„Benign-by-Design" ein Konzept der grünen und nachhaltigen Pharmazie zum Schutz von Wasserressourcen



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LEUPHANA

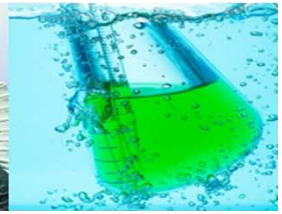
Institute of Sustainable and Environmental Chemistry
http://www.leuphana.de/en/institutes/isec.html

ISC3

International Sustainable Chemistry Collaborative Centre
http://isc3.org







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1. Das Konzept
2. Beispiele
3. Schlussfolgerungen

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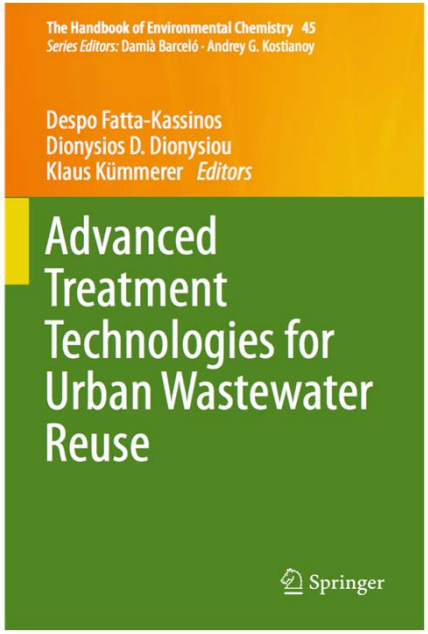
(Erweiterte) Abwasserreinigung stößt zunehmend an Grenzen!

1. Jedes Verfahren entfernt nur spezifische Minderheit von Substanzen
2. Oxidative Verfahren bilden Vielzahl von Abbauprodukten mit unbekannten Eigenschaften und Toxizität
3. Stoffe der Zukunft unbekannt
4. Zusätzlicher Energieverbrauch
5. Hochwasserentlastung
6. Infiltration in den Untergrund
7. Kosten?

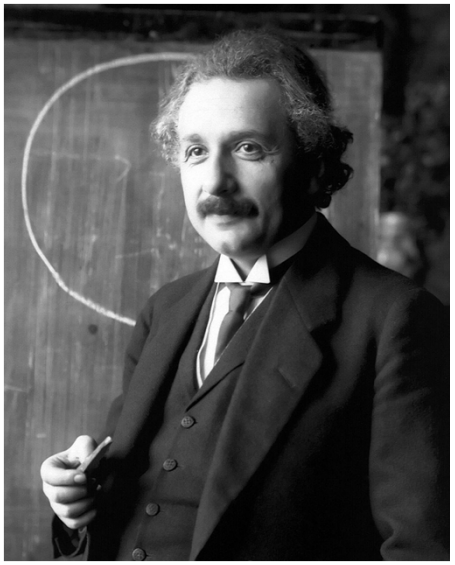


Die Idee dahinter

Ein schlauer Mensch löst ein Problem.

Ein weiser Mensch vermeidet es.

Einstein zugeschrieben



Maßnahmen an der Quelle

Member States should tackle the sources of pollution ... This is much preferable to using end-of-pipe treatment ... while avoiding high treatment costs and protecting the environment.

9.3.2015

COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL The Water Framework Directive and the Floods Directive: Actions towards the 'good status' of EU water and to reduce flood risks /* COM/2015/0120 final */., 9.3.2015

Eine politische Antwort

December 9, 2014 Council of the European Union

2018 EU strategy for a non-toxic environment: the Council calls for actions

The Commission and the Member States need to pave the way towards reaching a non-toxic environment in the EU. Actions are requested on substances of high concern, nanomaterials, endocrine disruptors, imported articles and REACH registration dossiers.

Europe

SVHC and restrictions | Nanomaterials | Regulatory | Innovation | REACH Registration | Endocrine disruptors

Council of the European Union

Brussels, 5 December 2014
(OR. en)

16361/14

At the Rio+20 Conference on Sustainable Development, the UN members reaffirmed their commitment to achieve, by 2020, sound management of chemicals throughout their life cycle in ways that lead to minimisation of significant adverse effects on human health and the environment.

In the EU, the REACH Regulation has now been functioning since 2007, and is unquestionably an improvement in the regulation of chemicals. However, there are still areas where both the efficiency and the effectiveness of REACH need improvement.

The 7th EAP calls on the Commission to develop, **by 2018**, a **Union strategy for a non-toxic environment that is conducive to innovation and the development of sustainable substitutes including non-chemical solutions, building on horizontal measures to be**

Worin besteht das Problem?

Persistenz von Chemikalien und Arzneimitteln in der Hydrosphäre!

Die Vermeidung

Stoffe

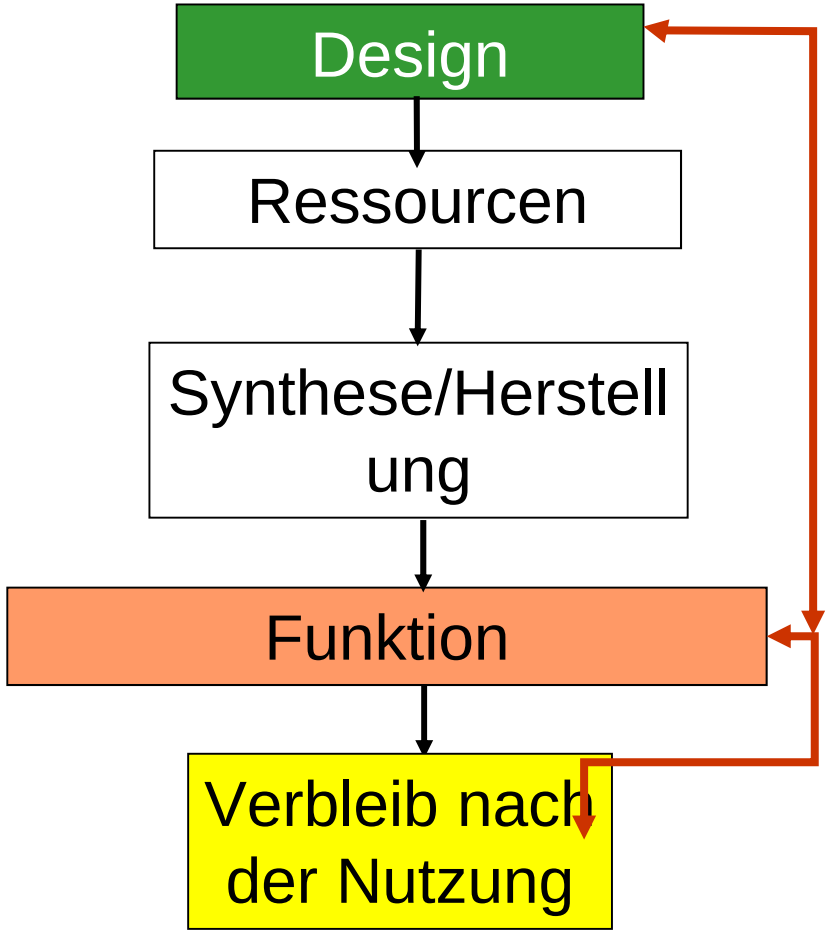
erfüllen ihren Anwendungszweck möglichst gut

