A sustainable chemistry solution to the presence of pharmaceuticals and chemicals in the aquatic environment-the example of re-designing β-blocker Atenolol

Rastogi, Tushar; Leder, Christoph; Kummerer, Klaus

Published in:
RSC Advances

DOI:
10.1039/C4RA10294K

Publication date:
2015

Document Version
Peer reviewed version

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A Sustainable Chemistry Solution to the Presence of Pharmaceuticals and Chemicals in the Aquatic Environment- the Example of Re-Designing β-blocker Atenolol

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

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Tushar Rastogi, Christoph Leder, Klaus Kümmerer*

Micro-pollutants in general as well as Pharmaceuticals in the environment (PIE) in particular are obstacles for sustainable chemistry and can be seen as one of the major challenges of sustainable management of water resources and a threat to health, water and food safety. Recent research has shown that this problem cannot be solved with advanced effluent treatment. Therefore, new approaches are urgently needed. This includes the new design of molecules or the re-design of existing molecules that present the functionality needed for their application and that are improved with regards to their biodegradability in the environment after their intended use. This paper presents a new approach for generating, identifying and testing biodegradable and drug-like molecules.

Micro-pollutants have gained more attention in the scientific community. They are increasingly seen as one of the major challenges to the sustainable management of water resources and a threat to health, water, and food safety. Due to their targeted design for bioactivity and stability, pharmaceuticals are leading hot spot micro-pollutants of the aquatic environment.[1–4] The most extensively discussed strategy for the prevention of the input of pharmaceuticals into the aquatic environment are advanced effluent treatment processes. However, these advanced effluent treatment processes, which are the end of pipe solution, have their own specific limitations and drawbacks such as the formation of toxic and stable reaction products and their very limited possibility of application on the global scale.[5–7]

The tenth principle of green chemistry is 'Design for Degradation'.[8] This means that 'Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment' as stated by the American Chemical Society on their webpage.[9] In other words, the goal is to design pharmaceutically active ingredients (APIs) that can mineralize at a reasonable rate and more or less completely in normal effluent treatment and in the aquatic environment. The concept of the benign by design is the key element in this respect.[10,11] It is an important concept within green and sustainable pharmacy and chemistry and very promising in terms of sustainability.[12] The concept of benign by design can be applied on two levels: the design of completely new molecules or the re-design of existing molecules. In both cases, small alterations in the chemical structure of an API may have a significant impact on the one hand, on its activity, solubility and polarity and on the other hand on biodegradability. Therefore it is reasonable to assume that a set of functionalities exists that can foster both and need to be explain in detail. Re-designing such biodegradable drugs is a challenge that is addressed in the research presented here.

The present study focuses on the re-design of the existing API β-blocker Atenolol (ATL), a selective β_1 blocker and reported to be largely excreted as unchanged from the human body.[13] In 2012, 45.7 million defined daily dose (DDD) of ATL [accounting for 75 mg of pure ATL taken either oral or parenteral[14]] were prescribed in Germany.[15] This corresponds to a total amount of 3.43 tonnes of ATL consumed by individuals in Germany who were insured by public health insurance in 2012. ATL is not biodegradable and has been frequently detected in the aquatic environment including drinking water at concentrations up to 120 μg L^{-1}.[2]

Atenolol was used as an example to incorporate the additional attribute biodegradability while preserving its substructures responsible for β adrenergic receptor blocker activity. An aromatic ring and a β-ethanolamine moiety are considered essential substructures of β-blockers responsible for their receptor blocking activity.[16,17]

The very first step in designing biodegradable β-blocker derivatives is to generate new molecules that possess substructures (both aromatic ring and β-ethanolamine) responsible for their specific action as β-blockers. New drug-like derivatives (photo-transformation products, photo-TPs) were generated by direct photolysis of ATL with no pre-treatment and no other oxidizing agents in order to exclude any other constituents that could interfere with the formation of derivatives (photo-TPs). Photolysis of ATL resulted in numerous derivatives. The kinetics of formation of derivatives (photo-TPs) and proposed molecular structures and reaction pathways were elucidated by ion-trap LC-MS/MS and by using the photodegradation dictionary of *in silico* MetaPC software (MultiCASE Inc.). *In silico* predicted molecular structures were

compared to the corresponding MS/MS spectra measured by LC-ESI-MS^n (ion-trap).

