1
Different Roles of Carboxylic Functions in Pharmaceuticals and Agrochemicals

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1.1
Introduction

Explaining the importance of carboxylic acid and its related derivatives in medicine and crop protection is best achieved by examining the number of endogenous processes and molecules that rely on the chemical nature of this functional group. From amino acid conjugation via peptide synthesis to proteins and posttranslational protein acylation to triglycerides, bile acids, and prostanoids, it is evident that carboxylic acid, ester, and amide functions contribute to the physiology of many living systems [1]. Not surprisingly then, there exists an extensive number of active ingredients bearing such functions. Roughly 25% of all commercialized pharmaceuticals contain a CO_2H group [2]; a similar portion (25%) is reported to bear an amide [3]. A similar ratio is true for agrochemicals; at least 40% of all marketed crop protection agents bear a carboxylic function [4]. Several sets of criteria for the definition of the preferred chemical composition leading to optimal bioavailability for active ingredients, such as Lipinski's "Rule of Five" for oral drugs [5], Astex's "Rule of Three" for fragment-based lead discovery [6], and Brigg's "Rule of Three" for agrochemicals [7], contain the need for the presence of hydrogen-bond donors and hydrogen-bond acceptors for ideal drugs, a requirement that several carboxylic functions fulfill. This book chapter tries to highlight the most important roles that carboxylic functions play in pharmaceuticals and agrochemicals.

1.2
Solubilizer

The introduction of carboxylic acid into a biologically active compound positively impacts the water solubility of the compound. Acids are generally highly ionized at physiological pH values and therefore solvated to a greater degree and display more favorable aqueous solubilities than neutral molecules of similar lipophilicity do. In addition, the counterion influences solubility and

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physicochemical properties of active ingredients bearing a carboxylate [8]. The presence of charges plays a significant role in modulating solubility, lipophilicity, and thus cell permeation. However, acidic compounds are also often associated with poor permeability because they are mainly present in the deprotonated state in this pH range and cannot readily cross negatively charged lipid membranes [2]. Such solubilizing effects are even more pronounced in the presence of two or more ionized groups, especially zwitterions. For example, because of the pH gradient unique to the gastrointestinal tract, it is the piperazine moiety in the quinolone antibiotic ciprofloxacin that governs the charge state within the acidic upper gastrointestinal tract (gastric region). The elevation of the pH value in the subsequent proximal intestine results in the zwitterionic state **2** (Figure 1.1) [1, 9]. In crop protection, carboxylic acids are known for their pronounced phloem mobility, which includes the basipetal movement of an active ingredient from the leaves to the roots within a plant.

Further proof for the effect of carboxylic acid functions on the solubility of pharmaceuticals is found in the history of antihistaminic drugs [10]. Several first-generation derivatives, such as hydroxyzine (**3**), were rather lipophilic compounds, which were able to cross the blood–brain barrier and had a sedating effect because they were no substrates for P-glycoproteins (P-gps). Owing to the replacement of the hydroxyl function by a carboxylic acid, cetirizine (**4**), a second-generation antihistaminic, is less lipophilic and therefore a P-gp substrate that limits the CNS exposure (Figure 1.2) [11, 12].

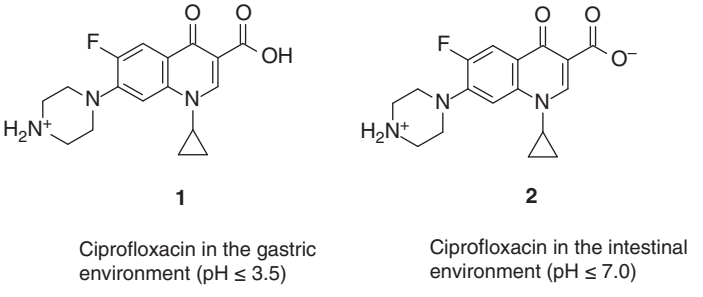


Figure 1.1 Ionization state of ciprofloxacin in the gastrointestinal tract [1].

