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Review Article

Carboxylic Acid Bioisosteres in Medicinal Chemistry: Synthesis and Properties

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Lead optimization represents the tedious process of fine-tuning lead compounds from biologically active hits to suitable drug candidates for clinical trials. By chemically modifying a hit structure, an improved compound can be obtained in terms of activity, selectivity, and pharmacokinetic ADME (absorption, distribution, metabolism, and excretion) properties. The carboxylic acid moiety is known to be a crucial functionality in many pharmaceutically active compounds. Despite its common use as a key functionality in drugs, its presence in a lead molecule is often associated with poor pharmacokinetic properties and toxicity. In this literature overview, we discuss how the shortcomings of a carboxylic acid can be circumvented by replacing this functionality with bioisosteres. In this way, the positive aspects of this moiety, such as its activity, for example, by virtue of its capacity to form hydrogen bonds, can be maintained or even improved. To that end, we provide an overview of the most promising carboxylic acid bioisosteres and discuss a selection of synthetic routes towards the main functionalities.

1. Introduction

Carboxylic acids are often called privileged structures for the binding of drugs to their target as they engage in specific charge-charge interactions [1]. In 2010, over 450 drugs containing a carboxylic acid moiety have been marketed worldwide, including among others nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, anti-coagulants, and cholesterol-lowering drugs (e.g., statins) [2]. This is not surprising since most of the corresponding protein targets have natural substrates that contain (carboxylic) acids, such as phosphorylated peptides, fatty acids, DNA, and RNA [1]. Carboxylic acids have a planar geometry and a pK_a value of around 5, depending on the neighboring groups in the structure, which means that at the physiological pH of 7.4, carboxylic acids are dissociated to carboxylate ions. This improves the overall water solubility of the drug as well as their ability to engage in relatively strong electrostatic interactions such as hydrogen bonds and dipole interactions [1, 3]. However, the presence of a carboxylic acid functional group in a drug or drug candidate may elicit undesired effects in terms of toxicity and ADME properties. The low lipophilicity of carboxylic acids can limit the permeability of the pharmaceutical agent across biological membranes, while the metabolic instability of the carboxylic acid moiety can lead to idiosyncratic toxicity and rapid elimination of the drug through rapid biotransformation or low bioavailability.

Both endogenous metabolites in a human's body and xenobiotic drugs can have a carboxylic acid functionality in their structures, which is beneficial for the interactions of drugs with their target molecule. A consequence thereof is that in biological systems, xenobiotic drugs are often metabolized via the same pathways as the endogenous metabolites [4]. The metabolites of carboxylic-acid-containing drugs are chemically reactive and bind covalently to endogenous macromolecules, such as proteins or DNA, which

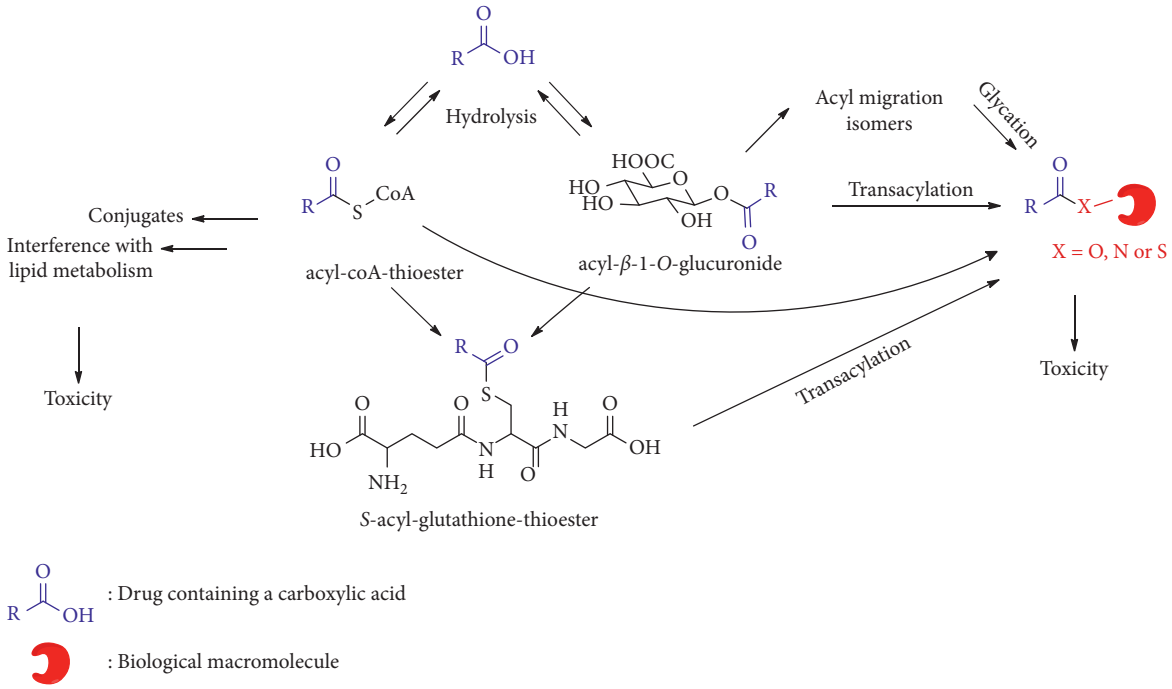


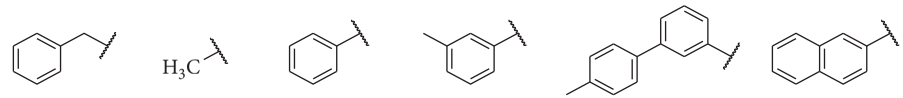
Figure 1: Overview of metabolic pathways of carboxylic-acid-containing drugs leading to idiosyncratic toxicity.

causes disruption of cellular functioning, resulting in haptenation, protein dysfunction, and disturbance in cell signaling, leading to a series of adverse side effects [5]. This has even led to the withdrawal of some already marketed drugs such as ibufenac and benoxaprofen for causing liver toxicity and zomepirac that could induce anaphylaxis [6]. The different routes for metabolization of carboxylic acids are summarized in Figure 1. The quantitatively most important route is glucuronidation, leading to reactive acyl glucuronides (AGs) that, directly or after acyl migration, are susceptible to nucleophilic attack by biological macromolecules such as proteins or DNA [7]. Besides glucuronidation, carboxylic acid-containing drugs can be metabolized by fatty coenzyme A (CoA) ligases to acyl-CoA thioester derivatives, which are even more reactive than AGs. Both AGs and acyl-CoA thioesters will also form *S*-acyl-glutathione thioesters (SGs) with the endogenous tripeptide glutathione, which are reactive as well. Furthermore, after subsequent reactions, CoA conjugates can also interfere with endogenous lipid metabolism [8, 9].

Unfortunately, not all mechanisms of carboxylic-acid-containing drugs that lead to idiosyncratic toxicity are known yet. As a result, it is difficult to predict the potential bioactivation of the carboxylic-acid-containing drugs, and therefore, during drug design, the carboxylic acid moiety needs to be handled as a "structural alert." The drawbacks of a carboxylic acid moiety in a lead compound, such as its potential for toxicity and low lipophilicity, can be obviated through replacement by suitable surrogates, called isosteres, that do not carry those unwanted properties. Bioisosteres are structurally related compounds, that is, single atoms, groups, or even whole molecules, that exhibit broadly similar biological activity [10]. They have similar volume, shape, and/or physicochemical properties. A distinction can be made between classical and nonclassical isosteres. Classical isosteres are functionalities that do not differ much from the original moiety in terms of valence electrons and size, while nonclassical isosteres may differ quite drastically from the original group with regard to sterics and the number of atoms [11]. Although the term "bioisostere," in the strict sense, is used for nonclassical isosteres and "isostere" for both classes, "bioisostere" will be used in this manuscript to assign both classes, as is often done in the literature.

The volume, shape, and charge distribution of the carboxylic acid bioisostere are the critical parameters that determine the strength of its interactions with the binding site, whereas lipophilicity and acidity are known to influence many key ADME properties of the drug [3, 12]. Unfortunately, although bioisosteres exhibit similar electron environments, the success of a bioisosteric replacement depends on the ability of the binding site to adjust to the surrogate structure. Since it is not always certain whether bioisosteric replacements will provide the desired improvements in properties, experimental data detailing the structure-property relationships (SPR) are useful, especially since the systematic assessment of carboxylic acid bioisosteres of the lead compound is often time-consuming and expensive. Using SPR, the physiochemical properties (Table 1) of a series of alternative carboxylic acid structures can be screened, from which the most promising bioisosteres can be selected for subsequent testing. Also, the historical success rate of a bioisostere, the synthetic accessibility, and the chemical and medicinal intuition influence this selection process [13]. Even though the proven effectiveness of a

Table 1: Experimental or calculated[c] properties of test compounds containing different carboxylic acid bioisosteres.

R: 

R^1 R^2 R^3 R^4 R^5 R^6

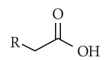
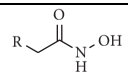
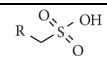
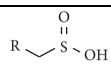
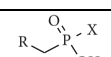
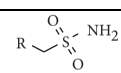
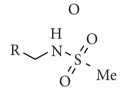
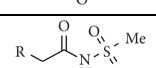
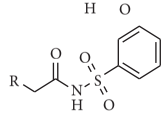
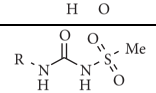
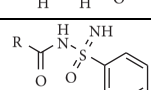
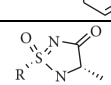
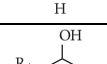
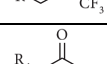
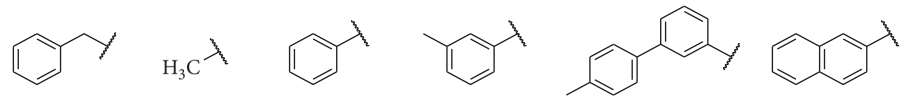
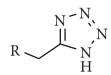
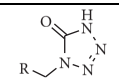
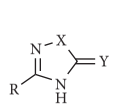
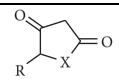
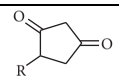
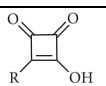
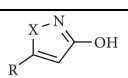
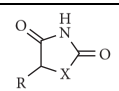
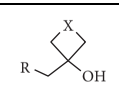
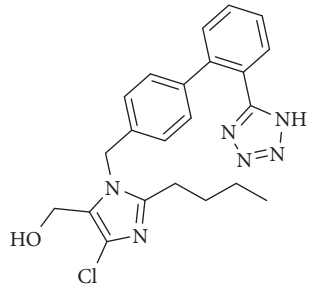
Isostere	Structure	R	pK_a	$logD_{7.4}$	LogP	$logP_{app}$	Ref
Carboxylic acid		R^1	4.64	−0.49 ± 0.19	ND	−5.79 ± 0.10	[13]
		R^2	4.76	−1.65[c]	ND	ND	[3]
		R^3	3.96	−1.5	ND	ND	[14]
		R^4	4.13 ± 0.01	ND	1.98 ± 0.04	ND	[15]
		R^5	4.0	ND	ND	ND	[16]
		R^6	6.52	ND	1.09	ND	[17]
Hydroxamic acid		R^1	8.18	0.71	ND	−5.30	[13]
Sulfonic acid		R^1	<2	−1.45	ND	−7.42	[13]
Sulfinic acid		R^1	2.1	−1.30	ND	ND	[13]
Phosphonic acid (X = OH)		R^1	2.34	−1.14	ND	−7.03	[13]
Phosphinic acid (X = H)		R^1	1.98	−1.44	ND	−7.77	[13]
Sulfonamides		R^1	10.04	0.96	ND	−5.67	[13]
		R^1	>12	1.42	ND	−4.98	[13]
Acyl sulfonamides		R^1	4.94	−1.02	ND	−6.46	[13]
		R^1	4.49 ± 0.04	−0.09	2.67 ± 0.01	−5.79	[18]
Sulfonylurea		R^1	5.04	−1.23 ± 0.06	ND	−6.61 ± 0.20	[13]
Acyl sulfonimidamide		R^3	7.38	1.2	ND	ND	[14]
Cyclic sulfonimidamide		R^5	6.0	1.6	ND	−4.18	[16]
Trifluoromethyl carbinol		R^2	ND	1.03[c]	ND	ND	[3]
Trifluoromethyl ketone		R^2	ND	0.25[c]	ND	ND	[3]

Table 1: Continued.

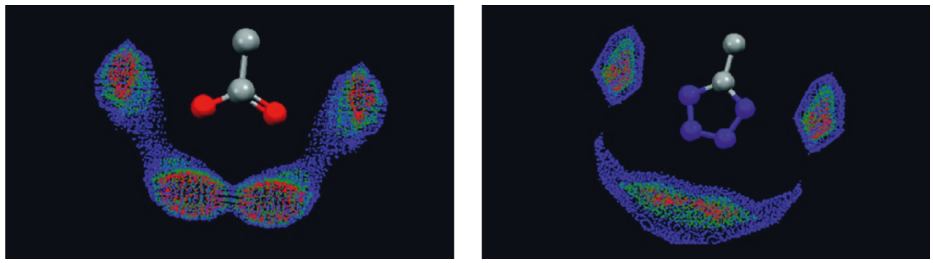
Isostere	Structure	R	pK_a	$logD_{7.4}$	LogP	$logP_{app}$	Ref
	R: 	R^1	5.09	-0.25 ± 0.10	ND	-6.33 ± 0.15	[13]
		R^2	ND	-0.37^c	ND	ND	[3]
Tetrazole		R^3	4.20	−1.0	ND	ND	[14]
		R^4	4.73 ± 0.03	ND	1.07 ± 0.01	ND	[15]
		R^5	4.0	1.3	ND	−5.14	[16]
Tetrazolone		R^6	6.36	ND	0.79	ND	[17]
5-Oxo-1,2,4-oxadiazole (X = O, Y = O)		R^1	5.73	0.32	ND	−5.91	[13]
		R^4	5.12 ± 0.04	ND	1.14 ± 0.04	ND	[15]
5-Oxo-1,2,4-thiadiazole (X = S, Y = O)		R^1	6.50	1.66	ND	−4.94	[13]
		R^4	5.99 ± 0.09	ND	2.22 ± 0.08	ND	[15]
5-Thio-1,2,4-oxadiazole (X = O, Y = S)		R^1	3.58	−0.25	ND	−6.49	[13]
		R^4	3.19 ± 0.02	ND	2.39 ± 0.02	ND	[15]
Tetronic acid (X = O)		R^2	ND	-0.06^c	ND	ND	[3]
Tetramic acid (X = H)		R^1	6.08	−0.35	ND	−5.60	[13]
Cyclopentane-1,3-diones		R^1	4.01	−0.70	ND	−6.67	[13]
Cyclopentane-1,2-diones		R^1	8.88	1.85	ND	−4.94	[13]
Squaric acid		R^1	<2	−0.84	ND	ND	[13]
3-Hydroxyisoxazole (X = O)		R^1	5.36	0.46	ND	−5.33	[13]
3-Hydroxyisothiazole (X = S)		R^2	ND	1.25^c	ND	ND	[3]
2-4-Oxazolidinedione (X = O)		R^1	5.86	−0.16	ND	−5.61	[13] [13]
2,4-Thiazolidinedione (X = S)		R^1	6.19	1.07 ± 0.03	ND	-5.06 ± 0.06	[19] [19]
Oxetan-3-ol (X = O)		R^1	>12	2.07	ND	−5.08	[19]
Thietan-3-ol (X = S)		R^1	>12	2.99	ND	−4.88	[19]
Thietan-1-oxide-3-ol (X = SO)		R^1	>12	1.22	ND	−5.21	[19]
Thietan-1,1,-dioxide-3-ol ($X = SO_2$)		R^1	9.31	1.24	ND	−4.91	[19]

Note: pK_a determined by capillary electrophoresis (higher values > less acidic); $logD_{7.4}$ determined by LC-MS (more positive values > higher lipophilicity); log P = octanol-water partition coefficient measured by Sirius T3 apparatus; and $logP_{app}$ = log of the apparent permeability coefficient experimentally determined in a parallel artificial membrane permeability assay (PAMPA; less negative values > higher permeability). Unless[c]: log $D_{7.4}$ calculated using Pipeline Pilot version 8.0 (Accelerys, Inc., San Diego, USA) [20]. ND: not determined.