In the next step, aerobic biodegradation tests (Closed Bottle test [CBT] OECD 301D[18] and the Manometric Respiratory Test [MRT] OECD 301 F[19]) were applied to the resulting mixture of photolytic treatment for the assessment of the derivatives' biodegradability in the environment. CBT was employed because it is the most stringent biodegradation test with low bacterial density and diversity in order to avoid any false positive results. Thereby, the derivatives (photo-TPs) that had improved biodegradability compared to the parent compound and that still possessed an aromatic ring and a β-ethanolamine moiety were selected. The ones that were found to be biodegradable were further assessed with the help of QSAR tools in order to get further insights.

In addition, the detainment of the drug-like properties (absorption, distribution, metabolism and excretion; ADME) of the better biodegradable derivatives (photo-TPs) that retained the aromatic ring and a β-ethanolamine moiety similar to ATL were investigated. The final step was an *in silico* toxicity assessment of those biodegradable and drug-like derivatives.

Proposed structures of derivatives: The structures as well as reaction pathways are illustrated in Scheme 1. Six major pathways were found to be involved in the formation of the derivatives:

I. The observed major pathway was hydroxylation by the attack of electrophilic hydroxyl radical ($HO^{\bullet}$) at the aromatic ring of ATL molecule, which was also reported by Ji et al.[20] However, Medana et al.[21] mentioned that the attack of $HO^{\bullet}$ on the benzene ring of ATL is preferred, but not limited to it. This could be the reason for the formation of various derivatives such as TP 295, TP 310, etc. Further attack of $HO^{\bullet}$ on mono- hydroxyl derivatives of ATL (TP 283) results in the formation of di-, tri-, tetra- and even penta- hydroxyl derivatives of ATL, as shown in Scheme 1. $HO^{\bullet}$ attack on the benzene ring often leads to ring opening, which results in the formation of two aldehyde moieties or an aldehyde and an alcohol moiety, respectively.[22]The derivatives that were found, such as TP 275, TP 285, TP 317, TP 318 and TP 336 are likely to be formed through this proposed mechanism.

II. Another pathway observed during photolysis was dealkylation, i.e. cleavage of isopropyl moiety from the isopropyl-amino-propoxy side chain of ATL, which results in the formation of TP 225, as shown in Scheme 1. The subsequent elimination of NO_2 from TP 225 through the formation of a nitroso intermediate could lead to the formation of TP 210.[23] TP 225 could also be a precursor of TP 193; TP 207; TP 223 and TP 194. Coupling reactions were observed, reaction that resulted in the formation of dimers of TP 194 and TP 210 as TP 387 and TP 419, respectively (Scheme 1).[23]

III. An *ipso* substitution of $HO^{\bullet}$ on a carbon atom of the aromatic ring[20] resulted in an intermediate radical (resonance-stabilized carbon-centered radical) which later resulted in derivatives such as TP 134 and TP 152, as shown in Scheme 1.

IV. The loss of the methanamide radical ($CONH_2^{\bullet}$) from the acetamide side chain of ATL was observed, which finally was oxidized to benzaldehyde and resulted in TP 238. Further electrophilic $HO^{\bullet}$ attack either on the *ortho*- and *meta*- position of aromatic ring of TP 238 resulted in a hydroxylated benzaldehyde derivative TP 254 (Scheme 1).

V. Another pathway could be the dehydration, i.e. elimination of water from the isopropyl-amino-propoxy side chain of ATL, as shown in Scheme 1. This mechanism would result in the formation of TP 249, which was also reported as UVA-UVB photo-TP of ATL.[24] Removal of the amino group from the acetamide side chain of TP 249 through the formation of a nitroso intermediate result in TP 232.