und

sind nach Gebrauch leicht und vollständig abbaubar

Rabsch W und Fritsche W (1976) Z Allg Mikkrobiol. 17, 139
Daughton CG (2003) Environ. Health Perspect. 111, 757
Boethling R et al. (2007) Chem. Rev.107, 2207
Kümmerer K (2007) Green Chem. 9, 899

Benign by Design: Gezieltes Design chemischer Stoffe



Das Ende von Anfang an im Blick!

📖 Kümmerer, K. (2007) Green Chemistry 9, 899-907, verändert

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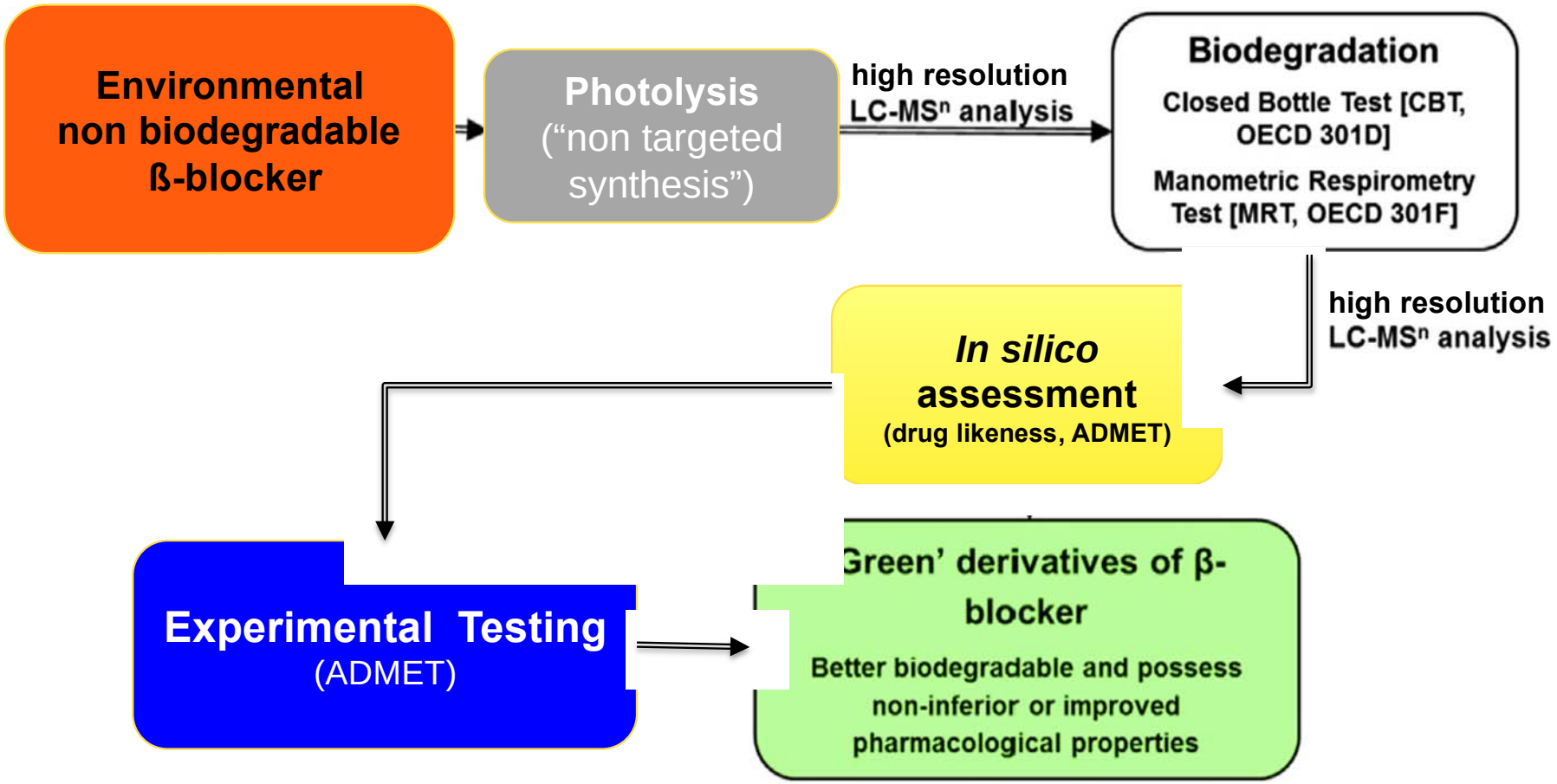
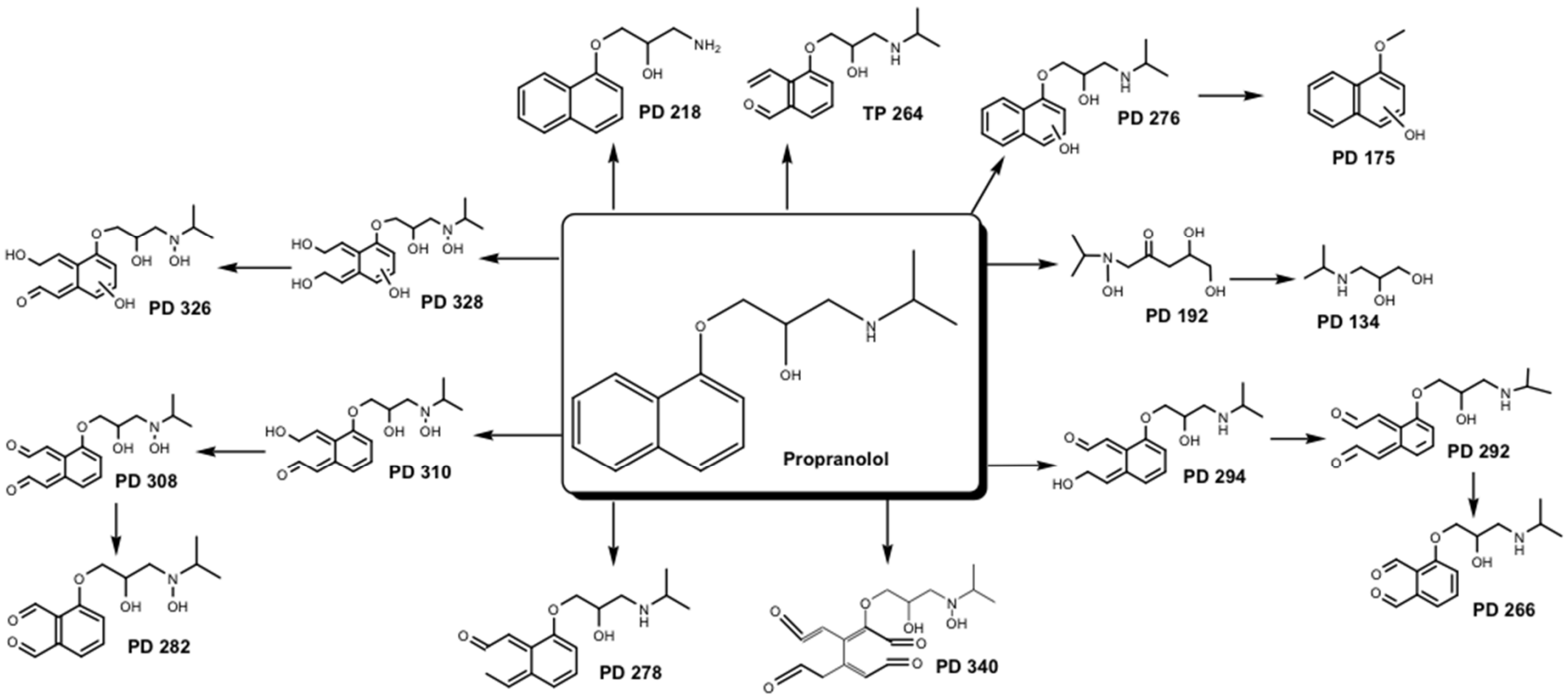

