IN VIVO ASSESSMENT OF THE ROLE OF LIVER METABOLISM IN SYDNONE IMINE BIOTRANSFORMATION

Popov NS[1] ✉, Terekhov VM[1], Baranov MS[2], Balabanyan VYu[2], Kaurova DE[2], Myasnyanko IN[2], Terekhova EA[1]

[1] Tver State Medical University, Tver, Russia

[2] Research Institute of Translational Medicine, Pirogov Russian National Research Medical University, Moscow, Russia

Assessment of pharmacologically active molecule biotransformation represents the most important phase of drug development, the results of which make it possible to identify active and toxic metabolites and provide a fundamental basis for the targeted design of new candidate drug molecules. The liver is the main organ involved in biotransformation of drugs. The currently widely used *in vitro* metabolism assessment methods do not allow one to identify products of extrahepatic drug molecule biotransformation. The study aimed to develop an *in vivo* approach to determination of the role of the liver in biotransformation of candidate drug molecules. The approach proposed is based on the vascular liver isolation performed surgically in laboratory rats. The organ involvement in biotransformation of pharmacologically active molecules is exemplified by the leader compound of the sydnone imine group possessing vasodilatory activity. It has been shown that elimination of the liver from systemic blood flow does not result in generation of the test compound metabolites identified by chromatography–mass spectrometry. The findings can provide the basis for prediction of drug pharmacokinetics, efficacy, and safety.

Keywords: biotransformation, pharmacokinetics, sydnone imines, vasodilators, chromatography–mass spectrometry

Funding: the study was carried out under the state assignment for the research project “Development of the Candidate Drug Possessing Mostly Central Vasodilatory Activity for Treatment of Cerebrovascular Disorders”, state registration number 124020900020-4.

Author contribution: Popov NS — search for the BBP2023 compound metabolites, bioanalytical method development, manuscript writing; Terekhov VM — developing the design of vascular liver isolation in rats, surgical procedure; Baranov MS — synthesis of the BBP2023 compound and its metabolites, manuscript writing; Balabanyan VYu — goal setting, developing the study design, manuscript writing, Kaurova DE — literature review, manuscript writing; Myasnyanko IN — synthesis of the BBP2023 compound and its metabolites, manuscript writing; Terekhova EA — developing the design of vascular liver isolation in rats, surgical procedure; all authors contributed to the publication equally, they confirm compliance of authorship with the ICMJE international criteria.

Compliance with ethical standards: the study was approved by the Ethics Committee of the Tver State Medical University (protocol No. 5 dated 19 June 2024). All experiments were conducted in accordance with the principles of Good Laboratory Practice (Order of the Ministry of Health of the Russian Federation No. 708n of 23.08.2010, Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes).

✉ **Correspondence should be addressed:** Nikita S. Popov
Sovetskaya, 4, Tver, 170100, Russia; ns.popov@mail.ru

Received: 16.04.2025 **Accepted:** 30.04.2025 **Published online:** 15.05.2025

DOI: 10.24075/brsmu.2025.026

ОЦЕНКА РОЛИ ПЕЧЕНОЧНОГО МЕТАБОЛИЗМА В БИОТРАНСФОРМАЦИИ СИДНОНИМИНОВ *IN VIVO*

Н. С. Попов[1] ✉, В. М. Терехов[1], М. С. Баранов[2], В. Ю. Балабаньян[2], Д. Е. Каурова[2], И. Н. Мяснянко[2], Е. А. Терехова[1]

[1] Тверской государственный медицинский университет, Тверь, Россия

[2] Научно-исследовательский институт трансляционной медицины, Российский национальный исследовательский медицинский университет имени Н. И. Пирогова, Москва, Россия

Исследование биотрансформации фармакологически активных молекул — важнейший этап разработки лекарственных средств, результаты которого позволяют выявить активные и токсичные метаболиты, прогнозировать лекарственные взаимодействия, а также являются фундаментальной основой для целенаправленного конструирования молекул новых лекарственных кандидатов. Основным органом, принимающим участие в биотрансформации лекарств, является печень. Широко используемые в настоящее время методы исследования метаболизма *in vitro* не позволяют выявить продукты внепеченочной биотрансформации лекарственных молекул. Целью исследования было разработать *in vivo* подход к определению роли печени в биотрансформации молекул лекарственных кандидатов. Предложенный подход основан на осуществлении сосудистой изоляции печени у лабораторных крыс, выполненной хирургическим путем. Участие данного органа в биотрансформации фармакологически активных молекул показано на примере соединения-лидера из группы сиднониминов, обладающего сосудорасширяющей активностью. Показано, что исключение печени из системного кровотока не приводит к образованию метаболитов изучаемого соединения, идентифицируемых с помощью хромато-масс-спектрометрии. Полученные результаты могут служить основой для прогнозирования фармакокинетики, эффективности и безопасности лекарственных средств.

Ключевые слова: биотрансформация, фармакокинетика, сиднонимины, вазодилататоры, хромато-масс-спектрометрия

Финансирование: исследование выполнено в рамках государственного задания, тема научно-исследовательской работы: «Разработка лекарственного кандидата, обладающего преимущественно центральным сосудорасширяющим действием для лечения цереброваскулярных патологий», номер госрегистрации — 124020900020-4.

