Effects of multi-kinase inhibitors on the activity of cytochrome P450 2J2

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ABSTRACT

1. Cytochrome P450 2J2 (CYP2J2) shows high expression in extrahepatic tissues, including the heart and kidney and in tumours. Inhibition of CYP2J2 has attracted attention for cancer treatment because it metabolises arachidonic acid (AA) to epoxyeicosatrienoic acid (EET), which inhibits apoptosis and promotes tumour growth. Multi-kinase inhibitor (MKI) is a molecular-targeted drug with antitumor activities. This study aimed to clarify the inhibitory effects of MKIs on CYP2J2 activity. We also investigated whether MKIs affected CYP2J2-catalysed EET formation from AA.

2. Twenty MKIs showed different inhibitory potencies against astemizole O-demethylation in CYP2J2. In particular, apatinib, motesanib, and vatalanib strongly inhibited astemizole O-demethylation. These three MKIs exhibited competitive inhibition with inhibition constant ($K_i$) values of 9.3, 15.4, and 65.0 nM, respectively. Apatinib, motesanib, and vatalanib also inhibited CYP2J2-catalysed 14,15-EET formation from AA.

3. In simulations of docking to CYP2J2, the $U$ energy values of apatinib, motesanib, and vatalanib were low, and measured $-84.5$, $-69.9$, and $-52.3$ kcal/mol, respectively.

4. In conclusion, apatinib, motesanib, and vatalanib strongly inhibited CYP2J2 activity, suggesting that the effects of a given CYP2J2 substrate may be altered upon the administration of these MKIs.

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Introduction

Cytochrome P450 2J2 (CYP2J2) is an abundant epoxygenase in the heart. Its expression is also high in the lung, skeletal muscle, kidney, and gastrointestinal tissues (Bièche et al. 2007). However, its hepatic expression is low measuring only 1–2% of the total P450 (Yamazaki et al. 2006). CYP2J2 is upregulated in various cancers (Xu et al. 2013). CYP2J2 expression is markedly elevated in human carcinoma tissues in 101 of 130 patients (77%) with various types of carcinomas, relative to adjacent non-tumour tissues (Jiang et al. 2005). It can metabolise endogenous polynsaturated fatty acids, such as arachidonic acid (AA) and linoleic acid. AA is converted into four epoxyeicosatrienoic acids (EET), namely 5,6-EET, 8,9-EET, 11,12-EET, and 14,15-EET (Wu et al. 1996; Chen et al. 2011). 8,9-EET, 11,12-EET, and 14,15-EET inhibit cell apoptosis and promote carcinoma growth (Jiang et al. 2005). These also promoted the proliferation and migration of cancer cells (Atone et al. 2020; Lai and Chen 2021). Therefore, owing to its epoxygenase activity, CYP2J2 has recently attracted attention.

Astemizole and terfenadine are well-known CYP2J2 substrates. CYP2J2 is partly responsible for the metabolism of molecular-targeted drugs, such as dasatinib, nilotinib, sorafenib, sunitinib, and regorafenib (Narjoz et al. 2014; Kojima et al. 2021). The latter three drugs are multi-kinase inhibitors (MKIs) as they inhibit multiple protein kinases involved in oncogenesis and angiogenesis. MKIs are used worldwide in clinical settings for the treatment of several cancers. To date, the effects of MKIs on CYP2J2 function remain unclear, although some MKIs may function as CYP2J2 substrates. This study aimed to elucidate the inhibitory effects of MKIs on CYP2J2 activity.

