Electronic Supplementary Material (ESI) for RSC Advances.

Potential metabolism determinants and drug-drug interactions of a natural flavanone bavachinin

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Table list

Figure caption

Figure S7 Kinetic profiles for the formation of M3 by CYP enzymes. (a) the formation of M3 by CYP1A1; (b) the formation of M3 by CYP1A2; (c) the formation of M3 by CYP2B6; (d) the formation of M3 by CYP2C19; (e) the formation of M1 by CYP3A5; All experiments were performed in triplicate.

Figure S8 Kinetic profiles for the formation of G1 by UGT enzymes. (a) the formation of G1 by UGT1A1; (b) the formation of G1 by UGT1A3; (c) the formation of G1 by UGT1A8; (d) the formation of G1 by UGT2B7; All experiments were performed in triplicate.

Figure S9 Kinetic profiles for the formation of M1-M3 by RLM and MLM. (a) the formation of M1 by RLM; (b) the formation of M2 by RLM; (c) the formation of M3 by RLM; (d) the formation of M1 by MLM; (e) the formation of M2 by MLM; (f) the formation of M3 by MLM; All experiments were performed in triplicate.

Figure S10 Kinetic profiles for the formation of M1-M3 by DLM and MpLM. (a) the formation of M1 by DLM; (b) the formation of M2 by DLM; (c) the formation of M3 by DLM; (d) the formation of M1 by MpLM; (e) the formation of M2 by MpLM; (f) the formation of M3 by MpLM; All experiments were performed in triplicate.

Figure S11 Kinetic profiles for the formation of G1 by animal liver microsomes. (a) the formation of G1 by RLM; (b) the formation of G1 by MLM; (c) the formation of G1 by DLM; (d) the formation of G1 by MpLM; All experiments were performed in triplicate.

Figure S12 Concentration-dependent inhibition of bavachinin towards expressed CYP and UGT enzymes. (a) concentration-dependent plot towards CYP2B6-mediated bupropion-hydroxylation; (b) concentration-dependent plot towards CYP2C9-mediated tolbutamide-4-hydroxylation; (c) concentration-dependent plot towards CYP2C19-mediated mephenytoin-4-hydroxylation; (d) concentration-dependent plot against UGT1A1-mediated β-estradiol-3-*O*-glucuronidation; (e) concentration-dependent plot against UGT1A9-mediated propofol-*O*-glucuronidation; (f) concentration-dependent plot against UGT2B7-mediated zidovudine-*N*-glucuronidation. All experiments were performed in triplicate. Data were presented as mean ± SD.

Figure S13 The inhibition curves and IC_{50} values of bavachinin against CYP2B6 (a),

CYP2C9 (b), CYP2C19 (c), UGT1A1 (d), UGT1A9 (e), UGT2B7 (f). The data were fit to log (bavachinin) and normalized response equations. Each data point represented the mean value ± the S.D. of triplicate determinations.

Table S1 Detailed UHPLC/Q-TOF-MS data for bavachinin and its related metabolites.

NO.	Time (min)	$[M+H]^+$ ion	Formula	(+) ESI-MS/MS	Identification
P0	6.71	339.161	$C_{21}H_{22}O_4$	283.096, 271.097, 219.103, 147.049	bavachinin
M1	5.75	355.158	$C_{21}H_{22}O_5$	337.144, 235.107, 217.087, 147.045	mono-oxidated bavachinin
M2	6.09	355.153	$C_{21}H_{22}O_5$	283.096, 181.050, 163.040, 133.030	mono-oxidated bavachinin
M3	6.58	355.155	$C_{21}H_{22}O_5$	299.092, 287.088, 219.101, 163.038	isomerized bavachinin
G1	6.13	515.195	$C_{27}H_{30}O_{10}$	459.133, 339.161, 283.095, 271.095 219.107, 147.047	bavachinin-glucuronide

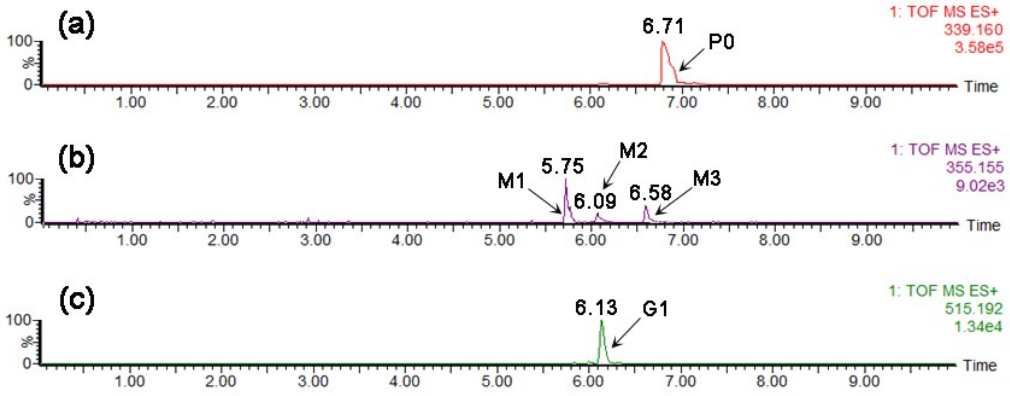
(a)
6.71
P0
1: TOF MS ES+
339.160
3.58e5
100
%
0
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
9.00
Time
(b)
M1
5.75
M2
6.09
6.58
M3
1: TOF MS ES+
355.155
9.02e3
(c)
6.13
G1
1: TOF MS ES+
515.192
1.34e4

