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The influence and manipulation of acid/base properties in drug discovery

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There is a growing awareness of the importance of acid/base properties in medicinal chemistry research. In many drug classes, ionisable groups are present that make critical interactions with the receptor and are essential for potency. Yet the presence of these groups may cause problems with oral bioavailability, pharmacokinetics, or toxicity. Manipulating pK_a values during drug development or applying pro-drug techniques are strategies that can overcome potential deficits in a variety of these areas. Knowledge of drug ionisation states coupled with a consideration of pH-specific cellular environments can be used advantageously to target chemoresistance. As modern drug research ventures into drug candidates that exceed the rule of 5, such exploration requires an understanding of drug acid/base properties and how these factors affect ADMET characteristics.

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Introduction

The attraction or repulsion between electrostatic charges underlies many chemical phenomena. Ionic interactions, hydrogen bonding and dispersion forces, are fundamentally charge–charge interactions, and the interaction between a drug and its protein binding site is dictated by the complementarity of drug and binding site charge and shape. Frequently, the binding of a drug to a protein target is dominated by a single strong electrostatic interaction that, in most cases, arises from the ionisation of weak to moderately-strong acids and bases present in the protein and drug. For example, in biogenic amine G protein-coupled receptors (GPCRs), such as the dopamine or serotonin receptors, an ionisable amino group in the ligand forms a strong ionic interaction (a ''salt-bridge'') with a negatively charged aspartic acid residue within the binding site [1]. Removal of either the positive charge from the ligand or the negatively charged residue from the protein generally abolishes biological activity. Other drug classes, for example the ''statin'' inhibitors of cholesterol biosynthesis, require an acidic functional group on the ligand in order to have sufficient potency. The carboxylate group of these drugs forms a strong ionic interaction with a charged lysine and an adjacent serine residue of HMG-CoA reductase, replicating a similar interaction made by the substrate, HMG-CoA [2]. Removal of the carboxylate greatly reduces potency.

The strength of the interaction between ionised acid/base pairs has important implications for drug development. In many drug targets, the contribution of the ionic interaction to ligand affinity makes it difficult (or impossible) for the medicinal chemist to substitute the ionisable functional group, leading to these groups being a 'non-negotiable' feature of many drug class chemotypes (Fig. 1). Recent reviews have given insights into the acid/base profiles of drugs [3,4], biologically active substances, and screening compounds [5]. Importantly, the presence of ionised functional groups within drugs broadly

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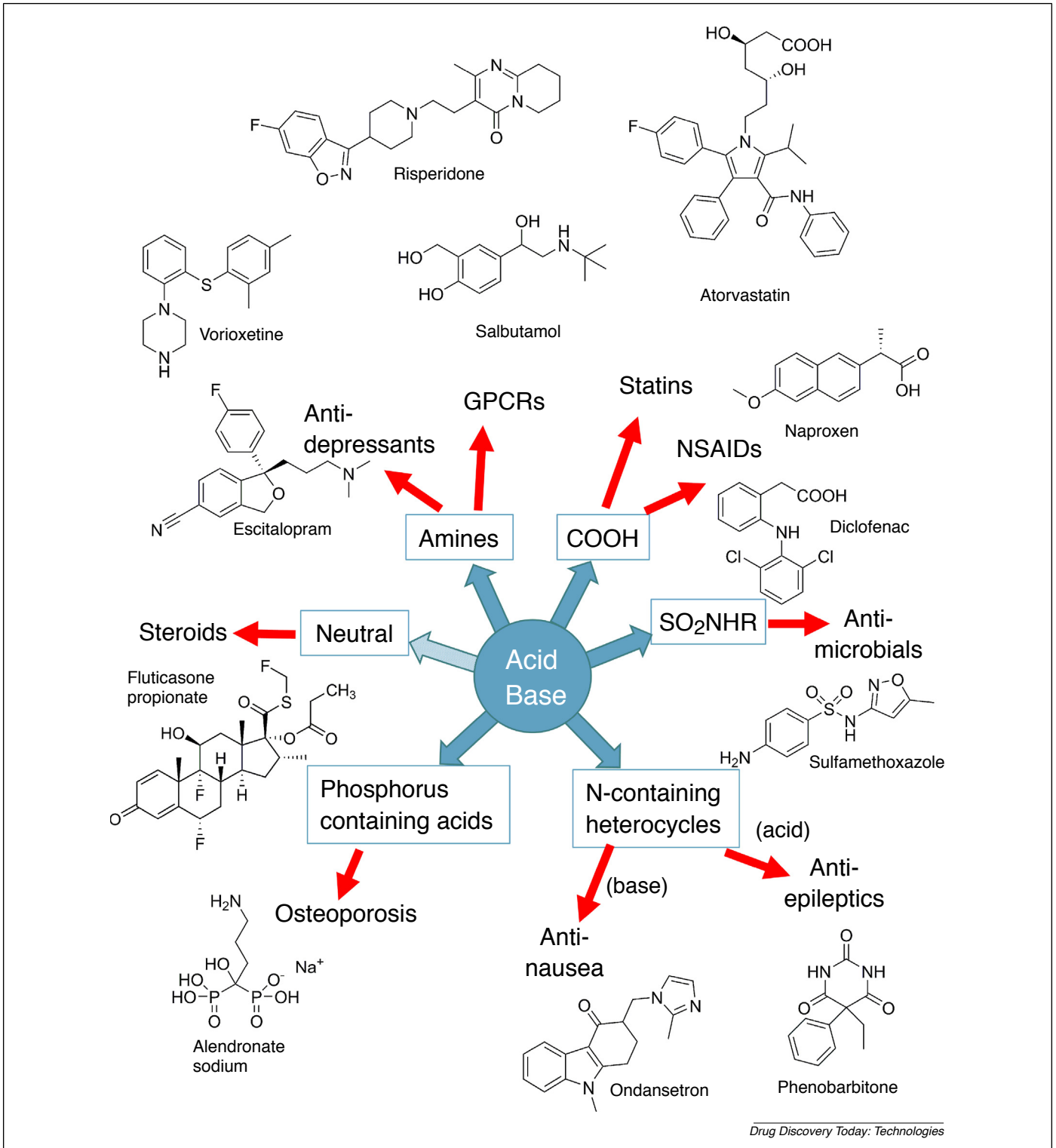

Fig. 1. Examples of compound or therapeutic drug classes and associated ionisable functional groups. ``Neutral'' refers to their molecular state under physiological conditions.

impacts drug behaviour within the body. Acidic and basic characteristics, in combination with whole molecule lipophilicity, affect drug behaviour in a number of broad areas:

- Molecular interactions with the target macromolecule
- Passage across cells [permeability, absorption and distribution]
- Toxicity [e.g. hERG channel blockade, phospholipidosis]
- Pharmacokinetics [clearance, plasma and tissue binding, metabolism]

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