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Purine metabolites regulate leukemic cell sensitivity toward cytarabine

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Contributions
H.Y. conceived the project, designed the experiments. H.Y. wrote the manuscript together with C.T.J. X.Z conducted most of the experiments and data analysis. Z.Z. and Y.W. assisted with HTS experiments. J.Y. and L.C. assisted with isotope labeling experiments. J.Z. assisted with patient sample experiments. A.J. and T.L. assisted with gene KD and KO experiments. L.H., X.D., T.Z and P.L. assisted with detection of tetramerization experiments.

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Data-sharing statement
Protocols and original data from this manuscript are available upon request by contacting the corresponding author.

While Cytarabine (Ara-C) remains a first-line chemotherapy drug for treating acute myeloid leukemia (AML), resistance to Ara-C and poor prognosis continue to be an unresolved clinical problem. Metabolites are involved in regulating leukemic cell chemosensitivity [1-4]. However, due to the complexity and diversity of metabolites, few chemosensitivity-modulating metabolites have been identified. To this end, we employed a library composed of 686 human endogenous metabolites and performed a high throughput screen (HTS) to examine the viability of leukemic cells upon Ara-C treatment in the presence or absence of these metabolites (Figure 1A). We first focused on the metabolites that promote the survival of MOLM-13 leukemic cells. We identified 25 metabolites increasing the cell viability by at least 2.5-fold upon Ara-C treatment (supplemental Table 1). Of these metabolites, 5'-methylthioadenosine (MTA), adenine, adenosine, inosine, and hypoxanthine are all involved in purine metabolism. Enrichment analysis also demonstrated that purine metabolism represents the most significantly enriched group (Figure 1A). Protective effects of these five metabolites are confirmed in leukemic cell lines and in leukemia stem cells (LSCs) enriched CD34+ AML patient cells (supplemental Figure 1A) (specimen acquisition was approved by Shenzhen People's Hospital Review Board, approval date Aug 09,2024; #LL-KY-2023089-01). Further, these metabolites are found to be enriched in the bone marrow (BM) serum of MOLM-13 leukemic mice following Ara-C treatment (supplemental Figure 1B) (animal experiments in this study were approved by Institutional Animal Care and Research Advisory Committee at Fudan University, approval date Jan 07,2024; #IDM2024017). This enrichment may result from metabolites released during chemotherapy-induced cell death, indicating that Ara-C chemotherapy might create a protective metabolic niche. Additionally, in two cohorts of AML patients, higher levels of related purine metabolism enzymes are associated with poorer survival outcomes (supplemental Figures 1C-1D).

We then investigated the underlying mechanisms for purine metabolites-induced chemoresistance. We first focused on MTA, which can be converted to adenine by methylthioadenosine phosphorylase (MTAP). Since adenine protects leukemic cells from Ara-C, we tested whether the protective effect of MTA depends on converting to adenine. Treatment with MT-DADMe-ImmA (MTDIA), an MTAP

inhibitor, eliminates MTA's protection against Ara-C (Figure 1B). Similar results were observed in MTAP-knockout (KO) and MTAP-knockdown (KD) cells (supplemental Figures 1E-1F). Adenine can be further converted to AMP by adenine phosphoribosyltransferase (APRT) or to 8-hydroxyadnine by xanthine dehydrogenase (XDH). Allopurinol, an XDH inhibitor, does not impact adenine-induced chemoresistance (supplemental Figure 1G). In contrast, adenine no longer protects leukemic cells against Ara-C in APRT-KO and APRT-KD cells (Figure 1C and supplemental Figure 1H).

Adenosine can enter multiple metabolic pathways. Given that inosine is identified as a protective metabolite, we postulated that adenosine promotes survival through the adenosine-to-inosine metabolic pathway. Surprising, Pentostatin, an adenosine deaminase inhibitor (ADAi), does not diminish the protective effect of adenosine; rather, it enhances adenosine-induced chemoresistance (supplemental Figure 1I). We then explored alternative metabolic pathways. Treatment with adenosine dialdehyde (ADDA), an Adenosyl homocysteinase inhibitor (AHCYi), does not affect the protective effect of adenosine (supplemental Figure 1J). In contrast, knocking down adenosine kinase (ADK) reduces adenosine protective effect (Figure 1D). Intriguingly, when the purine nucleoside phosphorylase inhibitor (PNPi), Forodesine, is employed, the protective effect of adenosine is also significantly reduced (Figure 1E). PNP is responsible for converting inosine to hypoxanthine. When PNP is inhibited, inosine-induced protection disappears (supplemental Figure 1K), indicating that conversion to hypoxanthine is necessary for inosine-induced chemoresistance. When ADK is knocked down in APRT-KO cells, a condition in which both ADK- and APRT-mediated AMP production is blocked, adenosine no longer promotes survival (Figure 1D). These results indicated that in leukemic cells, PNP also converts adenosine to adenine, which APRT then converts to AMP to induce Ara-C resistance. More importantly, PNPi can be utilized to chemo-sensitize leukemic cells in vivo (Figure 1F). Therefore, we identified two adenosine-mediated chemoprotective pathways, one involving PNP and the other ADK. Our results suggest that MTA, adenine and adenosine must be converted to AMP to protect leukemic cells from Ara-C. Similarly, inosine and hypoxanthine require conversion to AMP to induce Ara-C resistance, as knockdown of hypoxanthine guanine phosphoribosyltransferase (HPRT) or adenylosuccinate lyase (ADSL) eliminates their

protective effects (supplemental Figures 1L-1M).

To uncover why converting to AMP is critical for purine metabolites-induced Ara-C resistance, we labeled leukemic cells with either $^{13}C_1$-adenine or $^{13}C_{10}$, $^{15}N_5$-adenosine and analyzed the final metabolites produced, both with and without Ara-C treatment. dATP is the most increased labeled metabolite upon Ara-C treatment (Figure 2A). Interestingly, although GMP production from adenine is elevated, inhibiting inosine-5'-monophosphate dehydrogenase (IMPDH) does not impact adenine protective effect and supplementing with guanosine or guanine does not affect Ara-C toxicity toward leukemic cells (supplemental Figures 2A-2B).

With dual labeling by ^{13}C and ^{15}N, we traced adenosine metabolic pathways in leukemic cells. Consistent with Figure 1 results, adenosine can be converted to AMP by multiple pathways (Figure 2B). Interestingly, we found that ADK-generated AMP is converted to IMP, which can then be recycled back to AMP (Figure 2B). Further, in the presence of Ara-C, AMP production via the ADA-mediated pathway decreases, while AMP production through alternative pathways increases (Figure 2B). These data align with our findings that inhibiting ADK or PNP impairs adenosine-induced Ara-C resistance, while ADA inhibition does not affect this resistance. More importantly, dATP produced from all these pathways, including the ADA-mediated one, is increased in the presence of Ara-C (Figure 2B), suggesting that the machinery for dATP production from AMP is activated.

Next, we investigated whether dATP synthesis is essential for purine metabolite-mediated Ara-C resistance. Ribonucleotide Reductase Regulatory Subunit M2 (RRM2) is a key protein for dATP synthesis [5]. Treatment with hydroxyurea (HU), an RRM2 inhibitor (RRM2i), sensitizes leukemic cells to Ara-C and weakens purine metabolites-induced Ara-C resistance (Figure 2C). Knocking down RRM2 produces similar effects, while RRM2 overexpression confers resistance to Ara-C (supplemental Figures 2C-2D). Notably, the chemo-sensitizing effect of RRM2i is consistent with previous findings [6]. These results suggest that purine metabolites-induced chemoresistance is RRM2 dependent. We then investigated the mechanisms underlying RRM2-mediated Ara-C resistance.

RRM2 activation produces dATP from purines. An unbalanced increase in a single dNTP, such as dATP, acts as a cellular stress signal [7] that may trigger dNTPase activity in leukemic cells. SAMHD1 is a dNTPase that degrades dNTPs into nucleosides and functions as a detoxifier of Ara-CTP by converting it back to Ara-C [8]. Therefore, we reasoned that SAMHD1 may contribute to RRM2-mediated Ara-C resistance. We treated leukemic cells with ^{2}H labeled Ara-C and found that $^{2}H_{2}$-Ara-CTP levels are greatly reduced in the presence of purines metabolites (Figure 2D). Further, when SAMHD1 is KD or KO, leukemic cells are more sensitive to Ara-C and purine metabolites lose their protective effects (Figure 2E and supplemental Figure 2E). SAMHD1 demonstrates the maximal dNTPase activity in its homotetramer form [9]. We found that purine metabolites promote the formation of SAMHD1 tetramer, while the overall SAMHD1 protein levels remain unchanged by purine metabolites (Figure 2F and supplemental Figures 2F-2H). Leukemic cells survived Ara-C treatment also display an increased level of SAMHD1 tetramer and RRM2i significantly reduces SAMHD1 tetramerization induced by purine metabolites and Ara-C (Figure 2F and supplemental Figures 2F-2G). To directly demonstrate that elevated cellular dATP induces SAMHD1 tetramerization, we electroporated dATP into leukemic cells and observed that dATP indeed promotes SAMHD1 tetramer formation (supplemental Figures 2I-2J). Additionally, we found that higher expression levels of *Rrm2* and *Samhd1* are associated with poorer survival in AML patients (supplemental Figure 2K). These results suggest that purine metabolites induce Ara-C resistance via promoting SAMHD1 tetramerization.

