Optimizing Drug Therapy by Analogues

János Fischer
(Richter Plc, Budapest, Hungary)
Contents

1. Introduction: term „analogue”
2. Pioneer and analogue drugs
3. Optimization of pharmacodynamic properties
4. Optimization of pharmacokinetic characteristics
5. Summary
Analogue or analog

„Chemical compound having structural similarity to a reference compound”

Note: Despite the structural similarity, an analogue may display different chemical and/or biological properties, as is often intentionally the case during design and synthesis to optimize either efficacy or ADMET properties within a given series.

Pioneer and analogue drugs

Pioneer drug („first in class”) represents a breakthrough invention that affords a marketed drug where no structurally and/or pharmacologically similar was known before its introduction.

Analogue drug has a structural and pharmacological similarity to a pioneer and other analogue drugs.

Examples: cimetidine and analogues (ranitidine, roxatidine, nizatidine and famotidine)
chemical name: \( N\text{-cyano-}N'\text{-methyl-}N''\text{-}[2\text{-}[[\text{5-methyl-1H-imidazol-4-yl}methyl]thio]ethyl]guanidine \)

basic patent: SmithKline & French (1971) US 3 894 151
Discovery of cimetidine

burimamide

first lead compound
i.v. administration in human
oral inactivity

metiamide

second lead molecule
orally active in human
discontinued because of adverse effects
(low incidence of granulocytopenia)

Pioneer H₂ receptor histamine antagonist
for treatment of peptic ulcer disease
Launch year: 1976
First blockbuster drug
Pharmacodynamic characteristics

1. Potency
2. Improving the ratio of main activity and adverse effects
3. Improving the physicochemical properties with analogues
4. Decreasing resistance to anti-infective drugs
5. Decreasing resistance to anticancer agents
The potency of a drug refers to the amount of drug required to achieve a defined biological activity. The smaller the dose required, the more potent the drug.
Structures of H$_2$-receptor antagonists

- Cimetidine (1971)
- Ranitidine (1976)
- Roxatidine (1979)
- Famotidine (1979)
- Nizatidine (1980)
Inhibitory effects of various statins *in vitro*

<table>
<thead>
<tr>
<th>Drug</th>
<th>IC$_{50}$ (nM)</th>
<th>Molecular weight (Da)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pravastatin</td>
<td>44.1</td>
<td>424</td>
</tr>
<tr>
<td>simvastatin</td>
<td>11.2</td>
<td>419</td>
</tr>
<tr>
<td>atorvastatin</td>
<td>8.2</td>
<td>559</td>
</tr>
<tr>
<td>rosuvastatin</td>
<td>5.4</td>
<td>482</td>
</tr>
</tbody>
</table>

Statins are HMG-CoA reductase inhibitors. Rosuvastatin is the most potent analogue in rank order of atorvastatin, simvastatin and pravastatin.
Structures of HMG-CoA reductase inhibitors

simvastatin (1980)

pravastatin (1980)

rosuvastatin (1991)

atorvastatin (1986)
Improving the ratio of main activity and adverse effects

a.) Improving selectivity through receptor subtypes
b.) Improving selectivity through unrelated receptors
c.) Improving selectivity by tissue distribution
d.) Improving selectivity of nonreceptor-mediated effects
Improving selectivity through receptor subtype

Example: adrenergic $\beta$-receptor blockers

Propranolol (1961, ICI) blocks both $\beta_1$ and $\beta_2$ receptor subtypes

$\beta_1$ receptors occur predominantly in the heart
$\beta_2$ receptors are mainly found in the lungs

Blocking $\beta_2$ receptors in bronchitis and asthma is harmful. Analogue research focused on producing $\beta_1$–selective blockers
Structures of some adrenergic $\beta$-receptor blockers

propranolol (1962)

atenolol (1969)

metoprolol (1970)

bisoprolol (1976)
Phlorizin, a non-selective SGLT inhibitor

Phlorizin is naturally occurring in some plants (in the bark of pear, apple etc.). White to yellow crystalline solid, m.p. 106-109 °C.
1835 isolation
High dose caused glucosurea.
1990s cloning SGLT1 and SGLT2
Phlorizin was not used as a medication:
• poorly absorbed from the gastrointestinal tract (GI)
• Inhibits SGLT1 and SGLT2
• SGLT1 is mainly expressed in GI and inhibition would lead to GI side effects
SGLT2 inhibitors for the treatment of diabetes 2
(SGLT2 : sodium - glucose - transporter type 2)