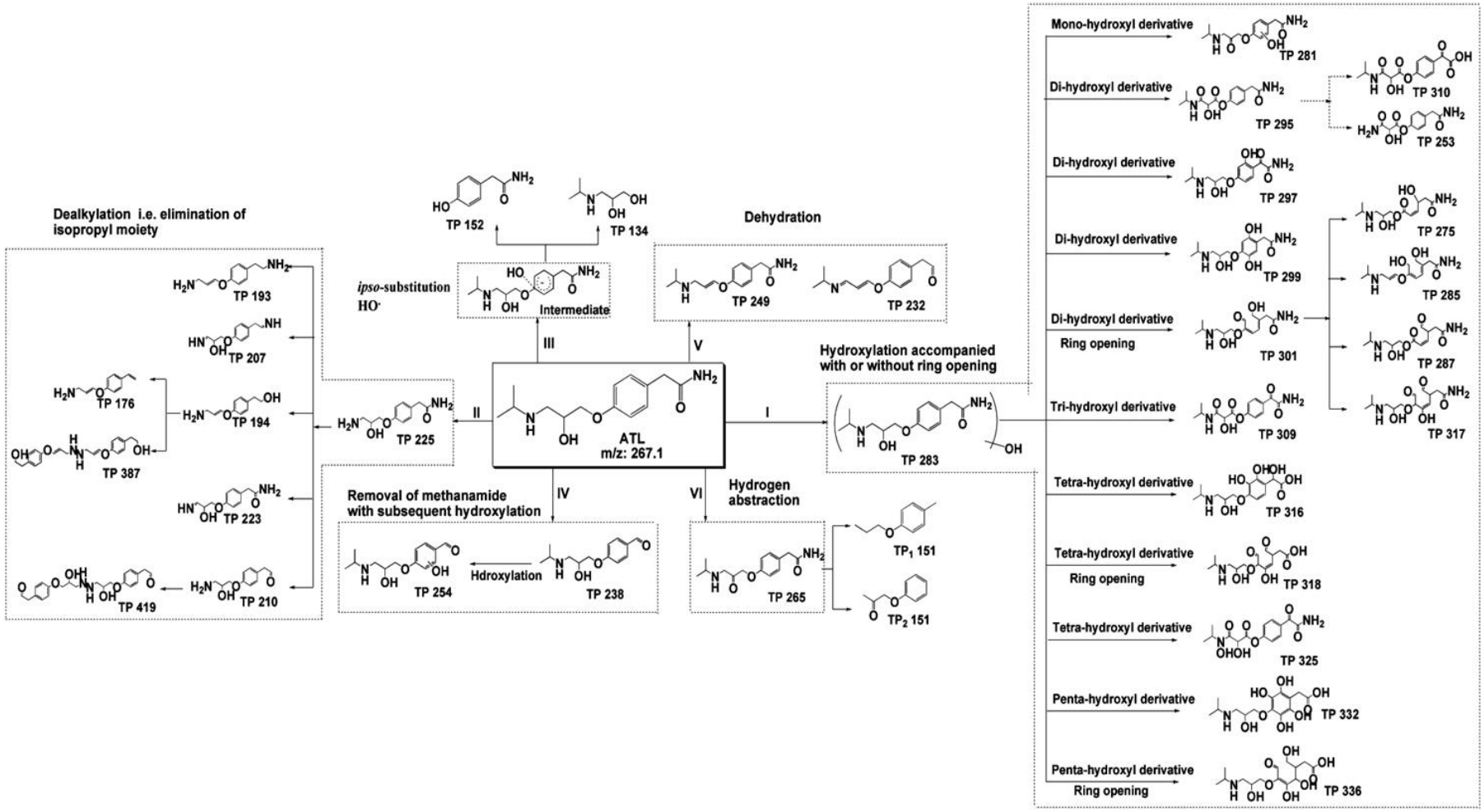
VI. The pathway leading to TP 265 could be hydrogen abstraction from the alcoholic moiety of the isopropyl-amino-propoxy side chain. TP 265 broke down further to $TP_{1\&2}$ 151 during photolysis (Scheme 1).

Biodegradability: The LC-MS analysis of sterile controls of MRT indicates that ATL was not abiotically eliminated, e.g. by hydrolysis, sorption etc. Samples from the start and the end of both biodegradation tests were analyzed through LC-UV-MS/MS, as illustrated in Figure S3 (in Supporting Information, SI). Both biodegradation tests, CBT and MRT, classified ATL as not readily biodegradable chemical. The LC-MS/MS analysis confirmed that ATL was not transformed or eliminated during biodegradation tests. These findings are in accordance with the presence of ATL in the aquatic environment. However, it was found that a few of the formed derivatives (summarized in Supporting Information, SI Table S6) were better biodegradable than ATL.

