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Minireview for special section entitled "Drug Metabolism and Mass Spectrometry to Enable Precision Medicine"

Title Page

Title: Combined oral contraceptives as victims of drug interactions

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Running Title Page

Running title: Drug interactions of oral contraceptives

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Nonstandard Abbreviations:

AUC area under the plasma concentration-time curve; **CAR** constitutive androstane receptor; **CDC** Centers for Disease Control and Prevention; **COCs** Combined oral contraceptives; **CIs** confidence intervals; **CYP** cytochrome P450; **DDIs** drug-drug interactions; **DRSP** drospirenone;

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DNG dienogest; **EE** ethinyl estradiol; **ENG** etonogestrel; **FDA** Food and Drug Administration; **IVIVE** in vitro-to-in vivo extrapolation; **LNG** levonorgestrel; **MDCK** Madin-Darby canine kidney; **MRP** multi-drug resistance protein; **NET** norethindrone; **NGM** norgestimate; **NGMN** norelgestromin; **OAT** organic anion transporters; **OATP** organic anion transporting polypeptide; **PD** pharmacodynamic; **P-gp** P-glycoprotein; **PK** pharmacokinetics; **PXR** nuclear pregnane X receptor; **SULTs** sulfotransferases; **UGTs** UDP-glucuronosyltransferases; **UK** United Kingdom; **US** United States; **UW DIDB** University of Washington Drug Interaction Database; **VTEs** venous thromboembolisms; **WHOMEC** World Health Organization updated Medical Eligibility Criteria for Contraceptive Use

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Abstract

Combined oral contraceptives (COCs) are widely used in women of reproductive age in the United States. Metabolism plays an important role in the elimination of estrogens and progestins contained in COCs. It is unavoidable that a woman using COCs may need to take another drug to treat a disease. If the concurrently used drug induces enzymes responsible for the metabolism of progestins and/or estrogens, unintended pregnancy or irregular bleeding may occur. If the concurrent drug inhibits the metabolism of these exogenous hormones, there may be an increased safety risk such as thrombosis. Therefore, for an investigational drug intended to be used in women with reproductive potential, evaluating its effects on the pharmacokinetics of COCs is important to determine if additional labeling is necessary for managing drug-drug interactions between the concomitant product and the COCs. It is challenging to determine when this clinical drug interaction study is needed, whether an observed exposure change of progestin/estrogen is clinically meaningful, and if the results of a clinical drug interaction study with one COC can predict exposure changes of unstudied COCs to inform labeling. In this review, we summarize the current understanding of metabolic pathways of estrogens and progestins contained in commonly used COCs, known interactions of these COCs as victim drugs, and discuss possible mechanisms of interactions for unexpected results. We also discuss recent advances, knowledge gaps, and future perspectives on this important topic. The review will enhance the understanding of DDIs with COCs and improve the safe and effective use of COCs.

Significance Statement

This minireview provides an overview of the metabolic pathways of ethinyl estradiol (EE) and progestins contained in commonly used COCs and significant drug interactions of these COCs as

victims. It also discusses recent advances, knowledge gaps, and future perspectives and provides insights on potential mechanisms for unexpected results of clinical drug interaction studies of COCs. This minireview will help the reader understand considerations when evaluating the drug interaction potential with COCs for drugs that are expected to be used concurrently.

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Body of Manuscript

Introduction

In the United States (US), approximately 45% of all pregnancies are unintended (Finer and Zolna, 2016; CDC, 2020) and about half of unintended pregnancies are among women who became pregnant despite reported use of contraception (Finer and Henshaw, 2006; Sundaram et al., 2017). As the most commonly used reversible method of contraception, oral contraceptives comprise 22% of all contraception in current users (Kavanaugh and Pliskin, 2020) and are highly effective (1% failure rate) when compliance is high. Data from the National Survey of Family Growth indicate that typical users report a 9% failure rate possibly due to incorrect or inconsistent use of contraceptives. It is possible that drug-drug interactions (DDIs) with a combined oral contraceptive (COC) may potentially contribute to the failure rate by compromising the effectiveness of these oral contraceptives. Based on data from the US Centers for Disease Control and Prevention (CDC), 46% of women ages 18-44 years use at least one prescription drug and 12% of women use three or more prescription drugs, suggesting a great potential for DDI to occur when COCs are concomitantly used with other drugs. Therefore, assessing the potential of DDIs with COCs and effectively communicating known interactions is critical to prevent unintended pregnancies which will provide substantial individual and public health benefits.

COCs contain a combination of an estrogen and a progestin, both of which are usually synthetic steroid hormones. A higher rate of venous thromboembolism (VTE) was reported in women taking COCs containing higher dose of estrogen (Gerstman et al., 1991). EE is the most widely used estrogenic component of COCs. Since the introduction of COCs in the 1960s, the dose of EE has been reduced from the initially approved dose of 50 mcg to the currently most prescribed

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doses of 15 - 35 mcg to reduce the risk of cardiovascular events. Commonly used progestins in COCs in the US include norethindrone (NET), levonorgestrel (LNG), norgestimate (NGM), and drospirenone (DRSP).

Metabolism plays a major role in the elimination of both estrogens and progestins. As a result, systemic exposures to these hormones may be significantly decreased or increased when used concurrently with drugs or herbal products that induce or inhibit the enzymes involved in the metabolism of these hormones. Reduced concentrations of estrogens and progestins may lead to unintended pregnancy and decreased exposures of estrogen can result in irregular (unscheduled) bleeding which may adversely affect patient compliance. Conversely, increased concentrations of estrogens or certain progestins can increase the risk of severe adverse cardiovascular events such as VTE (van Hylckama Vlieg et al., 2009; FDA, 2020).

Although COCs have been used for many years, the impact of these DDI effects on the efficacy and safety profile of COCs are still not fully understood. In this review, we summarize the metabolic and elimination pathways of estrogens and progestins contained in commonly used COCs, available clinical DDIs data with COCs, recent advances as well as knowledge gaps in this area, aiming to enhance the current understanding of the impact of drug interactions on COCs and improve the safe and effective use of COCs. It should be noted that in contrast to our review paper published in 2018 (Zhang et al., 2018) which focused primarily on assessing the role of cytochrome P450 (CYP) 3A in EE and progestin metabolism, the current manuscript extends the scope of discussion and contains information on possible mechanisms and clinical implications of COC DDIs, as well as FDA guidance recommendations regarding the need for conducting COC DDI studies.

Brief Historical Perspective

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The evaluation of DDI potential with COCs is challenging for several reasons. First, since most COCs were first developed over 50 years ago, the exposure-response relationships for efficacy and safety of COCs have not been well characterized. Consequently, when geometric mean ratios of COCs systemic exposure fall outside the default yet conservative no-effect boundary of 80 to 125 percent, it is difficult to translate the differences in pharmacokinetics (PK) observation into clinical outcomes and make labeling recommendations for risk mitigation. Another major barrier of understanding DDI for COCs is the lack of information on the relative contribution of each metabolic pathway to the clearance of progestins and estrogens. For instance, CYP3A-mediated metabolism is an established common feature of both EE and progestin clearance but the contribution of CYP3A to their elimination varies amongst the specific hormones and is not completely understood. As a result, when a clinical DDI study is conducted to investigate the effects of a drug on one COC, it can be challenging to predict effects of a concomitant drug on COCs with a different estrogen or progestin component. Also, previously observed increase in the area under the plasma concentration-time curve (AUC) of EE due to DDIs has been less than 2.4-fold (discussed in a later section). When the change in exposure is small, it is hard to predict what the exact magnitude of the change will be. Finally, Phase II drug metabolizing enzymes play a significant role in the biotransformation of certain estrogen and progestins. However, in vitro testing and in vitro-to-in vivo extrapolation (IVIVE) are lacking which makes it difficult to identify clinically significant DDIs via these metabolic pathways.

In recognition of the challenges in this area, the Food and Drug Administration (FDA) organized a public meeting entitled “Drug Interactions with Hormonal Contraceptives: Public Health and Drug Development Implications” in 2015 (Akbar et al., 2018). Key discussions in this meeting include when DDI studies with contraceptives are needed during drug development, what is the

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most appropriate study design, whether pharmacodynamic (PD) biomarkers can aid in better understanding DDI outcomes and in making clinical recommendations, and how to communicate DDI findings to clinicians and patients. Further, experts shared their perspectives on critical knowledge gaps, areas that require further investigation, and regulatory research opportunities that can be pursued to ensure the safe and effective use of COCs (e.g., differentiating DDI risks of COCs from that of non-oral and/or non-systemically acting hormonal contraceptives in drug labels). Following the workshop, tremendous efforts have been made. The Bill & Melinda Gates Foundation collaborated with University of Florida to quantitatively elucidate the impacts of DDI on unintended pregnancies and breakthrough bleeding, and to establish a DDI-prediction framework to inform optimal use of COCs (Lesko et al., 2018). In 2020, the FDA published a draft guidance, titled "Clinical Drug Interaction Studies with Combined Oral Contraceptives (COC)" (FDA-COC-DDI-Guidance, 2020). The draft guidance outlined the Agency's current thinking regarding how to determine the necessity of a clinical DDI study with COCs, how to design such studies, as well as how to interpret and report DDI study results with actionable risk mitigation strategies in drug product labeling.

Key Recent Advances

In this section, we present key recent advances in understanding of drug interactions of COCs. We summarize metabolic pathways and enzymes involved in the metabolism of EE and progestins (NET, LNG, NGM, and DRSP) and then describe the overall impact of CYP3A inhibition on the systemic exposure of these hormones. We then focus on the results of clinical DDI studies for perpetrators that increased the exposure of EE (which may result in severe adverse events such as VTE) and the impact of CYP3A inducers on the exposure of progestins and EE (which may cause unintended pregnancy and unscheduled bleeding) and discuss possible

mechanisms for these interactions based on current knowledge. We also discuss the considerations of the FDA COC DDI draft guidance when recommending a clinical DDI study for a drug that inhibits or induces the metabolism of EE and these progestins. In addition, we provide recent advances in the understanding of concomitant use of COCs with broad-spectrum antibiotics that are not enzyme-inducing but was thought to be associated with contraceptive failure.

Metabolic pathways of EE and progestins

Table 1 summarizes current understanding on the metabolic pathways of EE (as the most common estrogen contained in COCs) and several progestins (NET, LNG, NGM, and DRSP) that are commonly used in COCs in the US (Table 1). Figures 1-5 present their key metabolic pathways along with chemical structures of major metabolites.

EE: EE is a synthetic derivative of the natural estrogen estradiol. Following oral administration, EE undergoes substantial first pass metabolism with mean absolute oral bioavailability about 45% (ranging from 20% to 65%) (Stanczyk et al., 2013). The metabolism of EE is primarily mediated through hydroxylation by CYPs and conjugation via sulfotransferases (SULTs) and UDP-glucuronosyltransferases (UGTs) (Zhang et al., 2007). An in vitro study showed that hydroxylation of EE was mainly mediated by CYP3A and to a minor extent by CYP2C9 (Wang et al., 2004). Glucuronidation, primarily catalyzed by UGT1A1 in the liver (Guengerich, 1990), may contribute up to 20% of EE systemic clearance (Zhang et al., 2007). Sulfation has long been recognized as an important pathway for the gut and hepatic metabolism of EE (Ebner et al., 1993). It was reported that sulfate conjugation in the gut contributes to approximately 60% of the first-pass effect (Goldzieher, 1989). The sulfation metabolites EE-3-sulfate and EE-17-sulfate circulated at concentrations of about 10-fold higher than EE itself. Among various isoforms of

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SULTs, SULT1E1 was suggested playing a predominant role (≥ 70%) in the sulfation of EE in the intestine and liver (Schrag et al., 2004; Zhang et al., 2007).

NET: NET is a derivative of the 19-nortestosterone, a synthetic analogue of testosterone. After oral administration, it undergoes extensive metabolism, primarily via reduction and hydroxylation, followed by conjugation (Braselton et al., 1977; Stanczyk and Roy, 1990). Hydroxylation of NET is mostly mediated by CYP3A4 and to a lesser extent by CYP2C19 (Korhonen et al., 2008). Sulfate conjugates are major circulating metabolites in plasma while glucuronide conjugates account for most of the urinary metabolites (AYGESTIN, 2007).