Losartan

Figure 2: Structure of losartan.



(a) (b)

Figure 3: IsoStar and isoGen plots for the hydrogen bond environments of carboxylate (a) and tetrazolate (b), respectively. The plots highlight the key H-bond interaction areas and their preferred direction to the carboxylate and tetrazolate. The contour colors denote the regions preferred by the O–H and N–H donors whereby red denotes the most preferred region.

bioisostere in a specific biological setting does not predict its effectiveness in another biological setting, it is still worth testing a moiety that has been successful in a variety of different settings, such as the tetrazole moiety, a common carboxylic acid bioisostere [21].

2. Carboxylic Acid Bioisosteres

In this overview, a selection of carboxylic acid bioisosteres that have the greatest probability to improve drug-like properties of a lead compound will be discussed, as a complement to and extension of the seminal overview provided by Ballatore et al. [3]. This selection is based on several pharmacokinetic properties of the bioisostere relative to the corresponding compound that contains carboxylic acid functionality. These properties include acidity, lipophilicity, and permeability derived from SPR studies and are displayed in Table 1 in terms of pK_a value, the distribution coefficient between *n*-octanol and aqueous buffer at pH 7.4 ($logD_{7.4}$) or the octanol-water partition coefficient (LogP), and the permeability coefficient ($logP_{app}$), respectively [13]. These properties depend however on the neighboring group. Therefore, a given bioisostere should only be compared to the carboxylic acid that bears the same scaffold (R group; Table 1).

Lipophilicity and acidity influence many key ADME properties as well as toxicity. High lipophilicity ($logD_{7.4}$ more positive values) results in great permeability ($logP_{app}$ less negative values) of the drug through cell membranes and, consequently, results in higher potency. However, the ionization of the molecule also influences the permeability of the drug as neutral molecules diffuse more easily through the lipophilic membranes. Therefore, the lipophilicity is quantified at physiological pH as $logD_{7.4}$. Nevertheless, if the drug is too lipophilic, the compound has an increased likelihood to bind unwanted targets, resulting in toxicity as well as poor solubility and high metabolic clearance [12]. Thus, a balance must be found in terms of lipophilicity.

Besides improved lipophilicity, the selection criteria for bioisosteres are improved permeability and/or reduced toxicity as compared to carboxylic acids. Hydroxamic acids, known for their metal-chelating properties, have led to some successes as carboxylic acid bioisosteres [22–25]. However, although predicted to have both higher lipophilicity and permeability (Table 1), hydroxamic acids are said to have low bioavailability and to suffer from toxicity due to glucuronidation and mutagenicity [26–28]. Drugs containing thiazolidinedione (TZD) and oxazolidinedione (OZD) rings are reported to induce idiosyncratic adverse reactions as well, including liver toxicity. Indeed, the first marketed thiazolidinedione drug, troglitazone, was withdrawn from the market [3]. The thiazolidinedione ring is hypothesized to undergo an oxidative ring-opening reaction by cytochrome P450 that results in the formation of electrophilic metabolites [3, 29]. Squaric acids and their derivatives, squaramides, squaramines, and squarates, have also been successfully employed in some settings as carboxylic acid surrogates but contain a very reactive structure and therefore

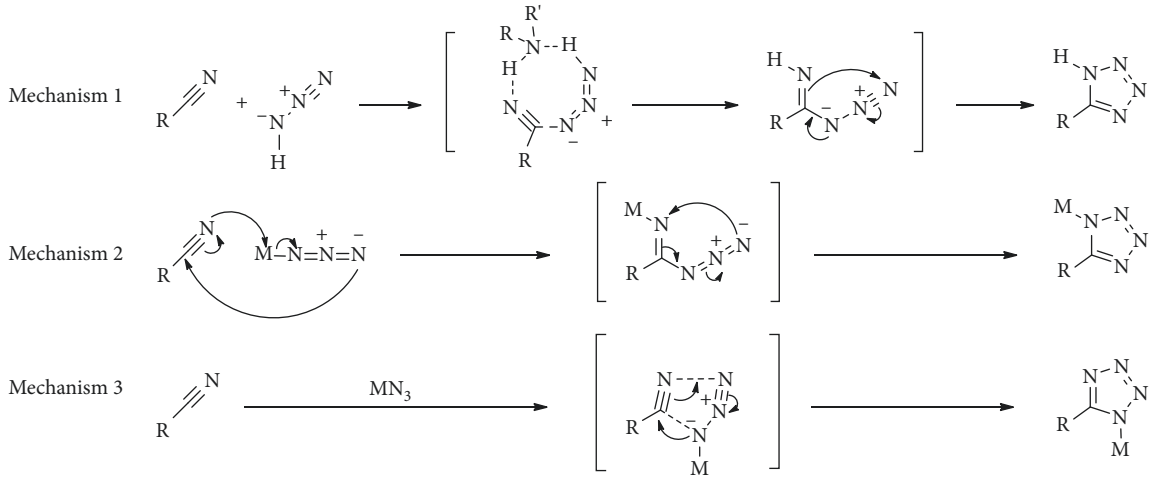


Figure 4: Three possible mechanisms whereby the addition of an inorganic azide to nitrile results in a tetrazole.

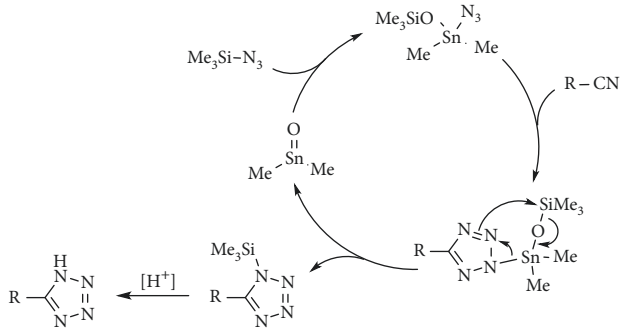


Figure 5: Proposed mechanism of tetrazole formation using trialkylsilyl azide.

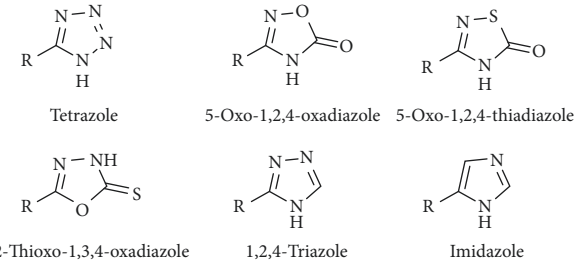


Figure 6: Overview of some aromatic heterocyclic bioisosteres of the carboxylic acid moiety.

are usually associated with toxicity, a lack of selectivity, and thus promiscuity towards several targets [30–32]. Meanwhile, phosphonic, phosphinic, sulfonic, and sulfinic acids are nonplanar and relatively highly acidic, leading to increased hydrophilicity and decreased permeability (Table 1) [33]. Nonetheless, these carboxylic acid bioisosteres can be of importance when, for example, cell penetration is not a requirement or when the design of derivatives that do not enter the CNS is desired. As a recent example, phosphonate analogs of 2-oxoglutaric acid and 2-oxoadipic acid have been shown to elicit selective inhibition of 2-oxoglutarate and 2-oxoadipate dehydrogenases [34].

3. Tetrazoles

The 5-substituted 1*H*-tetrazole is the best known and the most frequently used bioisostere of a carboxylic acid functionality. This moiety is found in more than 20 FDA-approved drugs that exhibit various anti-bacterial, anti-asthmatic, anti-cancer, anti-fungal, anti-hypertensive, anti-malarial, anti-tubercular, or anti-viral properties [35–37]. The most successful example of a bioisosteric replacement of the carboxylic acid moiety concerns the anti-hypertensive drug losartan (Figure 2), an antagonist of the angiotensin II type 1 receptor (AT_1) [38, 39]. More recent examples in preclinical studies are inhibitors of inflammatory kinases for the treatment of obesity and protein tyrosine phosphatase 1B inhibitors and G-protein receptor 40 (GPR40) inhibitors for the treatment of diabetes, where the introduction of a tetrazole improved the inhibitory activity of the lead compound [40–42]. Generally, tetrazoles are considered to be more lipophilic than carboxylic acids while having similar acidity (pK_a 4.5–4.9 vs. 4.2–4.4, respectively), as evidenced by SPR studies (Table 1) and researched by Hansch and Leo, who have shown that anionic tetrazoles are almost 10 times more lipophilic than corresponding carboxylates [43]. However, according to SPR studies (Table 1), the increased lipophilicity of tetrazoles does not lead to enhanced permeability of the moiety in contrast to the carboxylic acid [13]. This difference may be related, at least in part, to the fact that compounds bearing tetrazoles can establish considerably stronger hydrogen bond (HB) interactions compared to the corresponding compounds containing carboxylic acids. Stronger HB results in higher desolvation energies, and therefore, tetrazoles could exhibit lower permeability [13, 44, 45]. On the other hand, the stronger HB of the tetrazole moiety may improve the binding affinity of the compound for its receptor.

The tetrazole functionality is a typical example of nonclassical bioisosterism. It bears no resemblance to a

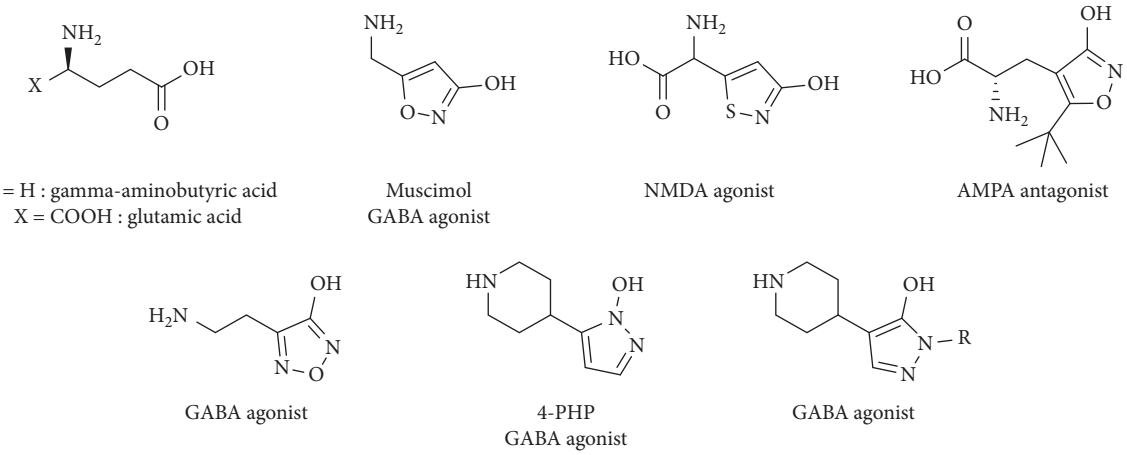


Figure 7: Structures of GABA agonists and antagonists.

carboxylic acid moiety in terms of the number of atoms, electron populations, electronic charges, or even volumes. Nevertheless, they share comparable average electron densities and electrostatic potentials [46]. Also, Allen et al. demonstrated that the HB environments of tetrazoles and carboxylic acids and their deprotonated species are topologically and energetically the same (Figure 3) [21]. Both the carboxylic acid and tetrazole functionalities exhibit a planar structure and are ionized at physiological pH [47]. The tetrazole moiety is able to stabilize its negative charge through delocalization around the ring, which results in the charge being distributed over a greater molecular surface area in contrast to carboxylic acids, where the negative charge is delocalized between two oxygen atoms [29, 48, 49]. However, depending on the local charge density at the interface, this is not always favorable for the binding interactions with the target [48]. Therefore, the binding affinity of a carboxylic acid-containing compound is not always enhanced by bioisosteric replacement with a tetrazole functionality. But when it does, this is probably due to the stronger HB interactions and to the high density of nitrogen atoms in the ring that provide more opportunities to form HB or π-stacking interactions with the interface [50]. Also, proteins have been shown to be able to adopt their conformation in order to accommodate the larger tetrazole moiety whose HB environment extends further by approximately 1.2 Å [21]. Finally, another major advantage of tetrazoles over carboxylic acids is that they escape many biological metabolic degradation pathways. Nevertheless, tetrazoles are susceptible to glucuronidation, but the resulting *N-β*-glucuronides are less reactive and allow the tetrazole-bearing drugs, by excretion and reabsorption, to exhibit longer half-life times [51, 52].

