminal amino acid side chains to a group that mimics the transition state of the enzymatic cleavage.
– For metalloprotease inhibitors, a metal-coordinating group is introduced at the amino-terminal side of the peptide.
– For serine and cysteine protease inhibitors, the groups that interact with the catalytic center are not necessarily but most often at the carboxy-terminal end of the peptide.

The chemogenomics strategy in the design of protease inhibitors will be illustrated by four examples: the design of HIV protease inhibitors, thrombin and factor Xa inhibitors, selective ACE and dual zinc protease inhibitors, and "dual warhead" MMP/cathepsin inhibitors. Renin is an aspartyl protease, which is involved in blood pressure regulation by converting angiotensinogen into angiotensin I, the substrate of angiotensin-converting enzyme (ACE). Hundreds of person years of research were invested to arrive at orally active peptidomimetics, without much success. When it became known that HIV protease is also an aspartyl protease, the accumulated experience on the design of transition state inhibitors could be transferred to this new project.

The same situation applies to inhibitors of the serine protease thrombin; here also all efforts to arrive at orally active analogs had only limited success. However, structural elements from inhibitors of another serine



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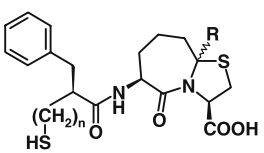

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Fig. 5. Captopril **12** was the very first marketed angiotensin-converting enzyme (ACE) inhibitor. The specific ACE inhibitor **13a** (n = 0, R = β-H; K_i ACE = 11.5 nM, K_i NEP24.11 = 2,820 nM) resulted from structural variation, as well as the dual zinc protease inhibitors **13b** (n = 0, R = α-H; K_i ACE = 16 nM, K_i NEP24.11 = 11.5 nM) and **13c** (n = 1, R = α-H; K_i ACE = 5.5 nM, K_i NEP24.11 = 1.1 nM)

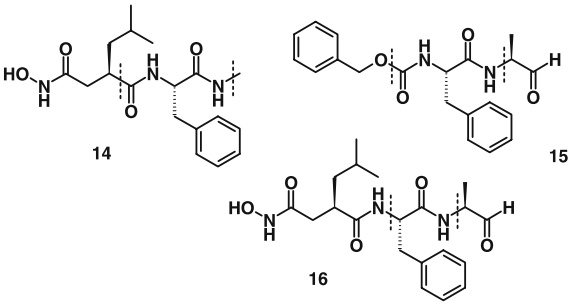

Fig. 6. Compound **14** is a nanomolar metalloprotease inhibitor (IC_{50} MMP-1 = 3 nM; IC_{50} Cat L > 1,000 nM), whereas compound **15** is a nanomolar cysteine protease inhibitor (IC_{50} MMP-1 > 1,000 nM; IC_{50} Cat L = 3 nM). Crossover of the two structures produces the dual inhibitor **16** (IC_{50} MMP-1 = 25 nM; IC_{50} Cat L = 15 nM); the *dashed lines* indicate the common center part of all three molecules

protease, elastase, e.g., the pyrimidone ring system as a substitute for a flexible amino acid, could also be applied to thrombin inhibitors. Later on, the search for inhibitors shifted from thrombin to factor Xa, a serine protease with similar specificity as thrombin.

Captopril **12** was the very first ACE inhibitor that was introduced into human therapy. A multitude of ACE-inhibiting analogs resulted from this drug, e.g., the ACE-specific inhibitor **13a** and the dual ACE/NEP24.11 inhibitors **13b** and **13c** (Fig. 5) (Slusarchyk et al. 1995).

A dual warhead inhibitor resulted from a merger of the structures of a selective matrix metalloprotease (MMP) inhibitor **14** with a cathepsin L inhibitor **15**. Although MMP-1 is a zinc protease and cathepsin L is a cysteine protease, the resulting inhibitor **16**, which bears both "warheads," inhibits both enzymes with nanomolar activity (Fig. 6) (Yamamoto et al. 2002).