Our study demonstrates that both RRM2 and SAMHD1 are promising targets to chemo-sensitize leukemic cells and are critical for purine metabolite-induced chemoresistance. However, currently reported SAMHD1 inhibitors lack cellular activities or exhibit extremely high IC 50 values [6]. Therefore, agents inhibiting SAMHD1 tetramerization could provide an alternative strategy to counteract SAMHD1-induced Ara-C resistance. Our HTS experiment also identifies metabolites sensitizing leukemic cells to Ara-C. We then focused on metabolites enhancing Ara-C toxicity 24 h post-treatment (Figure 3A). Among these, two adenosine derivatives, 1-methyladenosine (1-MA) and N6-methyladenosine (N6-MA), display potent chemo-sensitizing effects (Figure 3A). We validated

that both derivatives promote Ara-C killing effect in leukemic cell lines and CD34+ AML patient cells (Figure 3B and supplemental Figure 2L). Notably, 1-MA is more potent than N6-MA and chemo-sensitizes an Ara-C-resistant MOLM-13 line (supplemental Figure 2M). Further, 1-MA decreases SAMHD1 tetramerization upon Ara-C treatment (Figure 3C and supplemental Figure 2N). Interestingly, 1-MA chemo-sensitizes cells to Ara-C even with RRM2 inhibition, suggesting RRM2 independence (Figure 3D). Importantly, 1-MA displays significantly chemo-sensitizing effects in vivo (Figure 3E). These data indicate that 1-MA is a chemo-sensitizer through inhibiting SAMHD1 tetramerization.

Together, our data suggest that purine metabolites can be converted to AMP via multiple metabolic pathways, which is subsequently converted to dATP via RRM2. Increased dATP levels induce SAMHD1 tetramerization, which functions as a detoxifier of Ara-CTP, thereby promoting the survival of leukemic cells. We further identified that 1-MA serves as an inhibitor of SAMHD1 tetramerization and demonstrate that 1-MA acts as a potent chemosensitizer (Figure 3F). We propose that designing future AML therapies so as to target purine metabolism may improve therapeutic outcomes.

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Figures and legends

Figure 1. Purine metabolites induce Ara-C resistance

(A) A high throughput screen (HTS) was conducted to identify metabolites with chemosensitivity regulatory functions. The relative viability of leukemic cells post Ara-C (0.2 μM) treatment was examined. Enrichment analysis was performed on the 25 identified metabolites promoting survival of leukemic cells. The metabolic pathways of the five selected purine metabolites are showed, where red indicates the selected metabolites, blue denotes enzyme inhibitors, and red arrow represents pathway identified in this study. **(B)** Viability of MOLM-13 leukemic cells treated with Ara-C combined with 5'-methylthioadenosine (MTA) and the methylthioadenosine phosphorylase (MTAP) inhibitor MTDIA (10 nM) (n=3). **(C)** Viability of control and adenine phosphoribosyltransferase (APRT) KO cells treated with Ara-C combined with 10 μM adenine (n=3). **(D)** ADK was knocked down by siRNAs in control and APRT KO leukemic cells. Cells were then treated with Ara-C combined with 10 μM adenosine. Viability was accessed 48 h post-treatment (n=3). **(E)** The 48-h viability of leukemic cells treated with Ara-C combined with purine metabolites and the purine nucleoside phosphorylase (PNP) inhibitor Forodesine (100 nM) (n=3). **(F)** MOLM-13 leukemic mice were treated with Ara-C or Forodesine or Ara-C combined with Forodesine (combo) for 3 consecutive days. Leukemic cell number in one hindleg (tibia + femur) was accessed (n=5-6). All data are represented as mean ± SD. Quantification is provided for each gel image. *, $p \leq 0.05$; **, $p \leq 0.01$; ***, $p \leq 0.001$; ****, $p \leq 0.0001$.

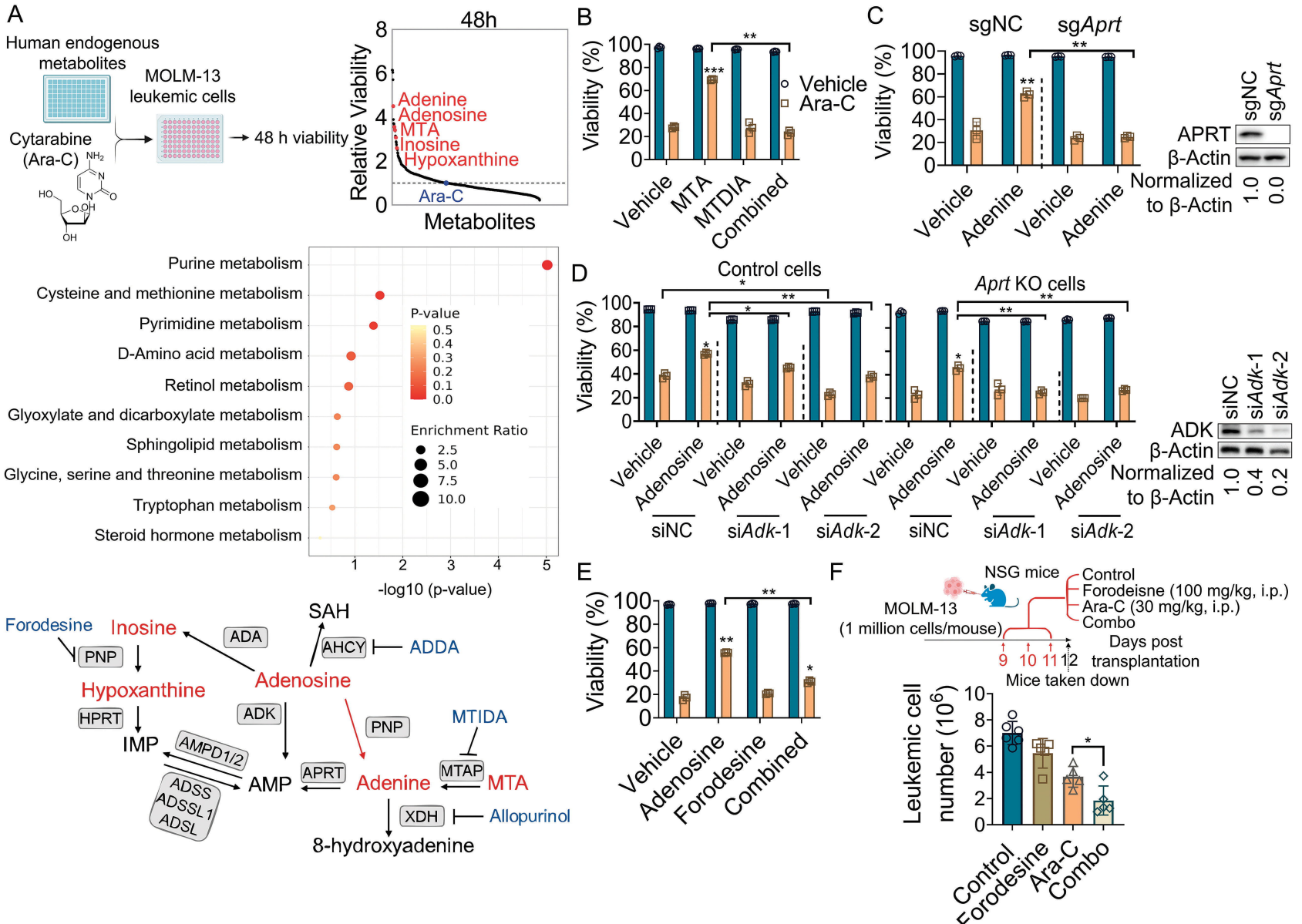
Figure 2. Purine metabolites are converted to dATP to induce SAMHD1 tetramerization in leukemic cells treated with Ara-C

(A-B) MOLM-13 cells were labeled with $^{13}C_1$-adenine or $^{13}C_{10,}$ $^{15}N_5$-adenosine with or without the presence of Ara-C. Eight hours post-labeling, leukemic cells were harvested for metabolic analyses (n=4-5). Hypo: hypoxanthine. **(C)** Viability of MOLM-13 cells treated with Ara-C combined with purine metabolites and the RRM2 inhibitor hydroxyurea (HU) (20 μM) (n=3). **(D)** MOLM-13 cells were treated with $^{2}H_2$-Ara-C with or without the presence of purine metabolites. $^{2}H_2$-Ara-CTP levels were assessed 8 h post-labeling (n=5). **(E)** SAMHD1 was knocked out by sgRNA in leukemic cells. Protection of

purine metabolites was assessed (n=3). **(F)** SAMHD1 tetramerization was examined in leukemic cells under indicated conditions by protein crosslinking. All data are represented as mean ± SD. Quantification is provided for each gel image. *, $p \leq 0.05$; **, $p \leq 0.01$; ***, $p \leq 0.001$; ****, $p \leq 0.0001$.