Figure S1

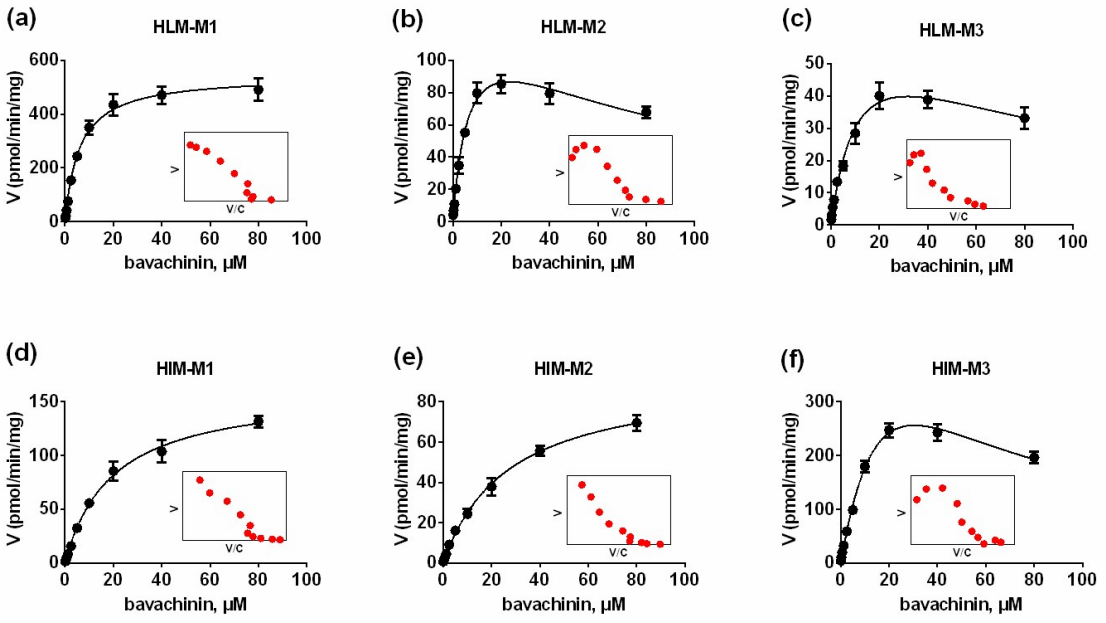
(a)
HLM-M1
V (pmol/min/mg)
bavachinin, μM
V
V/C
(b)
HLM-M2
V (pmol/min/mg)
bavachinin, μM
V
V/C
(c)
HLM-M3
V (pmol/min/mg)
bavachinin, μM
V
V/C
(d)
HIM-M1
V (pmol/min/mg)
bavachinin, μM
V
V/C
(e)
HIM-M2
V (pmol/min/mg)
bavachinin, μM
V
V/C
(f)
HIM-M3
V (pmol/min/mg)
bavachinin, μM
V
V/C

Figure S2

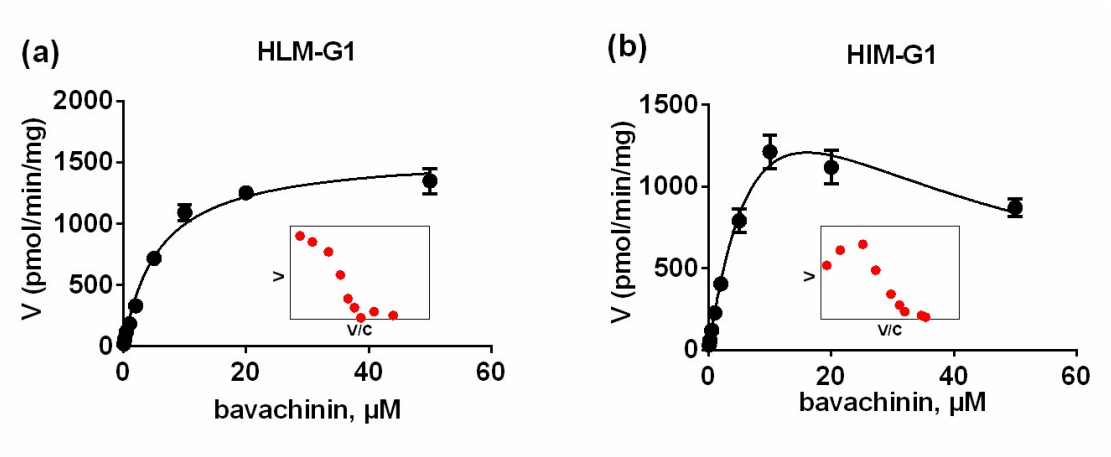
(a)
HLM-G1
V (pmol/min/mg)
2000
1500
1000
500
0
0
20
40
60
bavachinin, μM
v
v/c
(b)
HIM-G1
V (pmol/min/mg)
1500
1000
500
0
0
20
40
60
bavachinin, μM
v
v/c