Kinases play a most important role in cell signaling. More than 500 different kinases are coded by the human genome; after activation, they phosphorylate either a tyrosine hydroxyl group (tyrosine kinases) or a serine or threonine hydroxyl group (serine/threonine kinases). Some kinase mutants are constitutionally active: they activate a signaling cascade

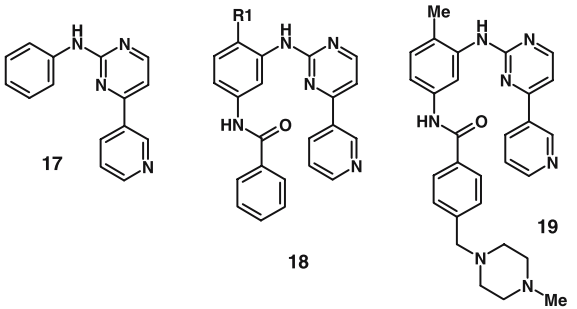

Fig. 7. Structural variation of the protein kinase C (PKC) inhibitor **17** produced the dual PKC/bcr-abl inhibitor **18a** (R = H). A minor structural modification to **18b** (R = CH_3) abolished the undesired PKC activity. After introduction of a methylpiperazine residue, to enhance the aqueous solubility, the bcr-abl inhibitor imatinib **19** (Glivec, Gleevec) resulted

without any external stimulus. Chronic myelogenous leukemia is caused by such a constitutionally active kinase. The coding regions of an abl tyrosine kinase at chromosome 9 and a bcr serine/threonine kinase at chromosome 22 form after reciprocal translocation a bcr-abl coding region at the new, shorter version of the chromosome 9, the so-called Philadelphia chromosome. The resulting bcr-abl tyrosine kinase is constitutionally active. At Novartis, a class of protein kinase C (PKC) inhibitors were optimized to the PKC inhibitor **17**. Amide analogs **18a** of this compound showed activity against PKC and bcr-abl kinase; surprisingly, the methyl analog **18b** inhibited only bcr-abl kinase; finally, an N-methyl-piperazine residue was added to increase solubility (Fig. 7). Imatinib (Gleevec, Glivec), **19**, was clinically developed and is successfully used for the treatment of chronic myelogenous leukemia (Capdeville et al. 2002).

Receptor Ligands

G protein-coupled receptors (GPCRs) are a large group of evolutionarily related seven-transmembrane proteins. They are activated by such different agents as light, ions, odorants, neurotransmitters, peptides, and proteins and transfer the stimulus by the G protein complex. Sero-

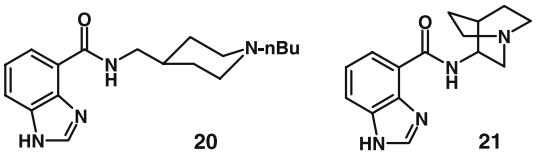

Fig. 8. Compound **20** is a highly selective 5-HT_3 antagonist (K_i 5-HT_3 = 3.7 nM, K_i 5-HT_4 > 1,000 nM), whereas the chemically closely related compound **21** is a selective 5-HT_4 antagonist (K_i 5-HT_3 > 10,000 nM, K_i 5-HT_4 = 13.7 nM)

tonin receptors are made up of 14 subtypes, 13 of which are GPCRs, whereas the 5-HT_3 subtype is a ligand-controlled ion channel. From pharmacophore models, Lopez-Rodriguez et al. designed the structure of a highly selective 5-HT_4 receptor ligand **20**, which shows a selectivity difference of more than five orders of magnitude to its closely related, 5-HT_3-selective analog **21** (Fig. 8) (Lopez-Rodriguez et al. 1997).

