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SHORT COMMUNICATION

In vitro assessment of cytochrome P450 inhibition and induction potential of azacitidine

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Abstract
Purpose To assess the potential inhibitory and inductive effects of azacitidine on cytochrome P450 isozymes in vitro.
Methods The inhibitory effects of azacitidine on various CYP isozymes were determined in human liver microsomes. In addition, the ability of azacitidine to induce CYP enzymes in cultured human hepatocytes was evaluated.
Results Azacitidine did not inhibit CYP2B6-, CYP2C8-, CYP2C9-, CYP2C19-, CYP2D6-, and CYP3A4-mediated activities in human liver microsomes up to a concentration of 100 μM, while weak inhibition (<30% inhibition) of CYP1A2 and CYP2E1 activities was observed at 100 μM azacitidine. In vitro azacitidine did not induce CYP1A2, CYP2C19, or CYP3A4/5 activities in cultured human hepatocytes.
Conclusions Azacitidine is not an inhibitor or inducer of the cytochrome P450 isozymes tested; therefore, clinically relevant pharmacokinetic drug–drug interactions are unlikely to occur between azacitidine and co-administered substrates of these CYP isozymes.

Keywords Azacitidine · Cytochrome P450 · CYP inhibition · CYP induction · Drug–drug interactions

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Introduction

Azacitidine (5-azacitidine) is an analogue of the naturally occurring pyrimidine nucleoside cytidine possessing pharmacological effects on cell differentiation, gene expression, and DNA synthesis and metabolism [1–4]. Mechanistically, azacitidine is believed to exert its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow [4, 5]. Azacitidine is used for the treatment of all subtypes of myelodysplastic syndrome. It has also demonstrated activity for the treatment of acute myelogenous leukemia [6, 7].

Cytochrome P450 (CYP) is a superfamily of mixed function oxidases that are responsible for the metabolism of many drugs including oral contraceptives, dexamethasone, and many anticancer agents such as taxanes. Some of these enzymes are polymorphically expressed (e.g., CYP2D6, CYP2C19) resulting in wide variability of pharmacokinetics of their substrate drugs. CYP isozymes are subject to inhibition via competitive or other mechanisms by drugs such as ketoconazole, ritonavir, and clarithromycin, leading to clinically relevant increases in the exposure of the affected drug. Further, some of the CYP isozymes are also subject to induction by xenobiotics via activation of nuclear receptors, with a consequent result of decreased exposure of the affected compound (e.g., rifampicin and oral contraceptive steroids) leading to therapeutic failure or toxicological implications due to higher levels of an undesired metabolite [8, 9].

For a new molecular entity, it is important to assess its likely inhibitory or inductive effects on the metabolic reactions catalyzed by CYP isozymes. Anticancer therapeutic regimens often involve polypharmacy comprising of multiple therapeutic agents and/or palliative therapies. Recent clinical studies have explored combinations of azacitidine

with other anticancer agents to enhance the therapeutic activity [10–13]. It is likely that azacitidine will be administered with other therapeutic agents in clinical settings.

This study was conducted to evaluate the potential for drug–drug interactions with azacitidine as an inhibitor or inducer of CYP enzymes. The clinical dosing regimen of azacitidine is by subcutaneous injection or intravenous infusion of 75 mg/m^2 for 7 days every 4 weeks (Vidaza® package insert). The peak plasma concentrations of azacitidine at the therapeutic dose are approximately 3 μM [14, 15]. The concentrations of azacitidine employed in this study span and exceed the therapeutic concentration range.