Figure 3. Purine derivatives chemo-sensitize leukemic cells by inhibiting SAMHD1 tetramerization

(A) Relative viability of leukemic cells 24 h post Ara-C treatment. **(B)** Viability of CD34+ AML patient cells treated with Ara-C combined with 1-methyladenosine (1-MA) (10 μM) (n=3). **(C)** SAMHD1 tetramerization was examined in cells treated with 1-MA, Ara-C, or Ara-C combined with 1-MA by Native PAGE. **(D)** Chemo-sensitizing effect of 1-MA was assessed with or without the presence of hydroxyurea (HU) (n=3). **(E)** MOLM-13 leukemic mice were treated with Ara-C, 1-MA, and Ara-C combined with Ara-C (Combo). BM leukemic cell number was accessed (n=6-7). **(F)** Working model. Purine metabolites is converted to AMP via differential enzymes. AMP is then converted to dATP via RRM2. Increased dATP promotes SAMHD1 tetramerization and detoxifies Ara-C. Purine derivatives such as 1-MA inhibits SAMHD1 tetramerization to chemo-sensitize leukemic cells. All data are represented as mean ± SD. Quantification is provided for each gel image. *, $p \leq 0.05$; **, $p \leq 0.01$; ***, $p \leq 0.001$; ****, $p \leq 0.0001$.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48 h viability
48h
Relative Viability
Adenine
Adenosine
MTA
Inosine
Hypoxanthine
Ara-C
Metabolites
Purine metabolism
Cysteine and methionine metabolism
Pyrimidine metabolism
D-Amino acid metabolism
Retinol metabolism
Glyoxylate and dicarboxylate metabolism
Sphingolipid metabolism
Glycine, serine and threonine metabolism
Tryptophan metabolism
Steroid hormone metabolism
P-value
Enrichment Ratio
-log10 (p-value)
Forodesine
Inosine
ADA
SAH
AHCY
ADDA
PNP
Hypoxanthine
Adenosine
HPRT
IMP
ADK
PNP
MTIDA
AMPD1/2
AMP
APRT
Adenine
MTAP
MTA
ADSS
ADSSL1
ADSL
XDH
Allopurinol
8-hydroxyadenine
B
Viability (%)
Vehicle
Ara-C
Vehicle
MTA
MTDIA
Combined
C
sgNC
sgAprt
Viability (%)
Vehicle
Adenine
APRT
β-Actin
Normalized to β-Actin
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Control cells
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Viability (%)
Vehicle
Adenosine
siNC
siAdk-1
siAdk-2
ADK
β-Actin
Normalized to β-Actin
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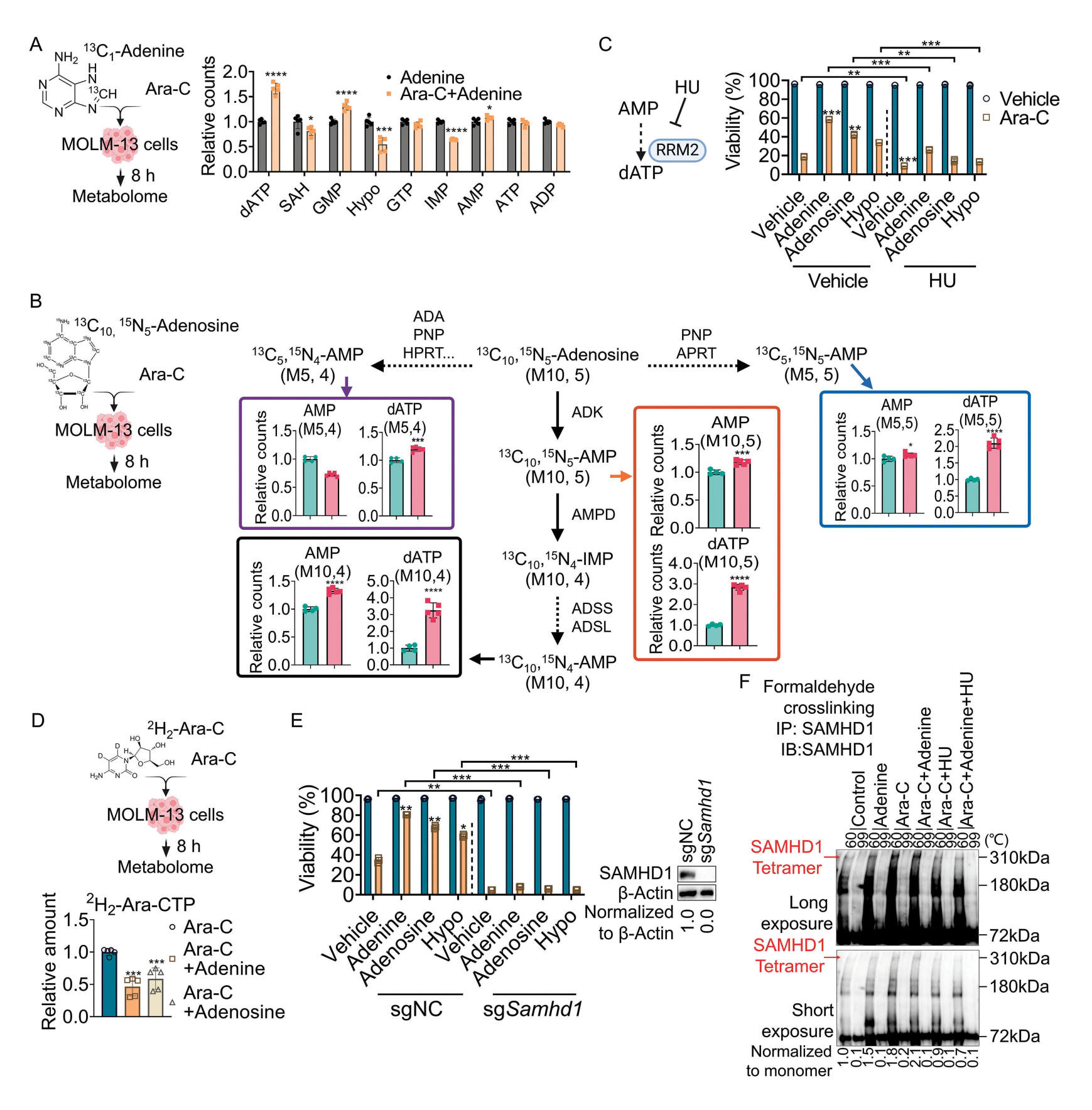
Viability (%)
Vehicle
Adenosine
Forodesine
Combined
F
NSG mice
MOLM-13
(1 million cells/mouse)
Control
Forodeisne (100 mg/kg, i.p.)
Ara-C (30 mg/kg, i.p.)
Combo
Days post transplantation
Mice taken down
Leukemic cell number (10^6)
Control
Forodesine
Ara-C
Combo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Metabolome
Relative counts
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GMP
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GTP
IMP
AMP
ATP
ADP
C
HU
AMP
RRM2
dATP
Viability (%)
Vehicle
Ara-C
Vehicle
Adenine
Adenosine
Hypo
HU
B
$^{13}C_{10}$, $^{15}N_5$-Adenosine
Ara-C
MOLM-13 cells
8 h
Metabolome
ADA
PNP
HPRT...
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ADSL
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(M10, 4)
AMP
dATP
(M5,4)
(M10,5)
(M10,4)
(M5,5)
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Ara-C
MOLM-13 cells
8 h
Metabolome
$^2H_2$-Ara-CTP
Relative amount
Ara-C
Ara-C +Adenine
Ara-C +Adenosine
E
Viability (%)
Vehicle
Adenine
Adenosine
Hypo
sgNC
sg*Samhd1*
SAMHD1
β-Actin
Normalized to β-Actin
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Formaldehyde crosslinking
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IB:SAMHD1
Control
Adenine
Ara-C
Ara-C+Adenine
Ara-C+HU
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SAMHD1 Tetramer
Long exposure
Short exposure
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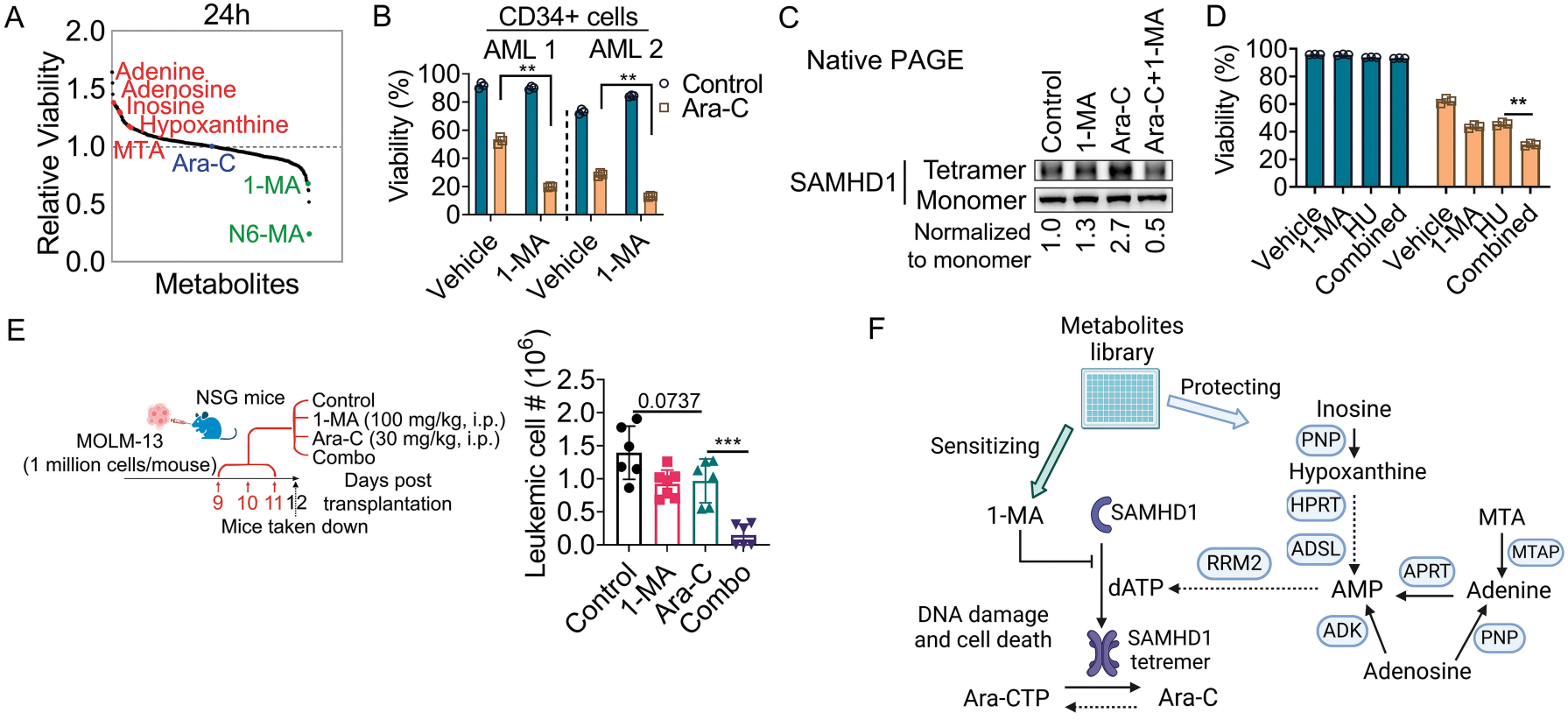
180kDa
72kDa
Normalized to monomer