Somatostatin receptors are made up of five subtypes: sst1–sst5. In their attempt to obtain selective, peptidomimetic ligands for each subtype, Rohrer et al. synthesized four β-turn-mimicking combinatorial libraries, with up to 350,000 compounds per library. Highly specific ligands resulted for all five subtypes (Rohrer et al. 1998).

Nuclear receptors are another important receptor family. They are made up of a ligand-binding domain and a DNA-binding domain. After activation by their specific ligands, e.g., the steroid hormones, the thyroid hormone or retinoic acid, receptor dimers bind to DNA and activate the expression of certain proteins.

Estrogen receptors exist as two distinct subtypes, ERα and ERβ, which are relatively abundant in several tissues. As their function in all those organs and potential interaction, forming ERα/ERβ heterodimers, has not been completely elucidated so far, it is most important to find selective ligands for both receptors. By homology modeling of the ligand-binding domain of the ERβ receptor, based on the corresponding 3D structure of the ERα receptor, Hillisch et al. inspected the minor differences in the estradiol binding site: in human ERβ, the leucine of ERα at the "top" of the binding site ("top" refers to the β side of the steroid ring) is replaced by a flexible, sterically less demanding methionine, whereas

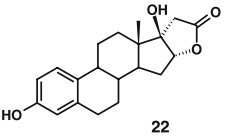

Fig. 9. The estradiol analogs **22** (40% of estradiol activity, ERα-selective) and **23** (50% of estradiol activity, ERβ-selective) have been designed as selective ERα and ERβ receptor ligands. Even though they are less active than estradiol, they show 300-fold and 190-fold selectivity for the different receptor subtypes

at the "bottom" of the binding site, close to ring D, a methionine in ERα is replaced by an isoleucine in ERβ. Using this information on the narrower binding pocket above and below the estradiol binding sites of ERα and ERβ, respectively, the selective ligands **22** and **23** could be designed (Fig. 9) (Hillisch et al. 2004a–c). Whereas **22** has only about 40% of the activity of estradiol at ERα, it shows a 300-fold selectivity against ERβ; on the other hand, compound **23** has only 50% of the activity of estradiol at ERβ but a 190-fold selectivity against ERα.

The thyroid hormone T3 and its less active storage form T4 are iodinated phenoxy-phenylalanines, which bind to two nuclear receptor subtypes TRα and TRβ. Unfortunately, the affinity of T3 to TRα is higher than to TRβ, which causes cardiac side effects, if hypothyroid patients are treated with T3. The alkyl analogs **24** and **25** are less active at TRα than at TRβ (Fig. 10) (Scanlan et al. 2001). Compound **26** binds to both receptor subtypes but has no agonistic activity at TRα and is only a weak partial agonist at TRβ; correspondingly, this compound might be used to treat hyperthyroid patients (Baxter et al. 2002). Other patients suffer from a R320C mutant of TRβ; due to the exchange of the strongly basic arginine side chain against the neutral cysteine, T3 binds with much lower affinity to this receptor, causing a hypothyroid condition. Treatment with T3 or compound **25** is impossible, due to the high affinity of these compounds to the TRα receptor. Conversion of the acid **25** into the neutral analog **27** solved the problem: **27** has a higher affinity to the TRβ mutant than to TRα (Fig. 10) (Ye et al. 2001).

Integrins are another group of receptors. They are expressed at cell surfaces and their endogenous ligands, e.g., fibrinogen at the GP IIb/IIIa integrin (also called fibrinogen receptor) or vitronectin at the $\alpha_v\beta_3$ TS[a]