2002  dapagliflozin : pioneer SGLT2 inhibitor
2003  canagliflozin
2004  empagliflozin

Dapagliflozin and analogues inhibit sodium glucose transport proteins. Natural product phlorizin served as a lead compound, a non-selective SGLT ½ inhibitor, with poor bioavailability and side effect profile.
Structure of dapagliflozin, canagliflozin and empagliflozin

Dapagliflozin and analogues are C-aryl glucosides, selective SGLT 2 inhibitors

Dapagliflozin (2002, BMS)

Canagliflozin (2003, Mitsubishi-Tanabe)

Empagliflozin (Boeringer-Ingelheim, 2004)
Improving selectivity through unrelated receptor

*Example*: selective aldosterone antagonists
Spirononactone has hormone-related side effects (eg. menstrual irregularity, gynecomastia etc. due to its low receptor selectivity.
Eplerenone has a selective mineralocorticoid selectivity.

spironolactone  (1958, Searle)  eplerenone  (1983, Ciba-Geigy)
Improving selectivity by tissue distribution

Example: *histamine H1 blockers*

- Diphenhydramine (1946, Parke-Davis)
  - Prototype of first-generation antihistamines
  - High incidence of sedation
  - Topical use

- Loratadine (1980, Schering-Plough)
  - Prototype of antihistamines that have a low incidence of sedative effects
Improving selectivity of nonreceptor mediated effects

Platinum compounds play a major role in oncology, eg. for the treatment of colon cancer. Cisplatin has nephrotoxic side effects, whose mechanism of action is not known.

The nephrotoxicity of carboplatin is lower, and oxaliplatin is devoid of nephrotoxicity.

Improving the physicochemical properties with analogues

Example: penicillin analogues

Ampicillin and amoxicillin can be given orally, because their acid sensitivity was reduced
Analogues to reduce the resistance to anti-infective drugs

(a) Resistance to antibiotics
(b) Resistance to antifungal drugs
(c) Resistance to antiviral drugs
(d) Resistance to anticancer drugs
Resistance to antibiotics

Oxacillin, cloxacillin, flucloxacillin and dicloxacillin have been discovered that were stable to β-lactamase enzyme of *S. aureus*.

The widespread use of penicillin G led to penicillin resistant *Staphylococcus aureus* infections. Meticillin was a penicillase-resistant analogue. It is no more used because of better analogues.

R = H, R₁ = H  oxacillin
R = H,  R₁ = Cl  cloxacillin
R = F,  R₁ = Cl  flucloxacillin
R = Cl,  R₁ = Cl  dicloxacillin
Antibacterial classes discovered per decade

A LOOK BACK ON ANTIBACTERIALS  Discovery of antibacterial classes has fallen off in recent decades.

Number of successful antibacterial classes discovered per decade

C and E News, January 12, 2015, p.3
Resistance to antifungal drugs

The use of oral ketoconazole has been discontinued in several countries. Less toxic and more effective triazoles are preferred for systemic use.

ketoconazole
first orally active antifungal azole
Janssen, 1977
EMA recommendation (2013)

fluconazole
Pfizer, 1981

voriconazole
Pfizer, 1990
Resistance to antiviral drugs

(a) Nucleoside reverse transcriptase inhibitors (NRTIs)
(b) Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
(c) Protease inhibitors

Human immunodeficiency virus-1 (HIV-1) inhibitors
Zidovudine and stavudine have a similarity to nucleoside thymidine.
Tenofovir has a structural similarity to nucleoside adenosine.
Tenofovir disoproxil is a prodrug.
Non-nucleoside reverse transcriptase inhibitors

nevirapine  (Boehringer-Ingelheim, 1996)

etravirine  (Tibotec, 2008)

rilpivirine  (Johnson & Johnson, 2011)
HIV-1 protease inhibitors

Cocrystal structure information of ritonavir, bound to HIV-1 protease, was used to design lopinavir.
Second generation of HIV-1 protease inhibitors

Darunavir is named after Arun K. Ghosh who discovered the molecule.
Resistance to drug therapies in cancer treatment

Imatinib (Novartis, 2001)
Bcr-Abl tyrosine kinase inhibitor
chronic myelogenous leukemia (CML)

Nilotinib (Novartis, 2007)

Nilotinib is approved for the treatment of imatinib-resistant CML
Pharmacokinetic characteristics

1. Improving oral bioavailability
2. Drugs with a long duration of action
3. Ultrashort-acting drugs
4. Decreasing interindividual pharmacokinetic differences
5. Decreasing systemic activity
6. Decreasing drug interactions
7. Increasing drug interactions
Improving oral bioavailability

(a) Improving absorption
(b) Improving metabolic stability
Improving oral bioavailability

A good oral bioavailability is necessary in most cases because the oral application of a drug is preferred to an injection therapy.