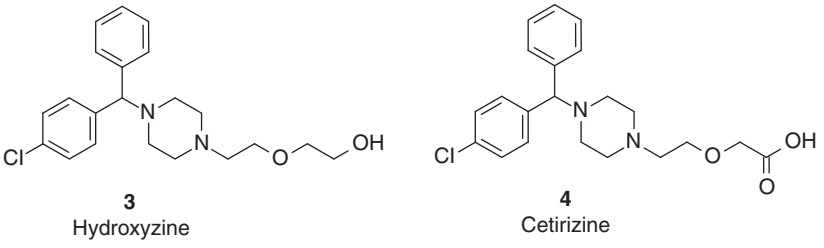


Figure 1.2 Increasing solubility of antihistaminic compounds by carboxylic acids.

1.3 Pharmacophore

A pharmacophore is the group of atoms and, therefore, also the ensemble of steric and electronic features of an active ingredient ensuring optimum molecular interactions with an enzyme and responsible for triggering or blocking its biological response [13]. The acidity of carboxylic acids, combined with the ability of all carboxylic acid derivatives to establish relatively strong electrostatic interactions and single or bifurcated hydrogen-bond bridges with the protein target, conferring both binding affinity and specificity to the drug–target interaction, is the reason that carboxylic acid functions are often the key determinant of pharmacophores [2]. Figure 1.3 shows only four examples of many pharmaceuticals and agrochemicals that rely on the presence of a carboxylic function in their pharmacophore. The terminal carboxylate of atorvastatin (**5**), a blood cholesterol-reducing blockbuster drug, forms a salt bridge with Lysine735 of its target enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase [14]. The carbonyl oxygen atom of the carboxylic acid function in the nonsteroidal anti-inflammatory acid flurbiprofen (**6**) builds a hydrogen-bond bridge with the phenol group of Tyrosine355 of cyclooxygenase-1 [15]. The broad-spectrum activity of azoxystrobin (**7**), the world's biggest selling fungicide, is due to the interaction of the carbonyl oxygen atom of its ester function with an amine proton of Glutamine272 in cytochrome bc1, the complex III of the respiratory