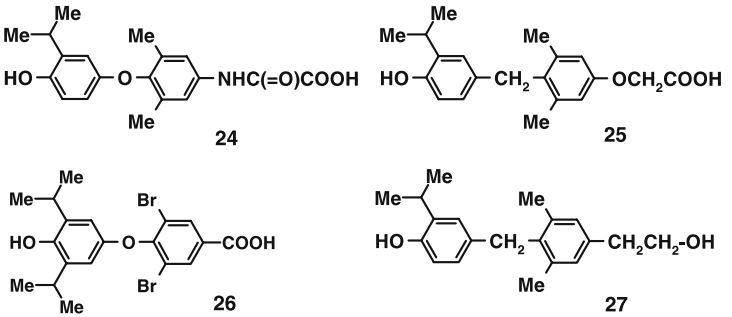

Fig. 10. Compounds **24** (CGS-23425) and **25** (GC-1, UCSF) are alkyl analogs of the thyroid hormone T3; in contrast to T3, which has a higher activity at TRα, these analogs have a higher activity at the TRβ. Compound **26** is a thyroid hormone antagonist at TRα and a weak partial agonist at TRβ. Neither T3 (EC_{50} hTRα = 0.14 nM, EC_{50} hTRβ = 0.66 nM, EC_{50} hTRβ R320C mutant = 4.3 nM) nor compound **25** (EC_{50} hTRα = 6.6 nM, EC_{50} hTRβ = 3.7 nM, EC_{50} hTRβ R320C mutant = 38 nM) has sufficient activity at a hTRβ R320C mutant. Compound **27** is a neutral, weakly active but TRβ R320C mutant-selective thyromimetic (EC_{50} hTRα = 38 nM, EC_{50} hTRβ = 32 nM, EC_{50} hTRβ R320C mutant = 7.0 nM)

integrin (also called vitronectin receptor), mediate cell–cell contacts. The recognition motif of these two receptors is the Arg-Gly-Asp (RGD) sequence of the ligands, obviously in different conformations. Research at SmithKline Beecham led to the discovery of ligands that showed, after minor chemical modification of a basic side chain, some selectivity

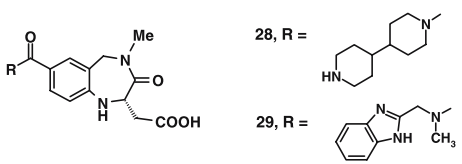

Fig. 11. Compound **28** (lotrafiban, K_i GP IIb/IIIa = 2.5 nM, K_i $a_v\beta_3$ = 10,340 nM; failed in phase III clinical trials) is a specific fibrinogen receptor antagonist, whereas compound **29** (K_i GP IIb/IIIa = 30,000 nM, K_i $a_v\beta_3$ = 2 nM) is a specific vitronectin receptor antagonist

for each of these two receptors (Samanen et al. 1996). After extensive structural modification, the highly selective ligands **28** (SB 214 857, lotrafiban) and **29** (SB 223 245) resulted in their selectivity (Fig. 11) (Samanen et al. 1996; Keenan et al. 1997; Miller et al. 2000). They differ by more than seven orders of magnitude.

1.5 Summary and Conclusions

Chemical similarity principles and bioisosterism are the guidelines of structural modification in classical medicinal chemistry. However, sometimes chemically similar compounds show very different biological activities and/or selectivities (Kubinyi 1998). In the early years of combinatorial chemistry, its potential output was significantly overestimated. An unprecedented number of new drugs was expected from chemistry-driven combinatorial syntheses. However, the output was just zero; sheer numbers did not contribute to drug discovery. Using the comparison of the "drug islands in an ocean," combinatorial chemistry was far away from those islands. The technology was able to deliver active analogs and to speed up drug discovery only after significant evolution. Instead of a combinatorial production of thousands of meaningless compounds, often in undefined mixtures, parallel syntheses of smaller libraries of single, purified compounds are now performed, driven by medicinal chemistry. In this manner, combinatorial chemistry is especially valuable in the very first steps of screening hit exploitation and lead structure optimization, in order to derive first structure–activity relationships (SARs) and to improve affinity, selectivity, and ADME properties to a certain point.