3.1. Synthesis of 5-Substituted 1H-Tetrazoles. Almost all methods to synthesize 5-substituted 1*H*-tetrazoles entail the addition of an azide ion to organic nitriles. In the earliest method, as reported by von Braun and Keller, the azide ion was added to organic cyanides under severe reaction conditions in the form of hydrazoic acid (HN_3) in the presence of

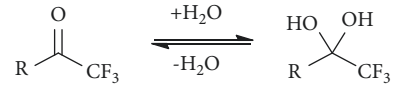


Figure 8: Hydration of trifluoromethyl ketones.

concentrated sulfuric acid [53]. A more convenient route entails the addition of an inorganic azide, sodium azide, to nitrile, generating the toxic and explosive hydrazoic acid only in situ [46, 54, 55]. The mechanism through which azide adds to a nitrile resulting in a tetrazole has been debated for a long time. A likely end to this debate is to accept that the reaction mechanism is different for different azide species (Figure 4). When a proton is available, for example, by the addition of ammonium chloride with sodium azide resulting in an ammonium azide, the proton activates the nitrile, hereby facilitating the azide attack on the carbon of the nitrile (Mechanism 1, Figure 4) [56]. In the other cases, without acid catalysis, the reaction proceeds either via a two-step mechanism (Mechanism 2, Figure 4) or a concerted [2 + 3] cycloaddition (Mechanism 3, Figure 4) [57]. Evidence was found for both mechanisms, but eventually, the actual transition states of the two-step and concerted mechanisms turned out to be almost identical to each other. Only with strong electron-withdrawing groups on the nitrile functionality, the intermediate of the two-step mechanism could be evinced [55]. The more electron-poor the nitrile is, the easier sodium azide reacts without additional reactants under mild conditions [58].

By the addition of a stoichiometric amount of $ZnBr_2$, the activation energy of the reaction is lowered, and thereby, the required reaction temperature is also lowered to 70–80°C. According to Himo et al., zinc acts as a Lewis acid and coordinates to the nitrile substrate [59, 60]. This protocol can be run in water as a solvent despite the insolubility of the starting product. It minimizes the risk of liberating hydrazoic acid, and usually after the reaction, only simple acidification is all that is needed to provide the pure tetrazole products. However, completion of the reaction can take some days, and the subsequent purification can be difficult when the end-product tetrazole is extremely nonpolar [59].

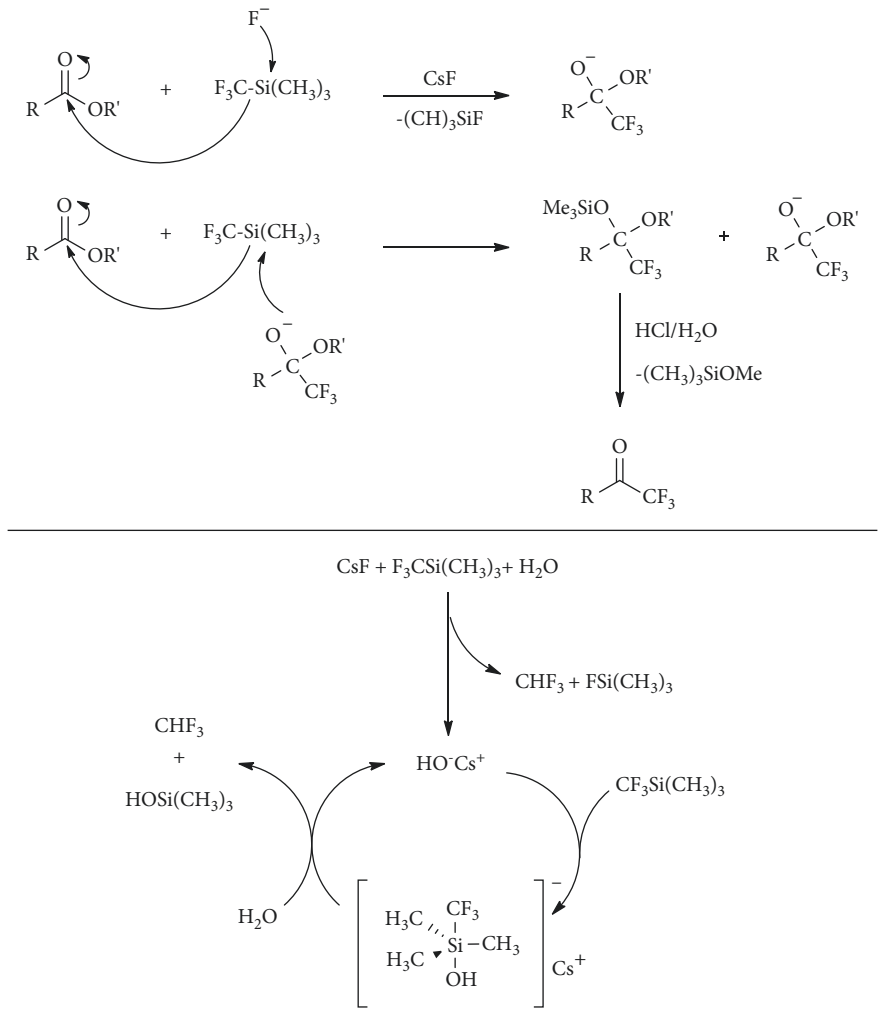


Figure 9: Mechanism of the direct synthesis of trifluoromethyl ketones from carboxylic esters (top) and scheme illustrating the formation of CHF_3 if water is present in the reaction mixture (bottom).

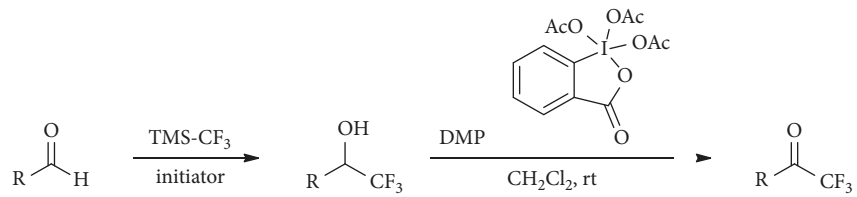


Figure 10: Preparation of TFMKs via a two-step protocol. The first synthesis of trifluoromethyl carbinol with TMS-CF_3 and TBAF or CsF as initiator, followed by oxidation using Dess–Martin periodinane as oxidant.

Other homogenous catalysts have also been reported. Examples include aluminium chloride ($AlCl_3$) [61], triethylamine hydrochloride ($Et_3N{\cdot}HCl$) in combination with *N*-methylpyrrolidinone as a solvent [62, 63], ammonium chloride in combination with DMF at 140°C [54, 64], boron trifluoride ($BF_3{\cdot}OEt_2$) [65], acetic acid [66], and zinc triflate ($Zn(OTf)_2$). However, they pose, just as $ZnBr_2$, difficulties in separation, recovery, and reusability of the catalyst, which results in tedious work-up. By using heterogeneous catalysts, this problem can be circumvented. A simple filtration suffices to retain the catalyst. However, reactions using heterogeneous catalysts require even longer reaction times and a large excess of sodium azide. Examples of these heterogeneous catalysts are among others Zn/Al hydrotalcites [67], tungstates (MWO_4, M = Ba, Ca, Zn, Cd, Cu, Na_2, H_2) [68], $FeCl_3$–SiO_2 [69], $NaHSO_4{\cdot}SiO_2$ [20], $Fe(HSO_4)_3$ [70], $CuSO_4{\bullet}H_2O$ [71–75], and a solid acid catalyst Amberlyst-15 [72].

As an alternative to the inorganic salts, organic soluble azide sources such as trialkyltin azide or trimethylsilyl azide have been introduced [46, 76–79]. However, reactions using toxic and volatile trimethylstannyl azide generate hazardous

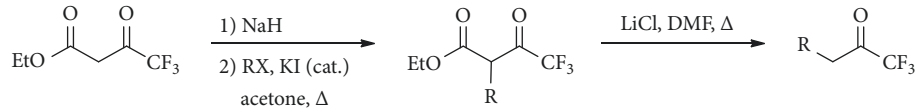


Figure 11: Preparation of TFMK through alkylation by activated halides (RX) and decarboxylation.

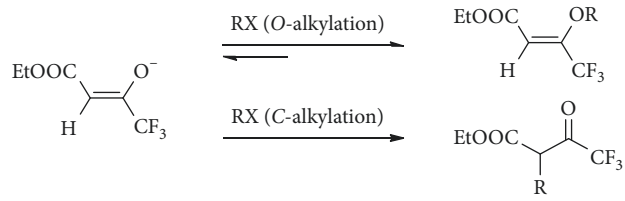


Figure 12: *O*-alkylation and *C*-alkylation of ethyl trifluoroacetoacetate by activated halides (RX).

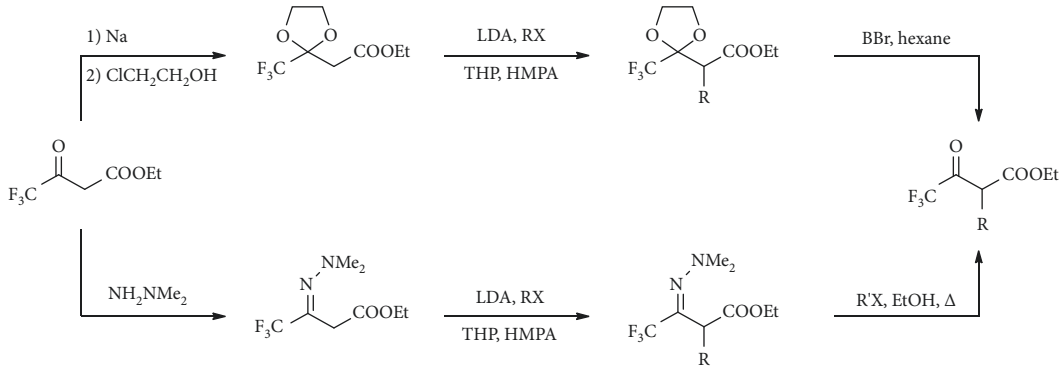


Figure 13: *C*-alkylation EFTAA through the preparation of dioxolane and *N*,*N*-dimethyl hydrazone derivatives of EFTAA.

tin products, which also can give purification problems. When reacting azidotrimethylsilane with a catalytic amount of dimethyltin oxide, only a small amount of this reactive alkyltin species is generated in situ (Figure 5) [80].

More recent methods entail among others nano-sized heterogeneous catalysts, which play an important role in green synthesis. Examples include $TiCl_4$•SiO_2 nanoparticles (NPs) [81], ZnO/Co_3O_4 NPs [82], Cu(II)-complex NPs [83, 84], and Ag NPs [85]. Their smaller size provides advantages such as higher availability of surface area to the reactant and the requirement of only a negligible amount of catalyst. Moreover, they achieve better selectivity, thus eliminating the formation of undesired products [86]. The long reaction times of these methods can be shortened under microwave-assisted conditions with monodisperse Pd/Co nanoparticles and Cu(II) as catalysts. Still, the development of cheap environmentally friendly, recyclable catalysts for microwave-assisted conditions remains a challenge [70, 85].

4. Other Aromatic Heterocycles as Bioisosteres

As previously discussed, although tetrazoles are more hydrophobic than carboxylic acids, some drugs containing tetrazoles, such as candesartan (another drug besides losartan that inhibits the AT_1 receptor and that lowers the blood pressure), still suffer from poor membrane permeability and low bioavailability [87]. This is because their acidity is similar to carboxylic acids. By replacement of this tetrazole moiety with other, slightly less acidic heterocycles such as 5-oxo-1,2,4-oxadiazole ($pK_a = 6.1$) and 5-oxo-1,2,4-thiadiazole ($pK_a = 6.6$), the oral bioavailability of the AT_1 inhibitor is increased (Figure 6) [47, 86]. This is also predicted by SPR studies (Table 1). In addition, other aromatic heterocycles such as 2-thioxo-1,3,4-oxadiazole, 1,2,4-triazole ($pK_a = 10.0$), and imidazole ($pK_a = 14.2$) have shown their effectiveness as carboxylic bioisosteres (Figure 6) in the search of novel inhibitors of β-secretase, a therapeutic target in Alzheimer's disease. This suggests that the delocalized π-orbitals or the proton of the amine on the heterocycles is important for inhibitory activity. They also share their planarity and two hydrophobic regions above and below the plane with the carboxylic acid moiety [47].

The planar heterocycle 3-hydroxyisoxazole and the corresponding isothiazole are also considered to be bioisosteres of carboxylic acids. They exhibit similar acidity ($pK_a = 4$–5) to carboxylic acids, and through SPR studies, they are considered to be more lipophilic and to have improved permeability (Table 1) [3]. 3-Hydroxyisoxazoles and thiazoles are incorporated in agonists and antagonists of the GABA (γ-aminobutyric acid) and

glutamate neurotransmitters, where 3-hydroxyisoxazoles and thiazoles displace the carboxyethyl group. The receptors that bind these neurotransmitters include the *N*-methyl-D-aspartic acid (NMDA) and ionotropic glutamate (AMPA) receptor [88–90]. Figure 7 displays some examples of the GABA, NMDA, and AMPA receptors agonists and antagonists. As permeability and lipophilicity are very important for neurotransmitters to surpass the blood-brain barrier [91], these 3-hydroxyisoxazole- or thiazole-bearing neurotransmitters confirm the findings of the SPR studies in Table 1 that these carboxylic acid bioisosteres have good properties in terms of lipophilicity and permeability. Also, 4-hydroxy-1,2,5-oxadiazole (pK_a~3), 1-hydroxypyrazole (pK_a~5), and 3-hydroxypyrazole (pK_a~7) units can be used as carboxylic acid bioisosteres as they show activity for a GABA receptor when incorporated in GABA-related compounds (Figure 7) [92–95]. Moreover, the 1-hydroxypyrazole derivatives of aldose reductase inhibitors exhibited improved membrane permeation and activity compared to the carboxylic acid counterpart [96].

5. Trifluoromethyl Ketones and α-Trifluoromethyl Alcohols

Trifluoromethyl ketones (TFMKs) and α-trifluoromethyl alcohols, also called trifluoromethyl carbinols, as bioisosteres of carboxylic acids are considered to increase the lipophilicity of the compound (Table 1). TFMKs are generally known as alternatives for hydroxamic acids as a zinc-binding group and have been found to be potent enzyme inhibitors [97]. There is only one example known where a TFMK and a trifluoromethyl carbinol replaced a carboxylic acid moiety in a drug. In the lead optimization of new antagonists of the brain-penetrant prostaglandin E (EP_1) receptor, the antagonists bearing TFMK and trifluoromethyl carbinol showed favorable ADME and pharmacokinetic properties including oral bioavailability and brain penetration in mice, which confirms the lipophilic character of the new compounds [3, 98, 99]. Under physiological conditions, TFMKs are present in the hydrate form and have a pK_a of about 7.5 (Figure 8) [3, 100].