Figure S3

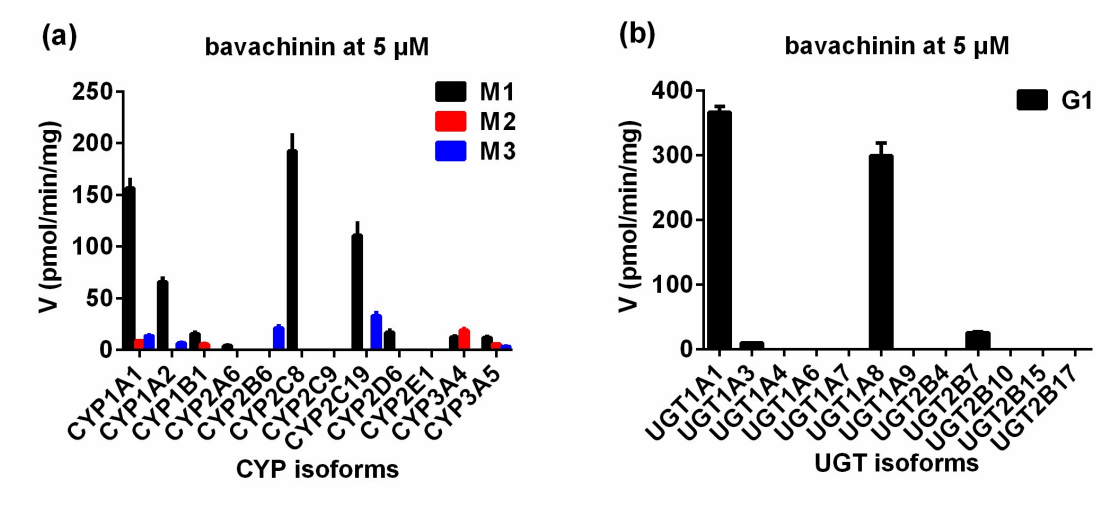
(a)
bavachinin at 5 μM
M1
M2
M3
V (pmol/min/mg)
250
200
150
100
50
0
CYP1A1
CYP1A2
CYP1B1
CYP2A6
CYP2B6
CYP2C8
CYP2C9
CYP2C19
CYP2D6
CYP2E1
CYP3A4
CYP3A5
CYP isoforms
(b)
bavachinin at 5 μM
G1
V (pmol/min/mg)
400
300
200
100
0
UGT1A1
UGT1A3
UGT1A4
UGT1A6
UGT1A7
UGT1A8
UGT1A9
UGT2B4
UGT2B7
UGT2B10
UGT2B15
UGT2B17
UGT isoforms

Figure S4

.