Environmental non biodegradable ß-blocker
Photolysis ("non targeted synthesis")
high resolution LC-MSⁿ analysis
Biodegradation
Closed Bottle Test [CBT, OECD 301D]
Manometric Respirometry Test [MRT, OECD 301F]
high resolution LC-MSⁿ analysis
In silico assessment
(drug likeness, ADMET)
Experimental Testing
(ADMET)
Green' derivatives of β-blocker
Better biodegradable and possess non-inferior or improved pharmacological properties

Photoprodukte Propranolol

Bundesministerium für Bildung und Forschung

📖 Rastogi T, Leder C, Kümmerer K (2015), ES&T, 49, 11756–11763

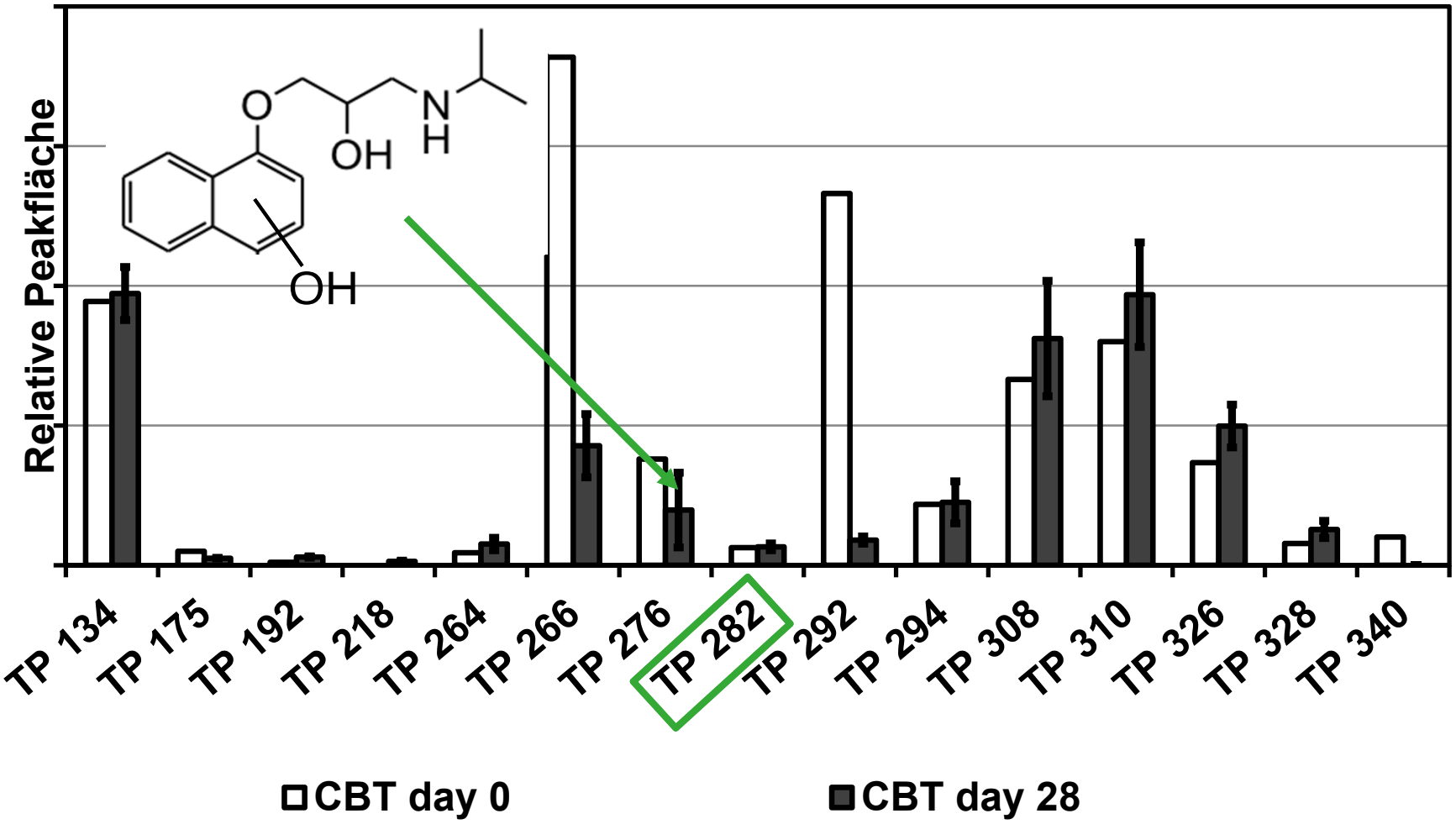


Biologische Abbaubarkeit der Photoprodukte

32 min Photolyse

Rastogi T, Leder C, Kümmerer K (2015), ES&T, 49, 11756–11763

Bundesministerium für Bildung und Forschung

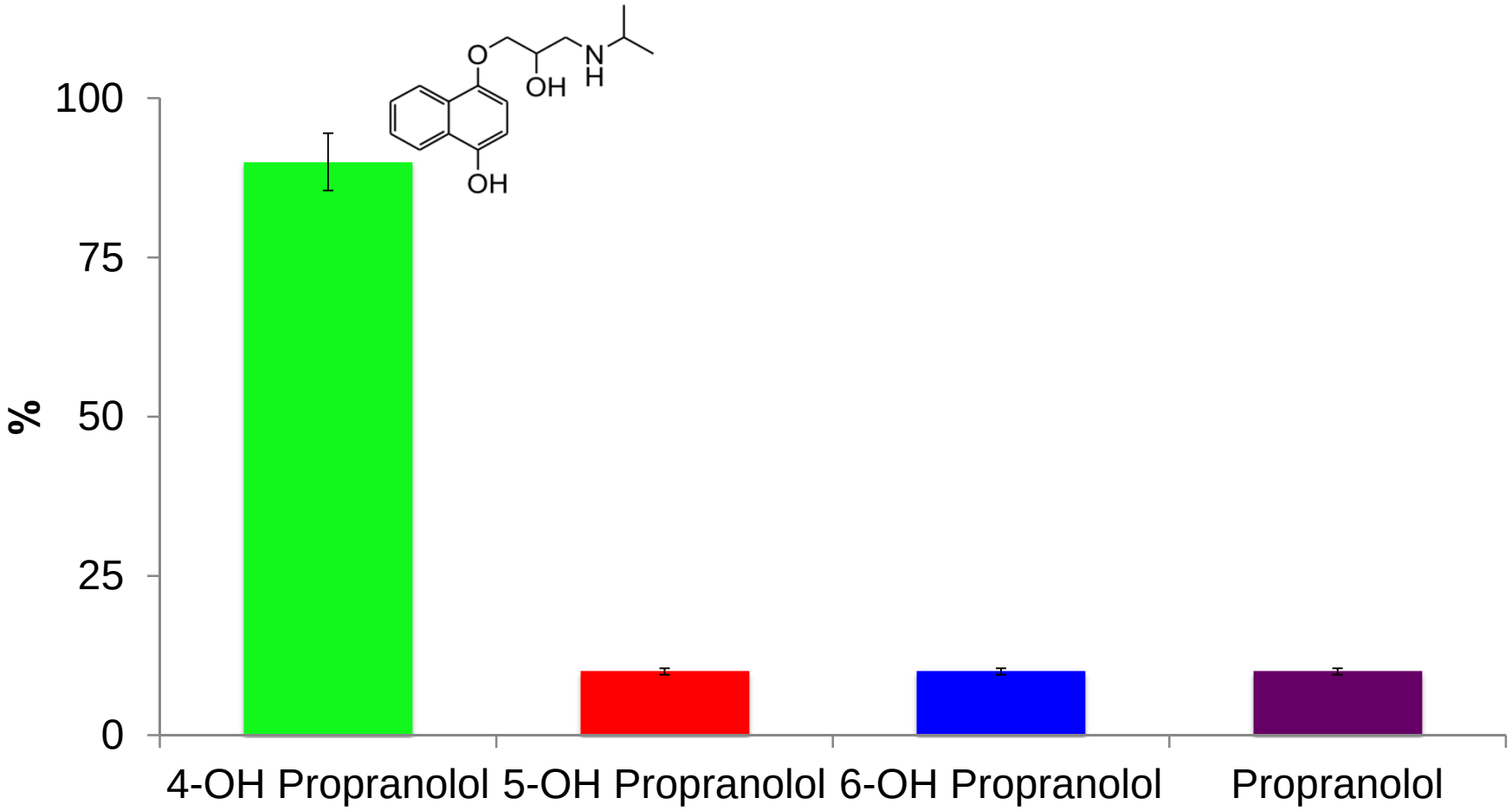


Biologische Abbaubarkeit Hydroxypropranolol

Closed Bottle Test (OECD 301D)

Rastogi T, Leder C, Kümmerer K (2015), ES&T, 49, 11756–11763

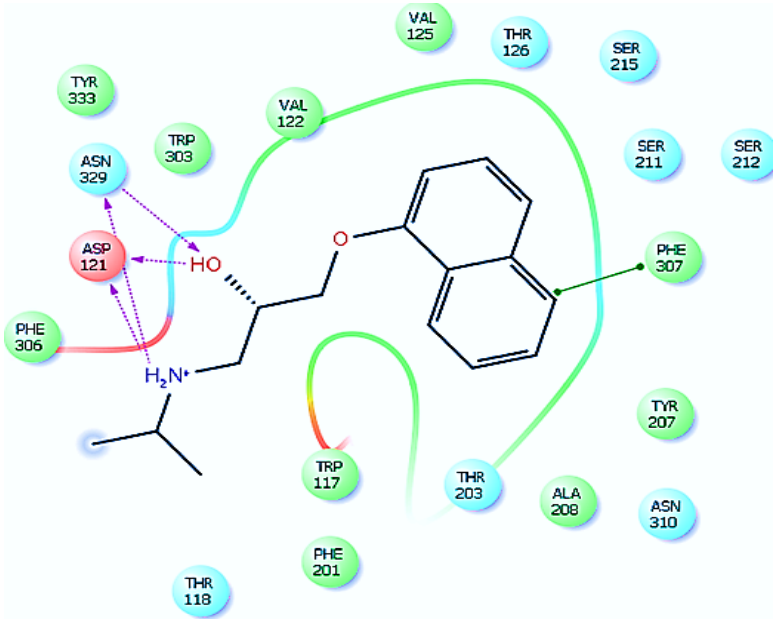
Bundesministerium für Bildung und Forschung