Вклад авторов: Н. С. Попов — поиск метаболитов соединения BBP2023, разработка биоаналитической методики, подготовка рукописи; В. М. Терехов — разработка дизайна сосудистой изоляции печени у крыс, выполнение оперативного вмешательства; М. С. Баранов — синтез соединения BBP2023 и его метаболитов, подготовка рукописи; В. Ю. Балабаньян — постановка цели, разработка дизайна исследования, подготовка рукописи, Д. Е. Каурова — обзор литературы, подготовка рукописи; И. Н. Мяснянко — синтез соединения BBP2023 и его метаболитов, подготовка рукописи; Е. А. Терехова — разработка дизайна сосудистой изоляции печени у крыс, выполнение оперативного вмешательства; все авторы внесли равнозначный вклад в подготовку публикации, подтверждают соответствие своего авторства международным критериям ICMJE.

Соблюдение этических стандартов: исследование одобрено этическим комитетом ФГБОУ ВО Тверской ГМУ Минздрава России (протокол № 5 от 19 июня 2024 г.). Все эксперименты выполнены в соответствии с Правилами лабораторной практики (приказ Минздрава России от 23.08.2010 № 708н, Директива Европейского парламента, Совет Европейского союза 2010/63/ЕС по защите позвоночных животных, используемых для научных целей).

✉ **Для корреспонденции:** Никита Сергеевич Попов
ул. Советская, д. 4, г. Тверь, 170100, Россия; ns.popov@mail.ru

Статья получена: 16.04.2025 **Статья принята к печати:** 30.04.2025 **Опубликована онлайн:** 15.05.2025

DOI: 10.24075/vrgmu.2025.026

Assessment of the candidate molecule biotransformation represents the most important phase of drug development [1]. Generation of toxic drug metabolites is a factor contributing greatly to safety of the ongoing drug therapy and the cause of the pre-clinical and clinical trial failure [2]. In contrast, generation of pharmacologically active metabolites can significantly increase the drug use efficacy [3] and can provide the basis for the design of new drug molecules [4]. The data on drug biotransformation are important at the stage of developing the dosage form composition and production technology [5]; these also allow one to predict many drug interactions [6]. Furthermore, the data on metabolic pathways of the known compounds provide the basis for the targeted design of new candidate drug molecules [7].

The liver is the main organ involved in biotransformation of drugs [8]. The drug candidate metabolism testing in the early development phase is most commonly conducted in vitro via incubation of substances with the liver microsomal fraction containing various enzymes [9–11]. This is a generally accepted, affordable and reproducible approach [12]. Furthermore, this allows one to identify certain cytochromes involved in metabolism of a specific substance [13]. However, such method has a number of fundamental flaws, among which impossibility of identifying products of extrahepatic drug biotransformation can be distinguished [14]. The alternative approach is *in vivo* biotransformation assessment, during which laboratory animals receive the test drug, and after that biomaterial (blood plasma, urine, internal organ fragments) is collected from these animals after a while. Biomaterial is tested in order to detect probable metabolites [15]. The results obtained also cannot give an accurate picture of the liver involvement in drug biotransformation processes.

One of the approaches to determination of the liver involvement in metabolism of pharmacologically active substances represents surgical elimination of the organ from systemic blood flow performed immediately before the test drug administration. Comparison of the results of determining probable metabolites in biomaterial collected from the laboratory animals with vascular liver isolation and without it by chromatography–mass spectrometry makes it possible to draw conclusions about the role of hepatocytes in the test molecule biotransformation.

The study aimed to develop an *in vivo* approach to determination of the role of the liver in biotransformation of candidate drug molecules.

METHODS

All experimental work, including pharmacological and bioanalytical phases, was performed at the research laboratory of the Tver State Medical University.

The BBP2023 leader compound representing a sydnone imine derivative that possessed vasodilator activity was used as an experimental object for assessment of the liver involvement in drug biotransformation (Fig. 1).

In the first phase of the study, the structure of probable BBP2023 compound metabolites, for which accurate monoisotopic mass values were calculated, was predicted based on the knowledge about common xenobiotic biotransformation pathways (Table 1).

In the second phase, a pharmacological experiment was conducted that was aimed at collecting biomaterial (blood plasma) containing probable metabolites. The testing involved male Wistar rats weighing about 250 g (SMK STEZAR LLC breeding nursery, Russia). Cages with animals were kept in a controlled environment (20–26 °C and relative humidity 30–70%). In the rooms, where the animals were kept, a 12 h light/dark cycle was used, along with 8-10 air changes per hour. Rats were fed with the PK-120 complete animal feed (Laboratorkorm LLC, Russia) and were given ad libitum access to filtered tap water. Cleaning of cages, mopping of rooms, and replacement of water bottles with new ones were carried out daily. The animals were deprived of food on the eve of the experiment.

During testing three rats underwent a single intragastric administration of the BBP2023 active pharmaceutical ingredient (API) in the form of the 10% corn oil emulsion in a dose of 1/100 LD_{50}. A total of 0.1 mL of blood was collected from the rat tail vein 3 h after administration of the drug using an insulin syringe containing 2 IU of sodium heparin. The collected blood was

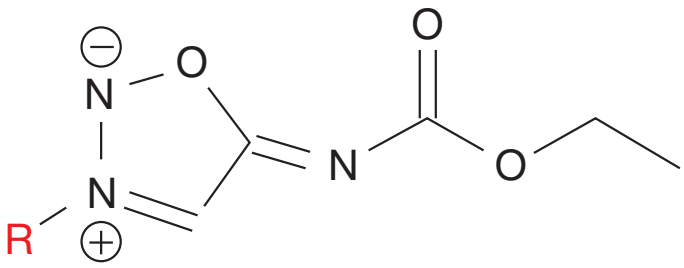


Fig. 1. BBP2023 structural formula, where R is a saturated branched hydrocarbon radical (C_7H_{15})