Materials and methods

Azacitidine was synthesized by Ash Stevens™ (Riverview, MI). Pooled human liver microsomes were obtained from In Vitro Technologies (NJ, USA), Tissue Transformation Technologies (T^3) (NJ, USA), BD Biosciences Discovery Labware (Woburn, MA), and CellzDirect™ Invitrogen Corporation (Durham, NC). NADPH was purchased from Sigma–Aldrich Co Ltd (St. Louis, USA). NADP+ (disodium salt) and glucose 6-phosphate (disodium salt) were obtained from Roche Products Ltd (Herts, UK), and glucose 6-phosphate dehydrogenase (from yeast) was obtained from Roche Diagnostics Ltd (East Sussex, UK). All radiolabelled substrates were purchased from Amersham Pharmacia Biotech UK Ltd (Bucks, UK). S-mephenytoin was purchased from Gentest Corp (Woburn, MA). 4′-Hydroxymephenytoin was purchased from Research Biochemicals International (Natick, MA). Resorufin and 7-ethoxyresorufin were purchased from Molecular Probes (Junction City, OR). All other reagents including rifampin, β-naphthoflavone (BNF), and testosterone were obtained from Sigma–Aldrich Chemical Company, Ultrafine Chemicals Ltd (Manchester, UK), Affiniti Research Products Ltd (Exeter, UK), FSA Laboratory Supplies (Loughborough, UK), BDH Ltd (Poole, UK), Helget Gas (Kansas City, MO), Gibco BRL (Grand Island, NY), Pierce Chemical Co (Rockford, IL), J.T. Baker Inc. (Phillipsburg, NJ), Fisher Scientific (Pittsburgh, PA), Cohesion (Santa Clara, CA), and Toronto Research Chemicals Inc (North York, ON, Canada). All chemicals were of analytical grade or higher.

Inhibitory effect on cytochrome P450s

Stock solution of azacitidine and subsequent serial dilutions were freshly prepared and refrigerated until use. Other stock solutions of substrates and inhibitors were made in either aqueous or organic solvents, and the final percentage of organic solvent in incubation mixture was less than 1%. Incubations were conducted at 37°C either in pH 7.4 potassium phosphate buffer or Tris buffer in the presence of human liver microsomes (concentrations from 0.05 to 2 mg/mL) and azacitidine at concentrations ranging from 0.1 to 100 μM. The incubation mixture was preincubated for 5 min prior to the initiation of metabolic reaction with NADPH cofactor, in either duplicate or triplicate (CYP2B6 and CYP2C8), alongside vehicle control. After incubation, the reactions were terminated by addition of quenching reagents such as acetonitrile, hydrochloric acid, or perchloric acid. Incubation conditions for evaluating CYP inhibition are summarized in Table 1. Experiments with positive control inhibitors were conducted in parallel, and furafylline as an inhibitor for CYP1A2 was preincubated for 15 min prior to initiation with substrate.

Inductive effect on cytochrome P450s

Human hepatocytes were prepared from three non-transplantable human liver tissue samples procured from Blue Color Scientific (Chapel Hill, NC). Fresh hepatocytes were isolated and cultured according to established methods [16–20]. Hepatocytes were seeded (approximately 1 million hepatocytes per mL) on 60-mm Permanox culture dishes (Fisher Scientific, Pittsburgh, PA), coated with collagen (PureCol), and placed in a humidified culture chamber (37 ± 1°C, at 95% relative humidity, 95/5% air/CO_2). After an attachment period of 2–3 h, media and dead or unattached cells were removed by aspiration, and the media were replaced with modified Eagle's medium Dr. Chee's modification containing ITS+ (6.13 μg/mL insulin, 6.13 μg/mL transferrin, and 6.13 ng/mL selenous acid), linoleic acid (5.25 μg/mL), BSA (1.23 mg/mL), penicillin (49 U/mL), streptomycin (49 μg/mL), dexamethasone (0.098 μM), and Matrigel (250 μg/mL). The viability of hepatocytes was assessed by the trypan blue exclusion method. Cultures were allowed to adapt to the culture environment for 3 days with daily media replacement. Hepatocyte cultures were treated once daily for three consecutive days, with medium containing 0.1% dimethyl sulfoxide (DMSO) (vehicle, negative control), one of the three concentrations of azacitidine (1.0, 10 or 100 μM), or one of the two known human CYP enzyme inducers (positive controls: 33 μM β-naphthoflavone and 20 μM rifampin). At the end of the treatment period, microsomal samples were prepared and stored at −80°C until analysis. Microsomal incubation was carried out with the CYP1A2, CYP2C19, and CYP3A4/5 isozyme-specific probe substrates at the concentrations and incubation conditions indicated in Table 2. The assessment of three CYP1A2, 2C19, and 3A4/5 activities was carried out as nuclear receptors, such as the aryl hydrocarbon receptor (AhR), pregnane X receptor (PXR), and constitutive androstane receptor (CAR), have been recognized as key mediators of drug-induced changes in the

Table 1 Inhibitory effect of azacitidine on isozyme-specific cytochrome P450 activities in human liver microsomes