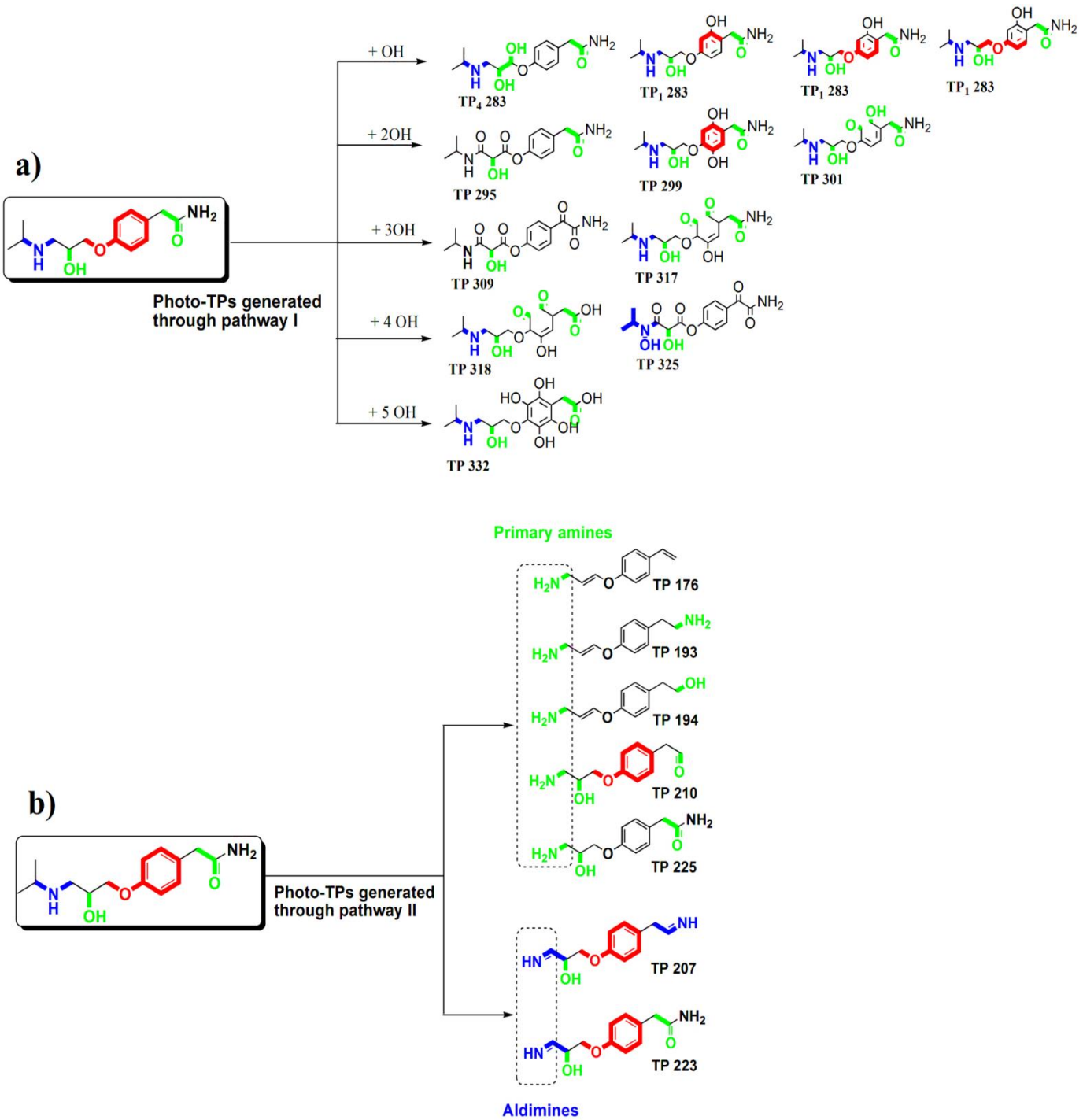
Biodegradable derivatives were then analyzed *in silico* by QSAR models (summarized in Table S5 in SI) for ready biodegradability to get a further insight of the structural alterations. The software package Case Ultra (Multicase Inc.) identifies the structural changes in the derivatives (photo-TPs) molecules that would modulate their biodegradability. The predictions and moieties of the derivatives that increase or reduce biodegradability are summarized in Table S9 in SI. This knowledge contributes to a better understanding of processes, which in turn could be the basis of a rational design of better biodegradable compounds in the future in accordance with the benign by design approach.