Table 1. Expected BBP2023 compound biotransformation products and their monoisotopic mass

Probable metabolite	Molecular mass, Da	Probable metabolite	Molecular mass, Da
BBP2023	255.16	R-NH_2	115.13
BBP2023 + OH	271.15	BBP2023 + OH + glucuronic acid	447.19
BBP2023 + 2OH	287.15	BBP2023 - (CO)OC_2H_5 + OH + glucuronic acid	375.16
BBP2023 + 3OH	303.15	R-NH_2 + OH	131.13
BBP2023 - (CO)OC_2H_5	183.14	R-NH_2 + OH + glucuronic acid	307.16
BBP2023 - (CO)OC_2H_5 + OH	199.13	BBP2023 + OH + sulfuric acid	351.11
BBP2023 - (CO)OC_2H_5 + 2OH	215.13	BBP2023 + glutathione	560.23
BBP2023 - (CO)OC_2H_5 - NO	154.15	BBP2023 - (CO)OC_2H_5 - NO+ OH + glucuronic acid	346.17

Note: R — saturated branched hydrocarbon radical (C_7H_{15})

Table 2. Chromatographic parameters for determination of the expected BBP2023 compound biotransformation products

Chromatography system	Agilent Technologies 1260 Infinity II (Agilent Technologies, USA)			
Chromatography column	Agilent InfinityLab Poroshell 120 EC-C18 4.6 × 100 mm, 2.7 µm			
Guard column	Zorbax Eclipse Plus C18 4.6 × 12.5 mm, 5 µm			
Elution solvent A	Deionized water + 0.1% formic acid			
Elution solvent B	Acetonitrile + 0.1% formic acid			
Gradient program	Time, min	Flow rate, mL/min	% A	% B
	0.0 1.0 4.0 8.0 8.01 12.0	0,4	90 90 5 5 90 90	10 10 95 95 10 10
Column thermostat temperature, °C	30			
Sample volume, µL	10			
Total analysis time, min	12			
Injector washing	Via washing port, 3 s, 50% aqueous methanol solution			

immediately transferred to 0.2 mL Eppendorf tubes; plasma was produced using the LMC-4200R laboratory centrifuge (Biosan, Latvia) at room temperature and rotor speed of 3000 rpm for 10 min. A total of 50 µL of plasma collected was combined with 800 µL of methanol supplemented with 0.5% formic acid; samples were vortexed using the Microspin FV-2400 vortex mixer (Biosan, Latvia) for 15 s, kept at a temperature of –40 °C — in the MDF-136 freezer (Sanyo, Japan) for 30 min; after that the supernatant was separated using the D-37520 centrifuge (Sigma, Germany) at 15,000 g and –10 °C — for 20 min. The