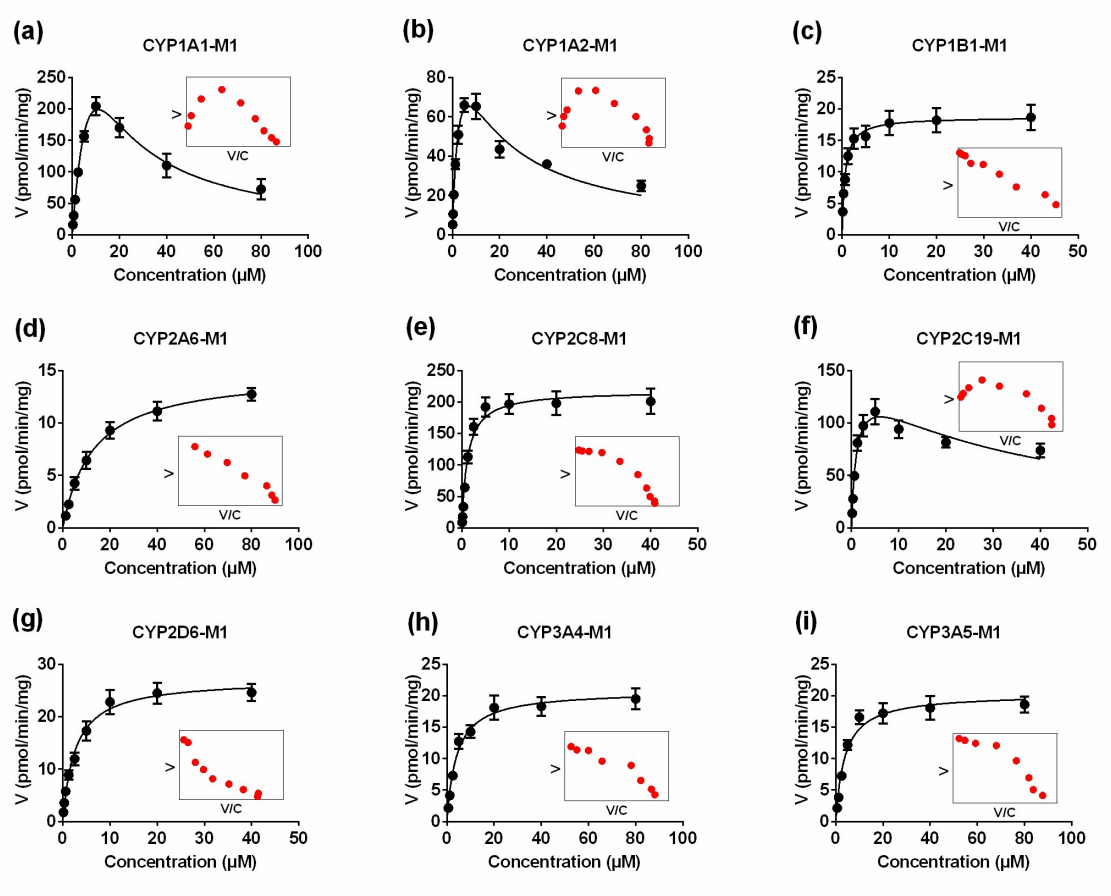
(a)
CYP1A1-M1
V (pmol/min/mg)
Concentration (μM)
V/C
(b)
CYP1A2-M1
V (pmol/min/mg)
Concentration (μM)
V/C
(c)
CYP1B1-M1
V (pmol/min/mg)
Concentration (μM)
V/C
(d)
CYP2A6-M1
V (pmol/min/mg)
Concentration (μM)
V/C
(e)
CYP2C8-M1
V (pmol/min/mg)
Concentration (μM)
V/C
(f)
CYP2C19-M1
V (pmol/min/mg)
Concentration (μM)
V/C
(g)
CYP2D6-M1
V (pmol/min/mg)
Concentration (μM)
V/C
(h)
CYP3A4-M1
V (pmol/min/mg)
Concentration (μM)
V/C
(i)
CYP3A5-M1
V (pmol/min/mg)
Concentration (μM)
V/C

Figure S5

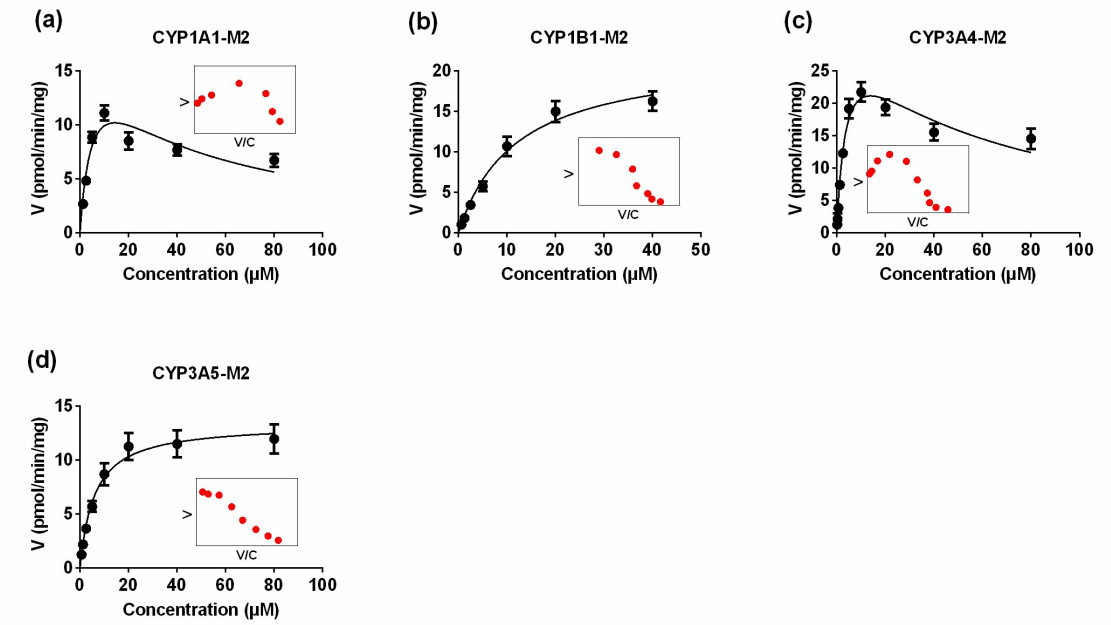
(a)
CYP1A1-M2
V (pmol/min/mg)
Concentration (μM)
V/C
(b)
CYP1B1-M2
V (pmol/min/mg)
Concentration (μM)
V/C
(c)
CYP3A4-M2
V (pmol/min/mg)
Concentration (μM)
V/C
(d)
CYP3A5-M2
V (pmol/min/mg)
Concentration (μM)
V/C

