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Electrosynthesis methods and approaches for the preparative production of metabolites from parent drugs

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ABSTRACT

Identification of potentially toxic metabolites is important for drug discovery and development. Synthesis of drug metabolites is typically performed by organic synthesis or enzymatic methods, but is not always straightforward. Electrochemical (EC) methods are increasingly used to study drug oxidation and to identify potential metabolites of new drug candidates, but the absolute yield of metabolites of these methods is low. This review discusses the challenges and recent developments of EC synthesis in terms of instrumental aspects, EC-reaction parameters and reaction-monitoring approaches, in an effort to produce drug metabolites selectively from parent drugs on a preparative scale (1–10 mg).

Contents

1. Introduction

Drug discovery and development is a high-cost, long-term process. It is therefore important to identify possibly toxic drug metabolites at the early stages of drug development [1–3]. Prior to clinical trials, drug-metabolism studies are often performed in experimental models *in vivo* and *in vitro* [4,5]. Animal and human liver microsomes, whole animal models, and isolated enzymes are used to investigate cytochrome P450 (CYP450)-mediated metabolic oxidation reactions [4–7]. However, scaling up *in vivo* or *in vitro* metabolite synthesis to mg levels, which is required for toxicity testing and structural characterization [e.g., by nuclear magnetic resonance (NMR)], is not straightforward, and metabolites have to be extensively purified. Also, these systems have limitations in isolating Phase-I metabolites, which can have a short half-life and eventually bind to cellular macromolecules or are further converted to Phase-II metabolites [8].

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Drug metabolites are generally synthesized via organic chemistry methods. Electrochemical (EC) synthesis methods, utilizing electron-transfer processes in an EC cell to oxidize drug compounds in a controlled manner, can offer an alternative for the production of drug metabolites [9,10]. Compared to organic synthesis methods, EC synthesis has several advantages including a limited number of reaction steps, mild reaction conditions, limited use of organic solvents and hazardous chemicals and the use of fairly simple equipment [11–13]. Electrochemistry can be readily combined with mass spectrometry (EC-MS) for product monitoring facilitating optimization of reaction conditions and is widely used as an analytical technique to study oxidative drug metabolism [14,15]. However, production of sufficient amounts of drug metabolites (1–10 mg) in a fast, specific manner requires careful adaptation of the existing analytical EC and EC-MS methods.

Conventional electrosynthesis methods have been used for a wide range of synthetic reactions using building blocks with redox-active functional groups. However, there are challenges in the synthesis of drug metabolites by EC modification of the parent-drug compound, due to the complex structure of many drug molecules. Moreover, there are technical challenges to the scaling up of electrosynthesis methods, including the geometry and the surface area of electrodes, which affect mass-transfer and conversion rates. Finally, the chemical properties of electrodes and substrates may lead to adsorption on the electrode surface, particularly at the high substrate concentrations required for preparative reactions [1,3,16]. Recent technological developments led to the more intensive application of electrochemistry for the synthesis of drug metabolites or active compounds in the pharmaceutical industry [17]. For example, Nematollahi et al. [18] have synthesized phenylpiperazine derivatives, which are biologically active compounds used in various therapeutic areas, in mg amounts using electrochemistry on carbon-rod electrodes (Fig. 1).

The approaches to metabolite electrosynthesis described in this review typically use the parent drug as the EC substrate, although analogues or prodrugs can also be considered in cases where they provide easier starting points for EC synthesis. For example, analgesic drug phenacetin is initially metabolized by O-dealkylation to

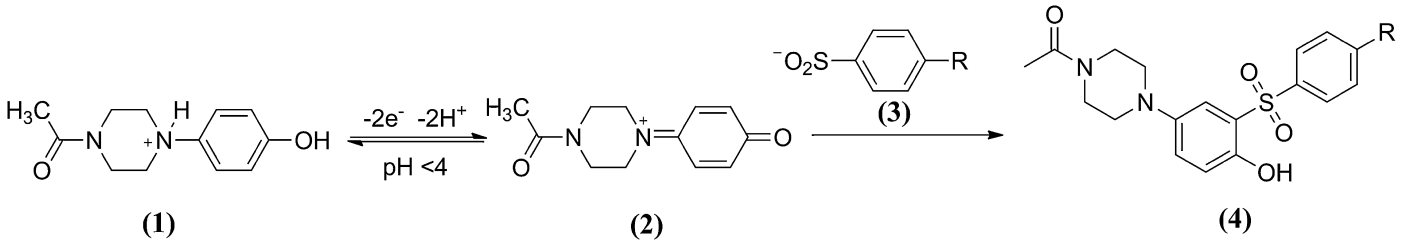

Fig. 1. Electrochemical (EC) synthesis of phenylpiperazine derivatives. EC oxidation of 4-acetyl-1-(4-hydroxyphenyl)piperazin-1-ium (1) forms a quinone-imine derivative (2) which allows a coupling reaction in the presence of arylsulfinic acid derivatives (3) to form phenypiperazine derivatives (4) [18].