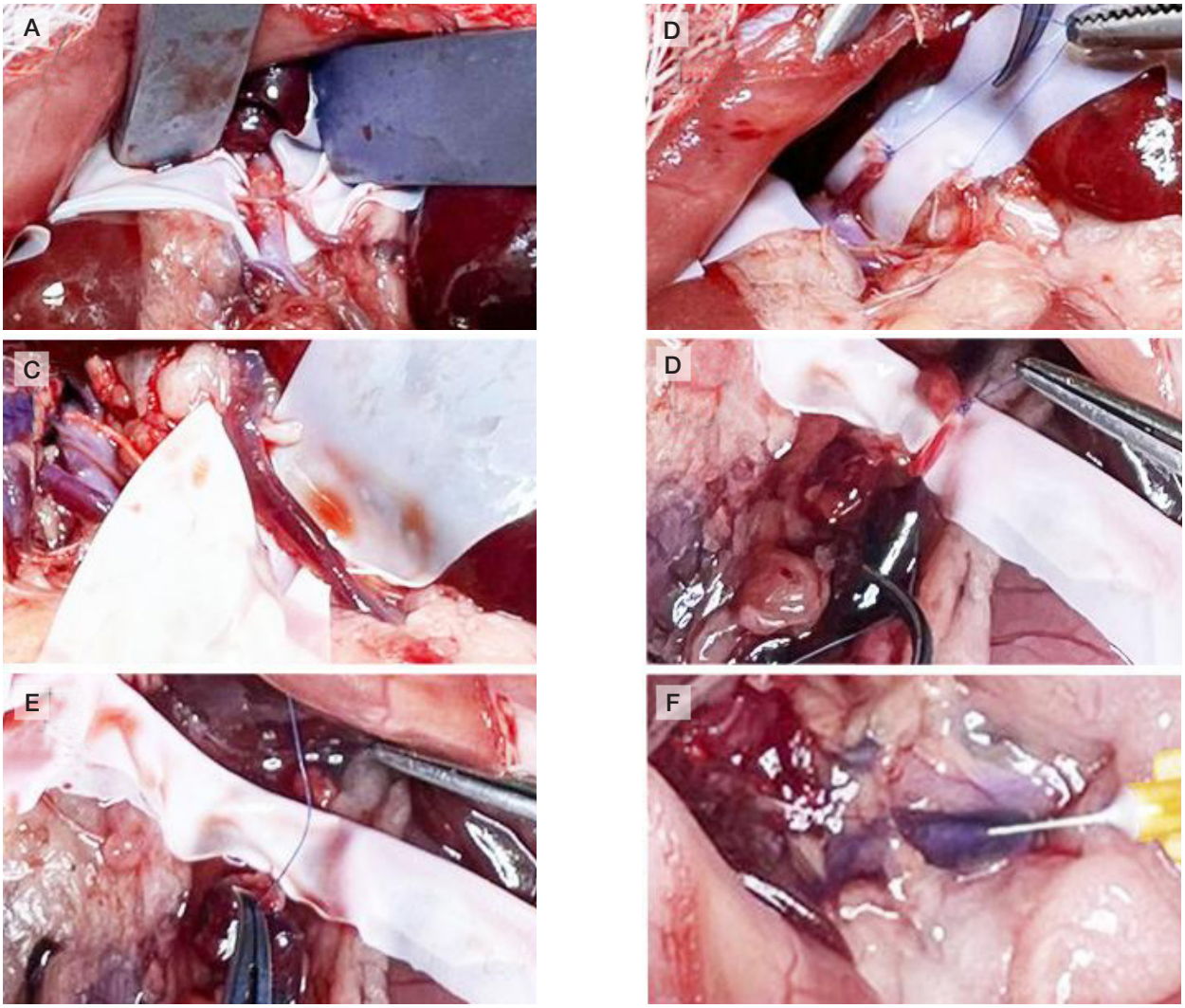
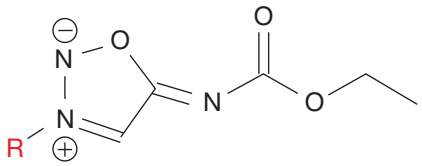
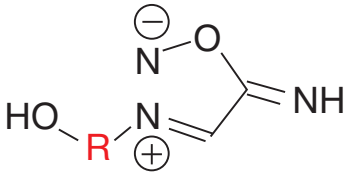
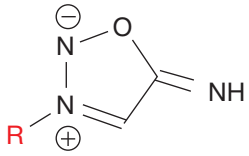
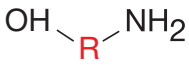
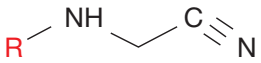
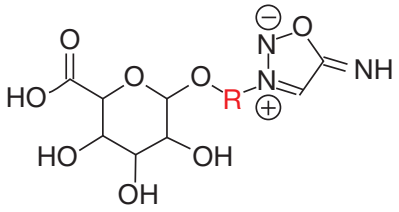
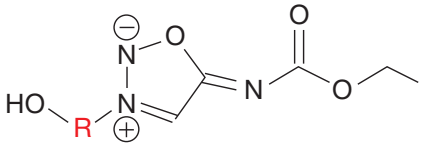
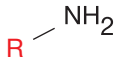
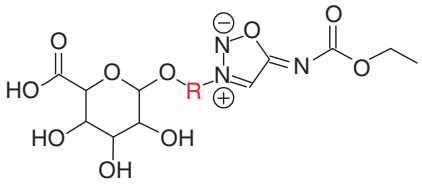
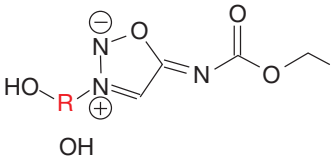


Fig. 2. A. Skeletonization of the abdominal aorta (*aorta abdominalis*) with the celiac trunk (*truncus celiacus*) **B**. Stumps of the celiac trunk with the ligatures placed. **C**. Portal vein (*vena portae*) isolation. **D**. Portal vein with the ligatures placed. **E**. Crossing the portal vein between the ligatures. **F**. Drug injection into the inferior vena cava (*vena cava inferior*). A sterile latex glove was used as a contrast medium during surgery in order to enhance the information content

Tabl3 3. Structural formulae of the identified BBP2023 compound metabolites and MRM transitions used for detection during chromatographic analysis

Structural formula	MRM transition, m/z	Structural formula	MRM transition, m/z
	256.2/57.1 256.2/102.1		200.1/73.1 200.1/86.1
	184.1/57.1 184.1/86.1		132.1/114.1 132.1/86.1
	155.2/57.1 155.2/95.0		376.2/86.1 376.2/115.1 376.2/183.1
	272.2/102.1 272.2/73.1		
	116.1/57.1 116.1/99.1		448.2/255.2 448.2/158.1 448.2/102.1
	288.2/102.1 288.2/89.1		

Note: R — saturated branched hydrocarbon radical (C_7H_{15}).

supernatant was filtered using the 0.22 μm membrane filter (Laboratoriya Vody, Russia), and injected directly into the electrospray ion source of the AB Sciex 3200 MD Qtrap mass spectrometer (Sciex, Singapore) using the built-in syringe pump at a rate of 10 μL/min. First, mass spectrometry analysis of the BBP2023 compound was conducted in order to identify characteristic product ions (Product Ion mode). Given that fragmentation of potential metabolites can yield product ions overlapping with the BBP2023 compound fragment ions based on the m/z value (mass divided by charge number), the reverse screening of molecular ions was performed for the corresponding product ions (Precursor Ion mode). The signals identified were compared with the theoretically calculated monoisotopic mass values of the expected metabolites. When these values coincided, the BBP2023 compound biotransformation products identified were tested by mass spectrometry in the Product Ion mode in order to indirectly confirm the chemical structure. The mass spectrometry testing results were later used to detect the expected metabolites in the multiple reaction monitoring (MRM) mode when performing chromatography analysis of blood plasma of intact rats and the animals administered the BBP2023 compound. For this purpose, chromatography conditions specified in Table 2 were selected.