A
24h
Relative Viability
Metabolites
Adenine
Adenosine
Inosine
Hypoxanthine
MTA
Ara-C
1-MA
N6-MA
B
CD34+ cells
AML 1
AML 2
Viability (%)
Control
Ara-C
Vehicle
1-MA
C
Native PAGE
Control
1-MA
Ara-C
Ara-C+1-MA
SAMHD1
Tetramer
Monomer
Normalized to monomer
1.0
1.3
2.7
0.5
D
Viability (%)
Vehicle
1-MA
HU
Combined
E
NSG mice
MOLM-13
(1 million cells/mouse)
Control
1-MA (100 mg/kg, i.p.)
Ara-C (30 mg/kg, i.p.)
Combo
Days post transplantation
Mice taken down
Leukemic cell # (10^6)
0.0737
Control
1-MA
Ara-C
Combo
F
Metabolites library
Protecting
Sensitizing
Inosine
PNP
Hypoxanthine
HPRT
ADSL
1-MA
SAMHD1
RRM2
dATP
AMP
APRT
MTA
MTAP
Adenine
DNA damage and cell death
SAMHD1 tetremer
ADK
PNP
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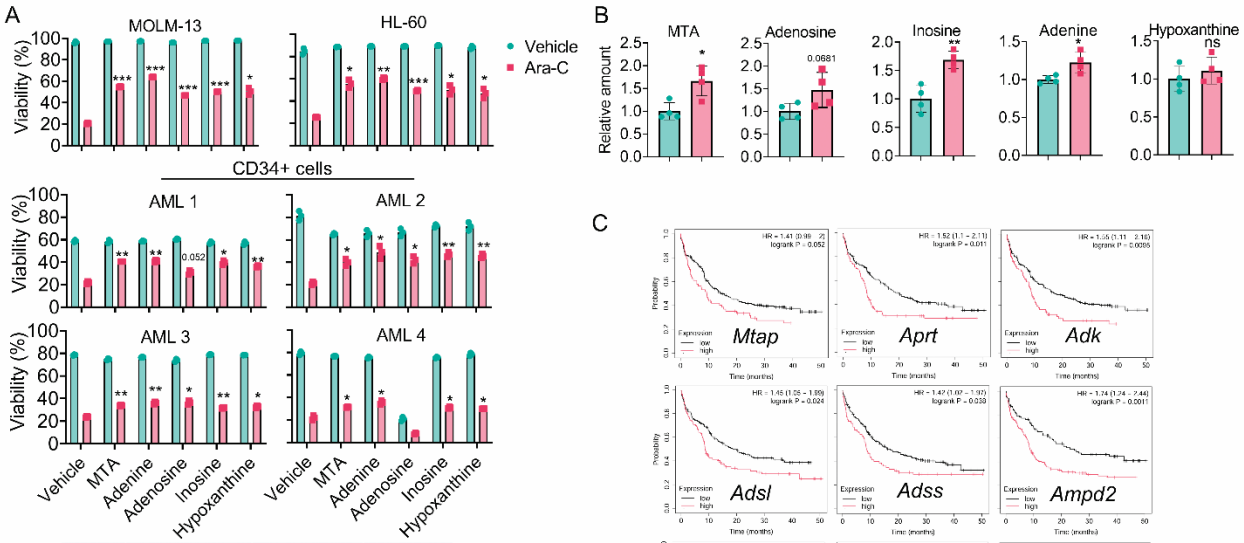
Ara-C



AML	Mutations	Cytogenetics	Diagnosis
AML 1	FLT3-ITD, NPM1, IDH1	46,XY, t(9;11)(p22;q23)	De novo AML
AML 2	FLT3-ITD, DNMT3A, CEBPA	Trisomy 8	Relapse
AML 3	N/A	45,X,-Y; t(9;11)(p22;q23)	De novo AML
AML 4	EZH2, ASXL1, GATA2, JAK2	Normal	De novo AML

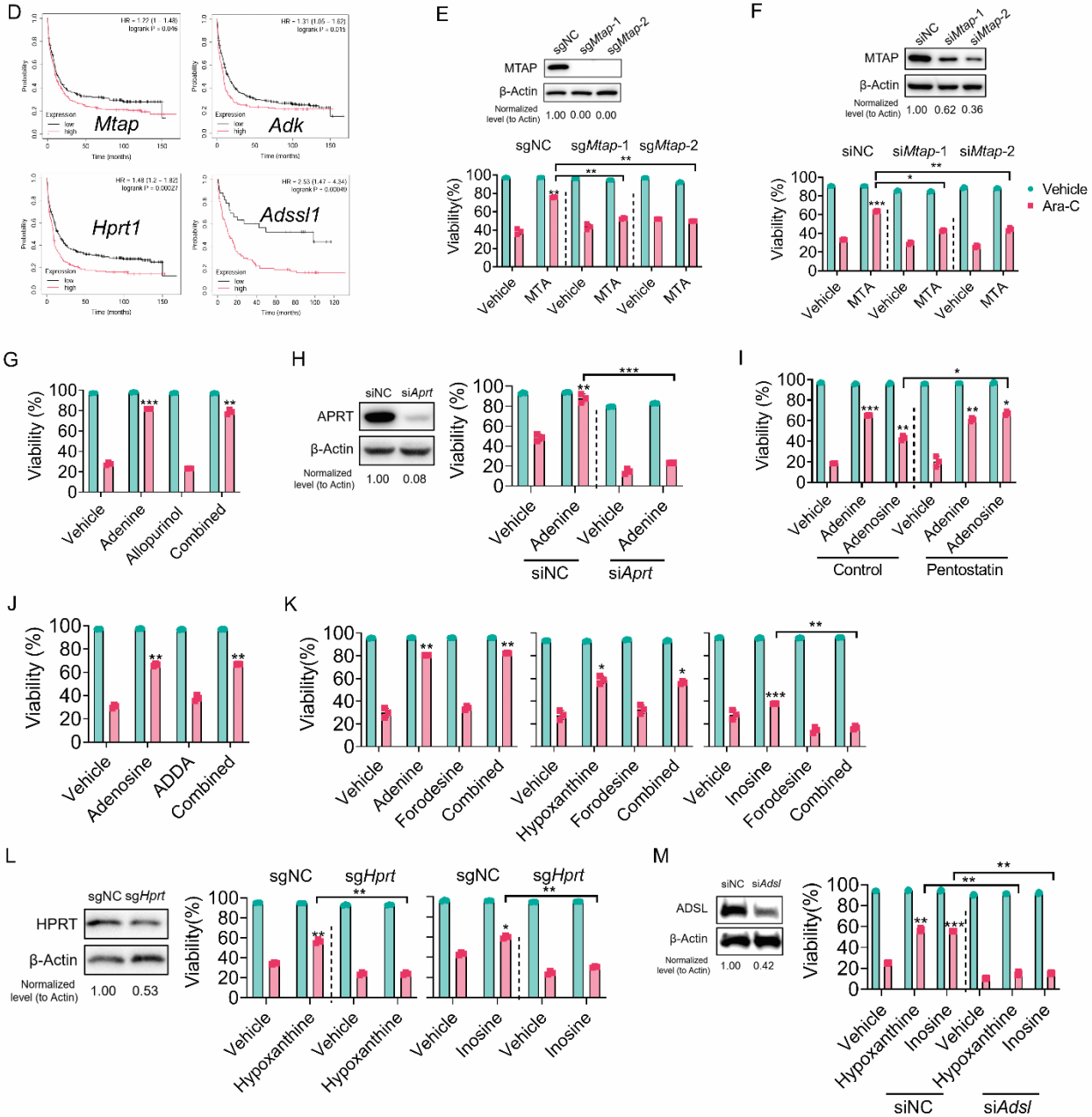


Figure S1. Purine metabolites induce chemoresistance

(A) Different leukemic cell lines and CD34+ AML patient cells were treated with Ara-C (0.2 μM) combined with the indicated purine metabolites (10 μM). Viability was accessed 48 h post-treatment (n=3). Information on the AML samples is provided. **(B)** BM serum was isolated from control and chemotherapy-treated mice. The levels of BM serum metabolites were examined (n=4). **(C-D)** Survival analysis was conducted on two AML patient cohorts, GSE12417 (C) and GSE37642 (D), based on the expression levels of enzymes involved in purine metabolism. **(E-F)** Methylthioadenosine phosphorylase (MTAP) was knocked out (KO) by sgRNAs (E) and knocked down (KD) by siRNAs (F) in leukemic cells. The protective effect of MTA against Ara-C was determined (n=3). **(G)** Leukemic cells were treated with Ara-C combined with adenine or the xanthine dehydrogenase (XDH) inhibitor Allopurinol (10 μM). Viability was accessed 48 h post-treatment (n=3). **(H)** Adenine phosphoribosyltransferase (APRT) was KD by siRNAs in leukemic cells. The protective effect of adenine was determined (n=3). **(I-J)** MOLM-13 leukemic cells were treated with Ara-C combined with adenine, adenosine, the adenosine deaminase (ADA) inhibitor Pentostatin (10 nM) (I), or the Adenosyl homocysteinase (AHCY) inhibitor ADDA (100 nM) (J). Viability was accessed 48 h post-treatment (n=3). **(L)** Control and hypoxanthine guanine phosphoribosyltransferase (HPRT) KD leukemic cells were treated with Ara-C combined with hypoxanthine (10 μM) or inosine (10 μM). Viability was accessed 48 h post treatment (n=3). **(M)** Adenylosuccinate lyase (ADSL) was KD in leukemic cells, followed by Ara-C treatment combined with inosine or hypoxanthine. Viability was accessed 48 h post treatment (n=3). All data are represented as mean ± SD. Quantification is provided for each gel image. *, $p \leq 0.05$; **, $p \leq 0.01$; ***, $p \leq 0.001$; ****, $p \leq 0.0001$.