LNG: LNG is also a derivative of the 19-nortestosterone. The most important metabolic pathways of LNG are reduction of the Δ4-3-oxo group and hydroxylation at positions 2α, 1β, and 16β, followed by conjugation. After oral administration, 3α, 5β-tetrahydro-levonorgestrel sulfate was the predominant circulating conjugated metabolite in plasma (Sisenwine et al., 1975). In vitro studies suggested that CYP3A4 was the predominant isoform in CYP-mediated clearance of LNG, followed by CYP2C9 and CYP3A5 to a lesser degree (Roberts et al., 2021).

NGM: Like LNG and NET, NGM is also a derivative of 19-nortestosterone. NGM is a prodrug that is extensively metabolized by first-pass mechanisms in the gastrointestinal tract and/or liver. Following oral administration, NGM is rapidly deacetylated to 17-deacetylnorgestimate (i.e., norelgestromin or NGMN), an active metabolite that has concentrations far exceeding the concentrations of the parent drug and thus significantly contributes to the efficacy of NGM. NGMN is further converted to LNG which is another active metabolite of NGM but may contribute less to the efficacy of NGM, compared to NGMN (Hammond et al., 2003). In vitro studies show that CYP3A4 plays a key role in NGMN metabolism with a fraction metabolized

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(fm) of 0.57. CYP2B6 and to a lesser extent CYP2C9 were also involved in the metabolism of NGMN (Ahire et al., 2017).

DRSP: DRSP is a derivative of spironolactone. Following oral administration, it is extensively metabolized into two major pharmacologically inactive metabolites: an acid form of DRSP generated by opening of the lactone ring, and 4,5-dihydrodrospirenone-3-sulfate formed by reduction and subsequent sulfation. Some metabolites of DRSP are further converted to glucuronide conjugates that are excreted in the feces or urine (Krattenmacher, 2000). Although the aforementioned two major metabolites were reported to be formed independently of CYPs, coadministration of strong CYP3A inhibitors, boceprevir and ketoconazole, increased the exposure of DRSP by 2- to 2.68-fold, indicating that DRSP is also oxidized by CYP3A4 (Bayer, 2015; Wiesinger et al., 2015; VICTRELIS, 2017; YASMIN, 2022).

Besides metabolic enzymes, it is known that transporters also play a role in the disposition of many drugs. We searched via the University of Washington Drug Interaction Database (UW DIDB) (https://www.druginteractionsolutions.org/) for studies evaluating NET, LNG, NGM, NGMN, and DRSP as substrates of drug transporters. There is only one publication reporting an efflux ratio of 1.3 for NET in Madin-Darby canine kidney (MDCK) cells transfected with P-glycoprotein (P-gp) (Kim and Benet, 2004). The net efflux ratio for NET was 2.2 when the efflux ratio was corrected with that in un-transfected MDCK cells. This is just marginally above 2, a commonly used threshold to determine whether a compound is transported by P-gp. The result indicates that NET may be a rather weak substrate of P-gp and thus its PK may not be significantly affected by P-gp modulation. The same study also examined transport of EE by P-gp and reported a net efflux ratio of 11, implying that EE is a P-gp substrate in vitro. However, ketoconazole, a strong inhibitor of CYP3A that also inhibits P-gp, increased the AUC of EE only

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by 40% in humans (Wiesinger et al., 2015). In contrast, voriconazole, another strong inhibitor of CYP3A that does not inhibit P-gp, increased AUC of EE by 61% (Andrews et al., 2008). Further, dronedarone, a moderate inhibitor of CYP3A that inhibits P-gp, increased EE AUC by 28% while fluconazole, a moderate inhibitor of CYP3A that does not inhibit P-gp, increased the AUC of EE by 24%-38% (Sinofsky and Pasquale, 1998; Hilbert et al., 2001; NDA022425, 2009; DIFLUCAN, 2022). The results of these clinical DDI studies showed that dual inhibitors of CYP3A and P-gp did not have a larger effect on the exposure of EE compared to inhibitors of CYP3A alone, indicating that P-gp may not play a significant role in the PK of EE. Therefore, the focus is on metabolic enzymes in this review.

The impact of enzyme inhibition on the exposure of EE and progestins

While CYP3A is the major isoenzyme responsible for the oxidative metabolism of EE and most of the progestins, the impact of CYP3A inhibition on the exposure of these drugs varies (Zhang et al., 2018; Sun et al., 2020). This may be due to varying degrees of the contribution from other metabolic pathways (e.g., reduction, direct glucuronidation or sulfation) to their overall clearance. For EE, NET, and LNG, their exposures were generally increased by up to ~50% in the presence of moderate or strong inhibitors of CYP3A (defined as drugs that increase AUC of sensitive substrates of CYP3A 2-5 folds or ≥ 5 folds, respectively). For example:

- Ketoconazole, a strong CYP3A inhibitor, increased the AUC of orally administered EE by 40% (Wiesinger et al., 2015).
- Fluconazole, a moderate inhibitor of CYP3A and a strong inhibitor of CYP2C19, had a modest effect on AUC of NET (increased by 13%) (Hilbert, et al. 2001).

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- Voriconazole, a strong inhibitor of CYP3A and a moderate inhibitor of CYP2C19, elevated the AUC of NET by 53% (Andrews et al., 2008).
- Telithromycin, another strong CYP3A inhibitor, increased the AUC of LNG by 50% (KETEK, 2015).

Compared to EE, LNG, and NET, the impact of CYP3A inhibition on the exposure of NGMN was larger, as indicated by an increase of 85% in NGMN AUC when it was given along with the combination of atazanavir and ritonavir (a moderate-to-strong inhibitor of CYP3A) (Zhang et al., 2011). The impact of CYP3A inhibition on the exposure of DRSP is even larger. As mentioned above, results of clinical studies showed 2- to 2.68-fold higher exposure of DRSP when DRSP was co-administered with ketoconazole or boceprevir, two strong inhibitors of CYP3A (Wiesinger et al., 2015; VICTRELIS, 2017).

As mentioned earlier, most prescribed COCs in the US contain EE at a dose of 35 mcg or lower due to known increased risk of VTE and other thrombotic complications at doses of 50 mcg or higher (Gerstman et al., 1991). Thrombotic safety concerns arise when drug interactions could potentially elevate EE exposure of those lower doses to that corresponding to a level of 50 mcg EE or greater. For example, an approximately 40% increase in EE AUC for COCs containing 35 mcg EE is anticipated to result in exposure similar to 50 mcg EE and therefore, is likely to result in an increased risk of VTE and other thrombotic complications. To identify perpetrators that can cause such DDIs, we gathered results of clinical DDI studies conducted with strong or moderate CYP3A inhibitors and COCs containing EE as victim drugs through the UW DIDB (Table 2). This approach is similar to that applied in our previous review published in 2018 (Zhang et al., 2018) but in the current review, we also included the results of clinical studies evaluating the

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impact of these perpetrators on the substrates of CYP2C9 and UGT1A1, since these enzymes are also involved in metabolism of EE.

As shown by Table 2, inhibition of CYP3A alone (e.g., telithromycin) does not seem sufficient to cause an increase in EE AUC of more than 40%, which may be due to the involvement of multiple metabolizing enzymes in EE biotransformation. However, when an inhibitor of CYP3A also inhibits other enzyme(s) including CYP2C9 and UGT1A1, it may reduce the metabolism of EE to a greater extent and thus lead to exposure increase exceeding 40%. For example, voriconazole increased the AUC of EE by 61% on average (Andrews et al., 2008). Besides being a strong CYP3A inhibitor, voriconazole is known as an inhibitor of CYP2C9 leading to an 81% increase in the AUC of phenytoin, a substrate of CYP2C9 (Purkins et al., 2003). Atazanavir, a moderate-to-strong inhibitor of CYP3A, increased the AUC of EE by 48% (REYATAZ, 2020). It also inhibits UGT1A1 as demonstrated by studies where atazanavir increased the AUC of dolutegravir and raltegravir, two drugs mainly metabolized by UGT1A1, by 91% and 72%, respectively (Iwamoto et al., 2008a; Song et al., 2011a). In addition, atazanavir inhibited CYP2C9 with K_i of 12 μM and an unbound C_{max}/K_i ratio of 0.035 (NDA021567, 2003), thus the possibility of atazanavir to inhibit CYP2C9 in humans cannot be ruled out. Based on these observations, in the recently issued FDA's draft guidance on 'Clinical Drug Interaction Studies With Combined Oral Contraceptives', a clinical DDI study with EE-containing COCs is recommended when an investigational drug is a moderate or strong inhibitor of CYP3A and also inhibits other metabolizing enzymes of EE such as CYP2C9, UGT1A1, and SULT1E1 (FDA-COC-DDI-Guidance, 2020).

Review of the available literature data also revealed that the above recommendation does not capture all the situations where EE AUC increases by 40% or more (Table 3). Some of the

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interaction pathways that can lead to this increase are not readily apparent or not routinely assessed through in vitro experiments include sulfation inhibition as described below. Sulfation seems to be a major metabolic pathway of EE. Thus, a drug that inhibits sulfation (mainly mediated by SULT1E1) without inhibiting CYP3A could result in a significant increase of EE AUC. An article published in the 1980s suggests that ascorbic acid (vitamin C) and paracetamol (acetaminophen) increased plasma levels of EE possibly by competing for sulfation in the gut (Back et al., 1981). The impact of SULT1E1 inhibition on EE exposure is perhaps best demonstrated by a recent clinical DDI study of ziritaxestat with an EE/DRSP containing COC (Helmer et al., 2022). In this study, co-administration with ziritaxestat at 600 mg once daily for 18 days resulted in about 2.8-fold and 2.4-fold increase in EE C_{max} and AUC, respectively, but no significant changes on DRSP exposure, indicating that ziritaxestat did not potently inhibit CYP3A. The ratios of EE AUC with/without hydrolysis by arylsulfatase and glucuronidase on Day 18 versus Day 1 demonstrated a potent inhibition of sulfation by ziritaxestat but not for glucuronidation. This finding is consistent with in vitro data that ziritaxestat may be a potent inhibitor of SULT1E1 at clinically relevant doses. Another example is etoricoxib which increased the AUC of EE by 50%-60% at a dose of 120 mg administered once daily (Schwartz et al., 2009), but did not alter the exposure of S-warfarin, a probe substrate of CYP2C9 (Schwartz et al., 2007). Inhibition of SULT1E1 may be a possible mechanism for the increased EE exposure because etoricoxib inhibited SULT1E1 in vitro (Takemoto et al., 2008).

Despite the recognition that sulfation plays an important role in EE metabolism, the effect of an investigational drug on sulfotransferases (e.g., SULT1E1) is not routinely assessed in in vitro experiments during drug development. A recently published review article also underscores the importance of including SULT1E1 (and UGT1A1) during drug development when evaluating

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the DDI potential with EE-containing COCs (Rodrigues, 2022). As this is a recently recognized interaction, clinical studies evaluating the impact of SULT inhibition on EE clearance are limited. Thus, further research is needed to better understand the contribution of SULT inhibition to EE exposure increase and to explore approaches predicting in vivo DDI potential based on in vitro data.

The impact of CYP3A induction on the exposure of progestins

Drug interactions resulting in decreased exposure of progestins will lead to increased risk of contraception failure. Concomitant use of COCs with CYP3A4 inducers such as phenytoin and phenobarbital has been reported to be associated with unintended pregnancies (Kenyon, 1972; Shane-McWhorter et al., 1998). Table 4 lists DDIs where the mean AUC values of NET, LNG, NGMN, and DRSP were reduced by 20% or more by perpetrator drugs through a search of the UW DIDB for clinical DDI studies (up to September 2022). The results of the survey suggested that all the identified perpetrators are inducers of CYP3A except for brivaracetam, mavoglurant, and perampanel, for which the in vivo induction strength has not been classified. This is not surprising because CYP3A inducers may also induce other enzymes (e.g., CYP2C9, CYP2C19, and UGT1A1) involved in the metabolism of the progestins, as CYP3A inducers are usually agonists of nuclear pregnane X receptor (PXR), a shared pathway co-regulating the expression of these genes (Sonoda et al., 2002). Thus, the induction effect of an investigational drug on CYP3A determined from a clinical study may be utilized to qualitatively estimate its effect on COCs.