Bindung an Rezeptor - Docking

Bundesministerium für Bildung und Forschung

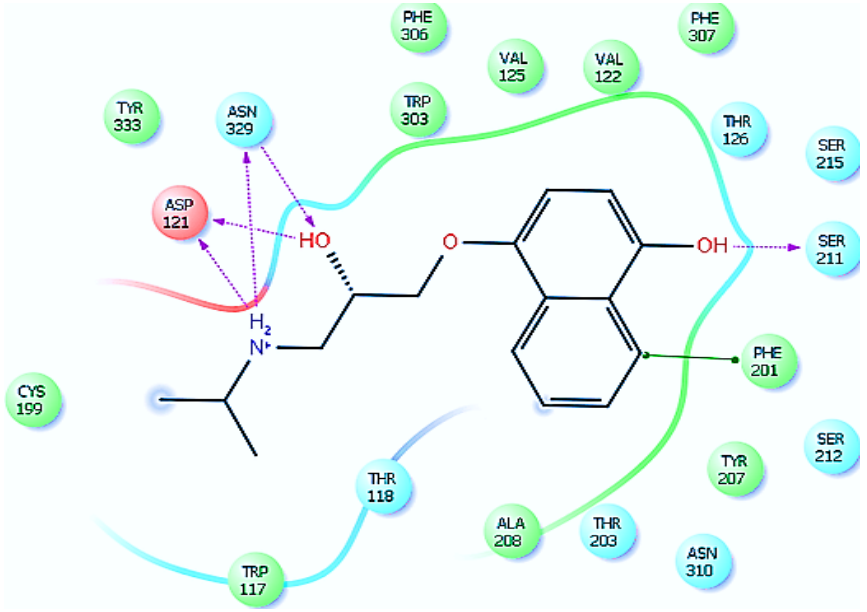
Rastogi T, Leder C, Kümmerer K (2015), ES&T, 49, 11756–11763



PPL (S)

Docking Score:

- 9.1



4-OH PPL (S)

Docking Score:

- 9.3

Mutagenität, Gentoxizität und Karzinogenität von 4-Hydroxypropranolol (In Silico)

Bundesministerium für Bildung und Forschung

📖 Rastogi T, Leder C, Kümmerer K (2015), ES&T, 49, 11756–11763

QSAR Software	Models	End points	Propranolol	4-OH Propranolol
CASE Ultra v. 1.5.2.0 (as per ICH M7 guidelines)	Salmonella mutagenicity	Mutagenicity	Known negative	Negative
	A-T site mutation	Mutagenicity	Inconclusive	Negative
	Expert rules for genotoxicity	Genotoxicity	Known negative	**Positive**
	E.coli mutagenicity	Mutagenicity	Negative	Negative
	Salmonella mutagenicity	Mutagenicity	Known negative	Negative
Leadscope Model Applier Version: 1.8.6 (as per ICH M7 guidelines)	ICH M7 Genetox Consensus	Genetox Consensus	Negative	Negative
	E Coli - Sal 102 A-T mutagenicity	Mutagenicity	Negative	Negative
	Salmonella mutagenicity	Mutagenicity	Negative	Negative
	Bacterial Mutation	Mutagenicity	Negative	Negative
	Human carcinogenicity	Carcinogenicity	Negative	Negative
CASE Ultra v.1.4.5.1	Micronucleus formation in vivo composite	Genotoxicity	**Positive**	Negative
	Chromosome aberration in vitro composite	Mutagenicity	**Marginal positive**	Negative
OASIS Catalogic	In vitro Ames model	Mutagenicity	Negative	Negative

ADME Eigenschaften von 4-Hydroxypropranolol (In Silico)

Bundesministerium für Bildung und Forschung

📖 Rastogi T, Leder C, Kümmerer K (2015), ES&T, 49, 11756–11763

ADME properties	Description	Range or recommended values	Atenolol	Metoprolol	Propranolol	4-Hydroxy propranolol
Rule of 5	Lipinski's rule of five.	Fewer or no violations	0	0	0	0
Rule of 3	Jorgensen's rule of three.	Fewer or no violations	0	0	0	0
log $P_{o/w}$	Octanol/water partition coefficient.	-2.0 to 6.5	0.17	1.9	3.1	2.1
log S	Aqueous solubility	-6.5 to 0.5	-1.3	-1.4	-3.5	-2.1
log HERG	IC50 value for blockage of HERG K^+ channels.	Concern below -5	-4.5	-6.1	-5.9	-5.9
P Caco	Apparent Caco-2 cell permeability	<25 poor and >500 great	33.9	733.9	1147.9	320.7
log BB	Brain/blood partition coefficient	–3.0 to 1.2	-1.21	-0.22	0.22	-0.4
P MDCK	Apparent MDCK cell permeability	<25 poor and >500 great	32.0	391.7	635.3	160.1
log K_p	Skin permeability	–8.0 to –1.0	-5.2	-3.2	-2.6	-3.7
Human-oral absorption		1, 2, or 3 for low, medium or high, respectively	2	3	3	3
log K_{hsa}	Binding to human serum albumin	–1.5 to 1.5	-0.76	-0.15	0.05	-0.12
CNS	Central nervous system activity	–2 (inactive) to 2 (active)	1	-2	1	0