Figure S6

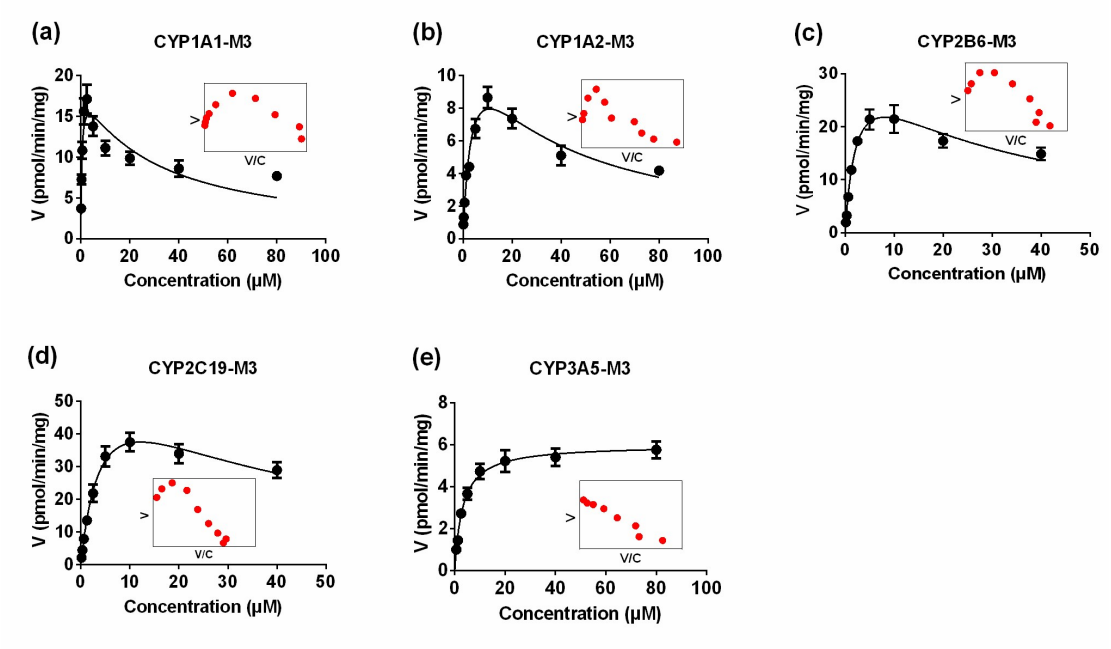
(a)
CYP1A1-M3
V (pmol/min/mg)
Concentration (μM)
V/C
(b)
CYP1A2-M3
V (pmol/min/mg)
Concentration (μM)
V/C
(c)
CYP2B6-M3
V (pmol/min/mg)
Concentration (μM)
V/C
(d)
CYP2C19-M3
V (pmol/min/mg)
Concentration (μM)
V/C
(e)
CYP3A5-M3
V (pmol/min/mg)
Concentration (μM)
V/C

Figure S7

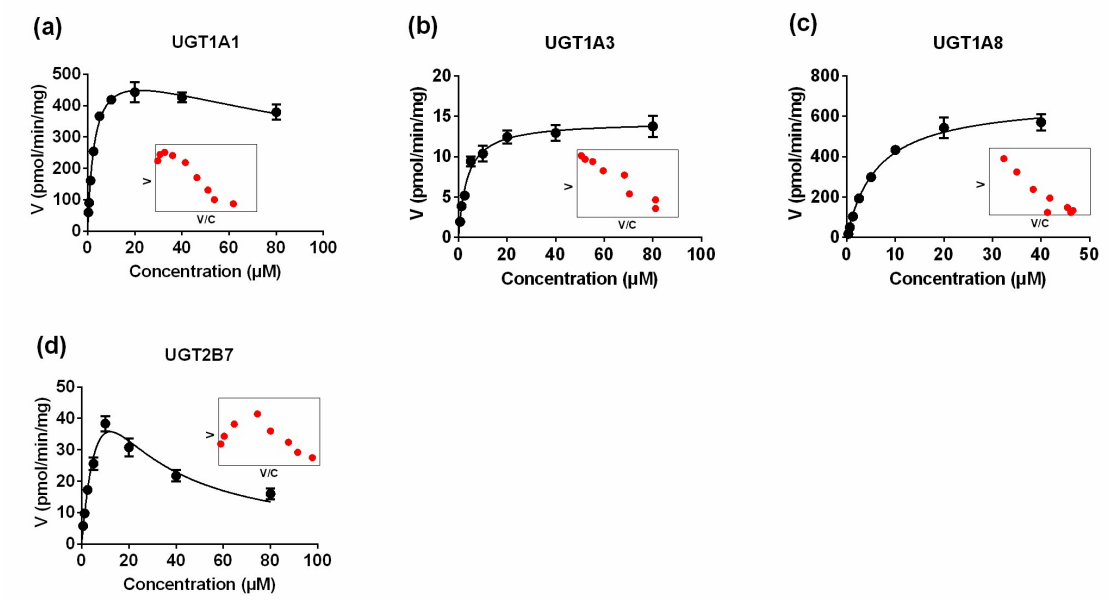
(a)
UGT1A1
V (pmol/min/mg)
Concentration (μM)
V
V/C
(b)
UGT1A3
V (pmol/min/mg)
Concentration (μM)
V
V/C
(c)
UGT1A8
V (pmol/min/mg)
Concentration (μM)
V
V/C
(d)
UGT2B7
V (pmol/min/mg)
Concentration (μM)
V
V/C