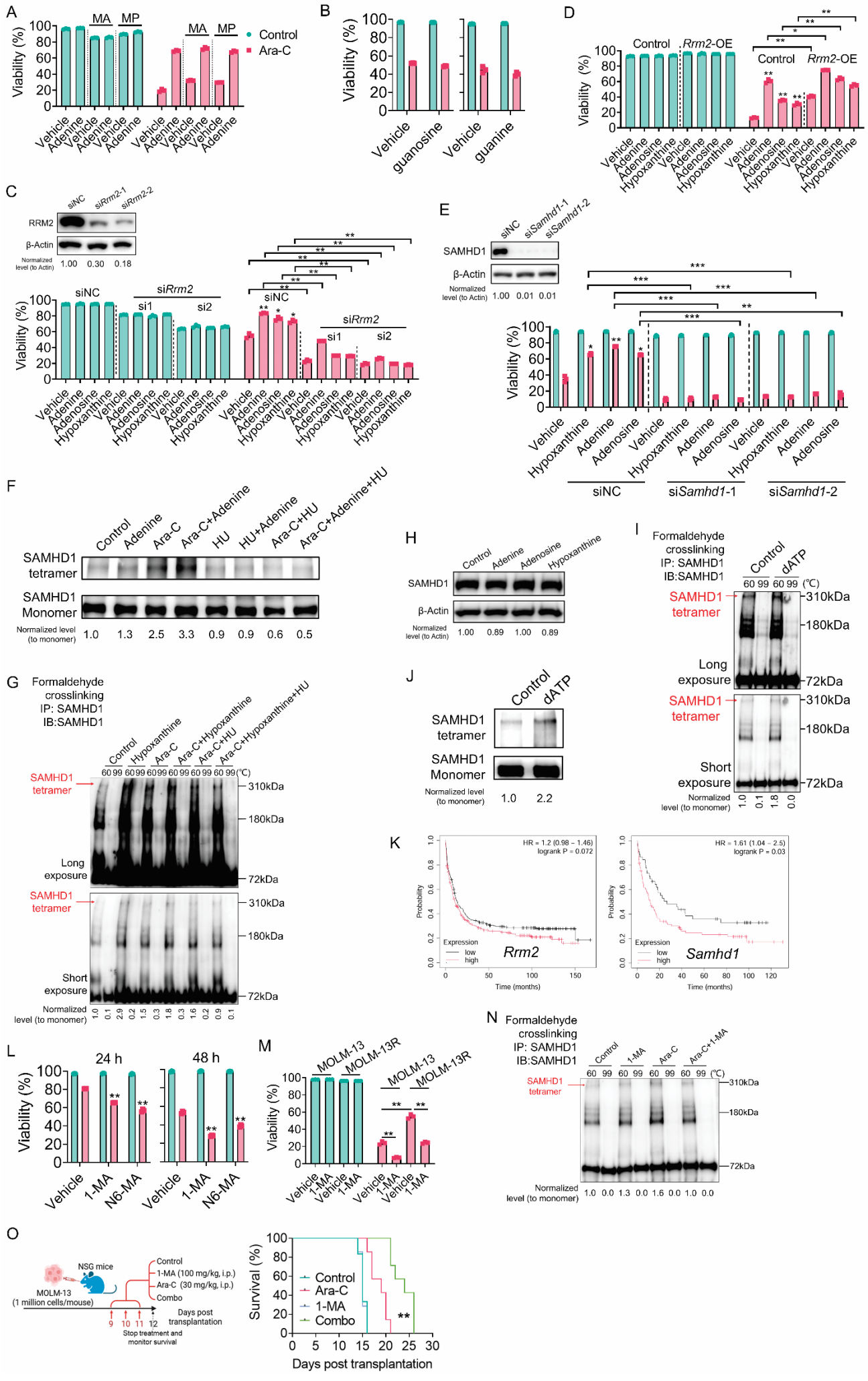

A
MA
MP
Control
Ara-C
Viability (%)
Vehicle
Adenine
B
guanosine
guanine
C
siNC
siRrm2-1
siRrm2-2
RRM2
β-Actin
Normalized level (to Actin)
1.00 0.30 0.18
siRrm2
si1
si2
D
Control
Rrm2-OE
E
siSamhd1-1
siSamhd1-2
SAMHD1
1.00 0.01 0.01
Hypoxanthine
Adenosine
F
Control
Adenine
Ara-C
Ara-C+Adenine
HU
HU+Adenine
Ara-C+HU
Ara-C+Adenine+HU
SAMHD1 tetramer
SAMHD1 Monomer
Normalized level (to monomer)
1.0 1.3 2.5 3.3 0.9 0.9 0.6 0.5
G
Formaldehyde crosslinking
IP: SAMHD1
IB:SAMHD1
Hypoxanthine
Ara-C+Hypoxanthine
Ara-C+HU
Ara-C+Hypoxanthine+HU
60 99
(℃)
310kDa
180kDa
72kDa
Long exposure
Short exposure
1.0 0.1 2.9 0.2 1.5 0.3 1.8 0.3 1.6 0.2 0.9 0.1
H
1.00 0.89 1.00 0.89
I
dATP
1.0 0.1 1.8 0.0
J
1.0 2.2
K
HR = 1.2 (0.98 – 1.46)
logrank P = 0.072
HR = 1.61 (1.04 – 2.5)
logrank P = 0.03
Probability
Expression
low
high
Rrm2
Samhd1
Time (months)
L
24 h
48 h
N6-MA
M
MOLM-13
MOLM-13R
N
1.0 0.0 1.3 0.0 1.6 0.0 1.0 0.0
O
NSG mice
MOLM-13
(1 million cells/mouse)
Control
1-MA (100 mg/kg, i.p.)
Ara-C (30 mg/kg, i.p.)
Combo
9 10 11 12
Days post transplantation
Stop treatment and monitor survival
Survival (%)
Days post transplantation

Figure S2. Purine metabolites-mediated Ara-C resistance is via RRM2-induced tetramerization of SAMHD1

(A) MOLM-13 leukemic cells were treated with Ara-C and adenine, with or without inosine-5'-monophosphate dehydrogenase (IMPDH) inhibitors mycophenolic acid (MA) (10 μM) or Merimepodib (MP) (10 μM). Viability was accessed 48 h post treatment (n=3). **(B)** MOLM-13 cells were treated with Ara-C combined with guanosine (10 μM) or guanine (10 μM). Viability was accessed 48 h post treatment (n=3). **(C-D)** The protective effect of purine metabolites against Ara-C was examined in RRM2 KD (C) and RRM2 overexpression (OE) (D) leukemic cells (n=3). **(E)** *Samhd1* was KD by siRNAs in leukemic cells. The protective effect of purine metabolites was determined (n=3). **(F)** SAMHD1 tetramerization was examined in leukemic cells under the indicated conditions by Native PAGE. **(G)** SAMHD1 tetramerization was examined in leukemic cells under the indicated conditions by protein crosslinking. **(H)** Protein levels of SAMHD1 in leukemic cells treated with purine metabolites. **(I-J)** Leukemic cells were electroporated with dATP and SAMHD1 tetramerization was examined by protein crosslinking (I) and by native PAGE (J). **(K)** Survival analysis of AML patients was performed based on RRM2 and SAMHD1 expression levels (GSE37642). **(L)** Leukemic cells were treated with Ara-C combined with 1-methyladenosine (1-MA) (10 μM) or N6-methyladenosine (N6-MA) (10 μM). Viability was accessed 24 h post-treatment (n=3). **(M)** MOLM-13 and Ara-C-resistant MOLM-13 cells (MOLM-13R) were treated with Ara-C, with or without 1-MA. Viability was assessed 48 h post treatment (n=3). **(N)** SAMHD1 tetramerization was examined in cells treated with 1-MA, Ara-C, or Ara-C combined with 1-MA by protein crosslinking. **(O)** MOML-13 leukemic mice were subjected to indicated treatments, followed by survival assessment (n=7). All data are represented as mean ± SD. Quantification is provided for each gel image. *, $p \leq 0.05$; **, $p \leq 0.01$; ***, $p \leq 0.001$; ****, $p \leq 0.0001$.