Materials and methods

Materials

AA, AEE788, apatinib, astemizole, axtinib, lervatinib, and pazopanib were purchased from Cayman Chemicals (Ann Arbor, MI, USA). Brivanib, cediranib, forestinib, linifanib, motesanib, orantinib, semaxinib, tivozanib, vandetanib, and vatalanib were obtained from AdooQ Biosciences (Irvine, CA, USA). Cabozantinib S-malate and nintedanib were purchased from LC Laboratories (Woburn, MA, USA) and MedChem Express (Monmouth Junction, NJ, USA), respectively. Danazol and midazolam were obtained from FUJIFILM Wako Pure Chemical Corporation (Osaka, Japan). O-Desmethylastemizole was purchased from ChemScene (Monmouth Junction, NJ, USA). Sunitinib was purchased from Selleck Chemicals (Houston, TX, USA).
Recombinant human CYP2J2 microsomes were purchased from Corning (Corning, NY, USA). The 14,15-EET/DHET ELISA kit was purchased from Detroit R&D Systems (Detroit, MI, USA).

Inhibition of MKIs on astemizole O-demethylation

Astemizole (1.0 μM) was incubated with recombinant human CYP2J2 microsomes (1.0 pmol) and 10 μM MKIs or 10 μM danazol, a strong inhibitor of CYP2J2, at 37 °C in a nicotinamide adenine dinucleotide phosphate generating system (5 mM MgCl₂, 5 mM glucose-6-phosphate, 1 U glucose-6-phosphate dehydrogenase, and 0.55 mM β-nicotinamide-adenine dinucleotide phosphate) and 100 mM potassium phosphate buffer (pH 7.4). The total reaction volume was 200 μL. MKIs and danazol were dissolved in dimethyl sulfoxide, and the content of organic solvent was less than 1% in the reaction mixtures. The reaction was initiated by the addition of a nicotinamide adenine dinucleotide phosphate generating system. After 20 min of incubation, the reaction was terminated with ice-cold acetonitrile and midazolam was added as an internal standard (500 pg). The samples were centrifuged at 20 600 g at 25 °C for 10 min, and the supernatant was collected and subjected to LC-MS/MS analysis.

Liquid chromatography was performed on the Prominence apparatus (Shimadzu, Kyoto, Japan) equipped with an InertSustain C18 (3 μm, 2.1 × 50 mm, GL Science, Tokyo, Japan) and set to a column temperature of 40 °C. The mobile phase consisted of 10 mM ammonium formate in 45% acetonitrile; the flow rate was 0.3 mL/min. The detection was similar to those of apatinib and motesanib. The reaction mixture exhibited a coefficient of variation of less than 10%.

The residual activity in the presence of MKIs was calculated and compared to that of the control (1% dimethyl sulfoxide). Data represent the mean ± SD of three independent experiments.

Determination of inhibition constants of MKIs on astemizole O-demethylation

Experiments were conducted at four astemizole concentrations (0.50–4.0 μM) at corresponding ranges of apatinib (5–60 nM), motesanib (10–60 nM), and vatalanib (50–400 nM). The inhibition constant (Kᵢ) and inhibition model were determined using GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA). Akaike’s information criterion was used as a measure of the goodness of fit.

Data were assessed for their fit to competitive inhibition (Equation 1), non-competitive inhibition (Equation 2), and un-competitive inhibition (Equation 3) as shown below.

\[
V = \frac{V_{\text{max}} \cdot [S]}{K_m \cdot [(1 + \frac{[S]}{K_i}) + [S]]}
\]  

where \( V \) is the velocity of the reaction, \( V_{\text{max}} \) is the maximum velocity, \( S \) is the concentration of the reaction, \( K_m \) is the Michaelis–Menten constant, and \( i \) is the concentration of inhibition.

Inhibition of MKIs on AA metabolism

The reaction mixture contained 10 μM AA as a substrate, MKIs (apatinib, motesanib, or vatalanib) at their \( K_i \) concentration, 100 mM potassium phosphate buffer (pH 7.4), and a nicotinamide adenine dinucleotide phosphate generating system. Danazol was used at 10 nM concentration since the \( K_i \) value against the CYP2J2 activity is 5–20 nM (Lee et al. 2012; Karkhanis et al. 2016). The enzyme reaction was conducted according to the methods described in the section of Inhibition of MKIs on astemizole O-demethylation. 14,15-EET was measured using a 14,15-EET/DHET ELISA kit, according to the manufacturer’s instructions.