As shown in Figure 6 and Table 4, strong inducers of CYP3A, defined as drugs that reduce the AUC of CYP3A substrates by 80% or more (e.g., carbamazepine, phenytoin, and rifampin at doses higher than 300 mg) resulted in around 50% reduction in the AUC of LNG and NET and a

larger (86%) reduction in the AUC of DRSP (CYP3A probe data shown in Supplemental Table 1). These results are consistent with the findings from DDI studies of COCs with CYP3A inhibitors which indicate a bigger role of CYP3A in the elimination of DRSP compared to LNG and NET, and the general recognition that CYP3A is more inducible than other enzymes such as CYP2C isoenzymes and UGT1A1 (Hariparsad et al., 2017). For NGMN, even though no DDI studies with strong inducers of CYP3A have been conducted so far, it is expected that strong inducers of CYP3A will result in significant reduction of NGMN because efavirenz, a moderate CYP3A inducer, reduced the AUC of NGMN by 64% (Sevinsky et al., 2011). As a strong inducer of CYP3A, rifampin at 600 mg/day was reported to also decrease the AUC of another two progestins, dienogest (DNG) and etonogestrel (ENG, an active metabolite of desogestrel), by 87% (Wiesinger et al., 2020). Based on these studies, if an investigational drug is a strong inducer of CYP3A, it is anticipated to significantly reduce the exposure of COCs when concomitantly used. Therefore, avoiding concomitant use with a strong CYP3A inducer is recommended to mitigate the risk of potential contraceptive failure (FDA-COC-DDI-Guidance, 2020).

Compared to strong inducers of CYP3A, there may be more variation in the effects of moderate CYP3A inducers on the exposure of progestins, because: 1) the potency of moderate inducers varies per the current definition, i.e., drugs leading to reduction from 50% to 80% in the AUC of a sensitive substrate of CYP3A, corresponding to 2- to 5-fold induction of clearance of a substrate. Thus, the induction effect of some moderate inducers may be close to strong inducers, while some others may lean towards weak inducers; 2) the contribution of CYP3A and other enzymes to the elimination of progestins vary, and thus one progestin may be less sensitive to inducers than another. Among the four progestins discussed here, there is no study conducted for

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DRSP and a moderate inducer of CYP3A. However, considering that DRSP is primarily metabolized by CYP3A and rifampin at 600 mg/day reduced the AUC of DRSP by 86%, it is likely that a moderate inducer may substantially decrease the exposure of DRSP. NGMN was significantly affected (AUC decreased by 64%) by efavirenz, a moderate CYP3A inducer. LNG appears to be less affected by moderate inducers (e.g., efavirenz, possibly eslicarbazepine and oxcarbazepine at higher doses) with AUC reduction ranging from 36% to 56% (Fattore et al., 1999; Carten et al., 2012; Falcao et al., 2013b), but the reduction was still significant. Compared to NGMN and LNG, NET seems to be less affected by moderate inducers. As summarized in Table 4, several moderate inducers (St. John's wort, bosentan, etravirine, elagolix (higher dose), and nevirapine) decreased the AUC of NET by ~20% or less, with an exception that, in one study, rifabutin (a moderate CYP3A inducer) reduced the AUC by 46% (LeBel et al., 1998). However, in another study conducted with rifabutin with similar study design, NET AUC was only decreased by 13% (Barditch-Crovo et al., 1999). Because the effects of moderate inducers of CYP3A on COCs vary depending on the inducer and the COC, the FDA's guidance recommends that, when an investigational drug is found to be a moderate CYP3A inducer, a clinical DDI study may be conducted to characterize the magnitude of exposure change of a COC to determine whether the COC can be used concomitantly with the investigational drug. If no clinical DDI studies are conducted, the labeling of the perpetrator drug should recommend avoiding use with COCs (FDA-COC-DDI-Guidance, 2020).

The impact of weak CYP3A induction on the exposure of different progestins was assessed in a study conducted with a low dose of rifampin (10 mg/day). Rifampin is considered as a weak inducer at this low dose since it reduced the AUC of midazolam by 46% (Wiesinger et al., 2020). At this dose of rifampin, AUC values of LNG and NET were decreased by 17% and 12%,

respectively. The results were generally consistent with literature studies conducted with other weak inducers of CYP3A (e.g., lersivirine, elagolix (lower dose), and St. John's wort (in that study)) (Hall et al., 2003; Davis et al., 2012; Falcao et al., 2013b; Feldman et al., 2021). Compared to these two progestins, DNG, DRSP, and ENG were more affected, with the AUC decreasing by 28%, 30%, and 37%, respectively by 10 mg/day rifampin. For an investigational drug that is found as a weak inducer of CYP3A, the FDA's draft guidance recommends a clinical DDI study to characterize the drug's effect on a COC to determine if the investigational drug can be used concomitantly with the COC. If a study is not conducted, justification is needed (FDA-COC-DDI-Guidance, 2020). One factor to be considered is the magnitude of the drug's effect on a sensitive CYP3A substrate. Since a weak inducer is defined as a drug that decreases the AUC of a sensitive substrate of CYP3A by 20% to 50%, some inducers that have effects close to moderate inducers may have a significant impact on COCs, while some others that are weaker inducers are less likely to result in clinically significant interactions with COCs.

When planning a COC DDI study, there can be different choices on which progestins will be studied while the estrogen component is usually EE. Among the four commonly used progestins in the US, DRSP is more sensitive to CYP3A modulation as described above. If a study is conducted with DRSP and the result suggests no interaction, then the observation can be extrapolated to LNG, NET, and possibly NGMN which are less sensitive than DRSP to CYP3A induction. On the other hand, if a less sensitive progestin is selected, compared to the choice of using DRSP, there is a higher chance that the study may be able to confirm the lack of impact of the drug on the contraceptive tested. The caveat is such a choice may limit the ability to extrapolate the study results to other progestins.

The impact of CYP3A induction on the exposure of EE

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Decreased exposure of EE may lead to unscheduled bleeding, which could result in COC discontinuation, and increased risk of contraception failure (Rosenberg and Waugh, 1998). In general, we may rely on the induction effect of a drug on CYP3A to have a rough estimate of its effect on COCs, however, there have been unexpected DDI results with EE.

For example, efavirenz as a moderate CYP3A inducer would be expected to decrease EE concentrations. In a clinical DDI study conducted with EE/NGM, efavirenz given at 600 mg once daily for 14 days decreased the AUCs of NGMN and LNG, by 64% and 83%, respectively, while EE exposure was just reduced by 10% (Sevinsky et al., 2011). Notably, in addition to CYP3A, efavirenz can also induce UGT1A1 (Swart and Dandara, 2019), and concomitant use of efavirenz increases the clearance of drugs that are primarily eliminated via UGT1A1 metabolism (e.g., dolutegravir and raltegravir) (TIVICAY, 2019; ISENTRESS, 2021). Therefore, it is intriguing that efavirenz treatment did not result in any significant changes in EE clearance even though both CYP3A and UGT1A1 are involved in the metabolism of EE. In vitro, efavirenz inhibited the metabolic activity of CYP2C9 with IC_{50} or Ki of 15 to 20 μM (von Moltke et al., 2001; Xu and Desta, 2013) but there were inconsistent results about the effects of efavirenz on CYP2C9 mRNA levels (Mattinen et al., 2014; Nagai et al., 2018). The impact of efavirenz on CYP2C9 in vivo remains unknown. In addition, the effect of efavirenz on SULT1E1 has not been evaluated. Therefore, the reason for the unaffected EE exposure by efavirenz is to be uncovered.

The other example is etravirine, which increased the AUC of EE by 22% but did not affect the AUC of NET (Scholler-Gyure et al., 2009). Etravirine decreased the AUC of sildenafil, a sensitive substrate of CYP3A, by 57%, indicating that etravirine is a moderate inducer of CYP3A (NDA022187, 2008) . Etravirine also reduced the AUC of dolutegravir (by 70%), and

raltegravir but to a much lesser extent (by 10%) (NDA022187, 2008; Song et al., 2011b). In vitro, etravirine inhibited CYP2C9 (NDA022187, 2008). Although etravirine did not alter the AUC of S-warfarin, the parent-to-metabolite AUC ratio (S-warfarin/7-OH-S-warfarin) was increased by 82%, after 2-week treatment of etravirine, implying that etravirine may inhibit CYP2C9 (Kakuda et al., 2014). The effect of etravirine on SULT1E1 remains unknown.

In addition, there is sparse information about induction of SULT1E1. The production of EE-3-sulphate in human hepatocytes was increased 1.5- to 3.3-fold by rifampicin, a prototype inducer of CYP3A and an agonist of PXR (Li et al., 1999). However, several more recent studies using primary or cryopreserved cultured hepatocytes demonstrated that rifampin repressed gene expression of SULT1E1, reducing its mRNA level by 25% to 70% (Kodama et al., 2011; Gufford et al., 2018; Moscovitz et al., 2018). Interestingly, in the study reported by Moscovitz et al., CITCO, a constitutive androstane receptor (CAR) agonist, increased the mRNA of SULT1E1 by 2.09-fold (Moscovitz et al., 2018). These limited results implied that SULT1E1 is regulated differently compared to CYP3A4 considering that CYP3A4 is upregulated primarily through PXR activation. Further research is needed to investigate the induction mechanisms and pattern of SULT1E1.

Current understanding of DDI with broad-spectrum antibiotics

COCs and antibiotics are both among the most frequently prescribed drugs in the US. For many years, women have been counseled that their birth control might become less effective during antibiotic treatment. Clinical concerns regarding drug interactions between COCs and non-enzyme inducing antibiotics are mainly based on anecdotal reports of unintended pregnancies that were associated with concomitant use of COCs and antibiotics, most frequently tetracycline and penicillin in the 1980s (Back et al., 1988). It has been postulated that antibiotics can reduce

the quantity of the intestinal bacterial flora participating in hydrolysis of the estrogen conjugates, resulting in impaired re-entry of steroids into the circulation. While enterohepatic recirculation has been shown to play a key role in the kinetics of endogenous estradiol, its contribution to the enterohepatic recirculation of EE and progestins has been questioned (Goldzieher and Brody, 1990; Elomaa et al., 2001; Edelman et al., 2010). An observation is that the concentration-time profile of EE lacks a pronounced 2nd peak, the characteristic indicator of a significant contribution from the enterohepatic recirculation (Vree and Timmer, 1998).A PK study evaluated the possible role of enterohepatic cycling on the bioavailability of NET and gestodene by orally administering activated charcoal at 3 hours after OC pill intake (Elomaa et al., 2001). The data showed no statistically significant difference in the PK parameters (C_{max}, $AUC_{0\text{-}24hrs}$) with or without activated charcoal administration, suggesting that enterohepatic circulation of gestodene and NET is not of clinical importance. Other progestins such as DRSP and LNG have not been reported to undergo enterohepatic recycling. As it has now become clear that the progestin provides a major part of the contraceptive effect of COCs, the commonly accepted mechanism of decreasing enterohepatic circulation of COCs does not appear to be supported by available scientific evidence.

Furthermore, many PK studies have been conducted to evaluate the effect of non-enzyme inducing antibiotics on the systemic exposure of COCs and demonstrated a lack of interaction between COCs and antibiotics. Particularly, no significant decrease in the plasma level of EE has been found when COCs were concomitantly used with ampicillin, ciprofloxacin, clarithromycin, doxycycline, metronidazole, ofloxacin, roxithromycin, temafloxacin, and tetracycline (Archer and Archer, 2002). Other studies evaluated the impact of non-rifamycin antibiotics on PD activities of COCs and found no differences in ovulation suppression or breakthrough bleeding.