Table S1. 24-h and 48-h relative viability of leukemic cells treated with Ara-C in combination with the indicated metabolites

24h	
Metabolites	Relative Viability
2'-Deoxycytidine	1.6437
Tryptamine	1.6412
5-Methyl-2'-deoxycytidine	1.5489
Deoxycorticosterone acetate	1.4516
Canrenone	1.3805
Quinolinic acid	1.3796
Adenine	1.3788
SDMA	1.3771
3-Hydroxybenzoic acid	1.3686
Phenoxyacetic acid	1.3644
Azelaic acid	1.3619
DL-Homocysteine thiolactone (hydrochloride)	1.3619
Diethyl phosphate	1.3525
Thyroxine sulfate	1.3449
Deoxycorticosterone	1.3449
p-Hydroxycinnamic acid	1.3441
21-Hydroxypregnenolone	1.3441
3-Amino-4-methylpentanoic acid	1.3432
(E/Z)-4-Hydroxytamoxifen	1.3415
11beta-Hydroxyprogesterone	1.3255
Gamma-Linolenic acid	1.3246
Ac-Ala-OH	1.3238
D-Ribonolactone	1.3170
Epiandrosterone	1.3170
Cortisone	1.3119
Cortodoxone	1.3060
Adenosine	1.3009
Uridine 5'-monophosphate	1.2992
Liothyronine	1.2925
Inosine	1.2899
Urolithin A	1.2882
Adenosine monophosphate	1.2823
Dichlorisone acetate	1.2671
2-(2-Methylbenzamido)acetic acid	1.2561
Pregnenolone	1.2535
D-Desthiobiotin	1.2518
4,4-Dimethoxy-2-butanone	1.2501
Desloratadine	1.2290
Androsterone	1.2256

5'-Deoxyadenosine	1.2230
Progesterone	1.2230
Retinoic acid	1.2214
Coniferyl alcohol	1.2180
(R)-pyrrolidine-2-carboxylic acid	1.2095
NADH (disodium salt)	1.2053
Mandelic acid	1.2044
L-SelenoMethionine	1.2027
Taurine	1.2010
2,6-Dimethoxybenzoic acid	1.1977
L-Glutamic acid	1.1960
N-Acetyl-L-methionine	1.1951
Aflatoxin B1	1.1943
Corticosterone	1.1850
Aminomalonic acid	1.1841
(-)-(S)-Equol	1.1833
Etiocholanolone	1.1833
Indole	1.1799
Docetaxel	1.1790
Fluticasone (propionate)	1.1765
5'-Methylthioadenosine	1.1757
Acetyl Coenzyme A (trisodium)	1.1757
NAD+	1.1740
Cytidine	1.1723
10-Undecenoic acid	1.1706
Flavin adenine dinucleotide (disodium salt)	1.1646
NADPH (tetrasodium salt)	1.1630
Hypoxanthine	1.1621
N-Acetylglycine	1.1613
Uridine triphosphate	1.1613
Substance P	1.1596
Isohomovanillic acid	1.1596
Chenodeoxycholic Acid	1.1596
Palmitic acid	1.1596
Prednisolone	1.1570
Hydrocortisone	1.1570
Ursodeoxycholic acid	1.1528
1,3-Dimethyluric acid	1.1511
2,6-Dihydroxyacetophenone	1.1503
3-Hydroxypicolinic acid	1.1494
4-Aminobenzoic acid	1.1486
Pantethine	1.1477
Oxoadipic acid	1.1477

3-Amino-2-piperidinone	1.1452
Indole-3-carboxylic acid	1.1443
Estradiol	1.1443
D-Panthenol	1.1426
Guanosine 5'-triphosphate (trisodium salt)	1.1418
3-Indolepropionic acid	1.1401
Arachidonic acid	1.1401
D-Mannose	1.1393
2-Methylbenzoxazole	1.1384
D-Alanine	1.1359
Histamine	1.1350
(S)-b-aminoisobutyric acid	1.1342
Methoxyacetic acid	1.1333
2',4'-Dihydroxyacetophenone	1.1316
D-Arabitol	1.1299
Adenosine 5'-diphosphate	1.1299
DL-O-Phosphoserine	1.1283
Isorhamnetin	1.1274
Oxalic Acid	1.1266
4-Hydroxy-3-methylbenzoic acid	1.1249
Dehydroepiandrosterone sulfate (sodium salt)	1.1249
Arachidic acid	1.1240
L-Hydroxyproline	1.1240
2-Methylbenzaldehyde	1.1215
Triacetin	1.1198
2-Hydroxyhexanoic acid	1.1198
Dihydrodaidzein	1.1172
Vanilpyruvic acid	1.1164
Myricetin	1.1156
Docosahexaenoic Acid	1.1147
Cytidine 5'-monophosphate	1.1147
Malic acid	1.1139
Trimethylamine N-oxide	1.1130
Isomaltose	1.1122
L-Glutamine	1.1113
3,3'-Diiodo-L-thyronine	1.1096
α-Pyridone	1.1096
4,6-Dioxoheptanoic acid	1.1062
L-Arginine	1.1062
Nicotinamide riboside (chloride)	1.1046
alpha-D-glucose	1.1003
Ergothioneine	1.1003
Coproporphyrin III	1.0995

Crustecdysone	1.0978
Isethionic acid	1.0969
AICAR (phosphate)	1.0969
2-Furoic acid	1.0969
Biocytin	1.0961
Glycocholic acid	1.0952
D-Sorbitol	1.0952
m-Anisaldehyde	1.0944
2-Acetyl-3-ethylpyrazine	1.0944
4-Hydroxybenzoic acid	1.0944
(-)-Aspartic acid	1.0944
2,4-Dihydroxybenzoic acid	1.0927
Benzophenone	1.0919
Meglutol	1.0910
Cinnamic acid	1.0910
all-trans-Anhydro Retinol	1.0902
Perillartine	1.0893
Bisphenol A	1.0885
Lornoxicam	1.0868
Dimethylmalonic acid	1.0851
4-Hydroxyphenylacetic acid	1.0842
4-Hydroxymethylpyrazole	1.0842
α-D-Glucose-1-phosphate (disodium hydrate)	1.0842
Squalene	1.0834
(R,R)-(+)-Hydrobenzoin	1.0825
Sorbic acid	1.0825
Menaquinone-4	1.0817
Ethylmalonic acid	1.0809
(S)-(+)-1,2-Propanediol	1.0809
5a-Pregnane-3,20-dione	1.0809
Vanillylmandelic acid	1.0792
Methyl 3-phenylpropanoate	1.0783
Dodecanedioic acid	1.0783
Glucosamine	1.0775
Taurolithocholic acid (sodium salt)	1.0758
Nerol	1.0749
Pimelic acid	1.0741
SAH	1.0732
Glycochenodeoxycholic acid	1.0732
Alanylphenylalanine	1.0724
L-Alanyl-L-leucine	1.0707
Raffinose	1.0699
D-(-)-Lactic acid	1.0699

β-Alanine	1.0699
D-(+)-Cellobiose	1.0690
Cytidine-5'-triphosphate	1.0682
17α-Hydroxyprogesterone	1.0673
Erucic acid	1.0673
Docosapentaenoic acid (22n-3)	1.0673
(Ethoxymethyl)benzene	1.0656
Glutathione oxidized	1.0656
Hydrocinnamic acid	1.0656
Medroxyprogesterone acetate	1.0648
L-Carnitine	1.0631
Palmitoylethanolamide	1.0622
DL-Norvaline	1.0622
Valdecoxib	1.0622
Royal Jelly acid	1.0614
Phloretin	1.0614
L-Azetidine-2-carboxylic acid	1.0614
Melatonin	1.0605
Ferulic acid	1.0605
γ-Aminobutyric acid	1.0605
p-Tolualdehyde	1.0597
2,6-Dibromophenol	1.0597
Lipoic acid	1.0588
L-Tartaric acid	1.0588
L-Methionine	1.0588
L-Cysteine	1.0580
N-Acetyl-L-phenylalanine	1.0572
2'-Deoxyadenosine-5'-monophosphate	1.0563
Hydroxyacetone	1.0555
Acetylcysteine	1.0546
Daidzein	1.0538
Thymine	1.0538
4-Aminohippuric acid	1.0529
Hydroxyphenyllactic acid	1.0529
H-Abu-OH	1.0529
Pyrogallol	1.0521
p-Anisic acid	1.0521
Maltose	1.0521
2-(4-Methoxyphenyl)acetic acid	1.0512
L-Palmitoylcarnitine (chloride)	1.0512
L-Arabinitol	1.0504
Ethoxyacetic acid	1.0504
Creosol	1.0495

3-(3-Hydroxyphenyl)propionic acid	1.0495
Zeaxanthin	1.0495
2'-Deoxyadenosine-5'-triphosphate (trisodium)	1.0495
11-Beta-hydroxyandrostenedione	1.0487
2-hydroxymethyl benzoic acid	1.0478
D-(+)-Glucono-1,5-lactone	1.0478
Methyl p-tert-butylphenylacetate	1.0478
LysoPC(14:0/0:0)	1.0478
L-Lactic acid	1.0462
Hippuric acid	1.0462
Folinic acid	1.0453
(-)-Fucose	1.0453
Levulinic acid	1.0453
Oleoylethanolamide	1.0453
Ursocholic acid	1.0445
Indole-3-acetamide	1.0436
Terephthalic acid	1.0436
5-Methoxyindole-3-acetic acid	1.0436
H-HoArg-OH	1.0436
Taurochenodeoxycholic acid (sodium salt)	1.0428
Fumaric acid	1.0428
Cholesterol	1.0428
Sucrose	1.0419
Taurocholic acid	1.0419
Ethynyl Estradiol	1.0411
Citicoline	1.0411
Oglufanide	1.0402
Urocanic acid	1.0394
Xylitol	1.0394
Uracil	1.0385
2,6-Dihydroxybenzoic acid	1.0385
2-O-Methylcytosine	1.0385
L-Thyroxine	1.0377
Theophylline	1.0377
L-Isoleucine	1.0377
D-Kynurenine	1.0360
5-Aminosalicylic Acid	1.0360
4-Pentenoic acid	1.0360
2-Hydroxy-4-methylbenzaldehyde	1.0351
3-Methyluridine	1.0343
N-Oleoyl glycine	1.0343
Nerolidol	1.0326
Heparan Sulfate	1.0318