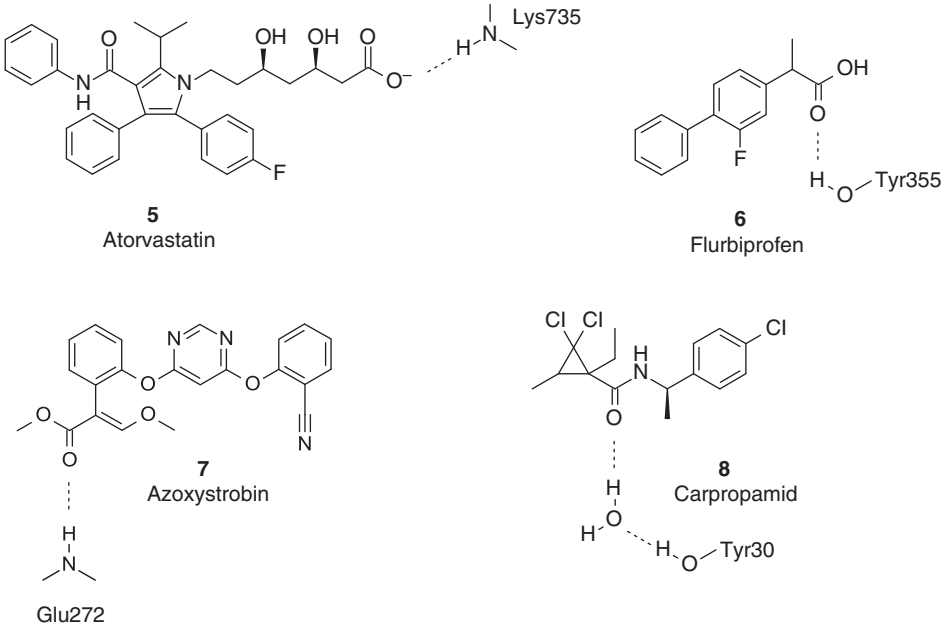


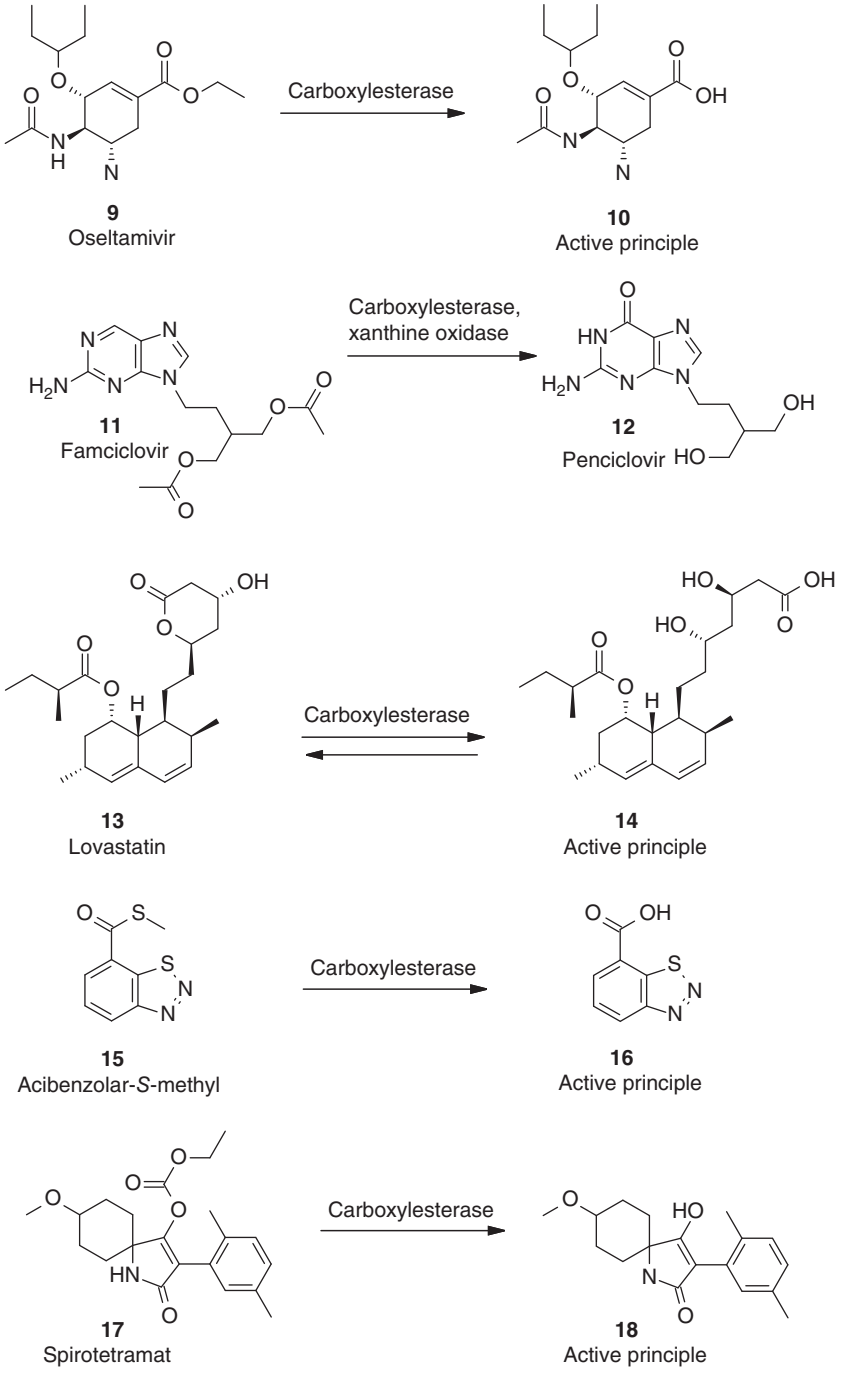
Figure 1.3 Examples for pharmacophores of active ingredients based on carboxylic acids, esters, and amides.

chain in the mitochondria of the fungi [16]. The carbonyl oxygen of the amide function of carpropamid (**8**), a melanin biosynthesis-inhibiting rice fungicide, accepts a hydrogen bond from a water molecule coordinated to Tyrosine30 of scytalone dehydratase [17].