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Despite criticisms that some of these studies were too small or poorly designed, the World Health Organization updated Medical Eligibility Criteria for Contraceptive Use (WHOMEC) in 2009 based on available evidence. This guideline states that there is intermediate level evidence that the contraceptive effectiveness of COCs is not affected by coadministration of most broad-spectrum antibiotics and recommends no restriction on use (WHOMEC Category 1) of COCs with antibiotics (WHOMEC 2009). This position has been adopted by the US Centers for Disease Control and Prevention in its Medical Eligibility Criteria for Contraceptive Use (CDC 2010). In 2015, the FDA also removed the relevant statement regarding the potential effects of antibiotics on COC effectiveness from the contraceptives class labeling. Interestingly, researchers from the United Kingdom (UK) published an observational "database" study, suggesting a higher risk of contraceptive failure associated with the concurrent use of broad-spectrum antibiotics and hormonal birth control such as COCs, patches or rings (Aronson and Ferner, 2021). Based on an analysis of reported unwanted side effects (referred to as Yellow Cards in the UK), the researchers found that compared with control medicines, unintended pregnancies were seven times more commonly reported with antibiotics (odds ratio 6.7, 95% CI 2.9-16.0) and 13 times more commonly reported with enzyme inducers (the positive controls). It should be noted that the value of this report is limited by the retrospective design recall bias, and lack of supporting data on the potential cause of DDI.

Current Challenges and Knowledge Gaps

During drug development, if in vitro data suggests an investigational drug may inhibit or induce CYP3A at clinically relevant doses, clinical DDI studies using CYP3A substrates are often conducted. Although CYP3A contributes to the metabolism of both progestins and estrogens, in vitro or in vivo data using CYP3A probe substrates may not always predict the clinical DDI

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results with COCs. This is likely due to the lack of information on fractional contribution (fm) of each metabolizing enzyme to the clearance of COCs and how these perpetrators may affect other metabolic pathways (e.g., sulfation and glucuronidation) of the steroids. The issue may be particularly relevant for EE, given the limited contribution of CYP3A to its overall clearance relative to Phase II enzymes such as SULT1E1. As discussed earlier, it has not been fully characterized what factors cause substantial increase in EE exposure. It appears that there are some known factors (i.e., a drug acts as a moderate or strong inhibitor of CYP3A and inhibits other enzyme(s) involved in EE metabolism) but these examples do not cover all the identified cases of DDIs where EE AUC was increased above a threshold of 40% (Table 3). Furthermore, currently the effect of an investigational drug on SULT1E1 is usually not evaluated but may help better interpret the findings about EE exposure change.

Besides this knowledge gap, interpretation of the inhibition potency of a perpetrator on SULT1E1 or UGT1A1 using in vitro data is challenging. For major CYP enzymes, there are available criteria for in IVIVE by comparing in vivo concentration of a perpetrator to its in vitro inhibition potency (FDA-In-vitro-DDI-Guidance, 2020). However, such criteria have not been established for SULT1E1 and UGT1A1, due to lack of sufficient in vitro (IC_{50} or K_i of perpetrators) and in vivo data (clinical studies conducted with typical substrates of UGT1A1 or SULT1E1). Thus, it is hard to determine whether a drug inhibiting these Phase II enzymes in vitro will exert inhibitory effects in humans and consequently affect the exposure of their substrates such as EE. Effort from stakeholders including industry and academia is encouraged to fill the knowledge gaps to increase our understanding of the role of SULT1E1 and UGT1A1 in DDIs with EE and improve our ability to predict the effects of these interactions.

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One aspect that could be considered is to incorporate measurement of EE conjugates in DDI studies. As exemplified by the recently published work by Helmer et al. describing the DDI between ziritaxestat and a EE-containing COC, changes in the plasma concentrations of glucuronide and sulfate conjugates of EE were measured to deconvolute the interacting mechanism (i.e., inhibition of sulfation pathway instead of glucuronidation by ziritaxestat (Helmer et al., 2022)). In the study evaluating the effect of etoricoxib (Schwartz et al., 2009), sulfate conjugate of EE was also measured providing direct evidence that sulfation of EE was inhibited. However, it should also be noted that some metabolites are substrates of drug transporters. For example, EE-3-sulfate was transported by hepatic uptake transporters organic anion transporting polypeptide (OATP) 1B1, OATP2B1, and sodium-taurocholate cotransporting polypeptide, hepatic efflux transporter breast cancer resistance protein, and renal transporters OAT (organic anion transporter) 3 and OAT4 (Han et al., 2010a; Han et al., 2010b). EE-3-glucuronide was shown to be transported by multi-drug resistance protein (MRP) 2 and MRP3 (Chu et al., 2004). If an investigational drug inhibits or induces transporters, it may potentially impact the concentrations of Phase II metabolites of EE. Thus, caution is needed when interpreting changes in the metabolite/parent ratio of EE when attempting to gain insight on the effect of a drug on UGTs/SULTs in humans.

The complexity of drug interactions involving EE as the substrate is also illustrated by an unexpected decrease in EE exposures by ritonavir, a strong CYP3A inhibitor. Ritonavir alone (100 mg once daily) decreased the AUC of EE by 29% (Kasserra et al., 2011). At a higher dose (500 mg twice daily), ritonavir reduced EE AUC by 39% (Ouellet et al., 1998). The observed reduction in EE exposure may be explained by the fact that ritonavir is not only an inhibitor but also an inducer of CYP3A and several other enzymes including CYP2C9 and UGT1A1 (Smith et

al., 2005; Nagai et al., 2018). At 100 mg (once daily and twice daily) or 400 mg (twice daily) dose levels, ritonavir reduced the AUC of CYP2C9 substrates, S-warfarin and tolbutamide, by 24% and 50%, respectively (Kirby et al., 2011; Morcos et al., 2013). Ritonavir at 100 mg twice daily dose led to a decrease of 16% in the AUC of raltegravir which is primarily metabolized by UGT1A1 (Iwamoto et al., 2008b). The effects of ritonavir on SULTs remain unknown. The unexpected changes in EE exposures underscore the necessity of evaluating the inhibition and induction potential of an investigational drug on enzymes other than CYP3A4 that play a significant role in the metabolism of COCs.

Perspective on Future Directions

The understanding of COC DDIs remains challenging in the following areas:

- Identification of clinically significant DDI with COCs based on in vitro and/or in vivo data obtained using CYP3A probe substrates without considering the contribution of other metabolizing enzymes
- Translation of clinical DDI study results between investigational drugs and COCs to better predict clinical outcomes (e.g., increased failure rate)
- Extrapolation of DDI study data from one COC to the larger COC class

Most COCs were developed decades ago when the original information (e.g., human mass balance studies) was published prior to the availability of modern bioanalytical techniques and standardized metabolism enzyme characterization. In particular, the metabolism pathways of progestins and EE need to be well characterized with definitive fm values. To fill these knowledge gaps, further studies are needed to characterize Phase I and Phase II enzymes involved in the metabolism of COC components and their relative contribution to the clearance

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of these hormones. Compared to Phase I enzymes, there is limited experience with modulation of Phase II enzymes when assessing DDI interactions. Thus, it is important to generate more data and conduct research to better understand the role of those enzymes in the PK and DDIs of COCs. For example, as sulfation plays a major role in the elimination of EE, it is important to evaluate the inhibition potential of investigational drugs on SULT1E1, the enzyme primarily responsible for sulfation of EE. Further research is also warranted to explore optimal IVIVE criteria to predict a drug's inhibitory effect in humans on SULT1E1 and UGT1A1 which is also involved in metabolism of EE. In addition, research is needed to understand the mechanisms of SULT1E1 regulation since there are only few studies evaluating the effects of inducers on SULT1E1 expression. Overall, the obtained information will help to reduce the risk of leaving out clinically significant DDIs with COCs, which would not be discovered solely based on the investigational drug's interaction potential with CYP3A. Additionally, elucidation of fractional contribution of various metabolic pathways (fm) is critical to build physiologically-based PK models and quantitatively and qualitatively predict clinical DDIs with different COCs or different routes of administration (Ezuruike et al., 2018; Cicali et al., 2021). The ability of extrapolating DDI results to unstudied COCs as a class preclude the need to conduct a more cost-intensive clinical study with multiple COC products.

A major challenge is extrapolating the findings from the DDI study to specific safety and efficacy outcomes for COCs. It is highly encouraged that research continues in this area to fill the knowledge gaps. For COCs with novel estrogen and progestin components, it is important to generate sufficient data during drug development to help establish exposure or dose-response relationship. This will aid data interpretation in the future as more COCs become available in the US market. Clinical DDI studies have evaluated the impact of DDI on both PK and PD activities

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of COCs using PD markers such as progesterone, luteinizing hormone, and follicle-stimulating hormone concentrations, but it is unclear how well changes in these PD markers can predict the effectiveness outcomes. Further research needs to establish the relationship of these PD markers to the efficacy and safety of COCs, to help determine the clinical significance of DDIs, especially for perpetrator drugs that have modest induction effects. It should be noted that, while PD data can aid clinical interpretation of DDI study results, such a study needs to be adequately powered to overcome the potentially large variability of these PD markers. Additionally, post-marketing pharmacovigilance studies using real-world data may also be a valuable tool in informing DDI risks. For example, researchers from University of Florida explored the possibility of using a pharmacoepidemiologic approach to evaluate real-world effectiveness of oral contraceptives in the presence of drug interaction (Sarayani et al., 2021). Continued collaborations among all parties, including academia, agencies, the pharmaceutical industry, and the funders are needed to fill the knowledge gap in understanding the impact of DDIs on COCs so that COCs can be used safely and effectively.

Conclusions:

Given that there is a large cohort of women in the US that use COCs, investigating the interaction potential of COCs as victim drugs is very important when developing drugs that are intended to be used in women of reproductive potential. Identifying the drug interaction potential with COCs and predicting the impact of drug interaction(s) on the safety and efficacy of COCs are challenging but can be performed. Additional effort is needed to characterize the relative contributions of each metabolic pathway to the overall clearance of steroid hormones contained in COCs. For investigational drugs, adequate characterization of the interaction potential of an investigational drug on the metabolizing enzymes of COCs, including CYP3A,

CYP2C9, SULTs, and UGTs, is needed to help determine if clinical drug interaction studies with COCs should be conducted and to aid in interpreting the results of clinical drug interaction studies. More work needs to be completed to determine how to apply findings of drug interactions from assessment of one COC to others.

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Data Availability Statement:

The authors declare that all the data supporting the findings of this study are available within the paper and its Supplemental Data.

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Figure Legends

Figure 1. Major metabolic pathways of ethinyl estradiol (EE). The bolded enzyme is the major one when multiple enzymes were reported to be involved. CYP = cytochrome P450; Glu = glucuronide; Sul = Sulfate; SULT1E1 = sulfotransferase 1E1; UGT1A1 = uridine diphosphate-glucuronosyltransferase 1A1.

Figure 2. Major metabolic pathways of norethindrone (NET). The bolded enzyme is the major one when multiple enzymes were reported to be involved. CYP = cytochrome P450; Glu = glucuronide; NGMN = 17-deacetyl-NGM; Sul = Sulfate; SULT = sulfotransferase; UGT = uridine diphosphate-glucuronosyltransferase.

Figure 3. Major metabolic pathways of levonorgestrel (LNG). The bolded enzyme is the major one when multiple enzymes were reported to be involved. CYP = cytochrome P450; Glu = glucuronide; Sul = Sulfate; SULT = sulfotransferase; UGT1A1 = uridine diphosphate-glucuronosyltransferase 1A1.

Figure 4. Major metabolic pathways of norgestimate (NGM). The bolded enzyme is the major one when multiple enzymes were reported to be involved. For metabolic pathways of levonorgestrel (LNG), a metabolite of NGMN, see Figure 3. CYP = cytochrome P450; NGMN = 17-deacetyl-NGM.

Figure 5. Major metabolic pathways of drospirenone (DRSP). CYP = cytochrome P450; Sul = Sulfate; SULT = sulfotransferase.