Figure S8

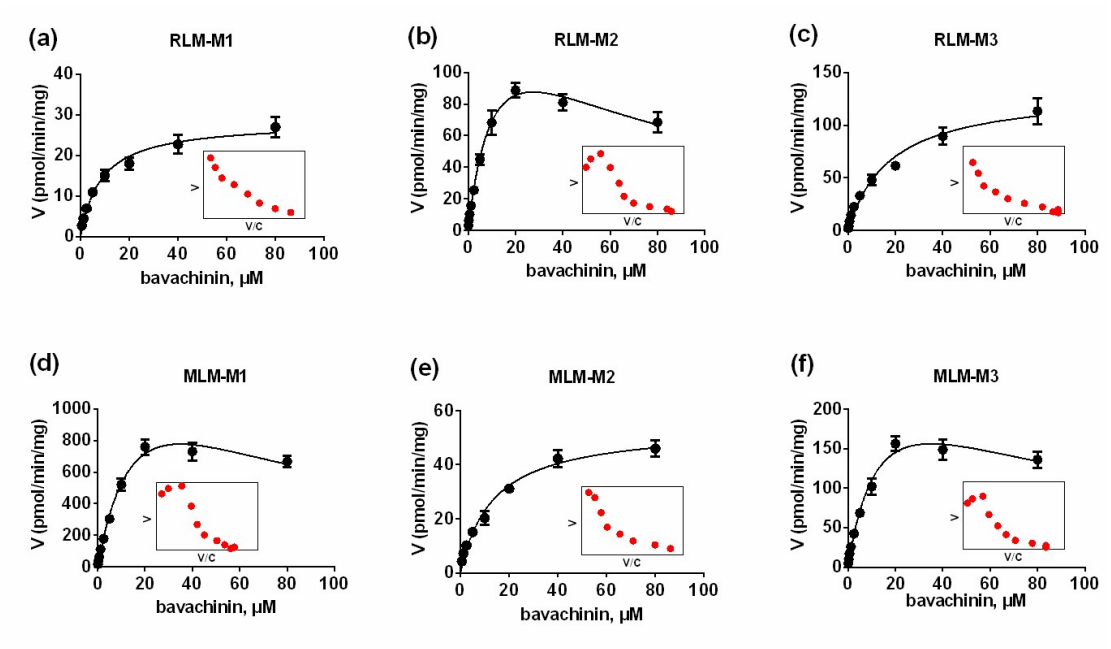
(a)
RLM-M1
V (pmol/min/mg)
bavachinin, μM
v
v/c
(b)
RLM-M2
V (pmol/min/mg)
bavachinin, μM
v
v/c
(c)
RLM-M3
V (pmol/min/mg)
bavachinin, μM
v
v/c
(d)
MLM-M1
V (pmol/min/mg)
bavachinin, μM
v
v/c
(e)
MLM-M2
V (pmol/min/mg)
bavachinin, μM
v
v/c
(f)
MLM-M3
V (pmol/min/mg)
bavachinin, μM
v
v/c