To assess the liver involvement in the BBP2023 compound biotransformation, surgery aimed to eliminate this organ from systemic blood flow was performed in three rats in the third phase of the experiment. The animal's fur was completely removed from skin in the surgical site; 0.1% atropine sulfate solution (Dalhimfarm, Russia) in a dose of 0.04 mg/kg was administered subcutaneously for premedication. Rats were in supine position. The upper midline laparotomy was performed under anesthesia achieved via subcutaneous administration of the combination of tiletamine hydrochloride 5 mg, zolazepam 5 mg (Zoletil, Virbac, France), and xylazine 4 mg (Nita-Farm, Russia); intestinal loops were retrieved, pulled to the left, wrapped in napkins soaked in warm sterile saline; the Adson retractor was installed. The portal vein (*vena portae*) and the celiac trunk (truncus celiacus) were isolated, tied up with the USP 3/0 lavsan thread (Medthekhnika, Russia), and crossed between the ligatures (Fig. 2). A key point of the portal vein ligation is that ligature is placed before the branches going to the liver begin to branch out from the vein. After vascular liver isolation, the BBP2023 compound solution (27.5 mg/mL) in a volume of 0.1 mL (1/100 LD_{50}) was injected into the subhepatic segment of the inferior vena cava (*vena cava inferior*) using the insulin syringe with the 30G needle (Inecta, China); a hemostatic sponge (Belcozin Factory, Luga, Russia) was placed onto the

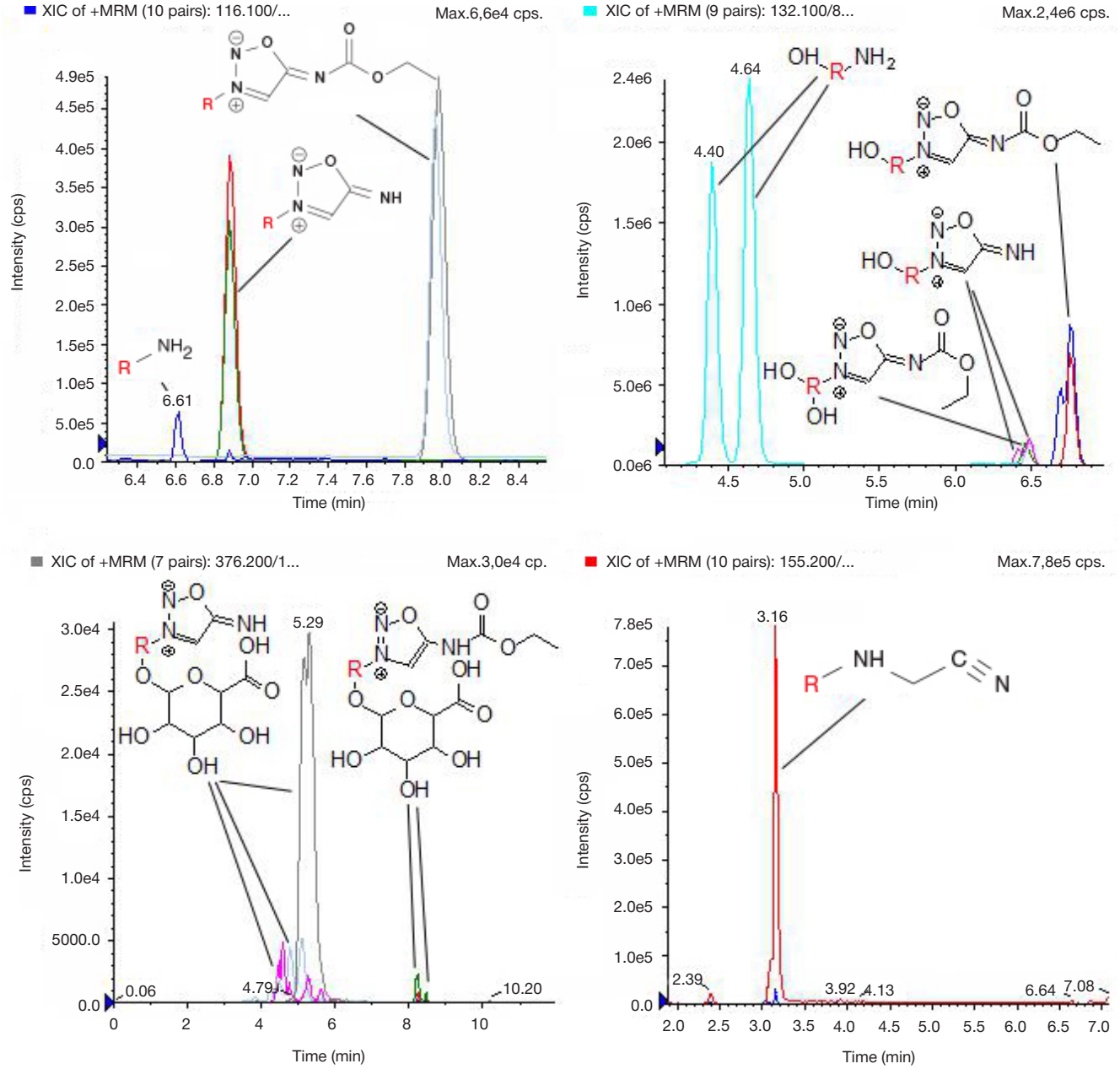


Fig. 3. Fragments of blood plasma chromatograms of the sham-operated animals, which were intravenously administered the BBP2023 compound in a dose of 1/100 LD_{50}. R — saturated branched hydrocarbon radical (C_7H_{15})

puncture site. After achieving hemostasis, the layer by layer closure of the laparotomy wound was performed.