Pharmakologische Aktivität 4-Hydroxypropranolol

In Vitro Analysis

📖 Rastogi T, Leder C, Kümmerer K (2015), ES&T, 49, 11756–11763

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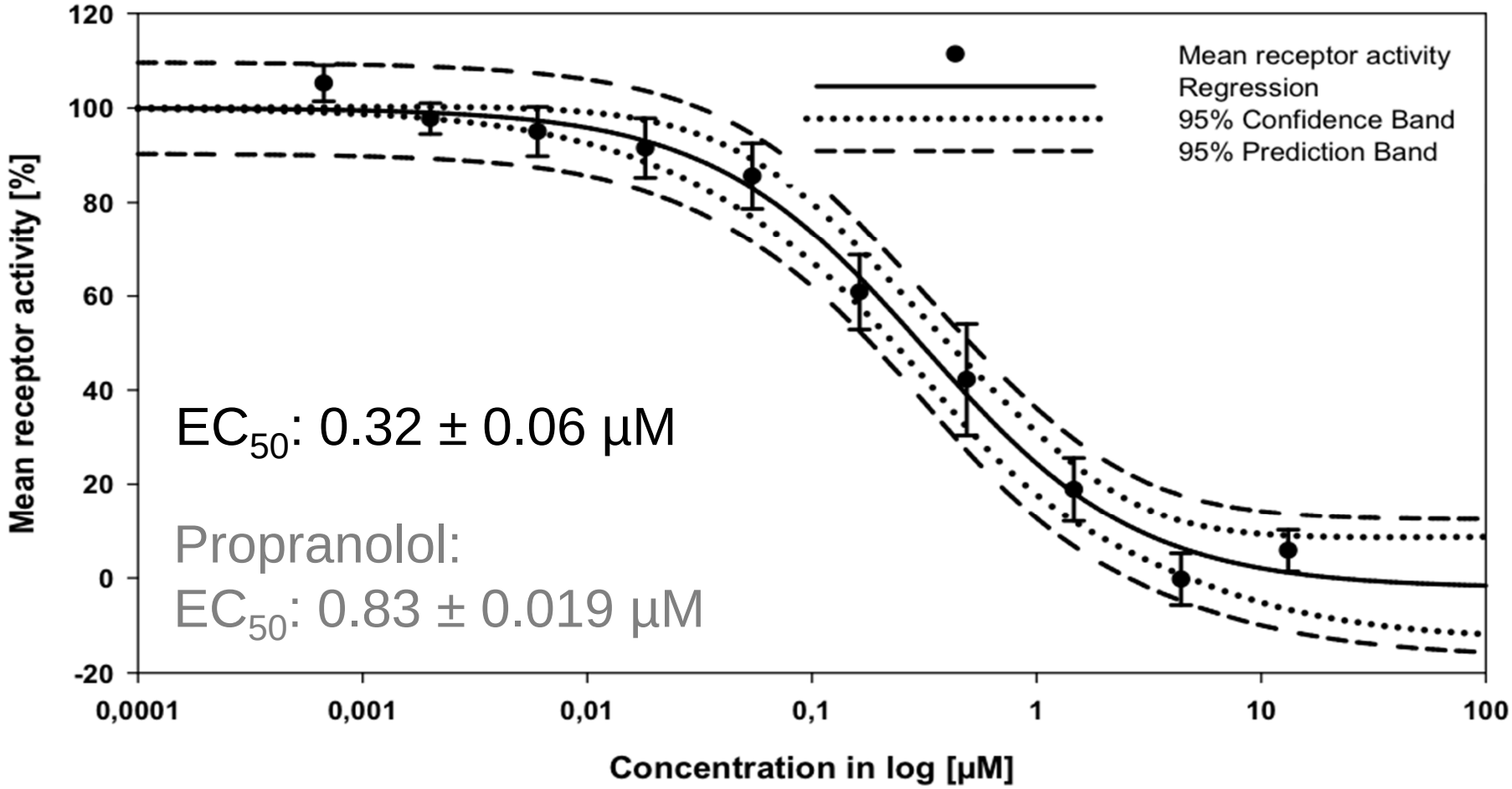

4-Hydroxypropranolol

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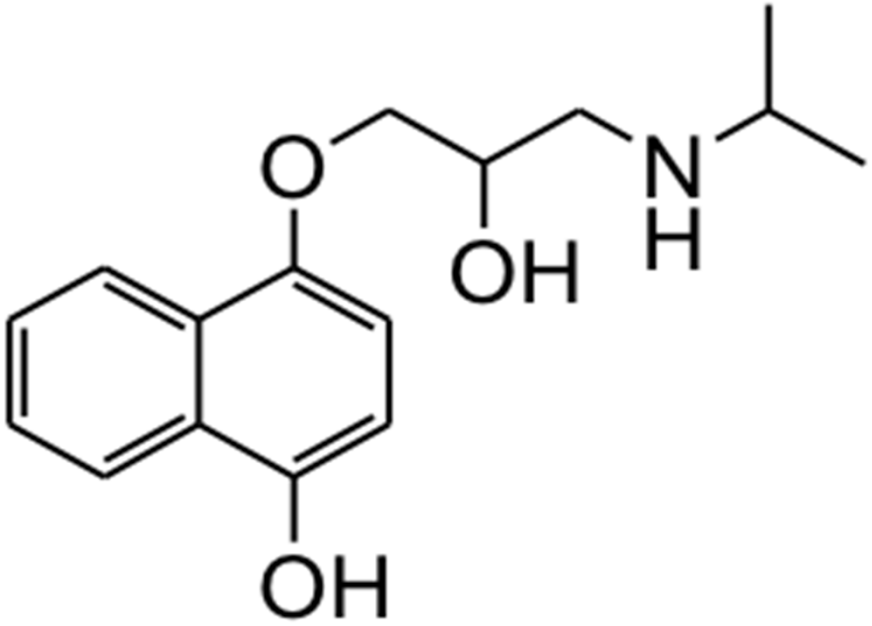
📖 Rastogi T, Leder C, Kümmerer K (2015), ES&T, 49, 11756–11763

Aktives Pharmakon

In der Umwelt biologisch abbaubar (einschließlich Metabolit)

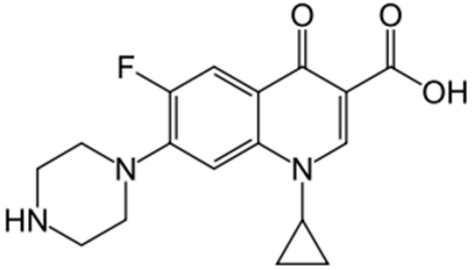


Analog:
Rastogi T, Leder C, Kümmerer K (2014) Chemosphere, 111, 493–499 (**Metoprolol**)
Rastogi T, Leder C, Kümmerer K (2015) RSC Advances, 5, 27-32 (**Atenolol**)