5.1. Synthesis of Trifluoromethyl Ketones and α-Trifluoromethyl Alcohols. The synthesis of TMFKs is not trivial. Early approaches involve the addition of Grignard species to trifluoroacetic acid (TFA) or derivatives. However, these methods lack general synthetic applicability [101]. Condensation reactions of trifluoro-organometallic reagents with carboxylic esters are widely used since the discovery of the Ruppert–Prakash reagent, (trifluoromethyl)trimethylsilane (TMS-CF_3) (Figure 9) [102]. The reaction has to be performed under dry conditions, as water competes with the carboxylic esters for the trifluoromethyl anion, which results in the formation of CHF_3 and $HOSi(CH_3)_3$ (Figure 9). Tetra-*n*-butylammonium fluoride (TBAF; hydrate or in solution in THF) was first used as initiator of the mechanism. However, as TBAF contains water that impedes the trifluoromethylation reaction, it was later replaced by another fluoride ion source, CsF [103]. Addition of activated molecular sieves to the reaction and changing the solvent from THF to nonpolar and aprotic solvents have also been successful strategies to avoid water [104].

Trifluoromethyl ketones can also be prepared via a two-step protocol starting with an aldehyde that is trifluoromethylated using TMS-CF_3 [101]. Afterwards, the corresponding trifluoromethyl carbinol is oxidized to a TFMK (Figure 10) [96]. The inductive effect of CF_3 raises the activation barrier for oxidation in the way that it lowers the nucleophilicity of the OH group or increases the strength of the α-C-H bond. Therefore, traditional oxidation protocols that rely on the attack of the oxygen on an activated complex fail to oxidize trifluoromethyl carbinols or require a large excess (15–20 equivalents) of oxidant [105]. The very powerful, but expensive, oxidant Dess–Martin periodinane (DMP) is the most successful, though sometimes 3.5 or 4 equivalents are required to ensure complete oxidation. It provides TFMKs in high yields under mild conditions and over short times [96, 100, 106]. More recently, new methodologies to oxidize trifluoromethyl carbinols were found using catalytic amounts of $RuCl_2(Biox)_2$ and sodium 2-iodobenzenesulfonate combined with $NaIO_4$ and Oxone® ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) as oxidants, respectively [107, 108]. Also, resin-bound permanganate oxidants that ease the purification of TFMK are used [109]. Overall, more rigorous conditions are required to oxidize alkyl-substituted trifluoromethyl carbinols as compared to aryl-substituted trifluoromethyl carbinols [96].

Another general approach to TMFK synthesis is the *C*-alkylation of enolates of ethyl trifluoroacetoacetate (ETFAA), a cheap substrate, followed by a decarboxylation step (Figure 11) [96]. The conditions of the first step should be carefully chosen to avoid *O*-alkylation. Especially, the use of dissociating solvents, such as acetone, that improve the reactivity of the enolates of ETFAA, is recommended. As such, the *O*-alkylation is kinetically favored but reversibility of this process eventually leads to the *C*-alkylated product (Figure 12) [104, 110]. This protocol, however, only works for activated halides (RX, Figure 11).

If ETFAA is masked into dioxolane or *N*,*N*-dimethyl hydrazone, it is easily alkylated independently of the alkyl halide, though at the expense of extra reaction steps (Figure 13) [111]. After *C*-alkylation, the TFMKs are easily obtained under Krapcho's decarboxylation conditions (LiCl and DMF at reflux) [112].

6. Sulfonamides and Derivatives

Sulfonamides are known to be carboxylic acid bioisosteres since the development in the 1930s and 1940s of the antibacterial agents sulfadiazine and sulfanilamide, the latter being the active form of prontosil. These drugs show activity because of the similarities of the sulfonamide moiety with the carboxylic acid of the natural substrate *para*-aminobenzoic acid (PABA) of the enzyme tetrahydropteroate synthetase that they inhibit (Figure 14) [3]. The sulfonamide analog of losartan (Figure 2) has shown good activity, which

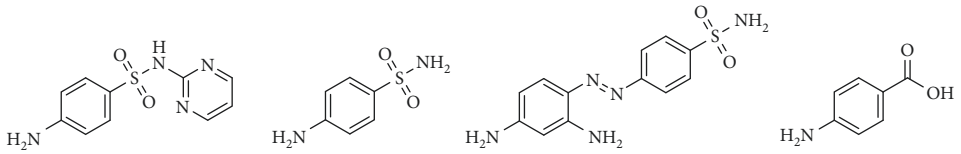


Figure 14: Sulfonamide-based anti-bacterial drugs and PABA.

also proves that the sulfonamide moiety is a potent carboxylic acid surrogate. Although being weakly acidic (pK_a ~10) and nonplanar in contrast to carboxylic acids, sulfonamides exhibit similar geometry of the hydrogen bond environment and a comparable average electron density to carboxylic acids [3,113]. Unlike the sulfonamide moiety, its derivatives such as acyl sulfonamides and sulfonylureas display pK_a values that fall within the range of carboxylic acids ($pK_a = 4–5$) [3].

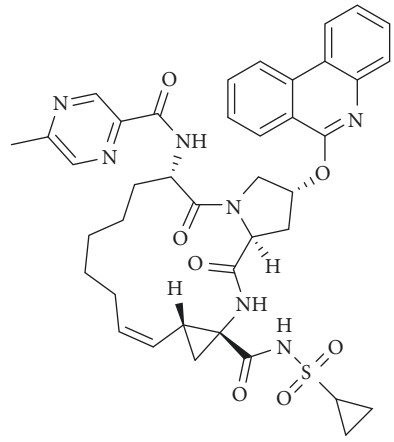
Acyl sulfonamides are well-known carboxylic acid bioisosteres in drugs as they have improved pharmacological properties compared to carboxylic acids, such as its metabolic resistance against glucuronidation, which is due to an enhanced chemical and enzymatic stability of the sulfonamide moiety as compared to carboxylic acids [3, 114]. However, the replacement of a carboxylic acid moiety by an acyl sulfonamide group does not enhance the permeability of the drug (Table 1). Interesting examples of bioisosteric modifications to acyl sulfonamides, which led to improved potency and/or pharmacological properties of the lead compound, are the inhibitors of several receptors including: (1) NS3 protease, important for treatment of hepatitis C virus, (2) PPARα, which is the molecular target of hypolipidemic drugs, and (3) EP_3 that has a role in many physiological effects such as hyperalgesia, platelet aggregation, thrombosis, and uterine contraction. Some of these inhibitors are currently in clinical trials, while others are already retailed such as paritaprevir (Figure 15), a drug against hepatitis C infections [113]. Notable examples of sulfonylurea as a carboxylic acid bioisostere include a β_3-adrenergic receptor agonist and an antagonist of the CXCR2 receptor, which had an improved oral bioavailability in mice [115, 116].

6.1. Synthesis of Sulfonamides. Various substrates have been deployed for the synthesis of sulfonamides. Still, protocols using sulfonyl chlorides and amines in organic solvents are best known because of their simplicity and reactivity (Figure 16). However, the methodology includes some drawbacks, such as the use of additional bases to scavenge the hydrochloric acid that is produced during the reaction, as well as the elevated temperatures needed for less reactive substrates and the side reactions that occur [117]. For example, bis-sulfonylation in the case of primary amines is a known side reaction [118]. To avoid the use of organic solvents, a protocol for synthesizing arylsulfonamides was developed in water where the pH is controlled at 8.0 using Na_2CO_3, and the end product can be filtered after bringing the pH to 2.0. Still, these conditions only result in good yields when the hydrolysis of the arylsulfonyl chlorides is not too fast [119]. In another protocol, sulfonyl chloride is slowly added to an amine solution in a biphasic system of organic solvents and basic aqueous solution (Na_2CO_3 or NaOH). Due to the hydrolysis of sulfonyl chlorides as a major competing reaction under these conditions (called modified Schotten–Baumann conditions), an excess of sulfonyl chloride is necessary to ensure complete conversion of the amine [120]. For both protocols, the isolation and purification of the sulfonamide are not always straightforward because of the side products that are formed [121].

Side reactions of alkyl sulfonyl chlorides attacking additional nucleophilic centers of the amines can be avoided when alkyl sulfonyl chlorides as sulfurated starting material are replaced by alkyl sulfonyl fluorides. Aliphatic sulfonyl fluorides are less active but more selective for the amino function compared to sulfonyl chlorides. In other cases, sulfonyl chlorides are still the recommended reagent. For example, the selectivity is of no importance when dealing with monofunctional aliphatic amines, and sulfonyl fluorides show in most cases no conversion towards amines bearing a sterically hindered amino group. In addition, sulfonyl chlorides are cheaper reagents than sulfonyl fluorides [122].

Thiols and sulfonic acids and their salts convert to sulfonamides through sulfonyl chlorides that are generated in situ. Sulfonic salts directly convert to sulfonamides using 2,4,6-trichloro[1,3,5]triazine [123]. Protocols with thiols as starting materials use an oxidizing chlorinating environment such as sodium hypochlorite, *N*-chlorosuccinimide, hydroperoxide combined with $SOCl_2$, or TMSCl and trichlorocyanuric acid [124–128]. Recently, Deeming et al. developed a methodology that avoids the use of sulfonyl chlorides by employing readily generated sulfinates that are formed from the corresponding Grignard reagents and DABSO (1,4-diazabicyclo[2,2,2] octane (DABCO) bis(sulfur dioxide)) as an SO_2 source [129]. These methods are displayed in Figure 17. Additionally, protocols using transition metals exist, but these are mostly limited to the preparation of aryl sulfonamides ($ArSO_2NHR$) [116].

6.2. Synthesis of Acyl Sulfonamides. Following the synthesis of sulfonamides, acyl sulfonamides are prepared by acylation of sulfonamides using classical acylation strategies (acylation route, Figure 18) [108].



Paritaprevir

Figure 15: Structure of paritaprevir.

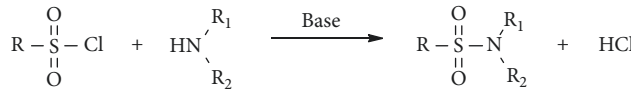


Figure 16: Synthesis of sulfonamides using sulfonyl chloride and a base.

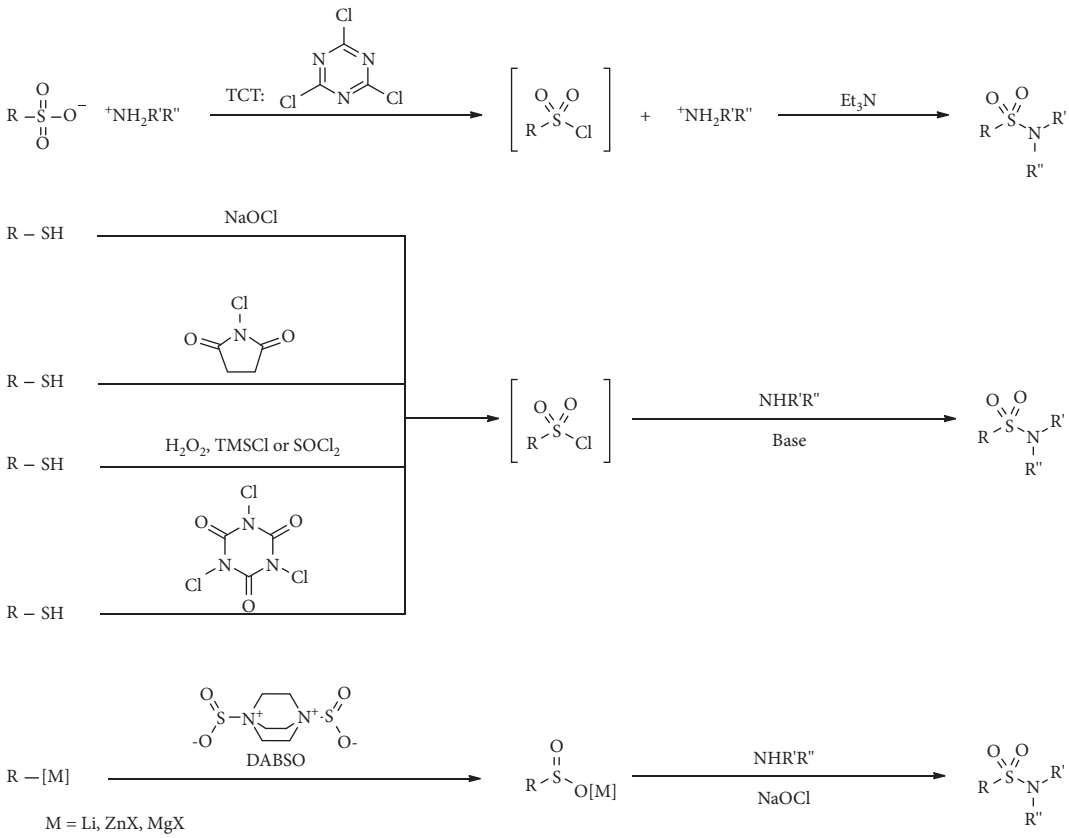


Figure 17: Direct conversions of sulfonic salts, thiols, and Grignard reagents to sulfonamides generating sulfonyl chloride in situ.

A common approach involves the reaction of a sulfonamide and a carboxylic acid in the presence of carbodiimides or *N*,*N*′-carbonyldiimidazole as dehydrating agents and 4-(dimethylamino)pyridine (DMAP) as activating agent [115, 130, 131]. Another, less common route to synthesize acyl sulfonamides is by sulfonylation of amides under basic

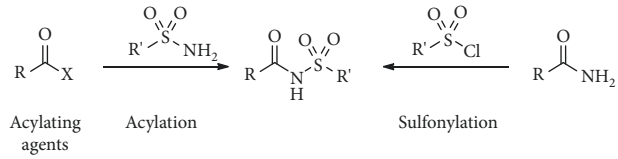


Figure 18: Synthetic routes to *N*-acylsulfonamides.

conditions. This method has as advantage that when there is a labile benzylic stereogenic center at the amide, the chirality of this center is preserved in the resulting acyl sulfonamide [132].

6.3. Synthesis of Sulfonylureas. Two synthetic routes to prepare sulfonylureas can be distinguished depending on the chemical bond of the urea moiety that is formed (Figure 19).