Blood was collected from the rat tail vein 3 h after administration of the drug; plasma collection and sample preparation were performed in accordance with the previously reported method. The samples processed were assessed by chromatography in order to detect the BBP2023 compound metabolites. Furthermore, biomaterial was tested that was collected from intact and sham-operated animals (without liver isolation), which were intravenously administered the drug in the same way. After blood collection the animals were euthanized through carbon dioxide inhalation.

Primary chromatography–mass spectrometry data were processed using the embedded AB Sciex Analyst 1.3.6 software (AB Sciex, USA).

RESULTS

Screening of blood plasma of the rats subjected to intragastric administration of the test drug revealed a metabolite representing the BBP2023 compound devoid of the ethoxycarbonyl group. Furthermore, a product was found formed after the nitrogen monoxide (NO) splitting off the above molecule. This fact may be an indirect evidence of the expected test leader compound pharmacodynamics. Moreover, screening revealed the mono- and dihydroxylated derivatives of the above metabolites and the original compound, as well as the glucuronic acid esters of these compounds (Table 3). Some metabolites identified were synthesized and used as standards when setting the method and performing further chromatographic analysis. The fact that the retention times of these compounds coincide confirms correctness of their identification in the screening phase.

The intact rat plasma testing revealed no chromatographic peaks corresponding to the BBP2023 compound and its metabolites, which confirmed selectivity of the identification method developed. The analysis of plasma samples collected from the sham-operated animals (without liver isolation), which were intravenously administered the test compound in a dose of 1/100 LD_{50} 3 h before blood collection, made it possible

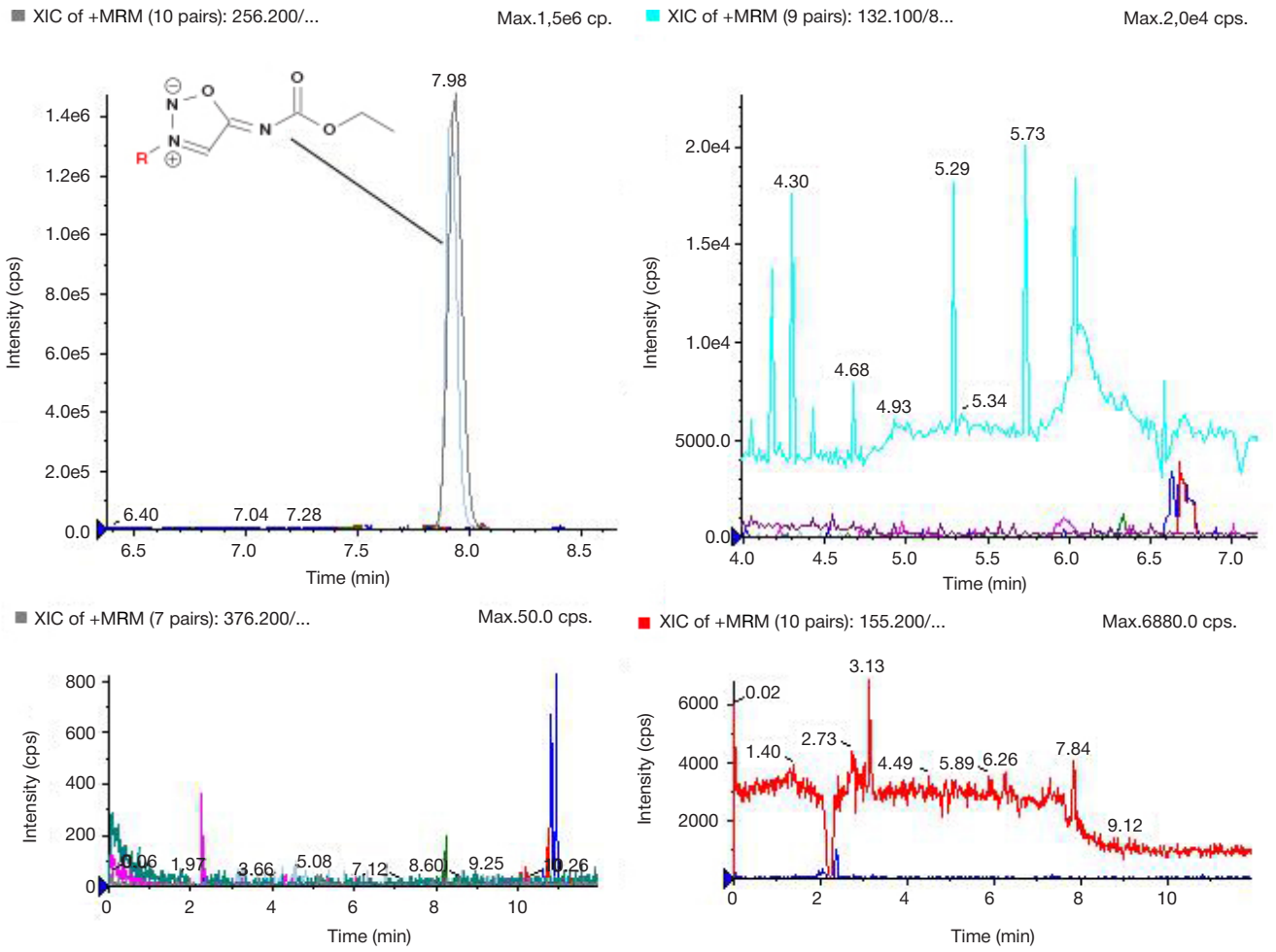


Fig. 4. Fragments of blood plasma chromatograms of the rats with vascular liver isolation, which were intravenously administered the BBP2023 compound in a dose of 1/100 LD_{50}. R — saturated branched hydrocarbon radical (C_7H_{15})

to detect chromatographic signals of all biotransformation products identified in the second phase (Fig. 3).