Figure S9

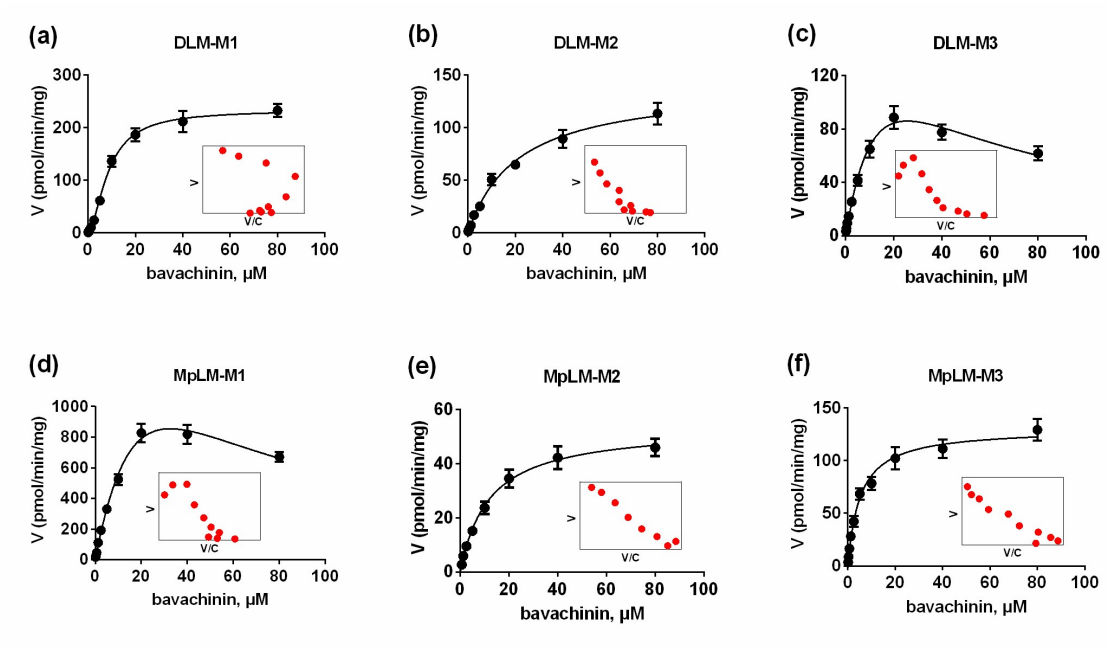
(a)
DLM-M1
V (pmol/min/mg)
bavachinin, μM
V
V/C
(b)
DLM-M2
V (pmol/min/mg)
bavachinin, μM
V
V/C
(c)
DLM-M3
V (pmol/min/mg)
bavachinin, μM
V
V/C
(d)
MpLM-M1
V (pmol/min/mg)
bavachinin, μM
V
V/C
(e)
MpLM-M2
V (pmol/min/mg)
bavachinin, μM
V
V/C
(f)
MpLM-M3
V (pmol/min/mg)
bavachinin, μM
V
V/C

Figure S10

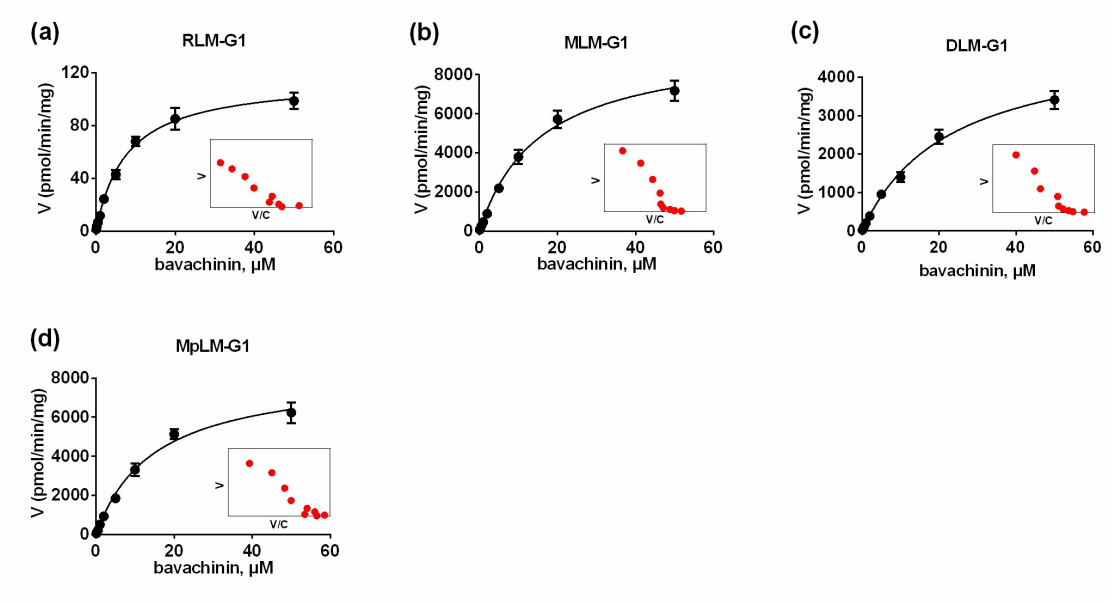
(a)
RLM-G1
V (pmol/min/mg)
bavachinin, μM
v
v/c
(b)
MLM-G1
V (pmol/min/mg)
bavachinin, μM
v
v/c
(c)
DLM-G1
V (pmol/min/mg)
bavachinin, μM
v
v/c
(d)
MpLM-G1
V (pmol/min/mg)
bavachinin, μM
v
v/c