Case Ultra software predicted that the methoxybenzene moiety at the aromatic ring weakens the biodegradability of ATL, as shown in Scheme 2. It also predicted moieties such as an OH group attached to the β-carbon of the ethanolamine side chain and the acetyl moiety on the acetamide side chain to assist biodegradability (Scheme 2). Moreover, the derivatives (photo-TPs) that were predicted to be better biodegradable were the same ones which were observed to be, according to analytical results, better biodegradable than ATL in the biodegradation test assays. Additionally, other moieties in the derivatives (photo-TPs) molecule such as alcohol, ketone, aldehyde and amine functionalities were predicted by Case Ultra software to foster biodegradability. This is also in accordance with the general understanding for biodegradability.[12,25] The structural alterations at the aromatic ring and side chains of ATL during photolysis that modulated the biodegradability of derivatives (photo-TPs) are summarized below.

Changes at the benzene ring: It was observed that the methoxybenzene moiety that weakens biodegradability was altered during photolysis of ATL, which resulted in the modulation of the biodegradability of the respective derivatives (photo-TPs). This alteration was mainly due to the attachment of functionalities like hydroxyl groups on a benzene ring according to the proposed photo-transformation pathway I i.e. hydroxylation (Scheme 2a). This phenomenon can be explained by the fact that the attachment of electron donating functionalities like oxygen or amine to the



Scheme 1: Proposed pathways of the generation of derivatives (photo-TPs).



Red: Moieties lowering biodegradability of the molecule
Green: Moieties increasing biodegradability of the molecule
Blue: Moieties recognized as unknown structure i.e. not included in the applicability domain of the model

Scheme 2: Observed structural changes responsible for the improved biodegradability of derivatives (photo-TPs) generated through a) pathway **I** i.e. hydroxylation; b) pathway **II** i.e. dealkylation.

aromatic ring of the molecule often increases the aerobic biodegradability of the molecule whereas the attachment of electron withdrawing functionalities do reduce it.[26,27]

The attachment of hydroxyl groups at the aromatic ring of ATL was often accompanied by ring-opening, which results in the formation of moieties such as alcohols and aldehydes that assist biodegradability. These modifications in the structure of derivatives such as TP 301, TP 317 and TP 318 provided a positive alert for biodegradation, as shown in Scheme 2a. This phenomenon i.e. the opening of the benzene ring due to the attachment of hydroxyl groups is considered the first step of aerobic biodegradation of aromatic compounds, which first turned into alcohols and acids and then subsequently mineralizes.[28,29]

The di- substitution of hydroxyl groups on the benzene ring of ATL without ring opening resulted into *p*-OH phenol moiety for TP 299 (Scheme 2a). This *p*-OH phenol moiety of TP 299 was predicted to deter biodegradability, which is in accordance with the fact that substitutions of OH, NO_2, NH_2, CH_3 and Cl groups at *o*- or *p*-position of a phenol alter the biodegradable phenol moieties to non-biodegradable substituted phenol.[30]

Changes at the side chains: When a hydroxyl group was attached to an α-carbon atom of the isopropyl-amino-propoxy side chain by replacing the hydrogen atom as in TP_4 283, the predicted moiety that weakens the biodegradability of ATL molecule was completely lost, and a new moiety was formed. This new moiety in TP_4 283 was predicted to assist biodegradation (Scheme 2a). Moieties that were predicted to reduce biodegradability of ATL were lost when two electron donating functionalities like oxygen were attached at the α- and γ-carbon atoms of the propoxy side chain as in TP 295 (Scheme 2a). The addition of three oxygen atoms to isopropyl-amino-propoxy and acetamide side chains of ATL (as in TP 309 and TP 325) also altered the biodegradability reducing moieties of ATL into the biodegradability assisting moieties.