In the first route (route 1, Figure 19), the SN-C bond is formed either by treatment of a sulfonamide with an isocyanate or activated carbamoyl in the presence of a base. Because the classical syntheses of isocyanates are based on the highly toxic and volatile phosgene, more environmentally friendly protocols have been developed in which isocyanates are generated in situ [133]. A convenient method concerns the isocyanation of sterically hindered amines with di-tert-butyl dicarbonate (Boc_2O) in the presence of a catalytic amount of DMAP. This reacts further with sulfonamides to sulfonylureas (Figure 20) [134].

Another mechanism to avoid phosgene in the synthesis of sulfonylureas is the Curtius rearrangement of an acyl azide, derived from diphenylphosphoryl azide (DPPA) and carboxylic acid, to an isocyanate intermediate that reacts with a sulfonamide (Figure 21) [135].

Lastly, after the synthesis of carbamates that contain good leaving groups from amines (LG_1 = OPhe [136], MeS [137], and benzotriazole (BTA) [138, 139]; Figure 19), the activated carbamates also generate the corresponding isocyanate intermediate in situ that reacts with sulfonamides or sulfonamide salts to sulfonylureas (Figure 22).

In the second synthetic route, the RN-C bond is formed by treatment of an amine with an *N*-sulfonylcarbamate or *N*-sulfonylisocyanate that is derived from the respective sulfonamides (route 2, Figure 19). Similar to route 1, the toxicity of phosgene used for the preparation of *N*-sulfonylisocyanates is problematic [132]. As an alternative, starting from sulfonyl chlorides, an intermediate isocyanate is formed with NaOCN that reacts further with amines to sulfonylureas (Figure 23). This single-step reaction is easily accessible for both aliphatic and aromatic sulfonylureas [140].

Similar to route 1 syntheses, also here, sulfonyl carbamates with good leaving groups (LG^2 = OPh, Figure 19) are used to prepare sulfonylureas directly (Figure 24) [132].

7. Recent Developments

Research towards new bioisosteres of the carboxylic acid moiety continues to grow. In this part, more recently developed bioisosteres are discussed that are still under further investigation and do not appear yet in examples of (candidate) drugs that are marketed or in clinical trials (Figure 25).

As a carboxylic acid bioisostere candidate, the monosubstituted 1,4-dihydro-5*H*-tetrazol-5-one moiety, as a derivative of the tetrazole moiety, called tetrazolone, exhibits favorable properties in terms of acidity (pK_a is around 6) and lipophilicity (Table 1). Also, an average electron density tool confirmed the bioisosteric similarity [141]. The acid-to-tetrazolone switch in telmisartan, a marketed inhibitor of the AT_1 receptor, yielded improved activity in vitro and an attractive pharmacokinetic profile in vivo. In particular, the data suggested that the replacement of an acid with a tetrazolone group could be a beneficial strategy to reduce rapid clearance in the body, as it has a longer half-life time. The replacement of an acid by a tetrazolone moiety was also tested on two inhibitors of two other receptors and did not result in improved activity. However, this is not different from a number of established bioisosteres as their success is also found to be case-dependent [17].

The pool of heterocyclic aromatic carboxylic acid bioisosteres is further expanded by 4-hydroxy-1*H*-1,2,3-triazoles (pK_a = 6–7, Figure 25). Pippione et al. have reported two C_5-substituted 4-hydroxy-1,2,3-triazole 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid (AMPA) analogs as antagonists of the AMPA receptor. This scaffold has the opportunity to regio-direct substituents in two different directions, reaching additional binding areas of the receptor to improve properties such as potency and selectivity, compared to one in the isoxazolyl moiety in AMPA [142, 143]. Also, the N_1- and N_2-substituted 4-hydroxy-1,2,3-triazole moieties act as a carboxylic acid bioisostere. They have been reported in some GABA analogs expressing affinities in the medium to lower molar range for the GABA receptor, just as the N_1-substituted hydroxytriazole is found in a new sortilin inhibitor replacing the carboxylic acid functionality [144, 145].

C_4- and C_3-substituted cyclopentane-1,3-diones (CPD1,3) and cyclopentane-1,2-diones (CPD1,2), respectively, have been reported by Ballatore et al. as carboxylic acid bioisosteres of a thromboxane A_2 prostanoid (TP) receptor antagonist in vitro [19,146]. The delocalization of the CPDs was found to be important for binding. They are derivatives of tetronic and tetramic acids that are rarely employed as bioisosteres of carboxylic acids, and according to SPR studies, CPD1,2 groups have improved lipophilicity and permeability as compared to carboxylic acid and tetronic and tetramic acids, whereas CPD1,3s show less favorable properties (Table 1). However, as the hydrophilic regions of CPDs are elongated to the distance of one covalent

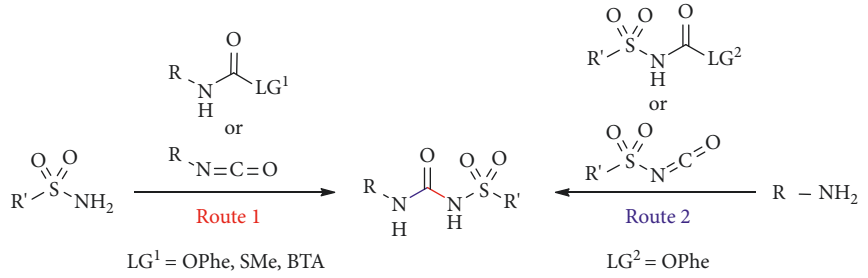


Figure 19: Syntheses of sulfonylurea from sulfonamides and electrophilic isocyanate or carbamates (route 1, formation of SN-C bond) and from amines and electrophilic sulfonyl isocyanate or *N*-sulfonyl carbamates (route 2, formation of RN-C bond).

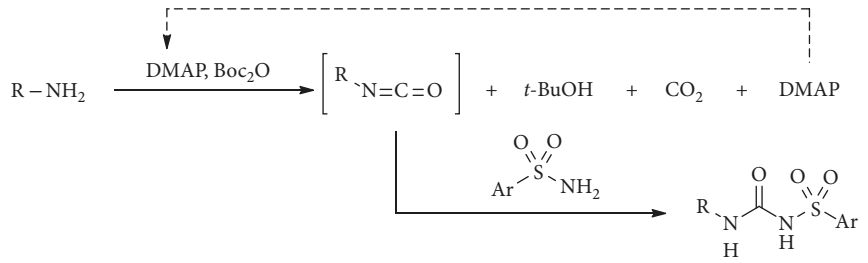


Figure 20: Synthesis of sulfonylurea with DMAP, Boc_2O.

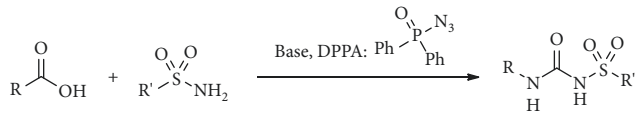


Figure 21: Synthesis of sulfonylureas via the Curtius rearrangement.

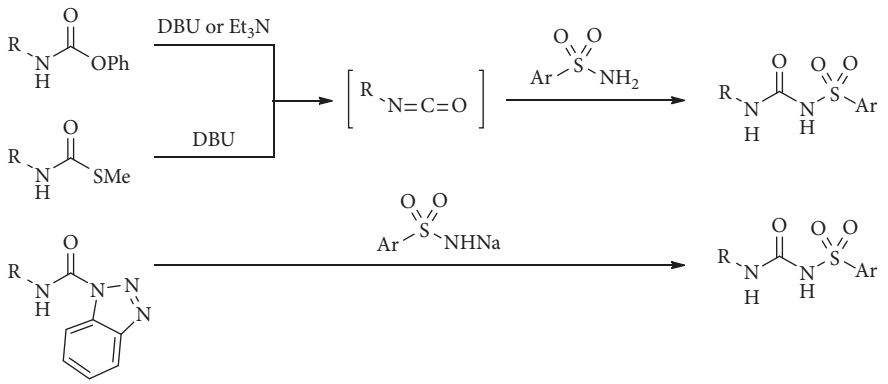


Figure 22: Syntheses of sulfonylureas using carbamates bearing good leaving groups (LG = OPh, SMe, and BTA).

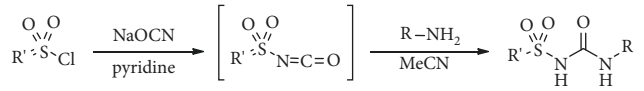


Figure 23: Synthesis of sulfonylureas through an intermediate isocyanate using NaOCN.

bond, CPDs are considered to be bioisosteres of the carboxymethyl group rather than of the carboxylic group. CPDs exist predominantly in the enol-ketone form, which presents two tautomers that can establish intermolecular hydrogen bonds such as carboxylic acids (Figure 26). Yet they are still called after their form with two ketones (diones). CPD1,3s have similar acidity ($pK_a = 4–5$) to carboxylic acid because of dissociation by the delocalization of π-electrons. Meanwhile, CPD1,2 are not vinylogous acid structures and thus have relatively high pK_a values [30, 147].

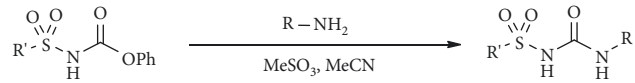


Figure 24: Syntheses of sulfonylurea using sulfonylcarbamates bearing a good leaving group (LG = OPh).

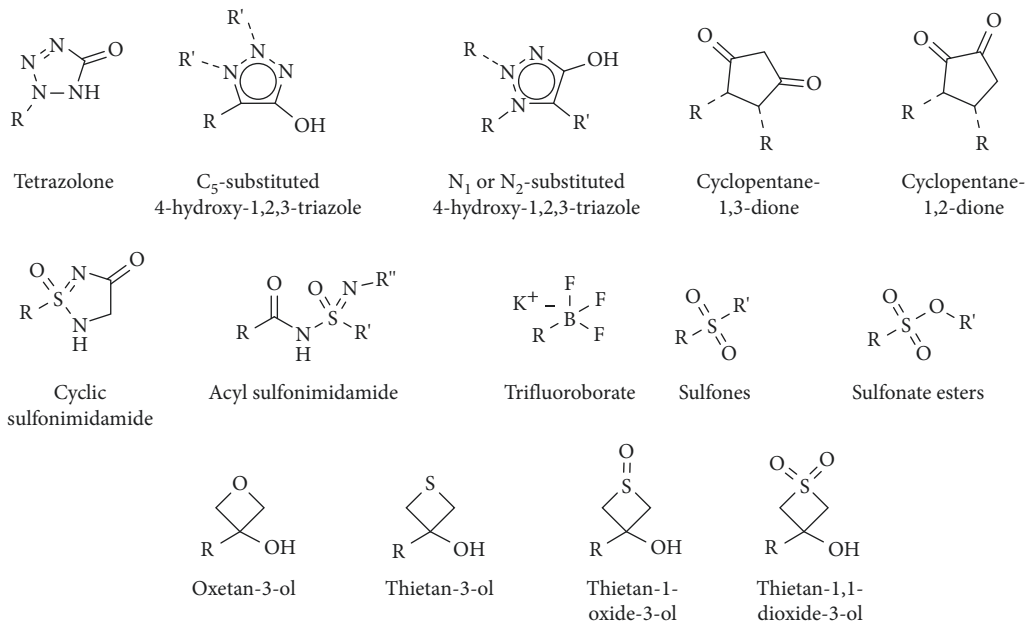


Figure 25: Overview of recent investigated carboxylic acid bioisosteres.

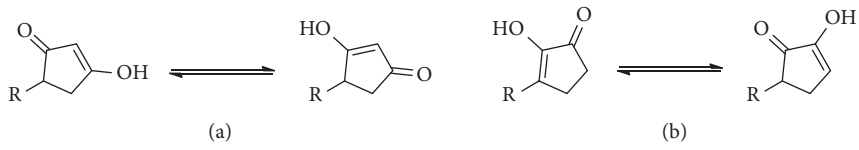


Figure 26: Tautomerization of CPD1,3 (a) and CPD1,2 (b).

Acyl sulfonimidamides, as alternatives to acyl sulfonamides, are explored as carboxylic acid bioisosteres [14]. A sulfonimidamide is a sulfonamide moiety in which one of the oxygen atoms on the sulfur has been replaced by a nitrogen atom. This makes the sulfur atom a chiral center. The additional nitrogen atom offers a reactive handle for chemical modifications, resulting in the further tuning of the physicochemical and biological properties [148]. For example, the acidity can be adjusted between the pH range of 5.9–7.6, which is still less acidic than acyl sulfonamides or carboxylic acids. The more acidic the moiety is, the less lipophilic and permeable, and vice versa. For example, the unsubstituted acyl sulfonamide moiety is less acidic but more lipophilic than carboxylic acid according to SPR studies (Table 1). Furthermore, the presence of a chiral sulfur center offers opportunities to exploit enantiomeric differences in drug optimization, regarding both pharmacokinetic and pharmacodynamic properties [14].

Cyclic sulfonimidamides have been designed as potential carboxylic acid bioisosteres [16]. In contrast to an acyclic sulfonimidamide that has properties that are less consistent with the ability to act as an acid surrogate ($pK_a = 9–11$ and lower lipophilicity and permeability) [14], the heterocycle exhibits similar lipophilicity and is slightly less acidic ($pK_a = 5–6$) compared to the corresponding carboxylic acid, plus, it even has a higher permeability than the corresponding tetrazole (Table 1). A distinctive feature of the sulfonimidamide heterocycle, next to the stereogenic tetrahedral sulfur center, is the presence of an sp^3 carbon that permits further tuning of physicochemical properties [3, 148].

Hong et al. researched the application of trifluoroborates, sulfones, and sulfonate esters (Figure 25), among others, as a replacement of the oseltamivir carboxylic acid. Although these moieties do not have acidic protons, they still exhibited significant influenza neuraminidase inhibitory activity, which indicated that the electronegative fluorine and oxygen atoms on the polarized B–F and S–O bonds still made sufficient electrostatic interactions with the receptor [149].

The oxetan-3-ol and thietan-3-ol rings and corresponding sulfoxide and sulfone structural units have also attracted some attention as a bioisosteric replacement of

carboxylic acid because this four-membered ring system is known to improve the lipophilicity and metabolic stability of a compound [19, 150]. Although these four-membered heterocycles have a limited acid character ($pK_a > 12$), they still have the capacity to establish hydrogen bonds as a hydrogen bond donor and acceptor. This combination of properties may be ideal in circumstances where the presence of a negatively ionizable acid in a compound may be responsible for its low permeability. Indeed, SPR studies revealed that the four-membered ring heterocycles are among the most permeable bioisosteres (Table 1) [19].