**Enalaprilat** (Merck, 1984) is not orally absorbed, requiring intravenous administration.

**Lisinopril**, a lysylproline analogue, has an acceptable bioavailability (Merck, 1987).

A good oral bioavailability is necessary in most cases because the oral application of a drug is preferred to an injection therapy.
Improving metabolic stability

The pioneer antifungal miconazole and its analogue tioconazole are administered by the topical route. Both are susceptible to metabolic inactivation, resulting in low bioavailability and low plasma levels.
Ketoconazole was the first orally active antifungal drug.
The 1,2,4-triazole analogues were 100 times more active, but UK-47265 proved to be hepatotoxic.
Fluconazole showed high efficacy without any safety problem.
Drugs with a long duration of action

<table>
<thead>
<tr>
<th>Drug</th>
<th>Elimination half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>captopril</td>
<td>2</td>
</tr>
<tr>
<td>enalapril</td>
<td>11</td>
</tr>
<tr>
<td>lisinopril</td>
<td>12</td>
</tr>
<tr>
<td>perindopril</td>
<td>&gt; 24</td>
</tr>
</tbody>
</table>

Captopril was the first orally active ACE-inhibitor (ACE : angiotensin-converting enzyme) It is used in emergency cases (onset time 1 h). Long-acting analogues are used for chronic treatment of hypertension.
Structures of captopril, enalapril, lisinopril and perindopril

- **Captopril** (1976, Squibb)
- **Enalapril** (1978, Merck)
- **Lisinopril** (1978, Merck)
- **Perindopril** (1980, Adir)
Calcium channel antagonists

The pioneer drug nifedipine has a short duration of action. The long-acting analogues are more convenient for lifelong treatment of hypertension.
Elimination half-life values of calcium antagonist dihydropyridines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Elimination half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>nifedipine</td>
<td>2-4</td>
</tr>
<tr>
<td>felodipine</td>
<td>10-15</td>
</tr>
<tr>
<td>lacidipine</td>
<td>7-18</td>
</tr>
<tr>
<td>amlodipine</td>
<td>30-50</td>
</tr>
</tbody>
</table>
GLP-1 (Glucagon-like peptide-1) is rapidly metabolized by the enzyme DPP-4. GLP-1 has a half-time of approximately 2 minutes. 2001: continuous infusion of GLP-1 gives an optimal glycemic control. Elimination half-time of liraglutide is between 11 - 15 h (subcutaneous injection)
Insulin analogues

G-I-V-E-Q$_5$-C-C-T-S-I$_{10}$-C-S-L-Y-Q$_{15}$-L-E-N-Y-C$_{20}$-N

F-V-N-Q-H$_5$-L-C-G-S-H$_{10}$-L-V-E-A-L$_{15}$-Y-L-V-C-G$_{20}$-E-R-G-F-F$_{25}$-Y-T-P-K-T$_{30}$

<table>
<thead>
<tr>
<th>Species</th>
<th>A$^8$</th>
<th>A$^{10}$</th>
<th>A$^{21}$</th>
<th>B$^3$</th>
<th>B$^{28}$</th>
<th>B$^{29}$</th>
<th>B$^{30}$</th>
<th>B$^{31}$</th>
<th>B$^{32}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>Thr</td>
<td>Ile</td>
<td>Asn</td>
<td>Asn</td>
<td>Pro</td>
<td>Lys</td>
<td>Thr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pork</td>
<td>Thr</td>
<td>Ile</td>
<td>Asn</td>
<td>Asn</td>
<td>Pro</td>
<td>Lys</td>
<td>Ala</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beef</td>
<td>Ala</td>
<td>Val</td>
<td>Asn</td>
<td>Asn</td>
<td>Pro</td>
<td>Lys</td>
<td>Ala</td>
<td></td>
<td></td>
</tr>
<tr>
<td>insulin lispro</td>
<td>Thr</td>
<td>Ile</td>
<td>Asn</td>
<td>Asn</td>
<td>Lys</td>
<td>Pro</td>
<td>Thr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>insulin aspart</td>
<td>Thr</td>
<td>Ile</td>
<td>Asn</td>
<td>Asn</td>
<td>Asp</td>
<td>Lys</td>
<td>Thr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>insulin glulisine</td>
<td>Thr</td>
<td>Ile</td>
<td>Asn</td>
<td>Lys</td>
<td>Pro</td>
<td>Glu</td>
<td>Thr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>insulin glargine</td>
<td>Thr</td>
<td>Ile</td>
<td>Gly</td>
<td>Asn</td>
<td>Pro</td>
<td>Lys</td>
<td>Thr</td>
<td>Arg</td>
<td>Arg</td>
</tr>
<tr>
<td>insulin detemir</td>
<td>Thr</td>
<td>Ile</td>
<td>Asn</td>
<td>Asn</td>
<td>Pro</td>
<td>Lys$^+$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>insulin degludec</td>
<td>Thr</td>
<td>Ile</td>
<td>Asn</td>
<td>Asn</td>
<td>Pro</td>
<td>Lys$^\ddag$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Long-acting insulin analogues: insulin glargine (Sanofi), duration 16-18 h
Fast-acting insulin analogues: insulin aspart (Novo Nordisk), onset time: 15 min., duration 3-5 h
Drug therapy of COPD
(chronic obstructive pulmonary disease)