Docking simulation

The human CYP2J2 structure was modelled using the MOE software (ver. 2018.0101; Chemical Computing Group, Montreal, QC, Canada) according to the method described by Ikemura et al. (2019). Chemical structures were obtained from PubChem and optimised using MOE. Docking simulations were also performed according to the method described by Ikemura et al. (2019). The lower the \( U \) value (kcal/mol), the more effective the docking into CYP2J2.

Data analysis

The significance of differences between the means of the various groups was evaluated using the Student’s t-test.

Results

Inhibition of MKIs on astemizole O-demethylation

Astemizole O-demethylation was inhibited by >50% by AEE788, apatinib, cabozantanib, motesanib, and vatalanib (Figure 1, Table 1). Apatinib, motesanib, and vatalanib strongly inhibited >80% of the control (Figure 2). The CYP2J2 substrates, sorafenib and sunitinib, exhibited weak inhibition, while regorafenib did not inhibit this activity. A well-known CYP2J2 inhibitor, danazol, also inhibited this activity to 5.7% of the control, whereby its inhibition potency was similar to those of apatinib and motesanib.

\( K_i \) values were calculated for three MKIs that exhibited strong inhibition. The \( K_i \) values of apatinib, motesanib, and vatalanib were 9.3, 15.4, and 65.0 nM, respectively (Figure 3, Table 2, Supplementary Figure 1). All three MKIs exhibited
competitive inhibition according to Akaike’s information criterion calculated on GraphPad Prism 8.

**Inhibition of CYP2J2-mediated AA metabolism**

14,15-EET was not detected in the presence of either apatinib or motesanib. The 14,15-EET concentrations in the reaction mixtures were 3.78 ± 2.84 and 1.62 ± 1.11 ng/mL in the presence of 1% dimethyl sulfoxide (control), and vatalanib, respectively. CYP2J2-mediated AA to 14,15-EET metabolism was inhibited by vatalanib (42.9% reduction) (Figure 4). These three MKIs inhibited 14,15-EET formation from AA. 14,15-EET formation was also inhibited completely by danazol.

**Docking simulation of MKIs into human CYP2J2**

Docking simulations were performed for apatinib, motesanib, and vatalanib, which strongly inhibited astemizole O-demethylation. The U energy values (kcal/mol) increased in the following order: apatinib (−84.5)< motesanib (−69.9)< vatalanib (−52.3). Figure 5 shows the models of probable interactions of apatinib, motesanib, and vatalanib with CYP2J2. The U energy value of astemizole was −79.9 kcal/mol.

**Discussion**

Twenty MKIs showed different inhibitory potencies against astemizole O-demethylation in CYP2J2. In this study, the $K_i$ values of apatinib, motesanib, and vatalanib on astemizole O-demethylation were 9.3, 15.4, and 65.0 nM, respectively. The $K_i$ value of danazol against astemizole O-demethylation is 5–20 nM (Lee et al. 2012; Karkhanis et al. 2016), suggesting that apatinib and motesanib can be categorised as strong CYP2J2 inhibitors. In clinical trials, the plasma concentrations of apatinib, motesanib, and vatalanib range from 956 to 2768 nM, from 47 to 2100 nM, and from 288 to 5718 nM, respectively (Sherman et al. 2008; Ding et al. 2012; Wang et al. 2014). Considering their plasma concentrations, these MKIs have inhibitory potency against CYP2J2 activity in vivo. Apatinib has been approved in China for the treatment of advanced or metastatic gastric cancer and advanced hepatocellular carcinoma (Tian et al. 2021), and several clinical trials have been conducted (Gao et al. 2022; Sun et al. 2022); however, motesanib and vatalanib have not been approved anywhere. Nevertheless, assessing CYP2J2 inhibition upon drug therapy using MKIs is crucial. Apatinib is metabolised primarily by CYP3A4/5 (Ding et al. 2013) and inhibits the activities of CYP2B6 with a $K_i$ value of 3.84 μM, CYP2C9 with 0.71 μM, CYP2D6 with 5.41 μM and CYP3A4 with 11.50 μM in human liver microsomes (Bao et al. 2018). Apatinib co-administration resulted in a significant increase in systemic exposure to nifedipine and S-warfarin (Zhu et al. 2020) and apatinib inhibits gefitinib metabolism, which may be mediated by CYP2D6 and CYP3A4 (Wang et al. 2021). In addition to CYP3A4, CYP2C9, and CYP2D6 inhibition, CYP2J2 inhibition during apatinib therapy should be considered.