1.4 Prodrug

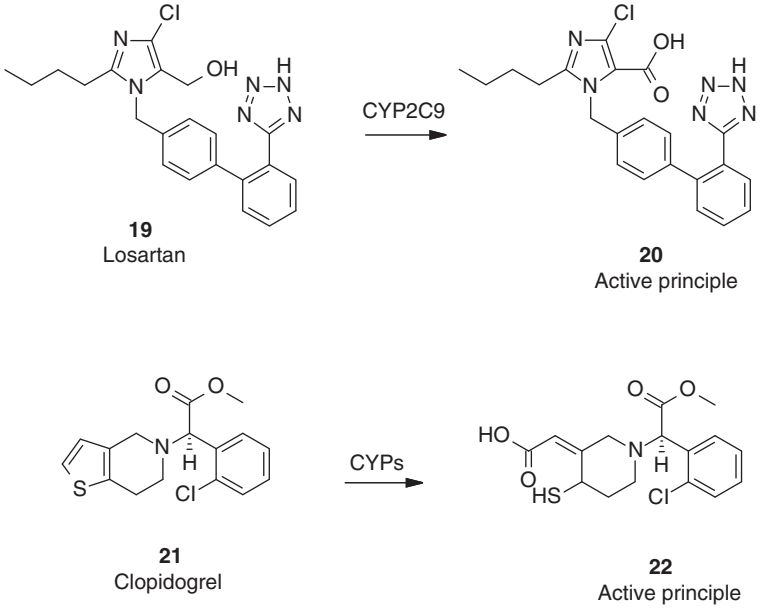
A carboxylic acid group, being usually ionized in the physiological pH range, adds to the hydrophilicity and polarity of the active ingredient. As a result, a large number of biologically active carboxylic acids display unfavorable pharmacokinetic properties such as low bioavailability because of limited uptake. Thus, the improvement of pharmacokinetic properties can be achieved by transferring the drug into a prodrug. A prodrug is a compound that itself is not biologically active, but is converted by enzymes, heat, moisture, or UV light into an intrinsically active derivative. Because of the ubiquitous availability of esterases and peptidases in many species, including human, the *in vivo* hydrolysis of esters and related carboxylic functions to the corresponding acids is one of the classical prodrug cases [18–23]. Such ester derivatives are called carrier prodrugs, because they often facilitate the adsorption and distribution of pharmaceuticals or agrochemicals to the desired location, followed by release of the active principle by cleavage of the carrier group through a hydrolytic reaction [19]. The ethyl ester in oseltamivir (**9**) increases the oral bioavailability in humans from less than 5% for the carboxylic acid parent **10** to 80% and, therefore, allows this anti-influenza antiviral agent to be administered orally [18, 20, 21]. Ester prodrugs that release a biologically active alcohol species instead of a carboxylic acid–containing drug are known to a lower content. The reason for this may be that the improvement of pharmacokinetic features is generally greater when masking the highly polar carboxylate rather than the less polar hydroxyl group [22]. An important example is the antiherpes virus agent famciclovir (**11**), which delivers *in vivo* penciclovir (**12**) by enzymatic ester cleavage and purine oxidation. The oral bioavailability of 4% for penciclovir is increased to 75% for famciclovir [20]. A special case of ester prodrugs are lactones, which are formed by intramolecular cyclization of hydroxyl acids and which liberate this function after cleavage. An example is the reversible ring opening of the lactone in 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor lovastatin **13** to its β-hydroxy acid open form **14** [21, 22]. The carbothioic acid *S*-methyl ester in the plant activator acibenzolar-*S*-methyl (**15**) [24] and the carbonate function in the insecticide spirotetramat (**17**) [25] are further examples of carboxylic acid derivatives, which can be employed as carrier prodrugs, and also carbamates have been used in this context (Scheme 1.1) [18, 19].

Another kind of prodrugs are bioprecursors, which deliver the biologically active compound via an *in vivo* transformation without the need to cleave a carrier moiety. Also here, the formation of carboxylic acids seems to play an important role. The angiotensin II receptor antagonist losartan (**19**), which



Scheme 1.1 Some examples of ester, carbonate, and carbothioic *S*-ester prodrugs.

is used in antihypertensive medication, can be seen as bioprecursor prodrug, because its primary alcohol is oxidized *in vivo* by the cytochrome P450 enzyme CYP2C9 to the carboxylic acid **20**, which represents the active principle [18, 19, 21]. In addition, the antithrombotic drug clopidogrel (**21**) is metabolized by cytochrome P450 enzymes to its active form **22** containing a carboxylic acid (Scheme 1.2) [18, 19].



Scheme 1.2 Losartan (**19**) and clopidogrel (**21**) as bioprecursors of carboxylic acid derivatives.