The second major photo-transformation pathway that could be assumed to alter the biodegradability of the derivatives was pathway II i.e. dealkylation. The dealkylation pathway resulted in primary amines and aldimines derivatives. Scheme 2b shows the structural changes due to the photo-transformation pathway II in an ATL molecule, which would assist the biodegradability of the resulting derivatives. The primary amine moiety (in TP 176, TP 193, TP 194, TP 210 and TP 225) that was formed was predicted to be responsible for the biodegradation, as shown in Scheme 2b. This is in accordance with the observation that primary amines are considered to be easily and rapidly biodegraded through the alkyl amine dehydrogenase pathway during biodegradation.[31] TP 207 and TP 223 had the aldimine moiety that could not be classified by the software, as this functionality is not included in the applicability domain of the model. Therefore, no reliable prediction is possible for these derivatives.

In general, it is difficult to quantify the effect of one certain structural alteration on biodegradability in total. However, the experimental results and QSAR predictions as well as the results of the other studies indicate that there are structural alterations that foster biodegradability. Therefore, the results presented here can serve as a good starting point for the rational design of improved biodegradable compounds.

Assessment of drug-likeliness: The software package Schrödinger QikProp 3.8 (Schrödinger, LLC) was employed for this assessment. It predicts the drug-likeness of the derivatives according to their ADME (absorption, distribution, metabolism and excretion) properties, which are described in detail in SI as Text S5. The QikProp predictions for the drug-likeness of the observed biodegradable derivatives are summarized in Table S7 in SI.

Biodegradable derivatives such as TP 176, TP 193 and TP 194 lack the β-ethanolamine moiety, which is an indispensable substructure of the pharmacophore of β-blockers. Therefore, these three derivatives were not further considered. QikProp software predicted that derivatives like TP 225, $TP_{1\text{-}7}$ 283, TP_1 295, TP 299, TP_2 309 and TP 325 to be drug-like but less orally available. This means that these derivatives also had to be omitted and that they were not considered for the further development of new ATL derivatives.

The biodegradable derivatives such as $TP_{1\text{-}6}$ 301, TP 317, and TP 318, which were formed by the opening of the aromatic ring due to the attachment of hydroxyl group, were predicted to be less drug-like and less orally available. These derivatives (photo-TPs) also lack the other essential substructure (benzene ring) responsible for their specific action as β-blockers. Therefore, these derivatives were also not further considered due to their unsatisfactory ADME properties prediction and activity.

The results show that remaining biodegradable derivatives such as TP 207, TP 210, TP 223, TP 238 and TP_2 295 were predicted to be drug-like and orally available (Table S7, SI). These derivatives also possess both essential substructures (aromatic ring and β-ethanolamine) of β-blockers. Thus, it can be concluded that the attachment or the removal of certain groups from either one of the side chains might not change the drug-likeness while opening of the aromatic ring decreases the drug-likeness and oral availability of the derivatives. Thus, derivatives such as TP 207, TP 210, TP 223, TP 238 and TP_2 295 might be considered to be the leading candidates for biodegradable drug-like molecules.

Toxicity assessment: Another important prerequisite for drug-like substances and APIs is that they should not be toxic. First of all, mutagenicity, genotoxicity and carcinogenicity have to be absent. Therefore, *in silico* predictions for these toxicity endpoints for the leading candidates (biodegradable drug-like derivatives) of ATL were performed by employing the QSAR toxicity models summarized in Table S5 in SI. The predictions of these QSAR models are summarized in Table S10 in SI.

The predictions indicate that some of the leading candidates such as TP 207, TP 210, TP 223 and TP 238, as shown in Figure 1, are possibly neither carcinogenic, genotoxic nor mutagenic in mammals, while TP_2 295 was predicted to be a carcinogenic. Therefore, TP_2 295 will not be considered to be a leading candidate for the development of new biodegradable ATL-derived entities anymore. However, the chromosome aberration model of Leadscope software provided a positive alert for all of the leading candidates mentioned above. Therefore, the next step would be to synthesize all these shortlisted biodegradable drug-like leading candidates and test them through various experimental assays to confirm the toxicity prediction and to investigate their pharmacological potency.

Figure 1 summarizes the leading candidates which are observed to be comparatively more biodegradable, drug-like and non-toxic. However, some of these shortlisted derivatives possess non-preferred functional groups such as aldehydes (non-preferred due to their toxicological potency and adverse effect in the human body) or imines (non-preferred due to their instability). Therefore, a comprehensive study is needed for the pharmacological, pharmacokinetic and toxicological assessment of these leading derivatives.