Chemogenomics is a complementary strategy for the investigation of chemically related compounds and libraries against various members of a target family. It is largely based on the proper application of automated parallel synthesis. The advantages of such a systematic approach are manifold:

- Specific analogs within a target family are discovered more easily.
- Results from one target may be used to explore a related target.
- Different subtype selectivities may be observed.
- Structure–activity relationships (SARs) result earlier.

– Coverage of chemical space and therefore patent coverage is more complete.

Of course, other rational approaches, such as molecular modeling, pharmacophore searches, virtual screening, and structure-based ligand design support this new strategy. The final steps of drug optimization will always need dedicated structural modifications, following the accumulated know-how of classical medicinal chemistry.

Only a few examples of chemogenomic applications could be discussed in this review. More illustrative applications are presented in a recent monograph on chemogenomics in drug discovery (Kubinyi and Müller 2004).

References

Austin CP, Brady LS, Insel TR, Collins FS (2004) NIH molecular libraries initiative. Science 306:1138–1139

Baxter JD, Goede P, Apriletti JW, West BL, Feng W, Mellstrom K, Fletterick RJ, Wagner RL, Kushner PJ, Ribeiro RC, Webb P, Scanlan TS, Nilsson S (2002) Structure-based design and synthesis of a thyroid hormone receptor (TR) antagonist. Endocrinology 143:517–524

Bishop AC, Ubersax JA, Petsch DT, Matheos DP, Gray NS, Blethrow J, Shimizu E, Tsien JZ, Schultz PG, Rose MD, Wood JL, Morgan DO, Shokat KM (2000) A chemical switch for inhibitor-sensitive alleles of any protein kinase. Nature 407:395–401

Bleicher KH (2002) Chemogenomics: bridging a drug discovery gap. Curr Med Chem 9:2077–2084

Bymaster FP, Calligaro DO, Falcone JF, Marsh RD, Moore NA, Tye NC, Seeman P, Wong DT (1996) Radioreceptor binding profile of the atypical antipsychotic olanzapine. Neuropsychopharmacology 14:87–96

Bymaster FP, Nelson DL, DeLapp NW, Falcone JF, Eckols K, Truex LL, Foreman MM, Lucaites VL, Calligaro DO (1999) Antagonism by olanzapine of dopamine D_1, serotonin$_2$, muscarinic, histamine H_1, and α_1-adrenergic receptors in vitro. Schizophr Res 37:107–22

Capdeville R, Buchdunger E, Zimmermann J, Matter A (2002) Glivec (ST571, Imatinib), a rationally developed, targeted anticancer drug. Nature Rev Drug Discov 1:493–502

Caron PR, Mullican MD, Mashal RD, Wilson KP, Su MS, Murcko MA (2001) Chemogenomic approaches to drug discovery. Curr Opin Chem Biol 5:464–470

Ding S, Wu TY, Brinker A, Peters EC, Hur W, Gray NS, Schultz PG (2003) Synthetic small molecules that control stem cell fate. Proc Natl Acad Sci U S A 100:7632–7637

Evans BE, Rittle KE, Bock MG, DiPardo RM, Freidinger RM, Whitter WL, Lundell GF, Veber DF, Anderson PS, Chang RSL, Lotti VJ, Cerino DJ, Chen TB, Kling PJ, Kunkel KA, Springer JP, Hirshfield JJ (1988) Methods for drug discovery: development of potent, selective, orally effective cholecystokinin antagonists. Med Chem 31:2235–2246

Hillisch A, Peters O, Kosemund D, Müller G, Walter A, Elger W, Fritzemeier KH (2004a) Protein structure-based design, synthesis strategy and in vitro pharmacological characterization of estrogen receptor α and β selective compounds. Ernst Schering Res Found Workshop 46:47–62

Hillisch A, Peters O, Kosemund D, Müller G, Walter A, Schneider B, Reddersen G, Elger W, Fritzemeier KH (2004b) Dissecting physiological roles of estrogen receptor α and β with potent selective ligands from structure-based design. Mol Endocrinol 18:1599–1609