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Figure 6. Effects of strong, moderate, and weak CYP3A inducers on the AUC of commonly used progestins (NET, LNG, NGM, and DRSP) in comparison to their effects on sensitive CYP3A substrates. Data are presented as geometric mean ratios of AUC and 90% confidence intervals (CIs) when the CIs were reported (probe data shown in Supplemental Table 1). Not all the studies described in Table 4 are listed. The in vivo induction potency on CYP3A of several perpetrators in Table 4 remained unknown at their dosing regimens evaluated in the DDI studies conducted with COCs. Thus, it is hard to make a classification on whether those drugs acted as moderate or weak inducers of CYP3A and therefore not included in this plot. Elagolix (for the study with LNG) and nevirapine are listed as weak/moderate inducers. In the study conducted with a COC containing 0.1 mg LNG, elagolix was administered as 200 mg twice daily (bid). The in vivo induction potency of elagolix at this dosing regimen has not been characterized. Elagolix 300 mg bid or 150 mg once daily (qd) reduced the AUC of midazolam by 54% and 35%, respectively, as presented, which correspond to moderate or weak induction of CYP3A4. The effect of nevirapine on NET was evaluated at 200 mg qd. At this dosing regimen, nevirapine reduced the AUC of indinavir by 31% and that of itraconazole by 62%. Thus, nevirapine was considered as a weak/moderate inducer of CYP3A4.

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Table 1. Phase I and II metabolism involved in the elimination of EE, NET, LNG, NGMN (the major active metabolite of NGM), and DRSP.

Compound name	**Phase I metabolism (P450s involved, if known)**	**Phase II metabolism (Isoenzymes involved, if known)**
EE	Hydroxylation [CYP3A (major), CYP2C9 (minor)] (Wang et al., 2004)	Sulfation [primarily by SULT1E1] and glucuronidation [primarily by UGT1A1] (Ebner et al., 1993; Schrag et al., 2004)
NET	Reduction; hydroxylation [CYP3A (major), CYP2C19 (minor)] (Stanczyk and Roy, 1990; Korhonen et al., 2008)	Sulfation and glucuronidation of NET metabolites (Stanczyk and Roy, 1990)
LNG	Reduction; hydroxylation [CYP3A (major), CYP2C9 (minor)] (Roberts et al., 2021)	Sulfation and glucuronidation of LNG metabolites (Stanczyk and Roy, 1990)
NGMN	Oxidation [CYP3A (major), CYP2B6 and CYP2C9 (minor)] (Ahire et al., 2017)	Glucuronidation of LNG (UGT1A1), an NGMN metabolite (Ahire et al., 2017)
DRSP	Reduction; oxidation [CYP3A] (Wiesinger et al., 2015; YASMIN, 2022)	Sulfation and glucuronidation of DSRP metabolites (Krattenmacher, 2000)

Table 2. Effects of Moderate or Strong inhibitors of CYP3A on the AUC of EE, CYP2C9 substrates, and UGT1A1 substrates

CYP3A Inhibitors[a]	Perpetrators	EE		CYP2C9 Substrates		UGT1A1 Substrates	
		Perpetrator Dose	AUCR (90% CI) of EE	Perpetrator Dose	AUCR of Substrates	Perpetrator Dose	AUCR (90% CI) of Substrates
Strong inhibitor	Ketoconazole	200 mg, bid	1.4 (1.31, 1.49) (Wiesinger et al., 2015)	200 mg, qd 200 mg, bid	tolbutamide (1.8) (Krishnaiah et al., 1994) phenytoin (1.07) (Touchette et al., 1992)	n/a	Did not affect ratio of SN-38 glucuronide/SN-38 (Kehrer et al., 2002)
	Voriconazole	200 mg, bid	1.61 (1.5, 1.72) (Andrews et al., 2008)	400 mg, bid	phenytoin (1.81) (Purkins et al., 2003)	n/a	n/a
	Telaprevir[b]	750 mg, tid	0.72 (0.69, 0.75) (Garg et al.,	750 mg, tid	phenytoin (1.31) not inhibitor in vitro	750 mg, tid	Dolutegravir (1.25) (Johnson et al., 2014) Raltegravir (1.31)

		2012)		(NDA201917, 2011)		(Milazzo et al., 2015)
Lopinavir and Ritonavir	400/100 mg, bid	0.58 (0.54, 0.62) (NDA021226, 2000)	400/100 mg, bid	phenytoin (0.69) (Lim et al., 2004) S-warfarin (0.71) (Yeh et al., 2006)	400/100 mg, bid	Dolutegravir (1.03) (Song et al., 2011c)
Paritaprevir/ Ritonavir/ Ombitasvir/ Dasabuvir combo	150 mg /100 mg /25 mg, qd /250 mg, bid	1.06 (0.96, 1.17) (NDA206619, 2014)	150 mg /100 mg /25 mg, qd /400 mg, bid	S-warfarin (0.88) (Menon et al., 2015)	150 mg /100 mg /25 mg, qd /250 mg, bid	Dolutegravir (1.38) (Khatri et al., 2016b) Raltegravir (0.82) (Venuto et al., 2020)
					150 mg /100 mg /25 mg, qd	Raltegravir (2.34) (Khatri et al., 2016a)

						/400 mg, bid	
	Telithromycin	800 mg, qd	1.02 (0.98, 1.07) (NDA021144, 2004)	800 mg, qd	S-warfarin (1.04) (NDA021144, 2004)	n/a	Unknown
Strong/ Moderate Inhibitor	Indinavir	800 mg, tid	1.22 (1.15, 1.30) (NDA020685, 1996)	n/a	not inhibitor in vitro (NDA020685, 1996)	n/a	An inhibitor in vitro (Ki or IC_{50}: 4.1 - 111 μM) (Boyd et al., 2006) (Zhang et al., 2005)
	Boceprevir	800 mg, tid	0.74 (0.68, 0.80) (Lin et al., 2014)	n/a	Not an inhibitor in vitro (NDA202258, 2011)	800 mg, tid	Not an inhibitor in vitro Dolutegravir (1.07) (NDA202258, 2011; Johnson et al., 2014) Raltegravir (1.04, 1.46) (de Kanter et al., 2013) (Kiser et al., 2017)

	Atazanavir	400 mg, qd	1.48 (1.31, 1.68) (REYATAZ, 2020)	n/a	in vitro inhibitor Ki: 12 μM (NDA021567, 2003)	400 mg, qd	Dolutegravir (1.91) Raltegravir (1.72) (Iwamoto et al., 2008a; Song et al., 2011a)
	Atazanavir and ritonavir	300 mg/ 100 mg, qd	0.81 (0.75, 0.87) (Zhang et al., 2011)	n/a	Ritonavir alone induced CYP2C9 S-warfarin (0.76) (Morcos et al., 2013)	300 mg/ 100 mg, qd	Dolutegravir (1.62) Raltegravir (1.41) (Iwamoto et al., 2008a; Song et al., 2011a)
Moderate inhibitor	Fluconazole	150 mg, single dose	1.3 (Sinofsky and Pasquale, 1998)	150 mg, single	Tolbutamide (1.9) (Lazar and Wilner, 1990) S-warfarin (1.86) S-warfarin (2) (Neal et al., 2003)	n/a	10 - 13% inhibition of substrate metabolism at 0.5-1 mM fluconazole (Lv et al., 2015) (Rong et al., 2018)
		200 mg, qd	1.38 (DIFLUCAN, 2022)	200 mg/day			
		300 mg, once weekly	1.24 (1.18, 1.31)	300 mg/day			

			(Hilbert et al., 2001)				
	Faldaprevir[c]	240 mg, qd	1.41 (1.34, 1.49) (Sabo et al., 2015b)	240 mg, bid	S-warfarin (1.29) (Sabo et al., 2015a)	240 mg, qd	Raltegravir (2.7) (Joseph et al., 2015)
	Letermovir	480 mg, qd	1.42 (1.32, 1.52) (Adedoyin et al., 2019)	n/a	Not an inhibitor in vitro (NDA209939, 2017)	n/a	An inhibitor in vitro (Ki: 16 μM) (Menzel et al., 2021)
	Isavuconazole	200 mg, qd	1.08 (1.03, 1.13) (Townsend et al., 2017)	200 mg, qd	S-warfarin (1.1) (Desai et al., 2017)	n/a	An inhibitor in vitro (IC_{50}: 9 μM) (Yamazaki et al., 2017)
	Dronedarone	800 mg, bid	1.28 (1.18, 1.38) (NDA022425,	600 mg, bid 400 mg, qd	S-warfarin (1.19) S-warfarin (0.97) (NDA022425,	n/a	n/a

			2009)		2009)		

n/a = not available; qd = once daily; bid = twice daily; tid = thrice daily

[a] The classification of a drug as a moderate or strong CYP3A inhibitor is based on clinical DDI studies with sensitive substrates of CYP3A. If a drug increases the AUC of a sensitive CYP3A substrate 5-fold or more, it is considered as a strong inhibitor of CYP3A. If the increase is 2- to 5-fold, the inhibitor drug is categorized as a moderate inhibitor.

[b] Per the FDA Clinical Pharmacology and Biopharmaceutics review for NDA 201917, telaprevir did not inhibit UGT1A1-catalyzed bilirubin glucuronidation (IC_{50} > 100 μM). While telaprevir increased raltegravir AUC, it also increased the AUC of raltegravir glucuronide metabolite by 37%, so that the ratio of raltegravir glucuronide/raltegravir ratio remained similar in the presence vs. absence of telaprevir.

[c] Faldaprevir inhibited UGT1A1 in vitro. Though faldaprevir increased raltegravir AUC in vivo, it only slightly decreased the ratio of raltegravir glucuronide to raltegravir ratio from 0.82 to 0.75. In addition, in that study, UGT1A1 polymorphism did not have a clear impact on the effect of faldaprevir on raltegravir AUC.

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Table 3. Clinical DDI studies with mean EE exposure (AUC) increase by ≥40% (except the ones already listed in Table 2)

Perpetrators	AUCR of EE (90% CI)	Effect on CYP3A Substrates (AUCR)	Effect on CYP2C9 Substrates (AUCR)	Effect on UGT1A1
Elagolix 200 mg bid	2.18 (1.99, 2.39) (ORILISSA, 2021)	Midazolam (0.46) (elagolix 300 mg bid) Midazolam (0.65) (elagolix 150 mg qd) (Polepally et al., 2020)	Not inhibitor in vitro (NDA210450, 2018)	n/a
Elagolix 150 mg qd	1.30 (1.19 – 1.42) (Feldman et al., 2021)			
Etoricoxib 120 mg qd	1.5 (1.39, 1.62) (Schwartz et al., 2009)	No impact on ^{14}C exhaled in the erythromycin breath test (Agrawal et al., 2004)	S-warfarin (1.0) (Schwartz et al., 2007)	n/a
Etoricoxib 120 mg qd separated by 12 hours from COC	1.60 (1.46, 1.75) (Schwartz et al., 2009)			
Fostemsavir 600 mg bid	1.40 (1.29, 1.51) (RUKOBIA, 2020)	Maraviroc (1.25) (RUKOBIA, 2020)	Not tested Its active moiety, temsavir, not an inhibitor in vitro	Not inhibitor in vitro (NDA212950, 2020)

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			(NDA212950, 2020)	
Rimegepant 450 mg qd	1.78 (1.56, 2.02) (NDA212728, 2020)	Midazolam (1.83) (Rimegepant 300 mg single dose) (NDA212728, 2020)	Not inhibitor in vitro (NDA212728, 2020)	Not inhibitor in vitro (NDA212728, 2020)
Rucaparib 600 mg bid	1.43 (1.15, 1.77) (Liao et al., 2021)	Midazolam (1.38) (Xiao et al., 2019)	S-warfarin (1.49) (Xiao et al., 2019)	Inhibitor in vitro (IC_{50}: 32 μM) (Liao et al., 2020)
Teriflunomide 14 mg qd	1.54 (1.46, 1.63) (NDA202992, 2012)	Midazolam (1.27) (NDA202992, 2012)	S-warfarin (1.12) (NDA202992, 2012)	n/a
Ziritaxestat 600 mg qd	2.39 (2.19, 2.60) (Helmer et al., 2022)	No effect on DRSP (Helmer et al., 2022)	n/a	n/a

n/a = not available; qd = once daily; bid = twice daily

Table 4. Systemic exposure changes of progestins and EE in clinical DDI studies that had progestin AUC decreases by ≥ 20% on average