CYP isozyme: Specific probe activity, probe concentration	Incubation time (min); HLM concentration (mg/mL); Buffer	Analytical method	Azacitidine*; positive control inhibitor concentration (μm)	Percent inhibition or IC_{50}
CYP1A2:				
Ethoxyresorufin *O*-deethylation, 0.4 μM	3; 0.1; 50 mM PPB	Fluorescence λex = 530 nm, λem = 585 nm	Azacitidine (0.1–100) Furafylline (10)	19.4% at 100 μM; 53.7%
CYP2C9:				
Tolbutamide 4-methyl hydroxylation, 100 μM	30; 2; 50 mM Tris	HPLC–UV/β-Ram Radiochemical	Azacitidine (0.1–100) Sulfaphenazole (10)	NI; 80.4%
CYP2C19:				
S-mephenytoin 4-hydroxylation, 96.4 μM	30; 2; 100 mM Tris	HPLC–UV/β-Ram Radiochemical	Azacitidine (0.1–100) Tranylcypromine (50)	NI; 51.8%
CYP2E1:				
Chlorzoxazone 6-hydroxylation, 40 μM	15; 0.8; 50 mM PPB	HPLC–UV (297 nm)	Azacitidine (0.1–100) Diethyldithiocarbamate (50)	27.1% at 100 μM; 75.0%
CYP2D6:				
Bufuralol 1′-hydroxylation, 10 μM	30; 0.05; 100 mM PPB	HPLC-Fluorescence, λex = 252 nm, λem = 302 nm	Azacitidine (0.1–100) Quinidine (1)	NI; 80.8%
CYP2B6:				
Bupropion Hydroxylation, 50 μM	20; 0.25; 100 mM PPB	HPLC–MS/MS	Azacitidine (0.1–100) DI: Orphenadrine	NI; 195 μM
CYP2C8:				
Paclitaxel 6α-hydroxylation, 10 μM	10; 0.5; 100 mM PPB	HPLC–MS/MS	Azacitidine (0.1–100) DI: Montelukast	NI; 0.46 μM
CYP3A4:				
Testosterone 6β-hydroxylation, 65 μM	10; 0.4; 50 mM PPB	HPLC–UV/β-Ram Radiochemical	Azacitidine (0.1–100) Ketoconazole (1)	NI; 70.8%

NI No inhibition, *DI* Direct inhibition, *HPLC* High performance liquid chromatography, *MS* Mass spectrometry, *PPB* potassium phosphate buffer

* Azacitidine concentration range for each CYP isozyme was 0.1–100 μM

Table 2 Experimental conditions for CYP induction study

CYP enzymes:	CYP1A2	CYP2C19	CYP3A4/5
CYP-mediated reactions:	7-Ethoxyresorufin *O*-dealkylation	S-mephenytoin 4′-hydroxylation	Testosterone 6β-hydroxylation
Microsome content; incubation time	0.1 mg; 30 min	0.04 mg; 240 min	0.05 mg; 20 min
Organic solvent (% in incubation mixture)	DMSO (0.4%)	Methanol (1.2%)	Methanol (2%)
Substrate; concentration	7-ethoxyresorufin; 10 μM	S-mephenytoin; 400 μM	Testosterone; 250 μM
Reaction stop reagents	Acetone	Methanol	Methanol
Metabolites monitored	Resorufin	4′-hydroxy-mephenytoin	6β-hydroxy-testosterone
Analytical method	Fluorimetric λ_{ex} = 535 nm, λ_{em} = 585 nm	HPLC–UV (204 nm)	HPLC–UV (254 nm)

HPLC–UV high performance liquid chromatography–ultraviolet detection

Ref [26, 27] for additional details

expression of CYP1A, CYP3A, CYP2B, and the CYP2C enzymes. All incubations were conducted in duplicate wells at 37 ± 1°C in incubation mixtures containing potassium phosphate buffer (50 mM, pH 7.4), $MgCl_2$ (3 mM), EDTA (1 mM), NADP (1 mM), glucose-6-phosphate (5 mM), and glucose-6-phosphate dehydrogenase (1 Unit/ mL). Reactions

were initiated by addition of the NADPH-generating system and were terminated after the appropriate incubation time by addition of acetonitrile. Precipitated protein was removed by centrifugation (920 g for 10 min at 10°C), and supernatants were analyzed for the respective metabolites (Table 2). The catalytic activities in cultures treated with azacitidine and positive control inducers were compared to DMSO-treated cultures. A one-way analysis of variance (ANOVA) for repeated measures was carried out to determine whether there were significant differences between the group means. The ANOVA was followed by a Dunnett's *post hoc* test to identify the group means that were significantly different from the controls ($P < 0.05$ or 5% level of significance). This statistical test is designed for multiple comparisons with a mean, such as comparing multiple treatment groups with a control group. Statistical analyses were performed using SigmaStat Statistical Analysis System (version 2.03, SPSS Inc, Chicago, IL).