Gezieltes Re-Design

In der Umwelt biologisch abbaubares Antibiotikum

Ausgangsverbindung: Ciprofloxacin



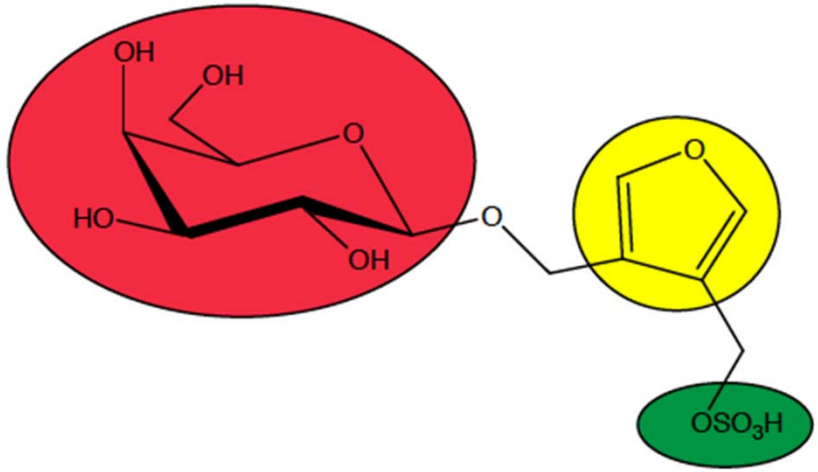
- Strukturvaianten der Leitstruktur
  - 20+ Jahre Erfahrung in biologischer Abbaubarkeit
  - In silico Evaluation (Aktivität, Drug-Likeness, ADMET)

- Synthese der erfolgversprechendsden Kandidaten
- Experimentelle Überprüfung

- 2 Patentanmeldungen eingereicht

De Novo Design
Neuer Wirkstoff

gefördert durch
DBU
Deutsche Bundesstiftung Umwelt
www.dbu.de



Ziel: Niedrigere Wirkschwelle & höhere biologische Abbaubarkeit in der Umwelt

<u>Systematische</u> Strukturvariation

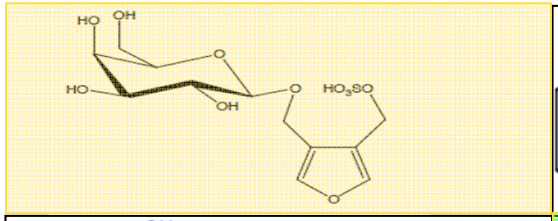
📖 Kümmerer K, Frei E, Marano G, in preparation

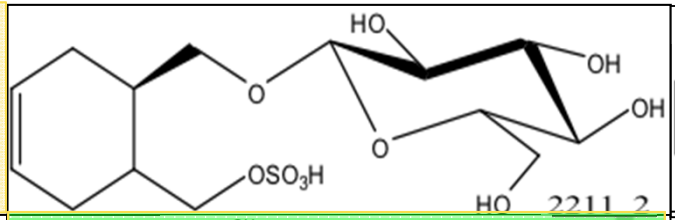
Systematische Strukturvariation

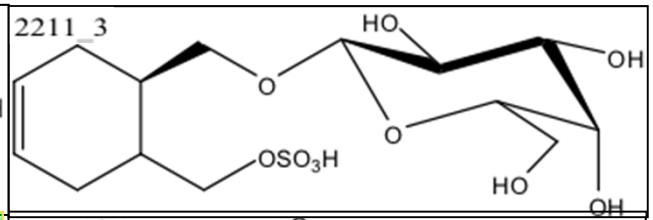
gefördert durch DBU Deutsche Bundesstiftung Umwelt www.dbu.de

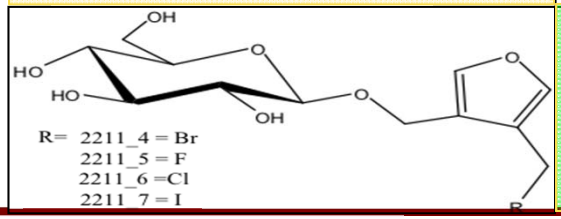
📖 Marano G. et al. EP 2 474 552 A1, Kümmerer submitted

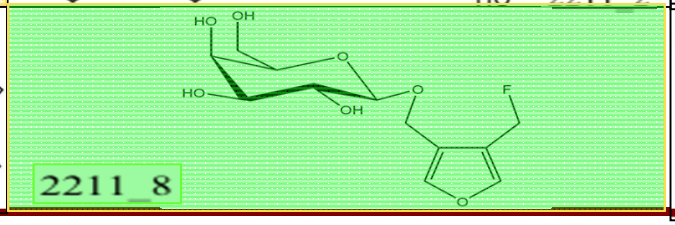
Struktur ID	Log Kow	Wirkschwelle (rel. Einheiten)	Biol. Abbaubarkeit [%]
GSF (D-Gal)	-2.1	1	19
2211_2 (Glu ,Cyclohex)	-1.8	> 1	37
2211_3 (Gal, Cyclohex)	-1.8	> 1	37
2211_4 (Glu-Br)	-0.5	> 1	14
2211_5 (Glu-F)	-0.9	> 1	14
2211_6 (Glu-Cl)	-0.7	> 1	14
2211_7 (Glu-I)	-0.5	> 1	14
2211_8 (Gal-F)	-2.0	<0,01	37
2211_9 (Desoxyglu)	-1.5	> 1	31