Figure S11

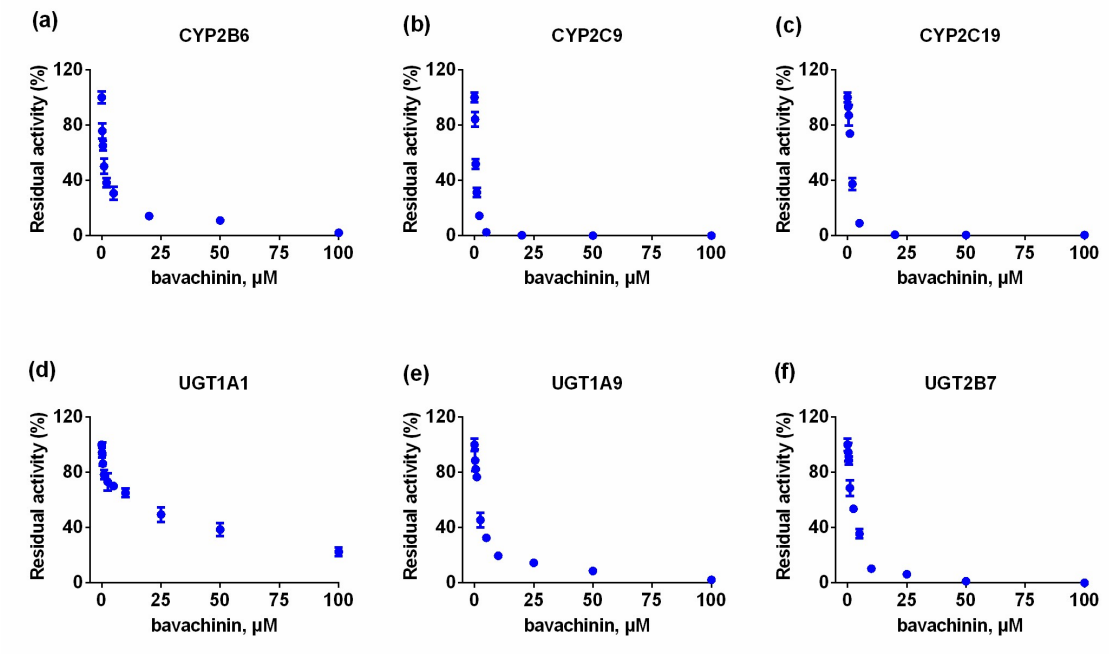
(a)
CYP2B6
(b)
CYP2C9
(c)
CYP2C19
(d)
UGT1A1
(e)
UGT1A9
(f)
UGT2B7
Residual activity (%)
0
40
80
120
0
25
50
75
100
bavachinin, μM

Figure S12

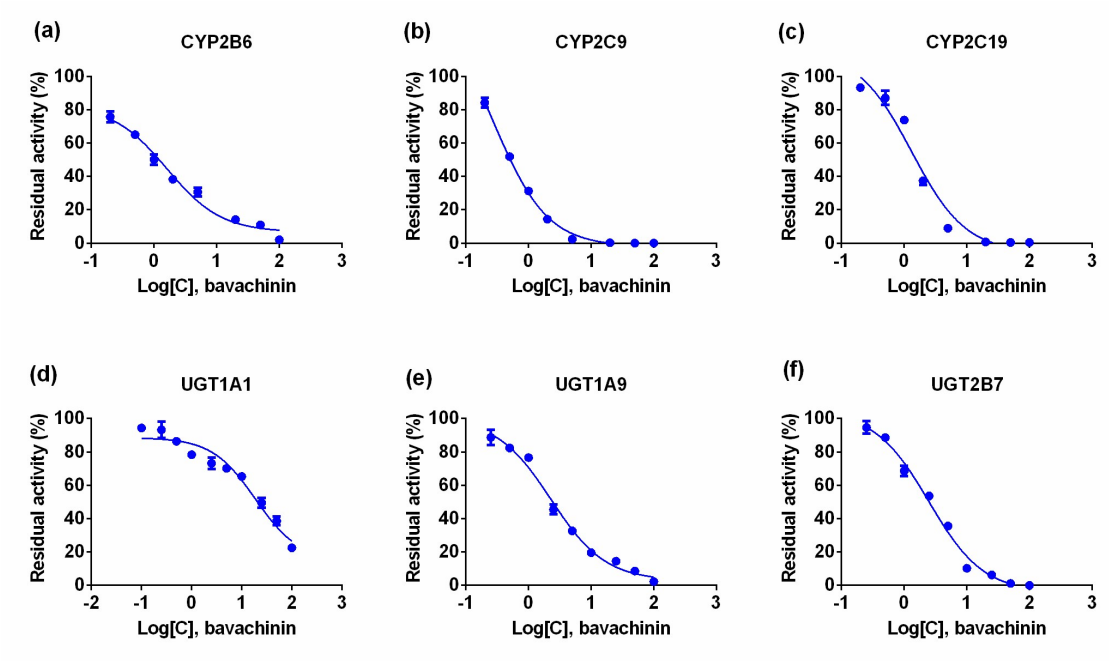
(a)
CYP2B6
(b)
CYP2C9
(c)
CYP2C19
(d)
UGT1A1
(e)
UGT1A9
(f)
UGT2B7
Residual activity (%)
Log[C], bavachinin

Figure S13