Results

Inhibitory effects on cytochrome P450s

The effect of azacitidine on isozyme-specific CYP activities in human liver microsomes is summarized in Table 1. As expected, all positive control inhibitors produced inhibitory effects on the respective catalytic activities. Azacitidine did not inhibit CYP2B6-, CYP2C8-, CYP2C9-, CYP 2C19-, CYP2D6- and CYP3A4-mediated activities up to 100 μM concentration under the in vitro conditions tested. Although limited inhibition of CYP1A2-dependent ethoxyresorufin *O*-dealkylation (19%) and CYP2E1-dependent chlorzoxazone 6-hydroxylation (27%) was observed at the highest concentration of azacitidine (100 μM) tested, no inhibition of these two CYP enzymes was observed at 70 μM or lower concentrations of azacitidine tested.

Inductive effects on cytochrome P450s

At the time of isolation, the viability of each hepatocyte preparation was between 73 and 89%. During the adaptation followed by a 72-h incubation period, human cultured hepatocytes were judged to be morphologically normal and adequately confluent for treatment with test and control articles. In general, the cells were characteristically cuboidal and contained intact cell membranes and granular cytoplasm with one or two centrally located nuclei. Enzymatic activities (pmol/mg protein/min) and fold-over DMSO (negative control) data are listed in Table 3. As expected, the positive control inducers produced marked elevations in most of the isozyme-specific catalytic activities tested. For all three CYP isozymes tested, (CYP1A2, CYP2C19, and CYP 3A4/5) treatment of azacitidine at 1 and 10 μM resulted in catalytic activities that were 0.86–1.20-fold of the catalytic activities of the vehicle-treated cultures, demonstrating no notable inductive effect of azacitidine. At 100 μM azacitidine, the CYP enzyme activities showed a 29% decrease of CYP1A2-mediated 7-ethoxyresorufin *O*-dealkylation, 56% decrease of CYP2C19-catalyzed *S*-mephenytoin 4′-hydroxylation, and a 78% decrease of CYP3A4/5-catalyzed testosterone 6β-hydroxylation. However, only the CYP3A4/5 activity decrease was statistically significant. Though morphologically azacitidine-treated hepatocytes were observed to be similar to those of vehicle-treated hepatocytes, it is possible that azacitidine, being a cytotoxic compound, may have adverse effects on primary hepatocytes at high concentrations. Overall, the results of this study demonstrate that treatment of cultured human hepatocytes with clinically relevant concentrations of

Table 3 Effect of azacitidine on isozyme-specific cytochrome P450 enzymatic activities in cultured human hepatocytes

Treatment	Concentration	Enzymatic activity (pmol/mg protein/min)[a] (Mean fold over control)		
		7-Ethoxyresorufin *O*-dealkylation (CYP1A2)	S-mephenytoin 4′-hydroxylation (CYP2C19)	Testosterone 6β-hydroxylation (CYP3A4/5)
DMSO	0.1% (v/v)	4.09 ± 0.86	7.80 ± 0.78	4190 ± 1350
Azacitidine	1 μM	4.11 ± 0.94 (1.0)	9.47 ± 4.76 (1.2)	4570 ± 1960 (1.1)
Azacitidine	10 μM	3.78 ± 0.72 (0.93)	6.82 ± 2.89 (0.86)	3650 ± 1320 (0.86)
Azacitidine	100 μM	2.91 ± 0.77 (0.71)	3.51 ± 1.16 (0.44)	936 ± 443* (0.22)
β-Naphthoflavone	33 μM	36.3 ± 1.5* (9.2)	33.6 ± 13.6* (4.4)	1880 ± 1150 (0.42)
Rifampin	20 μM	6.75 ± 1.29* (1.7)	59.0 ± 10.2* (7.5)	13100 ± 200* (3.3)

v/v volume/volume, *DMSO* dimethyl sulfoxide

[a] Values are the mean ± standard deviation of three human hepatocyte preparations

* Significantly different from control (0.1% DMSO) according to Dunnett's test ($P < 0.05$)

azacitidine, once daily for three consecutive days, did not induce CYP1A2, CYP2C19, and CYP3A4/5 activities.