Hillisch A, Pineda LF, Hilgenfeld R (2004c) Utility of homology models in the drug discovery process. Drug Discov Today 9:659–669

Jacoby E, Schuffenhauer A, Floersheim P (2003) Chemogenomics knowledge-based strategies in drug discovery. Drug News Perspect 16:93–102

Keenan RM, Miller WH, Kwon C, Ali FE, Callahan JF, Calvo RR, Hwang SM, Kopple KD, Peishoff CE, Samanen JM, Wong AS, Yuan CK, Huffman WF (1997) Potent, selective, orally active 3-oxo-1,4-benzodiazepine GPIIb/IIIa integrin antagonists. J Med Chem 40:2289–2292

Kubinyi H (1998) Similarity and dissimilarity – a medicinal chemist's view. In: Kubinyi H, Folkers G, Martin YC (eds) 3D QSAR in drug design, vol. II. Ligand–protein interactions and molecular similarity. Kluwer/ESCOM, Dordrecht, 1998, pp 225–252; also published in Persp Drug Design Discov 1998, 9–11:225–252

Kubinyi H (2004) Drug discovery from side effects. In: Kubinyi H, Müller G, (eds) Chemogenomics in drug discovery – a medicinal chemistry perspective, vol. 22 of Methods and principles in medicinal chemistry. Mannhold R, Kubinyi H, Folkers G (eds) Wiley-VCH, Weinheim, pp 43–67

Kubinyi H, Müller G (eds) (2004) Chemogenomics in drug discovery – a medicinal chemistry perspective, vol. 22, Methods and principles in medicinal chemistry. Mannhold R, Kubinyi H, Folkers G (eds) Wiley-VCH, Weinheim

Lipinski C, Hopkins A (2004) Navigating chemical space for biology and medicine. Nature 432:855–861

Lopez-Rodriguez ML, Morcillo MJ, Benhamu B, Rosado ML (1997) Comparative receptor mapping of serotoninergic 5-HT_3 and 5-HT_4 binding sites. J Comput-Aided Mol Design 11:589–599

Mayer TU, Kapoor TM, Haggarty SJ, King RW, Schreiber SL, Mitchison TJ (1999) Small molecule inhibitor of mitotic spindle bipolarity identified in a phenotype-based screen. Science 286:971–974

McGovern SL, Shoichet BK (2003) Kinase inhibitors: not just for kinases anymore. J Med Chem 46:1478–1483

McGovern SL, Caselli E, Grigorieff N, Shoichet BK (2002) A common mechanism underlying promiscuous inhibitors from virtual and high-throughput screening. J Med Chem 45:1712–1722

McGovern SL, Helfand BT, Feng B, Shoichet BK (2003) A specific mechanism of nonspecific inhibition. J Med Chem 46:4265–4272

Miller WH, Keenan RM, Willette RN, Lark MW (2000) Identification and in vivo efficacy of small-molecule antagonists of integrin $\alpha_v\beta_3$ (the vitronectin receptor). Drug Discov Today 5:397–408

Müller G (2003) Medicinal chemistry of target family-directed masterkeys. Drug Discov Today 8:681–691

Müller G (2004) Target family-directed masterkeys in chemogenomics. In: Kubinyi H, Müller G (eds) Chemogenomics in drug discovery – a medicinal chemistry perspective, vol. 22 of Methods and principles in medicinal chemistry. Mannhold R, Kubinyi H, Folkers G (eds) Wiley-VCH, Weinheim, pp 7–41

Patchett AA, Nargund RP (2000) Privileged structures – an update. Annu Rep Med Chem 35:289–298

Rival Y, Hoffmann R, Didier B, Rybaltchenko V, Bourguignon J-J, Wermuth CG (1998) 5-HT_3 Antagonists derived from aminopyridazine-type muscarinic M_1 agonists. J Med Chem 41:311–317