Perpetrators	Classification as CYP3A inducer	Victim drugs	Progestin GMR (90% CI)		EE GMR (90% CI)	
			AUC	C_{max}	AUC	C_{max}
NET						
Carbamazepine 600 mg qd x 21 days (Doose et al., 2003)	Strong	NET 1 mg/EE 0.035 mg qd	0.47 (0.34, 0.65)	0.63 (0.42, 0.96)	0.54 (0.42, 0.69)	0.77 (0.56, 1.04)
Rifampin 600 mg qd x 11 days (Wiesinger et al., 2020)	Strong	NET 0.35 mg SD	0.54 (0.49, 0.60)	0.81 (0.73, 0.91)	n/a	n/a
Rifampin 600 mg qd x 14 days (Barditch-Crovo et al., 1999)	Strong	NET 1 mg/EE 0.035 mg qd	0.49	No impact	0.34	0.57
Rifampin 450-600 mg/day x 3-12 months (Back et al.,	Strong	NET 1 mg/EE 0.05 mg SD	0.41	n/a	n/a	n/a

1979)						
Rifampin 300 mg qd x 10 days (LeBel et al., 1998)	Moderate	NET 1 mg/EE 0.035 mg qd	0.41	0.73	0.36	0.58
Rifabutin 300 mg qd x 10 days (LeBel et al., 1998)	Moderate	NET 1 mg/EE 0.035 mg qd	0.54	0.68	0.65	0.80
Rifabutin 300 mg qd x 14 days (Barditch-Crovo et al., 1999)	Moderate	NET 1 mg/EE 0.035 mg qd	0.87	0.87	0.64	0.91
St. John's wort 300 mg tid x 28 days (Murphy et al., 2005)	Moderate	NET 1 mg/EE 0.02 mg qd	0.87	No impact	0.86	No impact
Bosentan 125 mg bid x 7 days (van Giersbergen et al., 2006)	Moderate	NET 1 mg/EE 0.035 mg SD	0.86 (0.76, 0.97)	No impact	0.69 (0.60, 0.80)	No impact
Etravirine 200 mg bid x 15 days (Scholler-Gyure	Moderate	NET 1 mg/EE 0.035 mg qd	0.95 (0.90, 0.99)	1.05 (0.98, 1.12)	1.22 (1.13, 1.31)	1.33 (1.21, 1.46)

et al., 2009)						
Nevirapine 200 mg qd x 2 weeks then bid x 2 weeks (VIRAMUNE, 2022)	Weak/ moderate	NET 1 mg /EE 0.035 mg SD	0.79 (0.67, 0.96)	0.84 (0.72, 1.01)	0.73 (0.54, 1.02)	0.94 (0.78, 1.17)
Elagolix 300 mg bid x 9 days (Nader et al., 2021)	Moderate	NET 0.5 mg/ Estradiol 1 mg, SD	1.026 (0.957, 1.100)	0.975 (0.912, 1.042)	n/a	n/a
Elagolix 150 mg qd x 56 days (Feldman et al., 2021)	Weak	NET 0.35 mg qd	0.882 (0.788, 0.987)	0.947 (0.856, 1.047)	n/a	n/a
Rifampin 10 mg qd x 11 days (Wiesinger et al., 2020)	Weak	NET 0.35 mg SD	0.88 (0.79, 0.96)	0.90 (0.80, 1.00)	n/a	n/a
St. John's wort 300 mg tid x 28 days (Hall et al., 2003)	Weak[a]	NET 1 mg/EE 0.035 mg qd	0.88 (0.76, 1.0)	0.93 (0.88, 0.98)	0.68 (0.14, 1.23)	1.11 (0.33, 1.89)
Rufinamide 800 mg bid x 14 days (NDA021911,	Unknown[b] (weak inducer	NET 1 mg/EE 0.035 mg qd	0.861 (0.817, 0.907)	0.824 (0.742, 0.915)	0.777 (0.737, 0.819)	0.685 (0.631, 0.744)

2008)	as rufinamide 400 mg bid)					
Troglitazone 600 mg qd x 22 days (Loi et al., 1999)	Unknown[c] (weak inducer as troglitazone 400 mg qd)	NET 1 mg/EE 0.035 mg qd	0.7 (0.61, 0.82)	0.69 (0.61, 0.78)	0.71 (0.62, 0.81)	0.68 (0.61, 0.75)
LNG						
Rifampin 600 mg qd × 11 days (Wiesinger et al., 2020)	Strong	LNG 0.03 mg SD	0.43 (0.40, 0.46)	1.10 (0.99, 1.23)	n/a	n/a
Phenytoin 200-300 mg/day (8-12 weeks) (Crawford et al., 1990)	Strong (phenytoin 300 mg/day)	LNG 0.25 mg/EE 0.05 mg SD	0.58	n/a	0.51	n/a
Carbamazepine 600 mg qd for 2 months (Davis et al., 2011)	Strong	LNG 0.1 mg/EE 0.02 mg qd	0.54	0.78	0.55	0.65
Carbamazepine 300-600 mg/day (8-12	Strong (Carbamazepine	LNG 0.25 mg/EE 0.05 mg SD	0.6	n/a	0.58	n/a

weeks) (Crawford et al., 1990)	600 mg/day)					
Efavirenz 600 mg ×14 days (Carten et al., 2012)	Moderate	LNG 0.75 mg SD	0.44 (0.38, 0.51)	0.59 (0.50, 0.67)	n/a	n/a
Oxcarbazepine 600 mg bid x 26 days (Fattore et al., 1999)	Unknown[d]	LNG 0.25 mg/EE 0.05 mg qd	0.53	0.75	0.53	0.65
Oxcarbazepine 300 mg tid x 31 Days (Klosterskov Jensen et al., 1992)	Weak/Moderate[d] (oxcarbazepine 450 mg bid)	LNG 0.125 mg/EE 0.05 mg	0.64	0.93	0.53	0.75
Elagolix 200 mg bid x 15 days (ORILISSA USPI)	Weak (elagolix 150 mg qd)/ Moderate (elagolix 300 mg bid)	LNG 0.1 mg/EE 0.02 mg SD	0.73 (0.64, 0.82)	0.97 (0.88, 1.07)	2.18 (1.99, 2.39)	1.36 (1.27, 1.45)
Eslicarbazepine	Likely	LNG 0.15 mg/EE	0.64	0.87	0.58	0.80

1200 mg qd ×15 days (Falcao et al., 2013b)	moderate[e]	0.03 mg SD	(0.56, 0.72)	(0.78, 0.95)	(0.54, 0.62)	(0.70, 0.91)
Eslicarbazepine 800 mg qd ×15 days (Falcao et al., 2013b)	Moderate	LNG 0.15 mg/EE 0.03 mg SD	0.83 (0.76, 0.91)	1.04 (0.95, 1.14)	0.69 (0.64, 0.75)	0.91 (0.85, 0.97)
Rifampin 10 mg qd × 11 days (Wiesinger et al., 2020)	Weak	LNG 0.03 mg SD	0.83 (0.77, 0.90)	1.00 (0.90, 1.12)	n/a	n/a
Lersivirine 1000 mg qd x 10 days (Davis et al., 2012)	Weak	LNG 0.15 mg/EE 0.03 mg qd	0.87 (0.78, 0.97)	0.84 (0.69, 1.02)	1.10 (0.92, 1.31)	1.08 (0.85, 1.36)
Brivaracetam 200 mg bid for 21 days (Stockis and Rolan, 2013)	Unknown[f]	LNG 0.15 mg/EE 0.03 mg qd	0.78 (0.72, 0.83)	0.90 (0.85, 0.95)	0.73 (0.69, 0.78)	0.86 (0.79, 0.94)
Perampanel 12 mg qd x 21 days (NDA202834, 2012)	Unknown[g]	LNG 0.15 mg/EE 0.03 mg SD	0.60 (0.52, 0.68)	0.58 (0.50, 0.67)	1.05 (0.97, 1.14)	0.82 (0.73, 0.93)
Mavoglurant 100 mg bid	Unknown[h]	LNG 0.15 mg/EE	0.68	0.81	0.94	0.97

x 12 days (Sivasubramanian et al., 2015)		0.03 mg SD	(0.63, 0.73)	(0.75, 0.87)	(0.86, 1.03)	(0.90, 1.06)
NGM[i]						
Elagolix 150 mg qd × 56 days (Feldman et al., 2021)	Weak	NGM 0.25 mg/EE 0.035 mg qd	0.847 (0.782, 0.918)	0.871 (0.781, 0.973)	1.30 (1.186, 1.416)	1.15 (1.07, 1.25)
Efavirenz 600 mg qd × 14 days (Sevinsky et al., 2011)	Moderate	NGM 0.25 mg/EE 0.035 mg qd	0.36 (0.33, 0.38)	0.54 (0.48, 0.61)	0.90 (0.80,1.01)	1.06 (0.95, 1.19)
DRSP						
Rifampin 10 mg qd × 11 days (Wiesinger et al., 2020)	Weak	DRSP 3 mg/EE 0.03 mg SD	0.701 (0.657, 0.749)	0.931 (0.827, 1.05)	0.817 (0.730, 0.915)	0.997 (0.895, 1.11)
Rifampin 600 mg qd × 11 days (Wiesinger et al., 2020)	Strong	DRSP 3 mg/EE 0.03 mg SD	0.139 (0.130, 0.149)	0.605 (0.537, 0.680)	0.358 (0.320, 0.400)	0.782 (0.702, 0.871)

qd = once daily; bid = twice daily; tid = thrice a day; SD = single dose

[a] The induction effect of St. John's wort varies widely based on literature DDI studies and this may be preparation dependent. While St. John's wort more often behaved as a moderate inducer of CYP3A, in this study where the PK of midazolam was also evaluated besides COC, St. John's wort just reduced midazolam AUC by 35%. Thus, St. John's wort acted as a weak inducer of CYP3A in this study.

[b] Rufinamide at 400 mg bid dose was a weak inducer of CYP3A, as indicated by its effect on AUC (reduced by 36%) of triazolam, a sensitive substrate of CYP3A (NDA 21911).

[c] Troglitazone at 400 mg qd dose was a weak inducer of CYP3A, since it reduced the AUC of simvastatin, a sensitive substrate of CYP3A, by 38% (Prueksaritanont et al., 2001). It remains unknown whether at 600 mg qd dose it acted as a moderate or weak inducer of CYP3A.

[d] At 450 mg bid dose (900 mg/day), oxcarbazepine appeared to be a weak to moderate inducer. While it reduced the AUC of felodipine by 28%, a case report showed that oxcarbazepine decreased the average concentration (C_{avg}) of quetiapine by 73% (Zaccara et al., 1993; McGrane et al., 2015). Its effect at 1200 mg/day dose on CYP3A sensitive substrates has not been evaluated, there is possibility for oxcarbazepine to act as a moderate inducer though.

[e] Eslicarbazepine at 800 mg qd dose reduced the AUC of simvastatin (lactone form) and simvastatin acid by 50% and 46%, respectively, which is around the border of weak and moderate inducers (Falcao et al., 2013a). Thus, it is likely that eslicarbazepine at 1200 mg qd may act as a moderate inducer, while clinical DDI studies with sensitive substrate of CYP3A have not been conducted for this dose of eslicarbazepine.