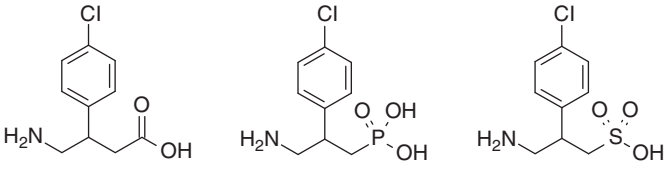
1.5 Bioisosteric Replacement

We have seen so far that carboxylic functions are often important constituents of active ingredients; however, the presence of such groups can also be responsible for significant drawbacks, such as metabolic instability, toxicity, and limited passive diffusion across membranes. To avoid some of these shortcomings while retaining the desired attributes of the carboxylic moiety, its replacement by a carboxylic bioisostere might be considered. The concept of bioisosterism is based on the notion that the exchange of single atoms or whole groups that exhibit similar size, shape, charge distribution, and physicochemical properties creates a new compound with similar biological properties to the parent active ingredient [13]. The same type of strategy can also be applied effectively for other purposes, for example, to increase the potency or selectivity of a biologically active compound or

to create own intellectual property. However, the outcome of any isosteric replacement cannot be readily predicted as the result is generally found to be dependent on particular properties of the drug and its target. As a result, screening of a panel of different isosteres is typically required; the more isosteres of one defined functional group are known, the higher the chances to find one with full preservation or even enhancement of the desired biological activity. As a matter of fact, several groups with an isosteric relationship to carboxylic functions are known, especially surrogates of carboxylic acids are really high in number [26, 27]. For example, several organic heteroatom acids, such as phosphonic acids, phosphinic acids, and sulfonic acids, are proven replacements of carboxylic acids, as demonstrated by the phosphonic acid phaclofen (**24**) and the sulfonic acid saclofen (**25**), two γ-aminobutyric acid $(GABA)_B$ antagonistic bioisosteres of the $GABA_B$-agonistic antispasmodic drug baclofen (**23**) (Figure 1.4) [26].

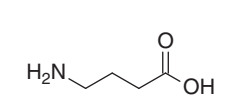
Another group of well-established bioisosteric functions of the carboxylic acid group are certain heterocycles, such as hydroxyisoxazole [28], hydroxyisothiazoles [29], thiadiazolidinediones [30], oxadiazolones [31], and of course especially tetrazoles [32]. The tetrazole moiety in losartan (**19**) mimics a carboxylic acid function. 3-Hydroxyisoxazole has been extensively applied as carboxylic acid bioisostere in the case of GABA and glutamate signaling drugs, which mimic GABA and glutamic acid, two essential neurotransmitters in the mammalian central nervous system [26, 29]. The $GABA_A$ agonists muscimol (**27**) and gaboxadol (**28**) are close analogs of GABA (**26**); their hydroxyisoxazole moiety resembles the acid group of **26** [26]. The naturally occurring heterocyclic amino acid ibotenic acid (**30**) and its synthetic analog thioibotenic acid (**31**) are hydroxyisoxazole and hydroxyisothiazole bioisosteres of glutamic acid (**29**), and, therefore, also potent glutamate receptor ligands [29]. The thiazolidinedione in the antidiabetic drug rosiglitazone (**33**) is probably required as carboxylic acid surrogate, because several other compounds with comparable activity against the targeted peroxisome proliferator-activated receptor, such as ragaglitazar (**32**), bear an acid function in the same region of the molecule (Figure 1.5) [30].

Several bioisosteric groups of other carboxylic functions, such as esters and amides, are clearly linked to related acid surrogates. Because 5-substituted tetrazoles are acid replacements, logically 1,5-disubstituted tetrazoles are effective bioisosteres for the amide bond [32]. In addition, the ability of 1,2,4-oxadiazoles to function as heterocyclic surrogate of the amide bond [33] is linked to the known

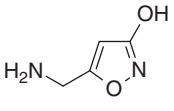


23 Baclofen **24** Phaclofen **25** Saclofen

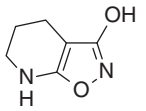
Figure 1.4 Baclofen (**23**) and its bioisosteres phaclofen (**24**) and saclofen (**25**) [26].