Discussion

Azacitidine is shown to undergo non-enzymatic degradation to N-formylamidinoribosyl guanylurea and is susceptible for further decomposition both in vitro and in vivo. In addition, cytidine deaminase and uridine-cytidine kinase play a role in the metabolism of azacitidine via deamination and phosphorylation, respectively [21–24]. In humans, azacitidine and/or its metabolites were eliminated renally, with 50–98% of the radioactive dose recovered in urine [24], and CYP enzymes do not play a role in metabolic clearance. Therefore, co-administration of potent CYP inhibitors (e.g., ketoconazole, fluconazole, fluoxamine, and quinidine) or inducers is not likely to result in clinically relevant effects on the exposure of azacitidine.

Based on early promising results in recent in vitro and in vivo studies, azacitidine could potentially be administered with other anticancer drugs in clinical settings [10, 12, 25], some of which are likely to be CYP substrates. It is important to understand any potential drug–drug interactions due to inhibition or induction of CYP enzymes by azacitidine. The results of these studies demonstrate that azacitidine does not inhibit or induce CYP enzymes in vitro. The peak plasma concentrations of azacitidine at therapeutic dose are approximately 3 μM, which are considerably lower than the highest concentration (100 μM) evaluated in this in vitro study. Hence, azacitidine is not anticipated to precipitate clinically relevant pharmacokinetic drug–drug interaction when co-administered with CYP substrates either due to inhibition or induction.

Conclusion

Azacitidine is not an inhibitor CYP enzymes nor inducer of CYP group of enzymes via activation of AhR, CAR, or PXR nuclear receptors; therefore, clinically relevant pharmacokinetic drug–drug interactions are unlikely to occur between azacitidine and co-administered substrates of these CYP isozymes.

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References

1. Vesely J, Cihak A (1978) 5-Azacitidine: mechanism of action and biological effects in mammalian cells. Pharmacol Ther 2:813–840
2. Jones PA (1985) Effects of 5-azacytidine and its 2′-deoxyderivative on cell differentiation and DNA methylation. Pharmacol Ther 28:17–27
3. Herman JG, Baylin SB (2003) Gene silencing in cancer in association with promoter hypermethylation. N Eng J Med 349:2042–2054
4. Stresemann C, Lyko F (2008) Modes of action of the DNA methyltransferase inhibitors azacytidine and decitabine. Int J Cancer 123:8–13
5. Fandy TE, Carraway H, Gore SD (2007) DNA demethylating agents and histone deacetylase inhibitors in hematologic malignancies. Cancer J 13:40–48
6. Von Hoff DD, Slavik M, Muggia FM (1976) 5-Azacytidine. A new anticancer drug with effectiveness in acute myelogenous leukemia. Ann Intern Med 85:237–245
7. Raza A, Mehdi M, Mumtaz M, Ali F, Lascher S, Galili N (2008) Combination of 5-azacytidine and thalidomide for the treatment of myelodysplastic syndromes and acute myeloid leukemia. Cancer 113:1596–1604
8. Back DJ, Orme ML (1990) Pharmacokinetic drug interactions with oral contraceptives. Clin Pharmacokinet 18:472–484
9. Park BK, Kitteringham NR, Pirmohamed M, Tucker GT (1996) Relevance of induction of human drug-metabolizing enzymes: pharmacological and toxicological implications. Br J Clin Pharmacol 41:477–491
10. Nand S, Godwin J, Smith S, Barton K, Michaelis L, Alkan S, Veerappan R, Rychlik K, Germano E, Stiff P (2008) Hydroxyurea, azacitidine and gemtuzumab ozogamicin therapy in patients with previously untreated non-M3 acute myeloid leukemia and high-risk myelodysplastic syndromes in the elderly: results from a pilot trial. Leuk Lymphoma 49:2141–2147
11. Gore SD (2005) Combination therapy with DNA methyltransferase inhibitors in hematologic malignancies. Nat Clin Pract Oncol 2 Suppl 1:S30–S35
12. Braiteh F, Soriano AO, Garcia-Manero G, Hong D, Johnson MM, Silva Lde P, Yang H, Alexander S, Wolff J, Kurzrock R (2008) Phase I study of epigenetic modulation with 5-azacytidine and valproic acid in patients with advanced cancers. Clin Cancer Res 14:6296–6301
13. Kuendgen A, Lübbert M (2008) Current status of epigenetic treatment in myelodysplastic syndromes. Ann Hematol 87:601–611
14. Marcucci G, Silverman L, Eller M, Lintz L, Beach CL (2005) Bioavailability of azacitidine subcutaneous versus intravenous in patients with the myelodysplastic syndromes. J Clin Pharmacol 45:597–602
15. Garcia-Manero G, Stoltz ML, Ward MR, Kantarjian H, Sharma S (2008) A pilot pharmacokinetic study of oral azacitidine. Leukemia 22:1680–1684
16. LeCluyse EL, Audus KL, Hochman JH (1994) Formation of extensive canalicular networks by rat hepatocytes cultured in collagen-sandwich configuration. Am J Physiol Cell Physiol 266:C1764–C1774
17. LeCluyse E, Madan A, Hamilton G, Carroll K, DeHaan R, Parkinson A (2000) Expression and regulation of cytochrome P450 enzymes in primary cultures of human hepatocytes. J Biochem Mol Toxicol 14:177–188
18. Madan A, Dehaan R, Mudra D, Carroll K, LeCluyse E, Parkinson A (1999) Effect of cryopreservation on cytochrome P-450 enzyme induction in cultured rat hepatocytes. Drug Metab Dispos 27:327–335
19. Mudra DR, Parkinson A (2001) Preparation of Hepatocytes; Unit 14.2. In: Maines MD (Ed.) Current Protocols in Toxicology,