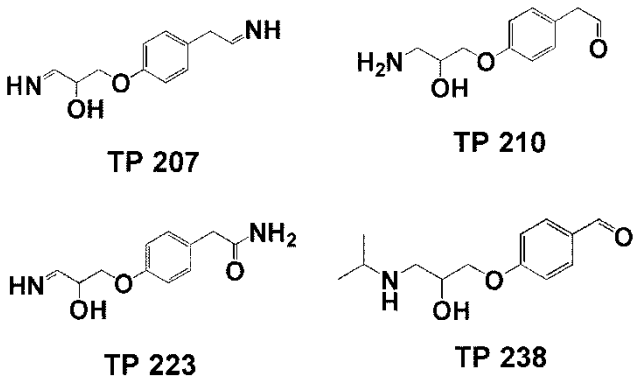


Figure 1: The shortlisted leading candidates, which were comparatively biodegradable and predicted to be drug-like, orally available, non-carcinogenic, non-genotoxic and non-mutagenic.

The limitation of this approach for re-designing ATL into biodegradable derivatives is the uncertainty of the pharmacological potency of the modified structures, which needs to be further investigated. However, a similar approach of re-designing existing pharmaceuticals was recently demonstrated for the alternative β-blocker Metoprolol.[32] This study concluded that it was possible to design new drug-like molecules of Metoprolol, which might have similar or non-inferior pharmacological properties with the additional attribute of biodegradability through small alterations of its structure during photolysis. Therefore, a thorough investigation of the pharmacological potency of the new derivatives of ATL is critically required. In addition, in the present study, photolysis was used as a method for the generation of derivatives, but other derivatisation processes (such as ozonation, fenton reaction etc.) are the possible alternatives for the future studies.

Furthermore, the approach presented here can be used to re-design existing pharmaceuticals as demonstrated, though it has to be confirmed with various other pharmaceuticals before being generalized. Further, it could be integrated into the lead optimization process of drug development as an addition to the pre-clinical development of novel pharmaceuticals. However, this was not the task of this initial work and this integration has to be explored in further studies.

Conclusions

Generally, studies like this will increase the knowledge about the role of the attachment of certain functionalities to the parent drug in order to improve its biodegradability while conserving pharmacological properties, an approach that was, in the past, neglected issue in drug development. A future goal should be to perform more of such studies with several other known pharmaceuticals in order to deepen the understanding concerning the approach as well as in order to understand the significance of the different functional groups that could alter the both biodegradability and activity of APIs.

Acknowledgement

The financial support from the German Ministry of Education and Research (NanoPharm, Project No. 03X0094C) is gratefully acknowledged. The authors also acknowledge Multicase Inc. and Leadscope Inc. for kindly providing the Case Ultra, MetaPC as well as the Leadscope QSAR software.

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Institute of Sustainable and Environmental Chemistry, Leuphana University Lüneburg, C13, DE- 21335 Lüneburg, Germany. Tel.: +49 4131 677 2893.
E-mail address: tushar.rastogi@leuphana.de, tushar1909@gmail.com (T. Rastogi), cleder@leuphana.de (C.Leder), Klaus.Kuemmerer@uni.leuphana.de (K. Kümmerer)
Electronic Supplementary Information (ESI) available: [[Experimental procedures, LC-MS/MS data and spectra of the derivatives, QSAR presiction, Biodegradation study results]. See DOI: 10.1039/c000000x/

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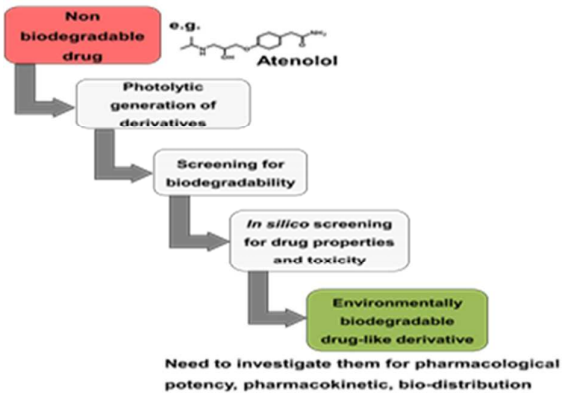

Text

Generation of new biodegradable, drug-like molecules through re-designing certain moieties from known drug molecules while preserving their pharmacophore