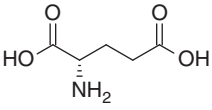
26
γ-Aminobutyric acid (GABA)



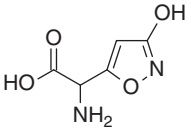
27
Muscimol



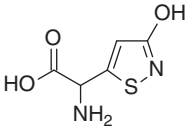
28
Gaboxadol



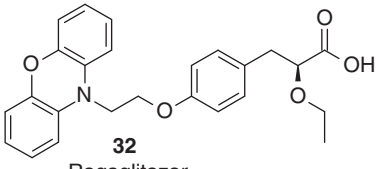
29
(S)-Glutamic acid



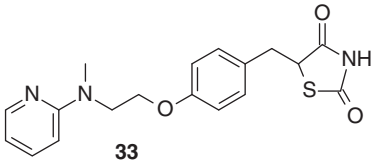
30
Ibotenic acid



31
Thioibotenic acid



32
Ragaglitazar



33
Rosiglitazone

Figure 1.5 Heterocyclic bioisosteres of carboxylic acid derivatives.

track record of related 1,2,4-oxadiazol-5-ones as good acid replacement [31]. As 2,2,2-trifluoroethan-1-ol is a highly viable carboxylic acid bioisostere [26], it is no surprise that α-trifluoromethyl-substituted amines can mimic amides [34].

1.6 Scaffold

Amides as stable and relatively neutral carboxylic acid derivatives play an important role in providing a three-dimensional scaffold required for optimum binding of the active ingredient to the target enzyme by linking elaborated acid and amide moieties together. Not only the potential of the amide group as hydrogen-bond donor as well as acceptor is an advantage, another reason for the vast amount of amides among pharmaceuticals and agrochemicals is their straightforward synthetic accessibility from carboxylic acids, chlorides, or esters with appropriate amines. The tyrosine kinase inhibitor imatinib (**34**) [35], the dopamine antagonist amisulpride (**35**) [36], the cellulose synthase inhibitor mandipropamid (**36**) [37], and the succinate dehydrogenase inhibitor (SDHI) isopyrazam (**37**) [38] are four examples of many pharmaceuticals and agrochemicals relying on an amide bridge (Figure 1.6).

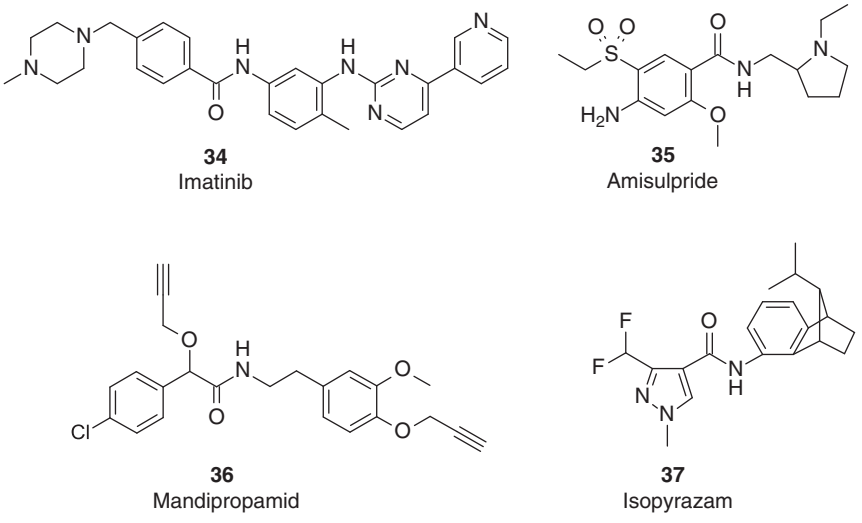


Figure 1.6 Four active ingredients, which rely on an amide function linking important parts of the molecule.

1.7 Conclusion

Carboxylic acid–containing drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), β-lactam antibiotics, and statins, have revolutionized the progress in the medical treatment of pain and diseases in the twentieth century. The history of chemical weed control and therefore the start of industrial agriculture would be unimaginable without carboxylic acid herbicide classes such as auxin mimics and sulfonylureas. Two out of the three currently most important fungicide classes, the inhibitors of complex II and complex III of the fungal respiratory chain (SDHIs and quinone outside inhibitor (QoI)s), are based on carboxylic functions. All these facts are proof for the fundamental importance of carboxylic functions for pharmaceuticals and agrochemicals.

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