The results of chromatographic analysis of blood plasma collected from rats, which received the BBP2023 API in the same dose after vascular liver isolation, confirmed the presence of the signal corresponding to the original compound. Furthermore, the chromatographic peak area was on average 2.8 times larger than that obtained when testing biomaterial collected from the sham-operated animals. Furthermore, it was found that there were no peaks corresponding to the earlier detected BBP2023 compound biotransformation products (Fig. 4).

DISCUSSION

The findings allow us to draw a conclusion that the liver is directly involved in production of the identified BBP2023 compound metabolites in rats. The use of perfectly healthy animals was an important factor of the above experiment, since any damage to hepatocytes leading to the emergence of hepatic enzymes in blood can considerably affect reliability of the results obtained. Impossibility of testing the drugs that have exclusively enteral dosage forms represents one of the disadvantages of this approach. In this case, the test substance cannot enter systemic bloodstream due to the ligature placed on the portal vein. Furthermore, one should consider possible interplay between the candidate drug and the components of anesthesia when conducting such an experiment.

One of the options for the implemented approach is the use of temporary restriction of blood flow through the liver by placing surgical clips on the corresponding blood vessels. Blood collection and subsequent blood flow restoration are accomplished after a certain time after drug administration. Blood re-collection after a specified time with subsequent testing of plasma for metabolites will allow one to consider the animal's individual characteristics in terms of certain drug candidate biotransformation. Perhaps, such an approach can be implemented with respect to other organs, such as the kidney.

CONCLUSIONS

The approach to assessment of the role of the liver in biotransformation of candidate molecules at the early stages of drug development proposed in this study is versatile and informative. It can be used as an independent in vivo metabolism assessment method, or to complement the widely used in vitro methods. The results obtained when applying this approach can provide the basis for prediction of drug pharmacokinetics, efficacy, and safety.

References

1. Shanu-Wilson J, Evans L, Wrigley S, Steele J, Atherton J, Boer J. Biotransformation: impact and application of metabolism in drug discovery. ACS Medicinal Chemistry Letter. 2020; 11 (11): 2087–2107. DOI: 10.1021/acsmedchemlett.0c00202.
2. Baillie TA, Rettie AE. Role of biotransformation in drug-induced toxicity: influence of intra-and inter-species differences in drug metabolism. Drug metabolism and pharmacokinetics. 2011; 26 (1): 15–29. DOI: 10.2133/dmpk.DMPK-10-RV-089.
3. Obach RS. Pharmacologically active drug metabolites: impact on drug discovery and pharmacotherapy. Pharmacological reviews. 2013; 65 (2): 578–640. DOI: 10.1124/pr.111.005439.
4. Fura A. Role of pharmacologically active metabolites in drug discovery and development. Drug discovery today. 2006; 11 (3–4): 133–42. DOI: 10.1016/S1359-6446(05)03681-0.
5. Mahanur V, Rajge R, Tawar MA. Review on emerging oral dosage forms which helps to bypass the hepatic first pass metabolism. Asian Journal of Pharmacy and Technology. 2022; 12 (1): 47–52. DOI: 10.52711/2231-5713.2022.00009.
6. Klomp F, Wenzel C, Drozdzik M, Oswald S. Drug–drug interactions involving intestinal and hepatic CYP1A enzymes. Pharmaceutics. 2020; 12 (12): 1201. DOI: 10.3390/pharmaceutics12121201.
7. Cerny MA, Kalgutkar AS, Obach RS, Sharma R, Spracklin DK, Walker GS. Effective application of metabolite profiling in drug design and discovery. Journal of Medicinal Chemistry. 2020; 63 (12): 6387–406. DOI: 10.1021/acs.jmedchem.9b01840.
8. Rai M, Paudel N, Sakhrie M, Gemmati D, Khan IA, Tisato V, Singh AV. Perspective on quantitative structure–toxicity relationship (QSTR) models to predict hepatic biotransformation of xenobiotics. Livers. 2023; 3 (3): 448–62. DOI: 10.3390/livers3030032.
9. Peeters L, Vervliet P, Foubert K, Hermans N, Pieters L, Covaci A. A comparative study on the in vitro biotransformation of medicagenic acid using human liver microsomes and S9 fractions. Chemico-Biological Interactions. 2020; 328: 109192. DOI: 10.1016/j.cbi.2020.109192.
10. Horspool AM, Wang T, Scaringella YS, Taub ME, Chan TS. Human liver microsomes immobilized on magnetizable beads: a novel approach to study in vitro drug metabolism. Drug Metabolism and Disposition. 2020; 48 (8): 645–654. DOI: 10.1124/dmd.120.090696.
11. Ooka M, Lynch C, Xia M. Application of in vitro metabolism activation in high-throughput screening. International journal of molecular sciences. 2020; 21 (21): 8182. DOI: 10.3390/ijms21218182.
12. Knights KM, Stresser DM, Miners JO, Crespi CL. In vitro drug metabolism using liver microsomes. Current protocols in pharmacology. 2016; 74 (1): 7–8. DOI: 10.1002/cpph.9.
13. Venkatakrishnan K, von Moltke LL, Greenblatt DJ. Human drug metabolism and the cytochromes P450: application and relevance of in vitro models. The Journal of Clinical Pharmacology. 2001; 41 (11): 1149–79. DOI: 10.1177/00912700122012724.
14. Pelkonen O, Raunio H. In vitro screening of drug metabolism during drug development: can we trust the predictions? Expert opinion on drug metabolism & toxicology. 2005; 1 (1): 49–59. DOI: 10.1517/17425255.1.1.49.
15. Zhu C, Wan M, Cheng H, Wang H, Zhu M, Wu C. Rapid detection and structural characterization of verapamil metabolites in rats by UPLC–MSE and UNIFI platform. Biomedical Chromatography. 2020; 34 (1): e4702. DOI: 10.1002/bmc.4702.
16. Lee K, Lee JY, Lee K, Jung CR, Kim MJ, Kim JA, Oh SJ. Metabolite profiling and characterization of LW6, a novel HIF-1α inhibitor, as an antitumor drug candidate in mice. Molecules. 2021; 26 (7): 1951. DOI: 10.3390/molecules26071951.