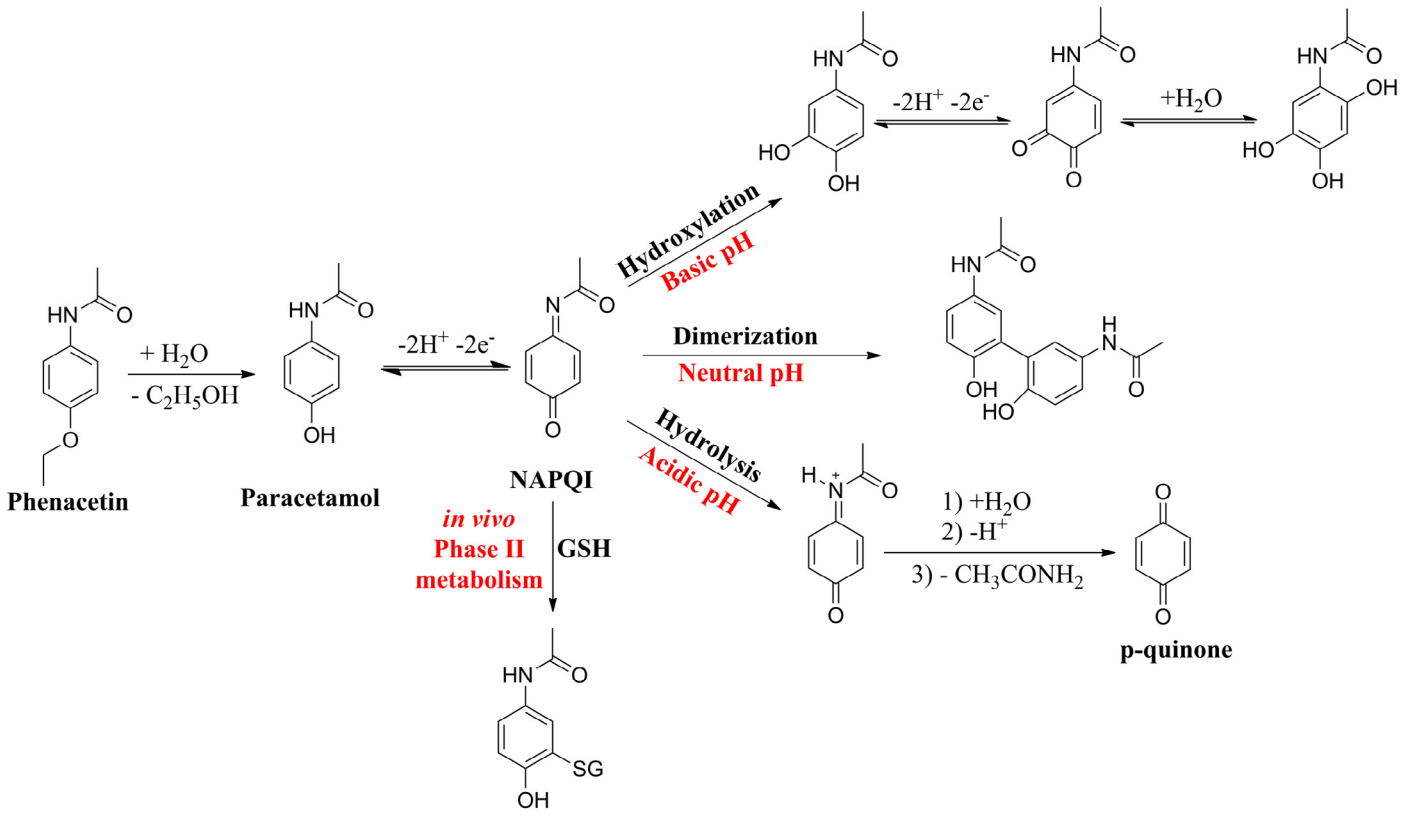

Fig. 2. Metabolic pathway of phenacetin to NAPQI. The NAPQI metabolite of phenacetin reacts at neutral pH to form a dimer. Hydroxylation occurs at basic pH and the amide of NAPQI is hydrolyzed to the *p*-quinone at acidic pH. *In vivo* NAPQI forms a Phase-II metabolite in the presence of glutathione (GSH) [19,20].