Cysteamine (hydrochloride)	1.0309
Stearic acid	1.0309
Norepinephrine	1.0301
3-Methoxybenzoic acid	1.0292
Indole-2-carboxylic acid	1.0292
α-Vitamin E	1.0292
2-Piperidone	1.0292
N-Acetyl-L-tryptophan	1.0292
(S)-2-Hydroxy-3-phenylpropanoic acid	1.0284
4-Methyl-1-phenyl-2-pentanone	1.0284
Xylose	1.0284
Thiamine (hydrochloride)	1.0284
Adipic acid	1.0267
α-Lipoic Acid	1.0267
4-Methoxycinnamic acid	1.0267
Octopamine (hydrochloride)	1.0267
Dimethyl trisulfide	1.0258
(S)-Malic acid	1.0258
Aminoadipic acid	1.0258
L-Homocitrulline	1.0258
3-Methyladipic acid	1.0250
3-Methyl-L-histidine	1.0250
Selenomethionine	1.0250
Xanthosine	1.0241
N-Methylnicotinamide	1.0241
Mesitaldehyde	1.0233
2-Hydroxy-2-methylbutanoic acid	1.0233
Eicosapentaenoic Acid	1.0225
Folic acid	1.0225
γ-Cyclodextrin	1.0225
4-Methylbiphenyl	1.0216
5,6-Dihydroxyindole	1.0216
Xanthine	1.0216
(-)-Menthol	1.0208
trans-Vaccenic acid	1.0208
O-Acetylserine	1.0208
L-Valine	1.0208
L-Alanine	1.0208
Undecanoic acid	1.0199
TFAP	1.0191
Cyclo(his-pro) (TFA)	1.0191
Estriol	1.0191
2-Methoxybenzoic acid	1.0182

Vanillic acid	1.0182
Butylparaben	1.0182
2-Methylacetophenone	1.0182
2-Ethylpyrazine	1.0174
2-Acetonaphthone	1.0174
2',4'-Dimethylacetophenone	1.0174
Natamycin	1.0174
D-Mannitol	1.0174
6-Mercaptopurine	1.0157
Hexadecanedioic acid	1.0157
Diphenyl disulfide	1.0157
N-Acetyl-D-glucosamine	1.0157
6-Thioguanine	1.0140
N2,N2-Dimethylguanosine	1.0140
D-Leucine	1.0140
H-D-Trp-OH	1.0140
N4-Acetylcytidine	1.0140
Coenzyme Q9	1.0131
5-Methyluridine	1.0131
7-Ketolithocholic acid	1.0114
Eriodictyol	1.0106
2-Naphthol	1.0098
Myristic acid	1.0098
Paraxanthine	1.0098
5-Methylcytosine	1.0098
D-(+)-Phenyllactic acid	1.0089
Pentadecanoic acid	1.0089
4-Carboxypyrazole	1.0089
L-Gulono-1,4-lactone	1.0089
2-Methoxyestrone	1.0081
D-Glucuronic acid	1.0072
1-Methylguanosine	1.0047
5-Hydroxymethyluracil	1.0047
3,5-Dihydroxyacetophenone	1.0047
Protoporphyrin IX	1.0038
Deoxycholic acid	1.0038
3-Methyl-2-oxobutanoic acid	1.0038
Prostaglandin E2	1.0038
Sucralose	1.0030
Oxytocin (acetate)	1.0030
Maltotetraose	1.0030
N-Acetylputrescine hydrochloride	1.0021
Coenzyme A	1.0021

Nudifloramide	1.0021
4-Hydroxycoumarin	1.0021
Lactose	1.0021
Dihydrocaffeic acid	1.0021
3-Methyl-2-cyclopenten-1-one	1.0021
6-Biopterin	1.0013
Ascorbyl palmitate	1.0013
Ara-C	1.0000
Dihydrouracil	0.9996
2-Naphthoxyacetic acid	0.9988
4,6-O-Ethylidene-α-D-glucose	0.9988
8-Hydroxyguanosine	0.9979
1-Methylinosine	0.9979
Oleic acid	0.9971
Aceglutamide	0.9971
4-Hydroxybenzyl alcohol	0.9971
L-Homocysteine	0.9971
Gamma-glutamylcysteine	0.9971
Guanidinosuccinic acid	0.9962
3-Methylcrotonylglycine	0.9954
N-Acetyl-5-hydroxytryptamine	0.9954
Succinic acid	0.9937
Spermidine	0.9937
2'-Deoxyuridine	0.9937
Scyllo-Inositol	0.9928
Chondroitin (sulfate)	0.9920
N2-Methylguanosine	0.9920
Methyl anisate	0.9920
5-Aminolevulinic acid (hydrochloride)	0.9894
Tetrahydrobiopterin	0.9886
N1,N8-Diacetylspermidine (hydrochloride)	0.9886
Agmatine (sulfate)	0.9886
D-Pipecolinic acid	0.9877
p-Coumaric acid	0.9869
17a-Hydroxypregnenolone	0.9869
4-Methoxybenzaldehyde	0.9869
2-Methylpentanedioic acid	0.9852
Docosanoic acid	0.9852
Sarcosine	0.9852
3-Hydroxycapric acid	0.9835
Pyrocatechuic acid	0.9835
Glycodeoxycholic Acid	0.9835
Vitamin K1	0.9835

Dulcite	0.9827
Pyridoxylamine	0.9818
2'-O-Methyladenosine	0.9818
Mevalonic acid (lithium salt)	0.9810
Benzamide	0.9810
Glycoursodeoxycholic acid	0.9810
i-Inositol	0.9810
Genistein	0.9801
Tauroursodeoxycholate	0.9801
Glycine	0.9793
Octanoic acid	0.9784
Ethyl glucuronide	0.9784
3-(Methylthio)propionic acid	0.9784
5α-Cholestan-3β-ol	0.9776
Dehydrocholate (sodium)	0.9776
Linalool	0.9776
2-Phenylpropionic acid	0.9767
2-Hydroxy-3-methylbutanoic acid	0.9767
N-Methylhydantoin	0.9759
1-Hydroxypyrene	0.9751
5,6-Dimethyl-1H-benzo[d]imidazole	0.9751
Phenylpropiolic acid	0.9751
SY-640	0.9751
1,2-Cyclohexanedione	0.9742
Melanin	0.9742
Pyridoxal phosphate	0.9742
L-Homocystine	0.9742
Sulcatone	0.9742
Isovalerylcarnitine	0.9734
Creatinine	0.9734
Triolein	0.9725
1-Hexadecanol	0.9717
6-Hydroxynicotinic acid	0.9700
Hypotaurine	0.9700
L-Alloisoleucine	0.9700
Benzylideneacetone	0.9683
4-Ethylphenol	0.9683
3-Indoleacetonitrile	0.9683
Creatine	0.9683
Guanidine (hydrochloride)	0.9674
Linoleic acid	0.9666
Isoprenaline (hydrochloride)	0.9657
Orotic acid	0.9657

Methyl Paraben	0.9657
Oxaloacetic acid	0.9649
7-Methylguanosine	0.9649
Cholic acid	0.9641
Dodecanoylcarnitine	0.9624
3,4-Dihydroxybenzeneacetic acid	0.9624
8-Hydroxy-2'-deoxyguanosine	0.9615
Undecanedioic acid	0.9607
N-Acetyl-L-leucine	0.9607
Methyl cyclohexanecarboxylate	0.9598
Phthalic acid mono-2-ethylhexyl ester	0.9590
D-Glutamine	0.9581
N-Acetyl-L-tyrosine	0.9581
Cytosine	0.9564
2-Hydroxyphenylacetic acid	0.9556
Hydrocortisone acetate	0.9556
1,3-Dithiane	0.9556
L-Tryptophan	0.9556
L-Aspartic acid	0.9556
Spinacine	0.9547
Pyrroloquinoline quinone	0.9547
Guanosine 5'-diphosphate (disodium salt)	0.9547
Chlorogenic acid	0.9539
7-Methylxanthine	0.9539
p-Toluic acid	0.9530
Guaiacol	0.9530
NSC 16590	0.9530
Leucyl-phenylalanine	0.9530
Cholesteryl oleate	0.9522
3-Hydroxyphenylacetic acid	0.9522
4-Amino-L-phenylalanine	0.9522
L-Norleucine	0.9514
L-Prolylglycine	0.9505
L-Pipecolic acid	0.9505
Palmitoleic acid	0.9488
Tyramine	0.9488
3-Hydroxyanthranilic acid	0.9488
5-Hydroxytryptophol	0.9480
Dimethyl sulfone	0.9471
trans-trans-Muconic acid	0.9463
Urea	0.9454
3-Chloro-L-tyrosine	0.9454
Ribitol	0.9446

β-Nicotinamide mononucleotide	0.9446
Propofol	0.9437
L-Valyl-L-phenylalanine	0.9437
D(-)-2-Aminobutyric acid	0.9437
Homogentisic acid	0.9429
D-(+)-Trehalose	0.9429
2-Phenylacetamide	0.9429
Niacin	0.9420
Lauric acid	0.9404
L-Homoserine	0.9404
Oxypurinol	0.9395
Thyminose	0.9395
DL-Tryptophan	0.9387
3-Nitro-L-tyrosine	0.9387
5-Aminovaleric acid	0.9387
2,4-Dihydroxybenzaldehyde	0.9378
DL-Asparagine	0.9370
7,8-Dihydro-L-biopterin	0.9361
5-Hydroxymethyl-2-furancarboxylic acid	0.9361
DL-Homocystine	0.9361
Riboflavin (phosphate sodium)	0.9361
[Leu5]-Enkephalin	0.9361
2'-Deoxyadenosine	0.9353
meso-Erythritol	0.9336
β-cyano-L-Alanine	0.9336
p-Synephrine	0.9336
PCL 016	0.9336
2,4-Di-tert-butylphenol	0.9327
Uridine	0.9310
Imidazol-1-yl-acetic acid	0.9310
Dimethyl fumarate	0.9302
D-Allothreonine	0.9302
Desaminotyrosine	0.9302
Isovaleric acid	0.9293
5-Amino-3H-imidazole-4-Carboxamide	0.9285
Urolithin B	0.9285
γ-Glu-Phe	0.9277
DL-Homocysteine	0.9260
L-Serine	0.9260
2-Methylsuccinic acid	0.9251
Glycohyodeoxycholic acid	0.9251
Dehydroascorbic acid	0.9251
5-Hydroxytryptophan	0.9243