Литература

1. Shanu-Wilson J, Evans L, Wrigley S, Steele J, Atherton J, Boer J. Biotransformation: impact and application of metabolism in drug discovery. ACS Medicinal Chemistry Letter. 2020; 11 (11): 2087–2107. DOI: 10.1021/acsmedchemlett.0c00202.
2. Baillie TA, Rettie AE. Role of biotransformation in drug-induced toxicity: influence of intra-and inter-species differences in drug metabolism. Drug metabolism and pharmacokinetics. 2011; 26 (1): 15–29. DOI: 10.2133/dmpk.DMPK-10-RV-089.
3. Obach RS. Pharmacologically active drug metabolites: impact on drug discovery and pharmacotherapy. Pharmacological reviews. 2013; 65 (2): 578–640. DOI: 10.1124/pr.111.005439.
4. Fura A. Role of pharmacologically active metabolites in drug discovery and development. Drug discovery today. 2006; 11 (3–4): 133–42. DOI: 10.1016/S1359-6446(05)03681-0.
5. Mahanur V, Rajge R, Tawar MA. Review on emerging oral dosage forms which helps to bypass the hepatic first pass metabolism. Asian Journal of Pharmacy and Technology. 2022; 12 (1): 47–52. DOI: 10.52711/2231-5713.2022.00009.
6. Klomp F, Wenzel C, Drozdzik M, Oswald S. Drug–drug interactions involving intestinal and hepatic CYP1A enzymes. Pharmaceutics. 2020; 12 (12): 1201. DOI: 10.3390/pharmaceutics12121201.
7. Cerny MA, Kalgutkar AS, Obach RS, Sharma R, Spracklin DK, Walker GS. Effective application of metabolite profiling in drug design and discovery. Journal of Medicinal Chemistry. 2020; 63 (12): 6387–406. DOI: 10.1021/acs.jmedchem.9b01840.
8. Rai M, Paudel N, Sakhrie M, Gemmati D, Khan IA, Tisato V, Singh AV. Perspective on quantitative structure–toxicity relationship (QSTR) models to predict hepatic biotransformation of xenobiotics. Livers. 2023; 3 (3): 448–62. DOI: 10.3390/livers3030032.
9. Peeters L, Vervliet P, Foubert K, Hermans N, Pieters L, Covaci A. A comparative study on the in vitro biotransformation of medicagenic acid using human liver microsomes and S9 fractions. Chemico-Biological Interactions. 2020; 328: 109192. DOI: 10.1016/j.cbi.2020.109192.
10. Horspool AM, Wang T, Scaringella YS, Taub ME, Chan TS. Human liver microsomes immobilized on magnetizable beads: a novel approach to study in vitro drug metabolism. Drug Metabolism and Disposition. 2020; 48 (8): 645–654. DOI: 10.1124/dmd.120.090696.
11. Ooka M, Lynch C, Xia M. Application of in vitro metabolism activation in high-throughput screening. International journal of molecular sciences. 2020; 21 (21): 8182. DOI: 10.3390/ijms21218182.
12. Knights KM, Stresser DM, Miners JO, Crespi CL. In vitro drug metabolism using liver microsomes. Current protocols in pharmacology. 2016; 74 (1): 7–8. DOI: 10.1002/cpph.9.
13. Venkatakrishnan K, von Moltke LL, Greenblatt DJ. Human drug metabolism and the cytochromes P450: application and relevance of in vitro models. The Journal of Clinical Pharmacology. 2001; 41 (11): 1149–79. DOI: 10.1177/00912700122012724.
14. Pelkonen O, Raunio H. In vitro screening of drug metabolism during drug development: can we trust the predictions? Expert opinion on drug metabolism & toxicology. 2005; 1 (1): 49–59. DOI: 10.1517/17425255.1.1.49.
15. Zhu C, Wan M, Cheng H, Wang H, Zhu M, Wu C. Rapid detection and structural characterization of verapamil metabolites in rats by UPLC–MSE and UNIFI platform. Biomedical Chromatography. 2020; 34 (1): e4702. DOI: 10.1002/bmc.4702.
16. Lee K, Lee JY, Lee K, Jung CR, Kim MJ, Kim JA, Oh SJ. Metabolite profiling and characterization of LW6, a novel HIF-1α inhibitor, as an antitumor drug candidate in mice. Molecules. 2021; 26 (7): 1951. DOI: 10.3390/molecules26071951.