8. Conclusion

The carboxylic acid is a highly versatile functionality in drug design. However, it can entail some downsides such as toxicity, poor lipophilicity, and membrane permeability. There are a plethora of possible replacements for the carboxylic acid functionality in a bioactive agent that could improve the activity, selectivity, and pharmacokinetics of the compound. Although the success of the replacements of these bioisosteres cannot be predicted, this paper gives a short overview of the most promising bioisosteres based on their ADME properties and their potential to avoid toxicity problems [151]. Examples of classical carboxylic acid bioisosteres are the trifluoromethyl ketones and the sulfonamide derivatives, even though they do not share the planarity of the carboxylic acid. On the other hand, the aromatic heterocycles (nonclassical bioisosteres) from which the tetrazole moiety is the best known and most investigated, do exhibit a planar geometry. Other heterocyclic bioisosteres could be worthy alternatives as they improve the bioavailability and permeability of the compound compared to the parent structure bearing a tetrazole moiety. By selecting these alternative heterocycles, the use of explosive and toxic azide reagents for the synthesis of tetrazoles is also avoided. Yet the search for new bioisosteres keeps advancing in the hope to find new potent drugs for use in the human body.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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References

[1] P. J. Hajduk, M. Bures, J. Praestgaard, and S. W. Fesik, "Privileged molecules for protein binding identified from NMR-based screening," *Journal of Medicinal Chemistry*, vol. 43, no. 18, pp. 3443–3447, 2000.

[2] A. S. Kalgutkar and J. Scott Daniels, "Chapter 3. carboxylic acids and their bioisosteres," *Drug Discovery Series*, vol. 1, pp. 99–167, 2010.

[3] C. Ballatore, D. M. Huryn, and A. B. Smith, "Carboxylic acid(bio)isosteres in drug design," *ChemMedChem*, vol. 8, no. 3, pp. 385–395, 2013.

[4] C. Skonberg, J. Olsen, K. G. Madsen, S. H. Hansen, and M. P. Grillo, "Metabolic activation of carboxylic acids," *Expert Opinion on Drug Metabolism & Toxicology*, vol. 4, no. 4, pp. 425–438, 2008.

[5] U. Boelsterli, "Xenobiotic acyl glicuronides and acyl CoA thioesters as protein-reactive metabolites with the potential to cause idiosyncretic drug reactions," *Current Drug Metabolism*, vol. 3, pp. 439–450, 2005.

[6] R. H. Sandler, "Anaphylactic reactions to zomepirac," *Annals of Emergency Medicine*, vol. 14, no. 2, pp. 171–174, 1985.

[7] E. M. Faed, "Properties of acyl glucuronides: implications for studies of the pharmacokinetics and metabolism of acidic drugs," *Drug Metabolism Reviews*, vol. 15, no. 5-6, pp. 1213–1249, 1984.

[8] M. Darnell and L. Weidolf, "Metabolism of xenobiotic carboxylic acids: focus on coenzyme a conjugation, reactivity, and interference with lipid metabolism," *Chemical Research in Toxicology*, vol. 26, no. 8, pp. 1139–1155, 2013.

[9] T. Lassila, J. Hokkanen, S.-M. Aatsinki, S. Mattila, M. Turpeinen, and A. Tolonen, "Toxicity of carboxylic acid-containing drugs: the role of acyl migration and CoA conjugation investigated," *Chemical Research in Toxicology*, vol. 28, no. 12, pp. 2292–2303, 2015.

[10] H. L. Friedman, "Influence of isosteric replacements upon biological activity," *NASNRS*, pp. 295–359, 1951.

[11] G. A. Patani and E. J. LaVoie, "Bioisosterism: a rational approach in drug design," *Chemical Reviews*, vol. 96, no. 8, pp. 3147–3176, 1996.

[12] P. D. Leeson and B. Springthorpe, "The influence of drug-like concepts on decision-making in medicinal chemistry," *Nature Reviews Drug Discovery*, vol. 6, no. 11, pp. 881–890, 2007.

[13] P. Lassalas, B. Gay, C. Lasfargeas et al., "Structure property relationships of carboxylic acid isosteres," *Journal of Medicinal Chemistry*, vol. 59, no. 7, pp. 3183–3203, 2016.

[14] S. R. Borhade, R. Svensson, P. Brandt, P. Artursson, P. I. Arvidsson, and A. Sandström, "Preclinical characterization of acyl sulfonimidamides: potential carboxylic acid bioisosteres with tunable properties," *ChemMedChem*, vol. 10, no. 3, pp. 455–460, 2015.

[15] M. Ferri, M. Alunno, F. A. Greco et al., "Fragment based drug design and diversity-oriented synthesis of carboxylic acid isosteres," *Bioorganic & Medicinal Chemistry*, vol. 28, no. 22, Article ID 115731, 2020.

[16] N. Pemberton, H. Graden, E. Evertsson et al., "Synthesis and functionalization of cyclic sulfonimidamides: a novel chiral heterocyclic carboxylic acid bioisostere," *ACS Medicinal Chemistry Letters*, vol. 3, no. 7, pp. 574–578, 2012.

[17] M. A. J. Duncton, R. B. Murray, G. Park, and R. Singh, "Tetrazolone as an acid bioisostere: application to marketed drugs containing a carboxylic acid," *Organic & Biomolecular Chemistry*, vol. 14, no. 39, pp. 9343–9347, 2016.

[18] K. R. Francisco, C. Varricchio, T. J. Paniak, M. C. Kozlowski, A. Brancale, and C. Ballatore, "Structure property relationships of N-acylsulfonamides and related bioisosteres," *European Journal of Medicinal Chemistry*, vol. 218, Article ID 113399, 2021.

[19] P. Lassalas, K. Oukoloff, V. Makani et al., "Evaluation of oxetan-3-ol, thietan-3-ol, and derivatives thereof as

bioisosteres of the carboxylic acid functional group," *ACS Medicinal Chemistry Letters*, vol. 8, no. 8, pp. 864–868, 2017.

[20] B. Das, C. Reddy, D. Kumar, M. Krishnaiah, and R. Narender, "A simple, advantageous synthesis of 5-substituted 1H-Tetrazoles[1]," *Synlett*, vol. 2010, no. 03, pp. 391–394, 2010.

[21] F. H. Allen, C. R. Groom, J. W. Liebeschuetz, D. A. Bardwell, T. S. G. Olsson, and P. A. Wood, "The hydrogen bond environments of 1H-tetrazole and tetrazolate rings: the structural basis for tetrazole-carboxylic acid bioisosterism," *Journal of Chemical Information and Modeling*, vol. 52, no. 3, pp. 857–866, 2012.

[22] R. De Vreese and M. D'hooghe, "Synthesis and applications of benzohydroxamic acid-based histone deacetylase inhibitors," *European Journal of Medicinal Chemistry*, vol. 135, pp. 174–195, 2017.

[23] R. De Vreese, N. Van Steen, T. Verhaeghe et al., "Synthesis of benzothiophene-based hydroxamic acids as potent and selective HDAC6 inhibitors," *Chemical Communications*, vol. 51, no. 48, pp. 9868–9871, 2015.

[24] R. De Vreese, Y. Depetter, T. Verhaeghe et al., "Synthesis and SAR assessment of novel tubathian analogs in the pursuit of potent and selective HDAC6 inhibitors," *Organic & Biomolecular Chemistry*, vol. 14, no. 8, pp. 2537–2549, 2016.

[25] R. De Vreese, L. Galle, Y. Depetter et al., "Synthesis of potent and selective HDAC6 Inhibitors bearing a cyclohexane- or cycloheptane-annulated 1,5-benzothiazepine scaffold," *Chemistry European Journal*, vol. 23, pp. 128–136, 2017.

[26] S. Shen and A. P. Kozikowski, "Why hydroxamates may not be the best histone deacetylase inhibitors-what some may have forgotten or would rather forget?" *ChemMedChem*, vol. 11, no. 1, pp. 15–21, 2016.

[27] K. Munakata, H. Mochida, S. Kondo, and Y. Suzuki, "Mutagenicity of N-acylglycinohydroxamic acids and related compounds," *Journal of Pharmacobio-Dynamics*, vol. 3, no. 11, pp. 557–561, 1980.

[28] J. Jochems, J. Boulden, B. G. Lee et al., "Antidepressant-like properties of novel HDAC6-selective inhibitors with improved brain bioavailability," *Neuropsychopharmacology*, vol. 39, no. 2, pp. 389–400, 2014.

[29] R. Alvarez-Sánchez, F. Montavon, T. Hartung, and A. Pähler, "Thiazolidinedione bioactivation: a comparison of the bioactivation potentials of troglitazone, rosiglitazone, and pioglitazone using stable isotope-labeled analogues and liquid chromatography tandem mass spectrometry," *Chemical Research in Toxicology*, vol. 19, pp. 1106–1116, 2006.

[30] C. Ballatore, B. Gay, L. Huang et al., "Evaluation of the cyclopentane-1,2-dione as a potential bio-isostere of the carboxylic acid functional group," *Bioorganic & Medicinal Chemistry Letters*, vol. 24, no. 17, pp. 4171–4175, 2014.

[31] J. Chasák, V. Šlachtová, M. Urban, and L. Brulíková, "Squaric acid analogues in medicinal chemistry," *European Journal of Medicinal Chemistry*, vol. 209, Article ID 112872, 2021.

[32] K. A. Agnew-Francis and C. M. Williams, "Squaramides as bioisosteres in contemporary drug design," *Chemical Reviews*, vol. 120, no. 20, pp. 11616–11650, 2020.

[33] R. G. Franz, "Comparisons of pKa and log *P* values of some carboxylic and phosphonic acids: synthesis and measurement," *AAPS PharmSci*, vol. 3, no. 2, pp. 1–13, 2001.

[34] A. V. Artiukhov, A. V. Kazantsev, N. V. Lukashev, M. Bellinzoni, and V. I. Bunik, "Selective inhibition of 2-oxoglutarate and 2-oxoadipate dehydrogenases by the phosphonate analogs of their 2-oxo acid substrates," *Frontiers of Chemistry*, vol. 8, Article ID 596187, 2021.

[35] Y. Zou, L. Liu, J. Liu, and G. Liu, "Bioisosteres in drug discovery: focus on tetrazole," *Future Medicinal Chemistry*, vol. 12, no. 2, pp. 91–93, 2020.

[36] C. Gao, L. Chang, Z. Xu et al., "Recent advances of tetrazole derivatives as potential anti-tubercular and anti-malarial agents," *European Journal of Medicinal Chemistry*, vol. 163, pp. 404–412, 2019.

[37] N. Dhiman, K. Kaur, and V. Jaitak, "Tetrazoles as anticancer agents: a review on synthetic strategies, mechanism of action and SAR studies," *Bioorganic & Medicinal Chemistry*, vol. 28, no. 15, Article ID 115599, 2020.

[38] D. J. Carini, J. V. Duncia, P. E. Aldrich et al., "Nonpeptide angiotensin II receptor antagonists: the discovery of a series of N-(biphenylylmethyl)imidazoles as potent, orally active antihypertensives," *Journal of Medicinal Chemistry*, vol. 34, no. 8, pp. 2525–2547, 1991.

[39] L. V. Myznikov, A. Hrabalek, and G. I. Koldobskii, "Drugs in the tetrazole series. (Review)," *Chemistry of Heterocyclic Compounds*, vol. 43, no. 1, pp. 1–9, 2007.

[40] T. S. Beyett, X. Gan, S. M. Reilly et al., "Carboxylic acid derivatives of amlexanox display enhanced potency toward TBK1 and IKKε and reveal mechanisms for selective inhibition," *Molecular Pharmacology*, vol. 94, no. 4, pp. 1210–1219, 2018.

[41] N. Maheshwari, C. Karthikeyan, S. V. Bhadada et al., "Synthesis and biological evaluation of some N-(3-(1H-tetrazol-5-yl) phenyl)acetamide derivatives as novel non-carboxylic PTP1B inhibitors designed through bioisosteric modulation," *Bioorganic Chemistry*, vol. 80, pp. 145–150, 2018.

[42] H. Huang, M. P. Winters, S. K. Meegalla et al., "Discovery of novel benzo[b]thiophene tetrazoles as non-carboxylate GPR40 agonists," *Bioorganic & Medicinal Chemistry Letters*, vol. 28, no. 3, pp. 429–436, 2018.

[43] C. Hansch, A. Leo, and D. J. Livingstone, "Fundamentals and applications in chemistry and biology," *Environmental Science & Technology*, vol. 29, p. 444, 1995.

[44] M. S. Karls, B. D. Rush, K. F. Wilkinson, T. J. Vidmar, P. S. Burton, and M. J. Ruwart, "Desolvation energy: a major determinant of absorption, but not clearance, of peptides in rats," *Pharmaceutical Research*, vol. 08, no. 12, pp. 1477–1481, 1991.

[45] J. M. Diamond and E. M. Wright, "Molecular forces governing non-electrolyte permeation through cell membranes," *Proceedings of the Royal Society of London Series B Biological Sciences*, vol. 171, pp. 273–316, 1969.

[46] C. F. Matta, A. A. Arabi, and D. F. Weaver, "The bioisosteric similarity of the tetrazole and carboxylate anions: clues from the topologies of the electrostatic potential and of the electron density," *European Journal of Medicinal Chemistry*, vol. 45, no. 5, pp. 1868–1872, 2010.

[47] R. J. Herr, "5-Substituted-1H-tetrazoles as carboxylic acid isosteres: medicinal chemistry and synthetic methods," *Bioorganic & Medicinal Chemistry*, vol. 10, no. 11, pp. 3379–3393, 2002.

[48] Y. Hamada and Y. Kiso, "The application of bioisosteres in drug design for novel drug discovery: focusing on acid protease inhibitors," *Expert Opinion on Drug Discovery*, vol. 7, no. 10, pp. 903–922, 2012.

[49] J. L. Kraus, "Isosterism and molecular modification in drug design: tetrazole analogue of GABA: effects on enzymes of

the γ-aminobutyrate system," *Pharmacological Research Communications*, vol. 15, no. 2, pp. 183–189, 1983.

[50] C. Liljebris, S. D. Larsen, D. Ogg, B. J. Palazuk, and J. E. Bleasdale, "Investigation of potential bioisosteric replacements for the carboxyl groups of peptidomimetic inhibitors of protein tyrosine Phosphatase 1B: identification of a tetrazole-containing inhibitor with cellular activity," *Journal of Medicinal Chemistry*, vol. 45, no. 9, pp. 1785–1798, 2002.