CYP2J2 protein is detected in all specimens of five types of gastric carcinoma and 10 of hepatocellular carcinoma (Jiang et al. 2009). CYP2J2 expression in hepatocellular carcinoma cell lines, HepG2 and Huh-7, is higher than that in

**Table 1. Inhibition of astemizole O-demethylation by multi-kinase inhibitors.**

| MKI       | Astemizole O-demethylation (% of control) |
|-----------|------------------------------------------|
| AE788     | 39.7 ± 1.4                               |
| Apatinib  | 5.4 ± 0.8                                |
| Axitinib  | 75.2 ± 1.9                               |
| Brivanib  | 98.1 ± 12.8                              |
| Cabozantinib | 43.7 ± 5.3                           |
| Cediranib | 88.7 ± 3.5                               |
| Foretinib | 54.6 ± 8.9                               |
| Lenvatinib | 118.5 ± 12.1                          |
| Linfatinib | 52.4 ± 10.5                             |
| Motesanib | 6.5 ± 0.7                                |
| Nintedanib | 85.8 ± 16.0                         |
| Orantinib | 122.2 ± 9.8                              |
| Pazopanib | 113.2 ± 11.7                             |
| Regorafenib | 105.8 ± 9.0                        |
| Semaxinib | 88.8 ± 12.5                              |
| Sorafenib | 74.7 ± 5.8                               |
| Sunitinib | 72.6 ± 9.0                               |
| Tivozanib | 56.6 ± 9.4                               |
| Vandetanib | 73.8 ± 21.1                          |
| Vatalanib | 12.4 ± 1.8                               |
normal liver epithelial cell line LO2 and the levels of 14,15-EET in HepG2 and Huh-7 were higher relative to those in LO2 cells (Gui et al. 2020). The treatment with a CYP2J2 inhibitor, acetylshikonin, inhibited the growth of HepG2 cells (Park et al. 2017) and the inhibition of CYP2J2 by tanshinone IIA induced apoptotic cell death in these cells (Jeon et al. 2015). Cabozantinib, which exhibits CYP2J2 inhibition by more than 50% as compared to the control (Figure 1), is approved in USA, EU, and Japan. Cabozantinib is used to treat patients with advanced renal cell carcinoma, hepatocellular carcinoma, and differentiated thyroid carcinoma.

### Table 2. Inhibition constants of multi-kinase inhibitors against CYP2J2 activity.

| MKI   | $K_i$ (nM) | Model of inhibition |
|-------|------------|---------------------|
| Apatinib | 9.3 ± 0.8 | Competitive          |
| Motesanib | 15.4 ± 0.8 | Competitive         |
| Vatalanib | 65.0 ± 20.0 | Competitive         |

Figure 2. Chemical structures of apatinib, motesanib, and vatalanib.

Figure 3. Inhibition of apatinib, motesanib, and vatalanib on astemizole O-demethylation. Lineweaver–Burk plots of apatinib (A), motesanib (B), and vatalanib (C). Each plot represents the mean ± SD of three independent experiments.