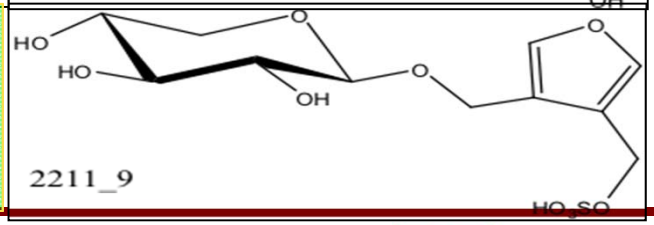






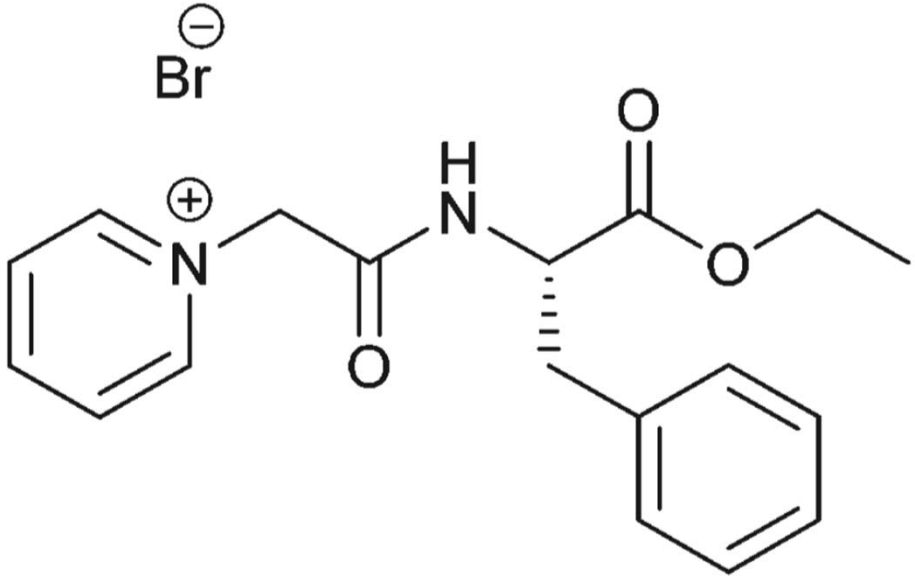






De-novo Design: Ionische Flüssigkeit

Pyridiniumderivat der Aminosäure Phenylanalin

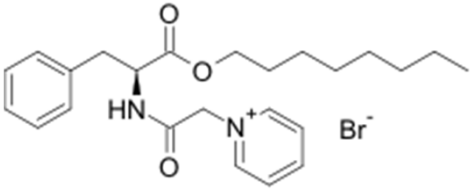


Primärelimination:

- 73 % ± 0.7 % (28d)
- 100 % ± 0.0 % (40d)
- Keine Transformationsprodukte (Orbitrap LC-MS)

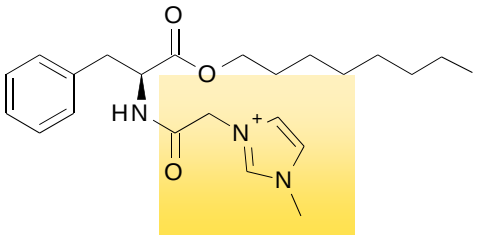
📖 Haiß A., Jordan A., Westphal J, Gathergood N., Kümmerer K (2016) Green Chem 18, 4361-4373

Regeln



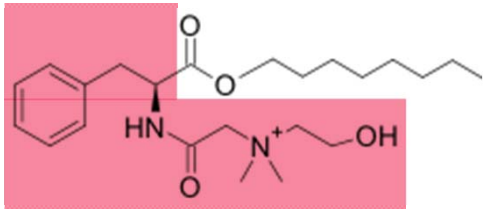
Phenylalanin-Pyridinium.

Komplette Mineralisation: Kette ≤ C_8



Phenylalanin-Imidazolium

Unvollständiger Abbau (AlkylKette, Phenylanalin)
persistentes Fragment



Phenylalanine-Cholinium-ILs

Nur Abbau der Alkylkette, nicht Phenylanalin
persistentes Fragment

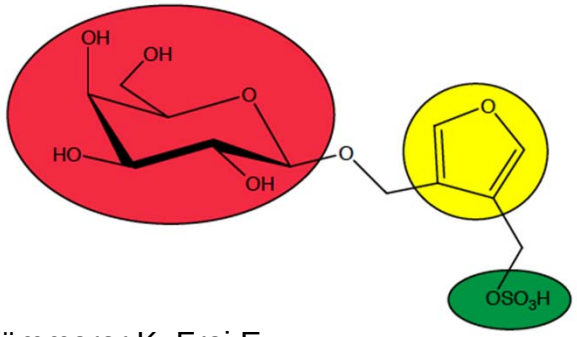
Nutze Phenylalanin basierte Pyridinium IF mit lineare Alkylkette ≤ C_8

Haiß et al. 2016, Green Chemistry 18, 4315-457
Haiß, et al., manuscript in preparation

Re-Design und De-Novo Design

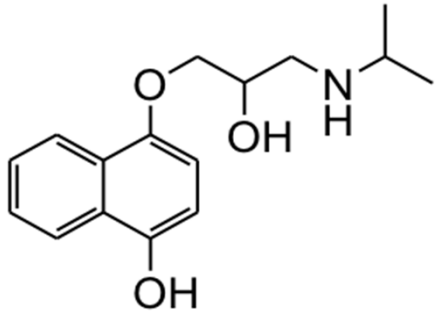
Beispiele

Krebsmedikament (patentiert)

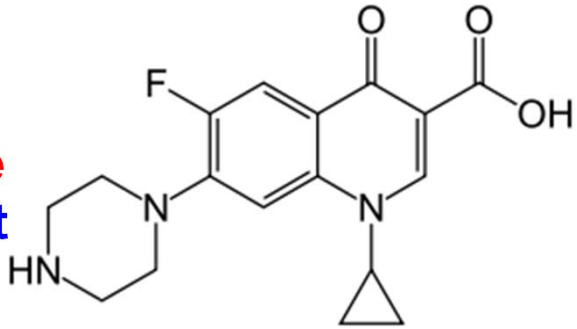


📖 Kümmerer K, Frei E, Marano G, Wiessler M., in Vorbereitung

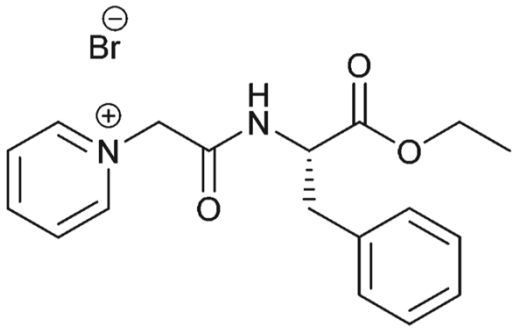
ß- Blocker



Antibiotika
Ciprofloxacinderivate
2 Patente angemeldet



Ionische Flüssigkeiten



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Was bedeutet das für die Entwicklung neuer Stoffe?

- Beginn mit einer Leitstruktur
- Optimierung

- Neu: Berücksichtigung des Schicksals in der Umwelt nach der Nutzung von Anfang an
  - Herausfordernd
  - **Neues Pardigma**
  - **Neue Chancen**

Schlussfolgerungen

1. Wirksamkeit und Umweltverträglichkeit sind kein unüberwindbarer Gegensatz
2. Kann auch bei Arzneimitteln gezielt eingebaut werden
3. Trägt zur Corporate Sustainable Responsibility bei
4. Eröffnet neue Marktchancen!