[51] L. Perrier, M. Bourrie, E. Marti et al., "In vitro N-glucuronidation of SB 47436 (BMS 186295), a new AT1 nonpeptide angiotensin II receptor antagonist, by rat, monkey and human hepatic micrisomal fractions," *Journal of Pharmacology and Experimental Therapeutics*, vol. 271, pp. 91–99, 1994.

[52] M. A. Malik, M. Y. Wani, S. A. Al-Thabaiti, and R. A. Shiekh, "Tetrazoles as carboxylic acid isosteres: chemistry and biology," *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, vol. 78, no. 1-4, pp. 15–37, 2014.

[53] J. Braun and W. Keller, "Synthese von tetrazol-verbindungen aus säurenitrilen," *Berichte der Deutschen Chemischen Gesellschaft*, vol. 65, no. 10, pp. 1677–1680, 1932.

[54] S. J. Wittenberger, "Recent developments in tetrazole chemistry. A review," *Organic Preparations and Procedures International*, vol. 26, no. 5, pp. 499–531, 1994.

[55] W. G. Finnegan, R. A. Henry, and R. Lofquist, "An improved synthesis of 5-substituted tetrazoles," *Journal of the American Chemical Society*, vol. 80, no. 15, pp. 3908–3911, 1958.

[56] F. Himo, Z. P. Demko, L. Noodleman, and K. B. Sharpless, "Mechanisms of tetrazole formation by addition of azide to nitriles," *Journal of the American Chemical Society*, vol. 124, no. 41, pp. 12210–12216, 2002.

[57] B. S. Jursic and Z. Zdravkovski, "Semiempirical and ab initio study of 1,3-dipolar addition of azide anion to organic cyanides," *Journal of Molecular Structure: THEOCHEM*, vol. 312, no. 1, pp. 11–22, 1994.

[58] J. Roh, K. Vávrová, and A. Hrabálek, "Synthesis and functionalization of 5-substituted tetrazoles," *European Journal of Organic Chemistry*, vol. 2012, no. 31, pp. 6101–6118, 2012.

[59] F. Himo, Z. P. Demko, L. Noodleman, and K. B. Sharpless, "Why is tetrazole formation by addition of azide to organic nitriles catalyzed by zinc(II) salts?" *Journal of the American Chemical Society*, vol. 125, no. 33, pp. 9983–9987, 2003.

[60] Z. P. Demko and K. B. Sharpless, "Preparation of 5-substituted 1H-tetrazoles from nitriles in water," *Journal of Organic Chemistry*, vol. 66, no. 24, pp. 7945–7950, 2001.

[61] D. P. Matthews, J. E. Green, and A. J. Shuker, "Parallel synthesis of alkyl tetrazole derivatives using solid support chemistry," *Journal of Combinatorial Chemistry*, vol. 2, no. 1, pp. 19–23, 2000.

[62] P. R. Bernstein and E. P. Vacek, "Improved conditions for the formation of tetrazoles," *Synthesis*, vol. 1987, no. 12, pp. 1133-1134, 1987.

[63] K. Koguro, T. Oga, S. Mitsui, and R. Orita, "Novel synthesis of 5-substituted tetrazoles from nitriles," *Synthesis*, vol. 1998, no. 06, pp. 910–914, 1998.

[64] U. J. Ries, G. Mihm, B. Narr et al., "6-Substituted benzimidazoles as new nonpeptide angiotensin II receptor antagonists: synthesis, biological activity, and structure-activity relationships," *Journal of Medicinal Chemistry*, vol. 36, no. 25, pp. 4040–4051, 1993.

[65] A. Kumar, R. Narayanan, and H. Shechter, "Rearrangement reactions of (hydroxyphenyl) carbenes," *Journal of Organic Chemistry*, vol. 61, no. 13, pp. 4462–4465, 1996.

[66] R. K. Russell and W. V. Murray, "Efficient synthesis of 5-(4'-methyl[1,1'-biphenyl]-2-yl)-1H-tetrazole," *Journal of Organic Chemistry*, vol. 58, no. 18, pp. 5023-5024, 1993.

[67] M. L. Kantam, K. B. Shiva Kumar, and K. Phani Raja, "An efficient synthesis of 5-substituted 1H-tetrazoles using Zn/Al hydrotalcite catalyst," *Journal of Molecular Catalysis A: Chemical*, vol. 247, no. 1-2, pp. 186–188, 2006.

[68] J. He, B. Li, F. Chen, Z. Xu, and G. Yin, "Tungstates: novel heterogeneous catalysts for the synthesis of 5-substituted 1H-tetrazoles," *Journal of Molecular Catalysis A: Chemical*, vol. 304, no. 1-2, pp. 135–138, 2009.

[69] M. Nasrollahzadeh, Y. Bayat, D. Habibi, and S. Moshaee, "FeCl3-SiO2 as a reusable heterogeneous catalyst for the synthesis of 5-substituted 1H-tetrazoles via [2+3] cycloaddition of nitriles and sodium azide," *Tetrahedron Letters*, vol. 50, no. 31, pp. 4435–4438, 2009.

[70] H. Eshghi, S. M. Seyedi, and E. R. Zarei, "Ferric hydrogensulfate [$Fe(HSO_4)_3$] as a reusable heterogeneous catalyst for the synthesis of 5-substituted-1H-tetrazoles and amides," *ISRN Org Chem*, vol. 2011, Article ID 195850, 5 pages, 2011.

[71] S. M. Joshi, R. B. Mane, K. R. Pulagam, V. Gomez-Vallejo, J. Llop, and C. Rode, "The microwave-assisted synthesis of 5-substituted 1H-tetrazoles via [3+2] cycloaddition over a heterogeneous Cu-based catalyst: application to the preparation of 13N-labelled tetrazoles," *New Journal of Chemistry*, vol. 41, no. 16, pp. 8084–8091, 2017.

[72] Z. Du, C. Si, Y. Li, Y. Wang, and J. Lu, "Improved synthesis of 5-substituted 1H-tetrazoles via the [3+2] cycloaddition of nitriles and sodium azide catalyzed by silica sulfuric acid," *International Journal of Molecular Sciences*, vol. 13, no. 4, pp. 4696–4703, 2012.

[73] R. Shelkar, A. Singh, and J. Nagarkar, "Amberlyst-15 catalyzed synthesis of 5-substituted 1-H-tetrazole via [3+2] cycloaddition of nitriles and sodium azide," *Tetrahedron Letters*, vol. 54, no. 1, pp. 106–109, 2013.

[74] B. Akhlaghinia and S. Rezazadeh, "A novel approach for the synthesis of 5-substituted-1H-tetrazoles," *Journal of the Brazilian Chemical Society*, vol. 23, no. 12, pp. 2197–2203, 2012.

[75] A. Khalafi-Nezhad and S. Mohammadi, "Highly efficient synthesis of 1- and 5-substituted 1H-tetrazoles using chitosan derived magnetic ionic liquid as a recyclable biopolymer-supported catalyst," *RSC Advances*, vol. 3, no. 13, pp. 4362–4371, 2013.

[76] P. L. Ornstein, D. D. Schoepp, M. B. Arnold et al., "4-(Tetrazolylalkyl)piperidine-2-carboxylic acids. potent and selective N-methyl-D-aspartic acid receptor antagonists with a short duration of action," *Journal of Medicinal Chemistry*, vol. 34, no. 1, pp. 90–97, 1991.

[77] P. Lin, J. M. Pisano, W. R. Schoen et al., "Acyclic structural variants of growth hormone secretagogue L-692,429," *Bioorganic & Medicinal Chemistry Letters*, vol. 9, no. 22, pp. 3237–3242, 1999.

[78] B. E. Huff and M. A. Staszak, "A new method for the preparation of tetrazoles from nitriles using trimethylsilylazide/trimethylaluminum," *Tetrahedron Letters*, vol. 34, no. 50, pp. 8011–8014, 1993.

[79] P. Kotian, S. W. Mascarella, P. Abraham et al., "Synthesis, ligand binding, and quantitative structure-activity relationship study of 3β-(4'-substituted phenyl)-2β-heterocyclic tropanes: evidence for an electrostatic interaction at the 2β-position," *Journal of Medicinal Chemistry*, vol. 39, no. 14, pp. 2753–2763, 1996.

[80] S. J. Wittenberger and B. G. Donner, "Dialkyltin oxide mediated addition of trimethylsilyl azide to nitriles. a novel preparation of 5-substituted tetrazols," *Journal of Organic Chemistry*, vol. 58, no. 15, pp. 4139–4141, 1993.

[81] L. Zamani, B. Mirjailli, K. Zomorodian, and S. Zomorodian, *South African Journal of Chemistry*, vol. 68, pp. 133–137, 2015.

[82] S. M. Agawane and J. M. Nagarkar, "Synthesis of 5-substituted 1H-tetrazoles using a nano ZnO/Co3O4 catalyst," *Catalysis Science & Technology*, vol. 2, no. 7, pp. 1324–1327, 2012.

[83] F. Dehghani, A. R. Sardarian, and M. Esmaeilpour, "Salen complex of Cu (II) supported on superparamagnetic Fe3O4@SiO2 nanoparticles: an efficient and recyclable catalyst for synthesis of 1- and 5-substituted 1H-tetrazoles," *Journal of Organometallic Chemistry*, vol. 743, pp. 87–96, 2013.

[84] H. Sharghi, S. Ebrahimpourmoghaddam, and M. M. Doroodmand, "Facile synthesis of 5-substituted-1H-tetrazoles and 1-substituted-1H-tetrazoles catalyzed by recyclable 4'-phenyl-2,2':6',2"-terpyridine copper (II) complex immobilized onto activated multi-walled carbon nanotubes," *Journal of Organometallic Chemistry*, vol. 738, pp. 41–48, 2013.

[85] P. Mani, C. Sharma, S. Kumar, and S. K. Awasthi, "Efficient heterogeneous silver nanoparticles catalyzed one-pot synthesis of 5-substituted 1H-tetrazoles," *Journal of Molecular Catalysis A: Chemical*, vol. 392, pp. 150–156, 2014.

[86] R. Mittal and S. K. Awasthi, "Recent advances in the synthesis of 5-substituted 1H-tetrazoles: a complete survey (2013-2018)," *Synthesis*, vol. 51, no. 20, pp. 3765–3783, 2019.

[87] T. Naka, K. Kubo, Y. Inada, and K. Nishikawa, "Discovery of a new class of antihypertensive agents, nonpeptide angiotensin II," *Drug Design and Discovery*, vol. 16, pp. 95–108, 1999.

[88] H. Bräuner-Osborne, J. Egebjerg, E. Nielsen, U. Madsen, and P. Krogsgaard-Larsen, "Ligands for glutamate receptors: design and therapeutic prospects," *Journal of Medicinal Chemistry*, vol. 43, pp. 2609–2645, 2000.

[89] P. Krogsgaard-Larsen, G. A. R. Johnston, D. Lodge, and D. R. Curtis, "A new class of GABA agonist," *Nature*, vol. 268, no. 5615, pp. 53–55, 1977.

[90] P. Krogsgaard-Larsen, G. A. R. Johnston, D. R. Curtis, C. J. A. Game, and R. M. McCulloch, "Structure and biological activity of a series of conformationally restricted analogues of gaba," *Journal of Neurochemistry*, vol. 25, pp. 803–809, 1975.

[91] H. Pajouhesh and G. R. Lenz, "Medicinal chemical properties of successful central nervous system drugs," *NeuroRx*, vol. 2, no. 4, pp. 541–553, 2005.

[92] M. L. Lolli, S. L. Hansen, B. Rolando et al., "Hydroxy-1,2,5-oxadiazolyl moiety as bioisoster of the carboxy function. synthesis, ionization constants, and pharmacological characterization of γ-aminobutyric acid (GABA) related compounds," *Journal of Medicinal Chemistry*, vol. 49, no. 14, pp. 4442–4446, 2006.

[93] P. Tosco and M. L. Lolli, "Hydroxy-1,2,5-oxadiazolyl moiety as bioisoster of the carboxy function. A computational study on γ-aminobutyric acid (GABA) related compounds," *Journal of Molecular Modeling*, vol. 14, no. 4, pp. 279–291, 2008.

[94] H. A. Møller, T. Sander, J. L. Kristensen et al., "Novel 4-(piperidin-4-yl)-1-hydroxypyrazoles as gamma-aminobutyric $acid_A$ receptor ligands: synthesis, pharmacology, and structure-acivity relationships," *Journal of Medicinal Chemistry*, vol. 53, pp. 3417–3421, 2010.

[95] J. Krall, K. T. Kongstad, B. Nielsen et al., "5-(Piperidin-4-yl)-3-Hydroxypyrazole: a novel scaffold for probing the orthosteric γ-aminobutyric acid type a receptor binding site," *ChemMedChem*, vol. 9, no. 11, pp. 2475–2485, 2014.

[96] N. Papastavrou, M. Chatzopoulou, K. Pegklidou, and I. Nicolaou, "1-Hydroxypyrazole as a bioisostere of the acetic acid moiety in a series of aldose reductase inhibitors," *Bioorganic & Medicinal Chemistry*, vol. 21, no. 17, pp. 4951–4957, 2013.

[97] C. B. Kelly, M. A. Mercadante, and N. E. Leadbeater, "Trifluoromethyl ketones: properties, preparation, and application," *Chemical Communications*, vol. 49, no. 95, pp. 11133–11148, 2013.

[98] Y. Ducharme, M. Blouin, M.-C. Carrière et al., "2,3-Diarylthiophenes as selective EP1 receptor antagonists," *Bioorganic & Medicinal Chemistry Letters*, vol. 15, no. 4, pp. 1155–1160, 2005.

[99] P. Clark, S. E. Rowland, D. Denis et al., "MF498 [N-{[4-(5,9-Diethoxy-6-oxo-6,8-dihydro-7H-pyrrolo [3,4-g]quinolin-7-yl)-3-methylbenzyl] sulfonyl}-2-(2-methoxyphenyl) acetamide], a selective E prostanoid receptor 4 antagonist, relieves joint inflammation and pain in rodent models of rheumatoid and osteoarthritis," *Journal of Pharmacology and Experimental Therapeutics*, vol. 325, no. 2, pp. 425–434, 2008.

[100] R. Jones, M. Giembycz, and D. Woodward, "Prostanoid receptor antagonists: development strategies and therapeutic applications," *British Journal of Pharmacology*, vol. 158, no. 1, pp. 104–145, 2009.