Volume 1 Supplement 8. Wiley, New York. doi:10.1002/0471140856.tx1402s08
20. Quistorff B, Dich J, Grunnet N (1989) Preparation of isolated rat liver hepatocytes. In: Pollard JW, Walker JM (eds) Methods in Molecular Biology, Vol. 5: Animal Cell Culture. Humana Press, Clifton, New Jersey, pp 151–160
21. Beisler JA (1978) Isolation, characterization, and properties of a labile hydrolysis product of the antitumor nucleoside, 5-azacytidine. J Med Chem 21:204–208
22. Plagemann PG, Behrens M, Abraham D (1978) Metabolism and cytotoxicity of 5-azacytidine in cultured Novikoff rat hepatoma and P388 mouse leukemia cells and their enhancement by preincubation with pyrazofurin. Cancer Res 38:2458–2466
23. Chabner BA, Drake JC, Johns DG (1973) Deamination of 5-azacytidine by a human leukemia cell cytidine deaminase. Biochem Pharmacol 22:2763–2765
24. Israili ZH, Vogler WR, Mingioli ES, Pirkle JL, Smithwick RW, Goldstein JH (1976) The disposition and pharmacokinetics in humans of 5-azacytidine administered intravenously as a bolus or by continuous infusion. Cancer Res 36:1453–1461
25. Gao S, Mobley A, Miller C, Boklan J, Chandra J (2008) Potentiation of reactive oxygen species is a marker for synergistic cytotoxicity of MS-275 and 5-azacytidine in leukemic cells. Leuk Res 32:771–780
26. Madan A, Graham RA, Carroll KM, Mudra DR, Burton LA, Krueger LA, Downey AD, Czerwinski M, Forster J, Ribadeneira MD, Gan LS, LeCluyse EL, Zech K, Robertson P Jr, Koch P, Antonian L, Wagner G, Yu L, Parkinson A (2003) Effects of prototypical microsomal enzyme inducers on cytochrome P450 expression in cultured human hepatocytes. Drug Metab Dispos 31:421–431
27. Luo G, Cunningham M, Kim S, Burn T, Lin J, Sinz M, Hamilton G, Rizzo C, Jolley S, Gilbert D, Downey A, Mudra D, Graham R, Carroll K, Xie J, Madan A, Parkinson A, Christ D, Selling B, LeCluyse E, Gan L (2002) CYP3A4 induction by drugs: correlation between a pregnane x reporter gene assay and CYP3A4 expression in human hepatocytes. Drug Metab and Dispos 30:795–804