Rohrer SP, Birzin ET, Mosley RT, Berk SC, Hutchins SM, Shen DM, Xiong Y, Hayes EC, Parmar RM, Foor F, Mitra SW, Degrado SJ, Shu M, Klopp JM, Cai SJ, Blake A, Chan WW, Pasternak A, Yang L, Patchett AA, Smith RG, Chapman KT, Schaeffer JM (1998) Rapid identification of subtype-selective agonists of the somatostatin receptor through combinatorial chemistry. Science 282:737–740; erratum Science 282:1646

Römer D, Büscher HH**,** Hill RC, Maurer R, Petcher TJ, Zeugner H, Benson W, Finner E, Milkowski W, Thies PW (1982) An opioid benzodiazepine. Nature 298:759–760

Russell K, Michne WF (2004) The value of chemical genetics in drug discovery. In: Kubinyi H, Müller G (eds) Chemogenetics in drug discovery. Wiley-VCH, Weinheim, pp 69–96

Samanen JM, Ali FE, Barton LS, Bondinell WE, Burgess JL, Callahan JF, Calvo RR, Chen W, Chen L, Erhard K, Feuerstein G, Heys R, Hwang S-M, Jakas DR, Keenan RM, Ku TW, Kwon C, Lee C-P, Miller WH, Newlander KA, Nichols A, Parker M, Peishoff CE, Rhodes G, Ross S,

Shu A, Simpson R, Takata D, Yellin TO, Uzsinskas I, Venslavsky JW, Yuan CK, Huffman WF (1996) Discovery of potent nonpeptide vitronectin receptor ($\alpha_v\beta_3$) antagonists. J Med Chem 39:4867–4870

Scanlan TS, Yoshihara HA, Nguyen N-H, Chiellini G (2001) Selective thyromimetics: tissue-selective thyroid hormone analogs. Curr Opin Drug Disc Dev 4:614–622

Schreiber SL (2000) Target-oriented and diversity-oriented organic synthesis in drug discovery. Science 287:1964–1969

Schreiber SL (2003) The small-molecular approach to biology. C&EN 81:51–61; cf. Rouhi AM (2003) Moving beyond natural products. C&EN 81:104–107

Seidler J, McGovern SL, Doman TN, Shoichet BK (2003) Identification and prediction of promiscuous aggregating inhibitors among known drugs. J Med Chem 46:4477–4486

Slusarchyk WA, Robl JA, Taunk PC, Asaad MM, Bird JE, DiMarco J, Pan Y (1995) Dual metalloprotease inhibitors. V. Utilization of bicyclic azepinonethiazolidines and azepinonetetrahydrothiazines in constrained peptidomimetics of mercaptoacyl dipeptides. Bioorg Med Chem Lett 5:753–758

Sneader W (1996) Drug prototypes and their exploitation. John Wiley, Chichester

Stockwell BR (2004) Exploring biology with small organic molecules. Nature 432:846–854

Tan DS, Foley MA, Shair MD, Schreiber SL (1998) Stereoselective synthesis of over two million compounds having structural features both reminiscent of natural products and compatible with miniaturized cell-based assays. J Am Chem Soc 120:8565–8566

Wermuth CG (2001) The "SOSA" approach: an alternative to high-throughput screening. Med Chem Res 10:431–439

Wermuth CG (2004) Selective optimization of side activities: another way for drug discovery. J Med Chem 47:1303–1314

Yamamoto M, Ikeda S, Kondo H, Inoue S (2002) Design and synthesis of dual inhibitors for matrix metalloproteinase and cathepsin. Bioorg Med Chem Lett 12:375–378

Ye HF, O'Reilly KE, Koh JT (2001) A subtype-selective thyromimetic designed to bind a mutant thyroid hormone receptor implicated in resistance to thyroid hormone. J Am Chem Soc 123:1521–1522