[101] R. J. Linderman and D. M. Graves, "Oxidation of fluoroalkyl-substituted carbinols by the dess-martin reagent," *Journal of Organic Chemistry*, vol. 54, no. 3, pp. 661–668, 1989.

[102] G. K. S. Prakash, R. Krishnamurti, and G. A. Olah, "Synthetic methods and reactions. 141. Fluoride-induced trifluoromethylation of carbonyl compounds with trifluoromethyltrimethylsilane(TMS-CF3). a trifluoromethide equivalent," *Journal of the American Chemical Society*, vol. 111, no. 1, pp. 393–395, 1989.

[103] R. P. Singh, G. Cao, R. L. Kirchmeier, and J. N. M. Shreeve, "Cesium fluoride catalyzed trifluoromethylation of esters, aldehydes, and ketones with (trifluoromethyl) trimethylsilane," *Journal of Organic Chemistry*, vol. 64, no. 8, pp. 2873–2876, 1999.

[104] J. Wiedemann, T. Heiner, G. Mloston, G. K. S. Prakash, and G. A. Olah, "Direct preparation of trifluoromethyl ketones from carboxylic esters: trifluoromethylation with (trifluoromethyl) trimethylsilane," *Angewandte Chemie International Edition*, vol. 37, no. 6, pp. 820-821, 1998.

[105] J. P. Bégué and D. Bonnet-Delpon, "Preparation of trifluoromrthyl ketones and related fluoriated ketones," *Tetrahedron*, vol. 47, pp. 3207–3258, 1991.

[106] R. J. Linderman and D. M. Graves, "An efficient procedure for the oxidation of fluorinated carbinols," *Tetrahedron Letters*, vol. 28, no. 37, pp. 4259–4262, 1987.

[107] V. Kesavan, D. Bonnet-Delpon, J.-P. Bégué, A. Srikanth, and S. Chandrasekaran, "New catalytic oxidation of trifluoromethyl carbinols by a ruthenium(II) complex," *Tetrahedron Letters*, vol. 41, no. 18, pp. 3327–3330, 2000.

[108] Y. Tanaka, T. Ishihara, and T. Konno, "A new entry for the oxidation of fluoroalkyl-substituted methanol derivatives: scope and limitation of the organoiodine(V) reagent-catalyzed oxidation," *Journal of Fluorine Chemistry*, vol. 137, pp. 99–104, 2012.

[109] I. Baxendale, S. Ley, W. Lumeras, and M. Nesi, "Synthesis of trifluoromethyl ketones using polymer-supported reagents," *Combinatorial Chemistry & High Throughput Screening*, vol. 5, pp. 197–199, 2012.

[110] J. P. Bégué, M. Charpentier-Morize, and G. Née, "Alkylation of ethyl 4,4,4-trifluoroacetoacetate. first example of a reversible O-alkylation process leading to C-alkylation," *Journal of the Chemical Society - Series Chemical Communications*, vol. 1989, pp. 83-84, 1989.

[111] C. Aubert, J.-P. Begue, M. Charpentier-Morize, G. Nee, and B. Langlois, "Alkylation du trifluoroacetylacetate d'ethyle methode generale d'acces aux trifluoromethylcetones. 2ème partie: alkylations indirects du TFAAE," *Journal of Fluorine Chemistry*, vol. 44, no. 3, pp. 377–394, 1989.

[112] A. P. Krapcho, J. F. Weimaster, J. M. Eldridge, E. G. E. Jahngen, A. J. Lovey, and W. P. Stephens, "Synthetic applications and mechanism studies of the decarbalkoxylations of geminal diesters and related systems effected in dimethyl sulfoxide by water and/or by water with added salts," *Journal of Organic Chemistry*, vol. 43, no. 1, pp. 138–147, 1978.

[113] A. A. Arabi, "Routes to drug design via bioisosterism of carboxyl and sulfonamide groups," *Future Medicinal Chemistry*, vol. 9, no. 18, pp. 2167–2180, 2017.

[114] A. Ammazzalorso, B. De Filippis, L. Giampietro, and R. Amoroso, "N -acylsulfonamides: synthetic routes and biological potential in medicinal chemistry," *Chemical Biology & Drug Design*, vol. 90, no. 6, pp. 1094–1105, 2017.

[115] M. P. Winters, C. Crysler, N. Subasinghe et al., "Carboxylic acid bioisosteres acylsulfonamides, acylsulfamides, and sulfonylureas as novel antagonists of the CXCR2 receptor," *Bioorganic & Medicinal Chemistry Letters*, vol. 18, no. 6, pp. 1926–1930, 2008.

[116] D. E. Uehling, K. H. Donaldson, D. N. Deaton et al., "Synthesis and evaluation of potent and selective β3 adrenergic receptor agonists containing acylsulfonamide, sulfonylsulfonamide, and sulfonylurea carboxylic acid isosteres," *Journal of Medicinal Chemistry*, vol. 45, no. 3, pp. 567–583, 2002.

[117] S. Mondal and S. Malakar, "Synthesis of sulfonamide and their synthetic and therapeutic applications: recent advances," *Tetrahedron*, vol. 76, no. 48, Article ID 131662, 2020.

[118] A. Yasuhara, M. Kameda, and T. Sakamoto, "Selective monodesulfonylation of N,N-disulfonylarylamines with tetrabutylammonium fluoride," *Chemical and Pharmaceutical Bulletin*, vol. 47, no. 6, pp. 809–812, 1999.

[119] X. Deng and N. S. Mani, "A facile, environmentally benign sulfonamide synthesis in water," *ChemInform*, vol. 38, pp. 835–838, 2007.

[120] C. M. R. Low, H. B. Broughton, S. B. Kalindjian, and I. M. McDonald, "Novel oxathiazinones as gastrin ligands: unexpected preducts from the schotten-baumann reaction of arylsulphonyl chlorides with derivatives of aspartic acid," *Bioorganic & Medicinal Chemistry Letters*, vol. 2, no. 4, pp. 325–330, 1992.

[121] Z. Almarhoon, S. M. Soliman, H. A. Ghabbour, and A. El-Faham, "A facile and eco-friendly method for the synthesis of sulfonamide and sulfonate carboxylic acid derivatives-X-ray structure, hirshfeld analysis and spectroscopic characterizations," *Crystals*, vol. 9, pp. 1–14, 2019.

[122] A. V. Bogolubsky, Y. S. Moroz, P. K. Mykhailiuk et al., "Sulfonyl fluorides as alternative to sulfonyl chlorides in parallel synthesis of aliphatic sulfonamides," *ACS Combinatorial Science*, vol. 16, no. 4, pp. 192–197, 2014.

[123] M. Soltani Rad, A. Khalafi-Nezhad, Z. Asrari, S. Behrouz, Z. Amini, and M. Behrouz, "One-pot synthesis of sulfonamides from primary and secondary amine derived sulfonate salts using cyanuric chloride," *Synthesis*, vol. 2009, no. 23, pp. 3983–3988, 2009.

[124] H. Veisi, R. Ghorbani-Vaghei, S. Hemmati, and J. Mahmoodi, "Convenient one-pot synthesis of sulfonamides and sulfonyl azides from thiols using N-chlorosuccinimide," *Synlett*, vol. 2011, no. 16, pp. 2315–2320, 2011.

[125] J. D. Bonk, D. T. Amos, and S. J. Olson, "Convenient one-pot synthesis of sulfonamides from thiols using trichloroisocyanuric acid," *Synthetic Communications*, vol. 37, no. 12, pp. 2039–2050, 2007.

[126] S. W. Wright and K. N. Hallstrom, "A convenient preparation of heteroaryl sulfonamides and sulfonyl fluorides from heteroaryl thiols," *Journal of Organic Chemistry*, vol. 71, no. 3, pp. 1080–1084, 2006.

[127] S. Sohrabnezhad, K. Bahrami, and F. Hakimpoor, "High yielding protocol for direct conversion of thiols to sulfonyl chlorides and sulfonamides," *Journal of Sulfur Chemistry*, vol. 40, no. 3, pp. 256–264, 2019.

[128] K. Bahrami, M. M. Khodaei, and M. Soheilizad, "Direct conversion of thiols to sulfonyl chlorides and sulfonamides," *Journal of Organic Chemistry*, vol. 74, no. 24, pp. 9287–9291, 2009.

[129] A. S. Deeming, C. J. Russell, and M. C. Willis, "Combining organometallic reagents, the sulfur dioxide surrogate DABSO, and amines: a one-pot preparation of sulfonamides, amenable to array synthesis," *Angewandte Chemie*, vol. 127, no. 4, pp. 1184–1187, 2015.

[130] C. F. Sturino and M. Labelle, "A convenient method for the preparation of acylsulfonamide libraries," *Tetrahedron Letters*, vol. 39, no. 33, pp. 5891–5894, 1998.

[131] M. Asada, T. Obitsu, A. Kinoshita et al., "Discovery of novel N-acylsulfonamide analogs as potent and selective EP3 receptor antagonists," *Bioorganic & Medicinal Chemistry Letters*, vol. 20, no. 8, pp. 2639–2643, 2010.

[132] D. Ellis, "Racemisation-free synthesis of chiral acylsulfonamides," *Tetrahedron: Asymmetry*, vol. 12, no. 11, pp. 1589–1593, 2001.

[133] T. De Ventura and V. Zanirato, "Recent advances in the synthesis of sulfonylureas," *European Journal of Organic Chemistry*, vol. 2021, no. 8, pp. 1201–1214, 2021.

[134] H.-J. Knölker, T. Braxmeier, and G. Schlechtingen, "A novel method for the synthesis of isocyanates under mild conditions," *Angewandte Chemie, International Edition in English*, vol. 34, pp. 2497–2500, 1995.

[135] C. A. Luckhurst, I. Millichip, B. Parker, J. Reuberson, and M. Furber, "A convenient synthesis of sulfonylureas from carboxylic acids and sulfonamides via an in situ curtius rearrangement," *Tetrahedron Letters*, vol. 48, no. 50, pp. 8878–8882, 2007.

[136] D. K. Tanwar, A. Ratan, and M. S. Gill, "A facile synthesis of sulfonylureas via water assisted preparation of carbamates," *Organic & Biomolecular Chemistry*, vol. 15, no. 23, pp. 4992–4999, 2017.

[137] T. Mizuno, T. Kino, T. Ito, and T. Miyata, "Synthesis of sulfonylurea derivatives used as oral antidiabetics by the selenium-assisted carbonylation using carbon monoxide with sulfur," *Synthetic Communications*, vol. 30, no. 17, pp. 3081–3089, 2000.

[138] I. Butula, V. Vela, and M. V. Prostenik, *Chem. Informationsd.*vol. 10, pp. 47–49, 1979.

[139] R. Hunter, A. e. Msutu, C. Dwyer, N. Emslie, R. Hunt, and B. Bezuidenhoudt, "Facile one-pot synthesis of carbamoylbenzotriazoles directly from CO2: synthesis of tolbutamide," *Synlett*, vol. 2011, no. 16, pp. 2335–2338, 2011.

[140] M. Hadianawala, A. Shaik, N. Hasija, A. K. Vasu, and D. B. Datta, "Sodium cyanate mediated synthesis of sulfonylurea and sulfonyltriuret from sulfonyl chloride and amine," *ChemistrySelect*, vol. 1, no. 10, pp. 2212–2216, 2016.

[141] A. A. Arabi, "Atomic and molecular properties of non-classical bioisosteric replacements of the carboxylic acid group," *Future Medicinal Chemistry*, vol. 12, pp. 1111–1120, 2020.

[142] A. C. Pippione, F. Dosio, A. Ducime et al., "Substituted 4-hydroxy-1,2,3-triazoles: synthesis, characterization and first drug design applications through bioisosteric modulation and scaffold hopping approaches," *MedChemComm*, vol. 6, no. 7, pp. 1285–1292, 2015.

[143] S. Sainas, P. Temperini, J. C. Farnsworth et al., "Use of the 4-hydroxytriazole moiety as a bioisosteric tool in the development of ionotropic glutamate receptor ligands," *Journal of Medicinal Chemistry*, vol. 62, no. 9, pp. 4467–4482, 2019.

[144] A. Giraudo, J. Krall, B. Nielsen et al., "4-Hydroxy-1,2,3-triazole moiety as bioisostere of the carboxylic acid function: a novel scaffold to probe the orthosteric γ-aminobutyric acid receptor binding site," *European Journal of Medicinal Chemistry*, vol. 158, pp. 311–321, 2018.

[145] J. L. Andersen, S. Lindberg, M. Langgård et al., "The identification of novel acid isostere based inhibitors of the VPS10P family sorting receptor sortilin," *Bioorganic & Medicinal Chemistry Letters*, vol. 27, no. 11, pp. 2629–2633, 2017.

[146] C. Ballatore, J. H. Soper, F. Piscitelli et al., "Cyclopentane-1,3-dione: a novel isostere for the carboxylic acid functional group. Application to the design of potent thromboxane(A2) receptor antagonists," *Journal of Medicinal Chemistry*, vol. 54, no. 19, pp. 6969–6983, 2011.

[147] B. M. Trost, G. Dong, and J. A. Vance, "Cyclic 1,2-diketones as core building blocks: a strategy for the total synthesis of (−)-Terpestacin," *Chemistry - A European Journal*, vol. 16, no. 21, pp. 6265–6277, 2010.

[148] F. Sehgelmeble, J. Janson, C. Ray et al., "Sulfonimidamides as sulfonamides bioisosteres: rational evaluation through synthetic, in vitro, and in vivo studies with γ-secretase inhibitors," *ChemMedChem*, vol. 7, no. 3, pp. 396–399, 2012.

[149] B.-T. Hong, Y.-S. E. Cheng, T.-J. Cheng, and J.-M. Fang, "Boronate, trifluoroborate, sulfone, sulfinate and sulfonate congeners of oseltamivir carboxylic acid: synthesis and anti-influenza activity," *European Journal of Medicinal Chemistry*, vol. 163, pp. 710–721, 2019.

[150] G. Wuitschik, M. Rogers-Evans, K. Müller et al., "Oxetanes as promising modules in drug discovery," *Angewandte Chemie*, vol. 118, no. 46, pp. 7900–7903, 2006.

[151] C. Horgan and T. P. O'Sullivan, "Recent developments in the practical application of novel carboxylic acid bioisosteres," *Current Medicinal Chemistry*, vol. 29, 2022.