Figure 4. Inhibitory effects of apatinib, motesanib, and vatalanib on 14,15-EET formation from arachidonic acid. Each column represents the mean ± SD of three independent experiments. N.D.: not detected.
Elevated levels of CYP2J2 expression are the most significant in kidney cancer among other tumours (Zou and Mo 2021). CYP2J2 inhibition by acetylshikonin is associated with acetylshikonin-induced apoptosis in renal cell carcinoma (Lim et al. 2022). Therefore, CYP2J2 inhibition may be a plausible mechanism for apoptotic cell death in CYP2J2-overexpressing cancer cells.

Apatinib, motesanib, and vatalanib showed competitive inhibition against CYP2J2 activity, indicating that these can bind to the catalytic site of CYP2J2. As apatinib and motesanib have similar chemical structures, we conducted a docking simulation of these compounds with CYP2J2. Interestingly, the $U$ energy values increased in the following order: apatinib < motesanib < vatalanib, which was the same as that of inhibition potency. Our molecular docking results also supported the potent inhibition of CYP2J2 by these three MKIs. Ikemura et al. (2019) reported that azelnidipine and manidipine showed potent inhibition of CYP2J2 activity with luciferin-2J2/4F12 as the substrate. The $U$ energy value of manidipine was $-56.9\text{ kcal/mol}$, which is higher than those of apatinib and motesanib. Therefore, apatinib and motesanib are very strong CYP2J2 inhibitors.

In the present study, apatinib, motesanib, and vatalanib were found to inhibit EET formation. Overexpression of CYP2J2 enhances the migration and invasion of breast cancer MDA-MB-231 cells (Jiang et al. 2007). Athymic BALB/C mice injected with recombinant adeno-associated viral vector-mediated delivery of antisense-CYP2J2 infected MDA-MB-231 cells inhibited tumour growth rate and size and suppressed lung metastases. Furthermore, the knockdown of CYP2J2 in Huh-7 and HepG2 cells significantly reduced the production of 11,12-EET and 14,15-EET and restricted cell proliferation (Gui et al. 2020). On the other hand, not only CYP2J2 but also CYP2C8 and CYP2C9 are responsible for the conversion of AA to 14,15-EET (Karkhanis et al. 2017). Vatalanib inhibited CYP2C8-catalysed amodiaquine $N$-desethylation with an IC$_{50}$ value of 593 nM (Filppula et al. 2018). Apatinib inhibits CYP2C9-catalysed tolbutamide
hydroxylation with a \( K_i \) value of 710 nM and shows a non-competitive inhibition (Bao et al. 2018). In a clinical study, the maximum concentration and area under the plasma concentration curve, \( C_{max} \), of warfarin, a CYP2C9 substrate, increased significantly upon co-administration with apatinib (Zhu et al. 2020). Apatinib, motesanib, and vatalanib inhibited the production of 14,15-EET, suggesting that these three MKIs could suppress tumour growth and proliferation by reducing 14,15-EET formation.

CYP2J2 is involved in the metabolism of 9,10-epoxy-12Z-octadecenoic acid (Askari et al. 2014), which induces peripheral neuropathy (Sisignano et al. 2016). Following oral administration of telmisartan, a CYP2J2 inhibitor, the plasma concentration of 9,10-epoxy-12Z-octadecenoic acid decreased, resulting in relief from pain caused by paclitaxel-induced peripheral neuropathy in mice (Sisignano et al. 2016). Thus, there is a possibility that apatinib, motesanib, and vatalanib may reduce such pain by inhibiting CYP2J2.

Recently, CYP2J2 inhibitors have emerged as attractive potential agents for cancer treatment. Some natural products such as acetylshikonin (Park et al. 2017), tanshinone IIA (Jeon et al. 2018), plumbagin (Lu et al. 2018), decursin (Lee et al. 2015), and 17-octadecynoic acid (Jiang et al. 2007; Jiang et al. 2015), which induces MKIs could suppress tumour growth and proliferation by increased significantly upon co-administration with apatinib (Zhu et al. 2020). Apatinib, motesanib, and vatalanib inhibited the production of 14,15-EET, suggesting that these three MKIs could suppress tumour growth and proliferation by reducing 14,15-EET formation.

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