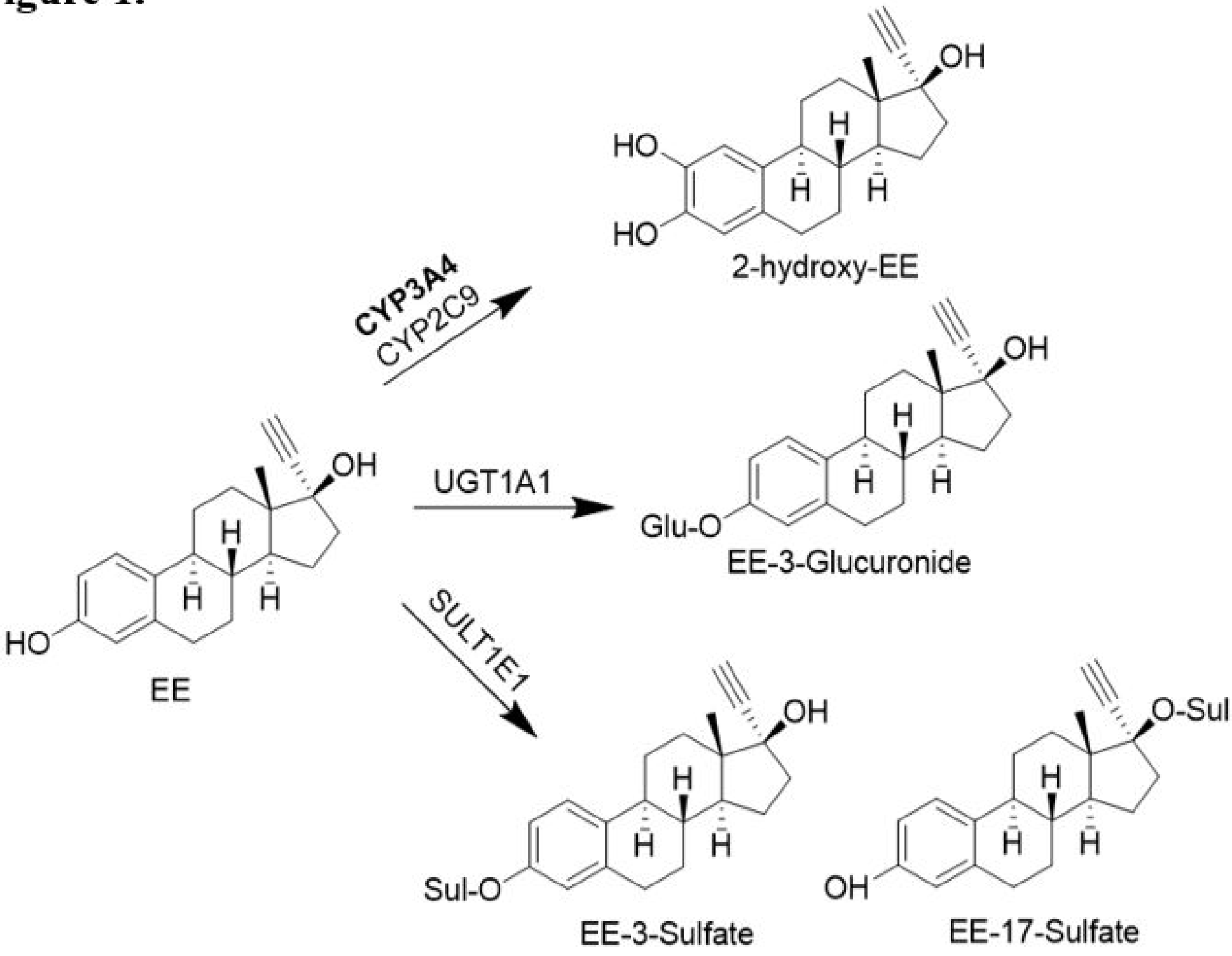
[f] The impact of brivaracetam on CYP3A was only tested at a dose of 75 mg bid, which slightly increased the AUC of midazolam by 8.5% (Stockis et al., 2015). Brivaracetam was an inducer of CYP3A *in vitro* based on CYP3A activity measurement (NDA205836, 2016). It remains unclear about its effect on CYP3A *in vivo* at 200 mg bid dose.

[g] Perampanel at 6 mg reduced midazolam AUC by 13% (NDA202834, 2012). The effect of 12 mg perampanel on CYP3A has not been evaluated *in vivo*.

[h] The impact of mavoglurant on CYP3A has not been assessed in clinical DDI studies.

[i] Data presented using the major active metabolite, 17-deacetyl norgestimate (NGMN), for NGM-containing COCs.

Figure 1.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HO
HO
H
H
H
2-hydroxy-EE
CYP3A4
CYP2C9
OH
H
H
H
Glu-O
EE-3-Glucuronide
UGT1A1
OH
H
H
H
HO
EE
SULT1E1
OH
H
H
H
Sul-O
EE-3-Sulfate
O-Sul
H
H
H
OH
EE-17-Sulfate

Figure 2.

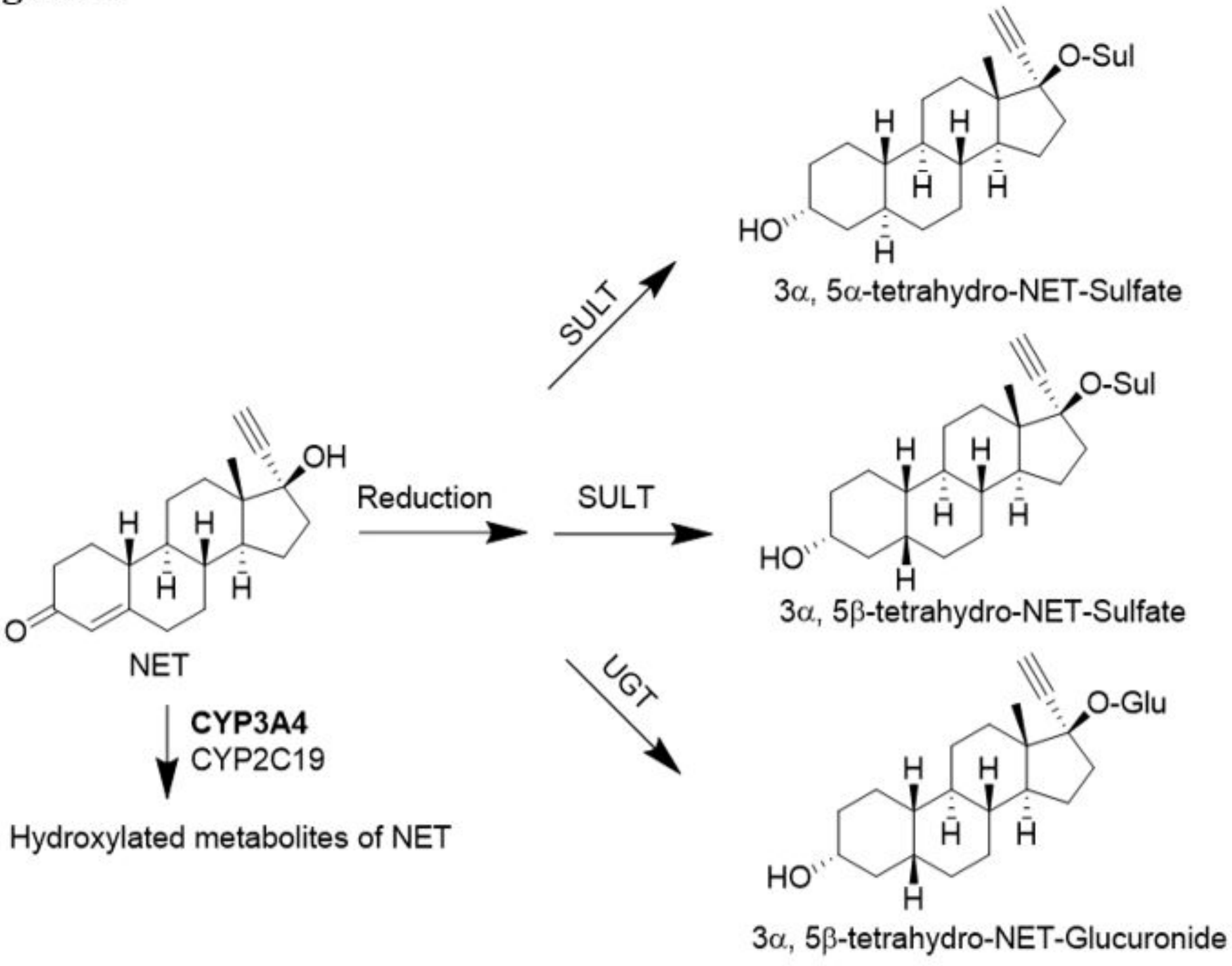

O-Sul
H
H
H
H
HO
3α, 5α-tetrahydro-NET-Sulfate
SULT
OH
Reduction
SULT
O-Sul
3α, 5β-tetrahydro-NET-Sulfate
O
NET
UGT
CYP3A4
CYP2C19
O-Glu
3α, 5β-tetrahydro-NET-Glucuronide
Hydroxylated metabolites of NET

Figure 3.

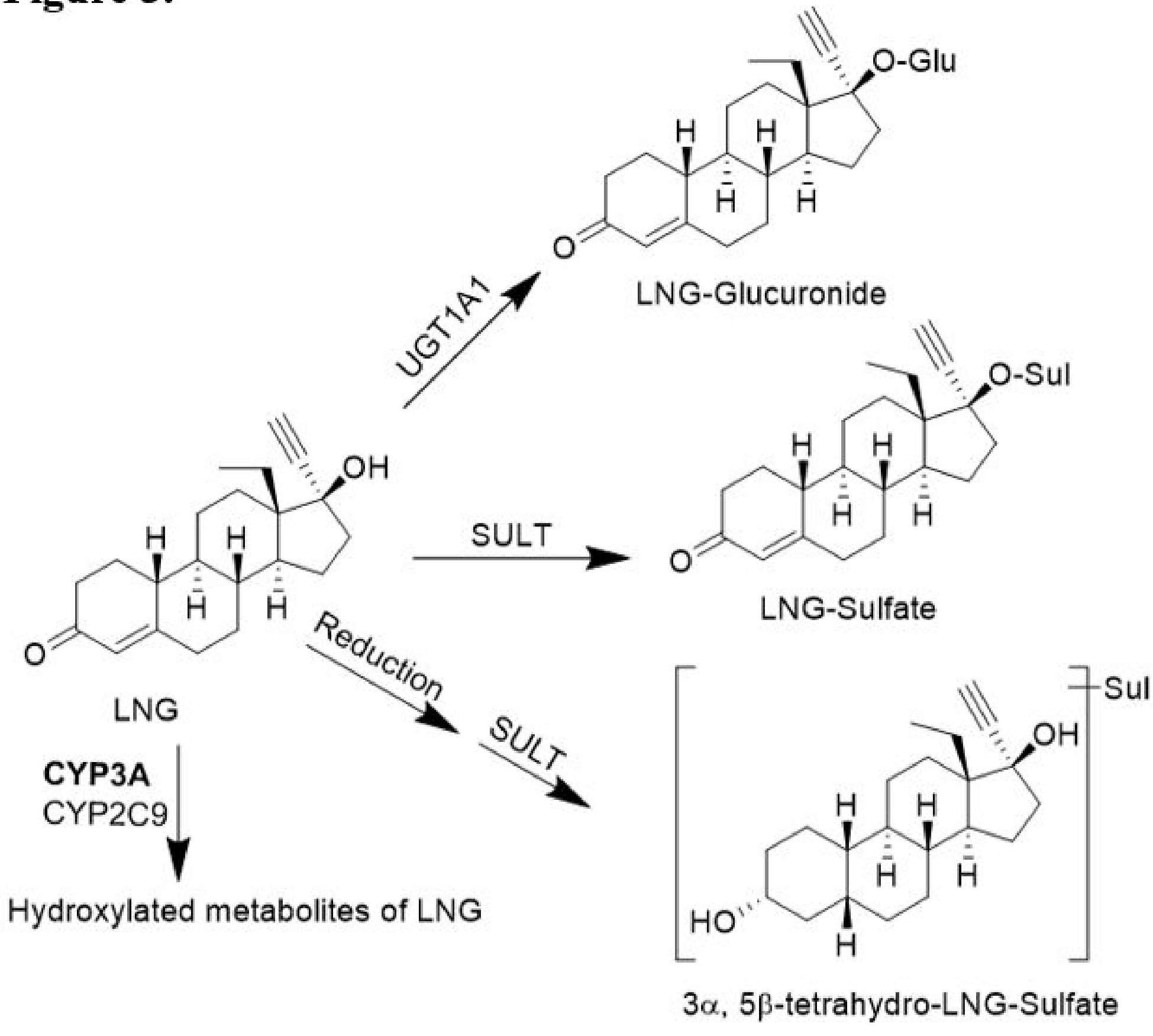

O-Glu
H
H
H
H
O
UGT1A1
LNG-Glucuronide
O-Sul
H
H
H
H
O
SULT
LNG-Sulfate
OH
H
H
H
H
O
LNG
Reduction
SULT
Sul
OH
H
H
H
H
HO
CYP3A
CYP2C9
Hydroxylated metabolites of LNG
3α, 5β-tetrahydro-LNG-Sulfate

Figure 4.