1966 salbutamol: short-acting β2-selective agonist
1972-1983 formoterol and salmeterol: long-acting analogues
Structures of salbutamol, formoterol and salmeterol

Salbutamol (albuterol) (Allen & Hanburys, 1966)

Salmeterol (Glaxo, 1983)

Formoterol (Yamanouchi, 1972)

Beta-2 selective agonists. Salbutamol is administered either by inhalation or orally for the symptomatic relief of bronchospams. Salmeterol and formoterol are long-acting drugs for the treatment of COPD.
Muscarinic receptor antagonists for the treatment of COPD

1974  ipratropium bromide
      (aerosol or solution)
      duration of action : 4 - 6 hours

2002  tiotropium bromide
      (dry powder)
      duration of action : 24 hours
Structures of ipratropium and tiotropium

ipratropium bromide
Boehringer Ingelheim, 1974
nonselective muscarinic (M₁, M₂, M₃)
short duration of action
three or four doses daily

tiotropium bromide
Boehringer Ingelheim, 2002
longer occupation at receptor M₃
long duration of action
once-daily treatment
Ultrashort acting drugs

esmolol  (Baxter, 1987)

beta-1 selective blocker
in emergency situation
during critical care medication
soft drug
active as an ester
distribution half-life 2 min.

corticosteroid
ophthalmology
for the treatment of inflammation of the eye
no systemic effect

loteprednol etabonate  (Bausch and Lomb, 1998)
Decreasing interindividual pharmacokinetic differences

omeprazole
Hässle / AstraZeneca, 1988
first PPI
(proton pump inhibitor)
interindividual variability of PK
(pharmacokinetics)

pantoprazole
Byk-Gulden, 1994
lower variability of PK
Decreasing systemic activity

It is important to decrease the systemic availability of corticosteroids in the intranasal and inhalation application to avoid their side effects, such as adrenocortical insufficiency and osteoporosis.

budenoside (AstraZeneca, 1981)
oral (systemic) bioavailability: 10%

fluticasone (GSK, 1990)
oral (systemic) bioavailability: < 2%
Drug interactions

(a) Decreasing drug interactions
(b) Increasing drug interactions
Decreasing drug interactions

cimetidine inhibits CYPs
e.g. CYP1A2, CYP2C9 and CYP2D6
interactions with several drug,
e.g. propranolol, warfarin, diltiazem, theophylline

cimetidine  (SmithKline & French, 1971)

ranitidine and famotidine have no such interactions

ranitidine  (Glaxo, 1980)

famotidine  (Yamanouchi, 1985)
Increasing drug interactions

Ritonavir (protease inhibitor) inhibits major P450 isoforms (CYP3A4 and CYP2D6), and it increases plasma level of lopinavir. The combination (Kaletra) is remarkable effective for the treatment of HIV infection.
Summary

1. Potency
2. Improving the ratio of main activity and adverse effects
3. Improving the physicochemical properties
4. Decreasing resistance to anti-infective drugs
5. Decreasing resistance to anticancer agents
6. Improving oral bioavailability
7. Drugs with a long duration of action
8. Ultrashort-acting drugs
9. Decreasing interindividual pharmacokinetic differences
10. Decreasing systemic activity
11. Decreasing drug interactions
12. Increasing drug interactions
Drug's Therapeutic Efficacy vs. Therapeutic Satisfaction

Source: Japan Health Science Foundation “Prospects on Medical Needs in Y2015”
Successful Drug Discovery
Volume 1

2015.
Hardcover-
ISBN: 978-3-527-33685-2