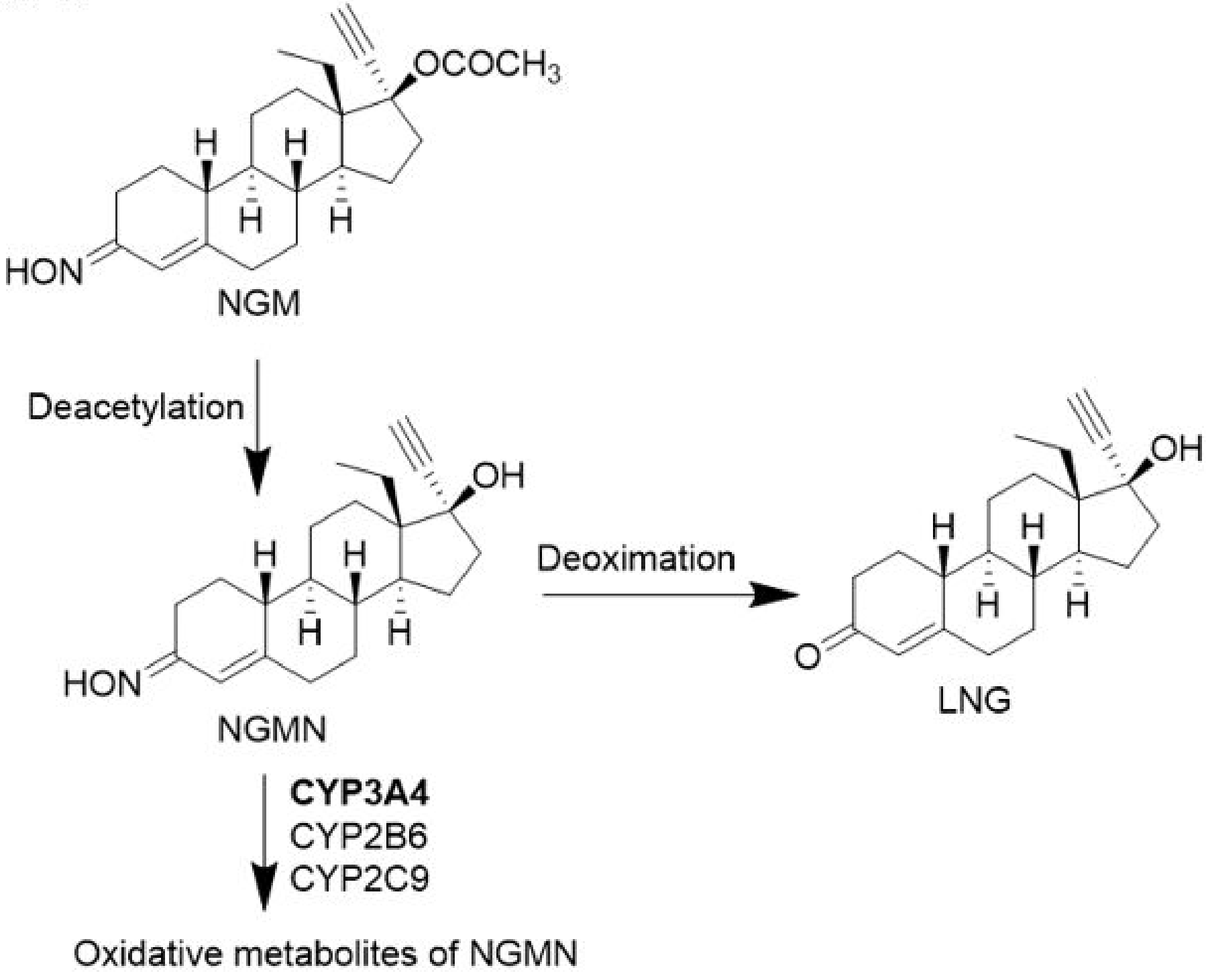

OCOCH3
H
H
H
H
HON
NGM
Deacetylation
OH
H
H
H
H
HON
NGMN
Deoximation
OH
H
H
H
H
O
LNG
CYP3A4
CYP2B6
CYP2C9
Oxidative metabolites of NGMN

Figure 5.

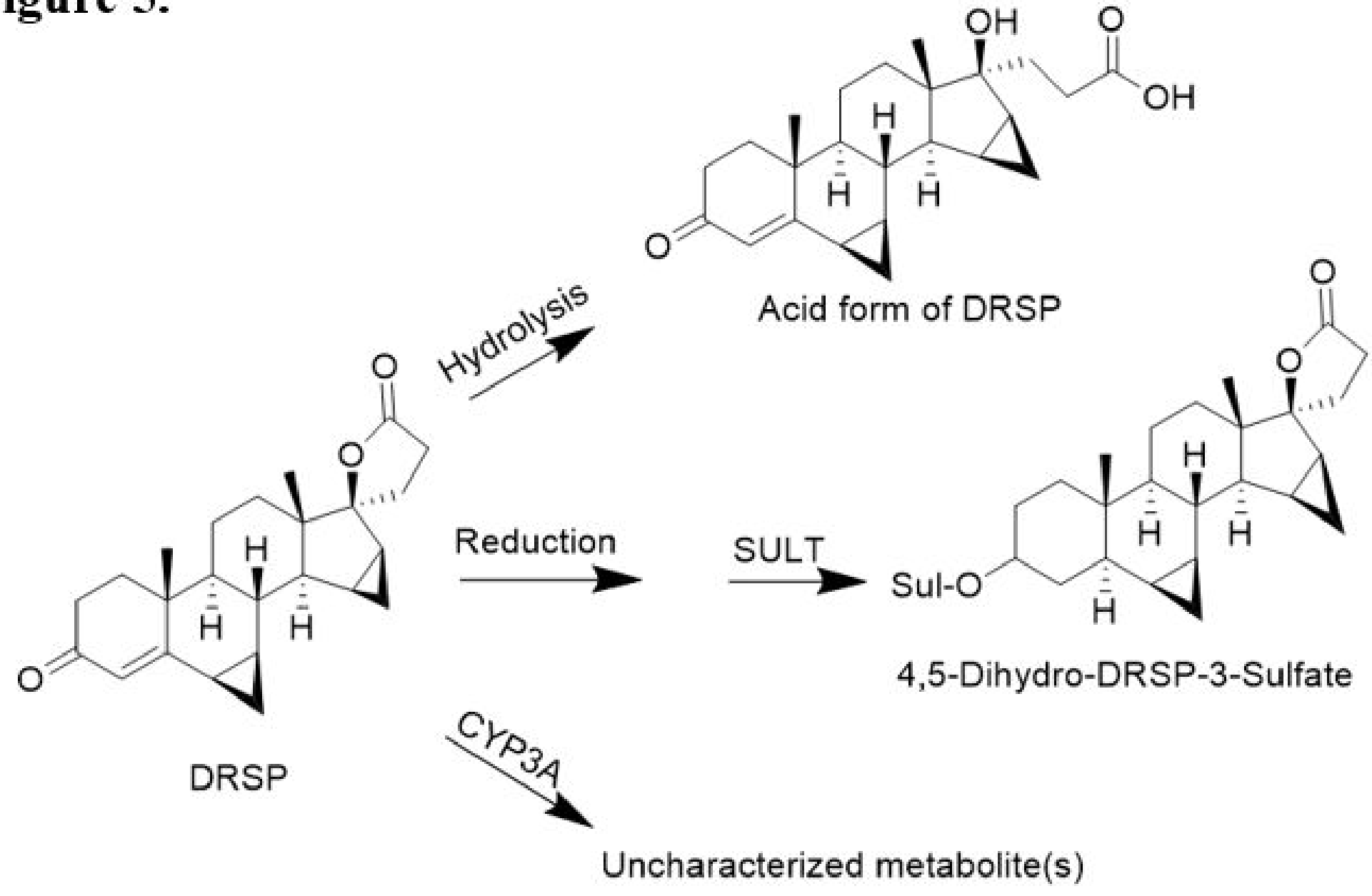
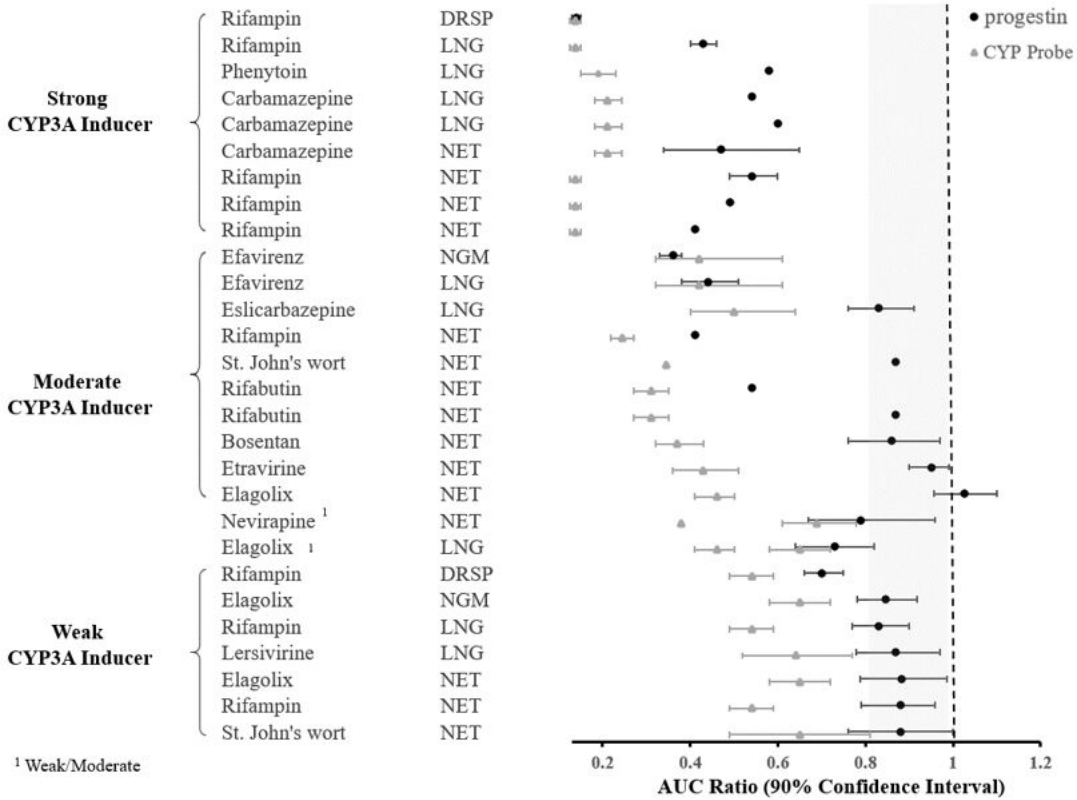

OH
O
OH
H
H
H
O
Acid form of DRSP
Hydrolysis
O
O
H
H
H
O
DRSP
Reduction
SULT
Sul-O
O
O
H
H
H
H
4,5-Dihydro-DRSP-3-Sulfate
CYP3A
Uncharacterized metabolite(s)

Figure 6.



[1] Weak/Moderate