Maltohexaose	0.9243
2'-Deoxyadenosine monohydrate	0.9234
Kynurenic acid	0.9209
Maltotriose	0.9200
2-Oxovaleric acid	0.9192
Cyclohexaneacetic acid	0.9192
Nicotinamide	0.9192
1-Dodecanol	0.9183
Glutaric acid	0.9183
N-Acetylhistamine	0.9175
Acetyl-L-carnitine (hydrochloride)	0.9175
N-Acetyl-L-arginine	0.9167
Elaidic acid	0.9133
L-Asparagine	0.9133
Ellagic acid	0.9124
L-Phenylalanine	0.9124
Suberic acid	0.9116
4-Methyl-2-oxopentanoic acid	0.9116
Phosphocreatine (disodium)	0.9116
2-Methylcitric acid	0.9107
3-Methylglutaric acid	0.9107
Norharmane	0.9107
3b-Hydroxy-5-cholenoic acid	0.9099
2,5-Dihydroxybenzoic acid	0.9099
Purine	0.9099
Antineoplaston A10	0.9090
D-α-Hydroxyglutaric acid (disodium)	0.9090
4-Hydroxybenzyl cyanide	0.9090
5-Methoxytryptophol	0.9082
Glycylglycine	0.9082
Tetrahydrothiophen-3-one	0.9073
3-Hydroxyisobutyric acid	0.9065
4-Acetamidobutanoic acid	0.9065
L-Alanyl-L-glutamine	0.9065
L-Kynurenine	0.9056
Glyoxalic acid	0.9056
Beta-Cortol	0.9056
Allantoin	0.9056
Pseudouridine	0.9048
D-Serine	0.9048
Oxytetracycline	0.9040
5-Methyltetrahydrofolic acid	0.9040
Homovanillic acid	0.9040

FAPy-adenine	0.9031
3-Methylbut-2-enoic acid	0.9031
L-Proline	0.9023
Lecithin	0.9014
Methylmalonic acid	0.9014
Glycolic acid	0.9014
Pyruvic acid	0.9006
5-Hydroxy-2'-deoxyuridine	0.9006
L-Citrulline	0.9006
(Z)-Aconitic acid	0.8997
L-Cystathionine	0.8997
L-Histidine	0.8989
Hyodeoxycholic acid	0.8980
(S)-3-Hydroxybutanoic acid	0.8980
Uridine-5'-diphosphate disodium salt	0.8972
3-Hydroxyglutaric acid	0.8963
Delta-Tocopherol	0.8955
Nervonic acid	0.8955
Benzoic acid	0.8955
Phosphorylcholine	0.8955
3-Indoleacetic acid	0.8946
Guanosine	0.8946
N-Acetyl-L-aspartic acid	0.8938
12-Hydroxydodecanoic acid	0.8921
3,4-Dimethoxyphenylacetic acid	0.8913
Phosphorylethanolamine	0.8904
Phenylephrine (hydrochloride)	0.8896
2,3,5-Trimethylpyrazine	0.8887
L-Ornithine	0.8887
Thymidine-5'-monophosphate (disodium) salt	0.8887
3-Hydroxybutyric acid	0.8887
2-(1H-Indol-3-yl)ethan-1-ol	0.8879
Deoxycholic acid sodium salt	0.8879
Phenylpyruvic acid	0.8870
Phosphonoacetic acid	0.8870
trans-Aconitic acid	0.8853
3-Methyl-2-oxovaleric acid	0.8845
H-Tyr(3-I)-OH	0.8845
Citraconic acid	0.8828
C16-PAF	0.8828
Thiamine pyrophosphate	0.8828
Cysteinylglycine (TFA)	0.8811
DL-3-Phenyllactic acid	0.8794

Pregnanediol	0.8786
Cyclic AMP	0.8777
Caffeic acid	0.8769
Nicotinuric acid	0.8760
H-Val-Tyr-OH	0.8760
(E)-Ferulic acid	0.8752
3-Methylxanthine	0.8752
(R)-3-Hydroxybutanoic acid	0.8752
3,4-Dihydroxymandelic acid	0.8743
DL-Glutamine	0.8743
L-DABA	0.8735
2,5-Furandicarboxylic acid	0.8735
Octadecanal	0.8726
Uric acid	0.8718
Nicotinamide N-oxide	0.8718
Pipecolic acid	0.8718
L-Lysine	0.8709
1-Methyl-L-histidine	0.8684
D-Cysteine	0.8659
L-Ascorbic acid 2-phosphate (trisodium)	0.8659
2(5H)-Furanone	0.8616
Maltopentaose	0.8616
L-Dihydroorotic acid	0.8599
DPPC	0.8566
Decanedioic acid	0.8557
3-Hydroxyisovaleric acid	0.8557
Spaglumic Acid	0.8557
1-Octanol	0.8557
Indolelactic acid	0.8540
γ-L-Glutamyl-L-alanine	0.8489
Butyrylcarnitine	0.8489
3,5-Dihydroxybenzoic acid	0.8472
3-Hydroxyvaleric acid	0.8472
25-Hydroxycholesterol	0.8464
L-Threonine	0.8464
Cholestenone	0.8447
Dinoprost	0.8439
2-(2-Phenylacetamido)acetic acid	0.8430
5'-Guanylic acid (disodium salt)	0.8430
sn-Glycerol 3-phosphate	0.8413
1,4-Dimethoxybenzene	0.8405
H-Phe-Phe-OH	0.8388
Glycyl-L-valine	0.8379

Ergosterol	0.8362
D-Ribose(mixture of isomers)	0.8362
N4-Acetylcytidine triphosphate (sodium)	0.8354
D-(-)-Quinic acid	0.8329
TRIA-662	0.8320
Methionine sulfoxide	0.8320
L-Carnosine	0.8303
3-Amino-2-methylpropanoic acid	0.8286
1-Naphthol	0.8261
(2-Aminoethyl)phosphonic acid	0.8252
4-Pyridoxic acid	0.8202
3-Methoxytyramine	0.8185
N-Methylsarcosine	0.8176
1,5-Anhydrosorbitol	0.8159
3-Hydroxyhippuric acid	0.8134
N-(5-Aminopentyl)acetamide	0.8100
Adrenosterone	0.8100
L-Methionine sulfoxide	0.8083
5,6-Dihydrouridine	0.8007
2'-Deoxyguanosine	0.7965
Sphingomyelin	0.7965
N-Acetylornithine	0.7922
1-Hydroxyoctadecane	0.7905
Pregnenolone monosulfate	0.7872
5-Hydroxyindole-3-acetic acid	0.7804
Galactose 1-phosphate Potassium salt	0.7728
Maleic Acid	0.7677
Cholesteryl palmitate	0.7643
5,6-Dihydro-5-methyluracil	0.7592
1-Methyladenine	0.7550
H-Gly-Pro-OH	0.7516
Citric acid	0.7491
Nepsilon-Acetyl-L-lysine	0.7448
2-Hydroxyadipic acid	0.7271
2'-Deoxyinosine	0.7093
Anserine	0.7008
1-Methyluric acid	0.6966
Thymidine	0.6873
Phenylacetylglutamine	0.6814
2,6-Diaminoheptanedioic acid	0.6788
1-Methyladenosine	0.6763
4-Methylcatechol	0.6238
4-Ethoxyphenol	0.6170

Kinetensin	0.5172
N6-Methyladenosine	0.2412

48h	
Metabolites	Relative Viability
N-Desmethyltamoxifen (hydrochloride)	6.1549
2'-Deoxycytidine	6.1420
Pimelic acid	6.1420
Tryptamine	6.0453
5-Methyl-2'-deoxycytidine	5.7134
Adenine	4.5082
m-Anisaldehyde	3.8959
Canrenone	3.7187
Uridine triphosphate	3.6961
Oxypurinol	3.6059
Adenosine	3.5576
Retinoic acid	3.4770
L-Serine	3.4641
5'-Methylthioadenosine	3.4158
Adenosine monophosphate	3.3739
Deoxycorticosterone acetate	3.1515
5'-Deoxyadenosine	3.0839
Inosine	3.0742
2-(2-Methylbenzamido)acetic acid	2.8873
all-trans-Anhydro Retinol	2.8358
Mandelic acid	2.7455
2'-Deoxyadenosine	2.6360
Hypoxanthine	2.5941
21-Hydroxypregnenolone	2.5618
Zeaxanthin	2.5167
2'-Deoxyadenosine-5'-monophosphate	2.3911
Squalene	2.3492
Ursodeoxycholic acid	2.2525
Deoxycorticosterone	2.2203
NAD+	2.1945
Adenosine 5'-diphosphate	2.1655
2,6-Dihydroxybenzoic acid	2.1268
Indole-2-carboxylic acid	2.1268
Epiandrosterone	2.1236
Acetyl Coenzyme A (trisodium)	2.0849
Progesterone	2.0269
Sorbic acid	2.0205
4,4-Dimethoxy-2-butanone	2.0140

11beta-Hydroxyprogesterone	1.9818
Chlorogenic acid	1.9594
Fluticasone (propionate)	1.9206
Etiocholanolone	1.9045
Undecanoic acid	1.8529
Cytidine 5'-monophosphate	1.8529
p-Hydroxycinnamic acid	1.8432
2-Naphthoxyacetic acid	1.8336
NADH (disodium salt)	1.8303
5a-Pregnane-3,20-dione	1.8078
2'-Deoxyadenosine monohydrate	1.7981
Thymine	1.7981
3-Hydroxycapric acid	1.7885
Glycoursodeoxycholic acid	1.7820
Guaiacol	1.7627
5-Hydroxymethyl-2-furancarboxylic acid	1.7530
5,6-Dimethyl-1H-benzo[d]imidazole	1.7466
Flavin adenine dinucleotide (disodium salt)	1.7466
Oxaloacetic acid	1.7369
Cortisone	1.7305
AICAR (phosphate)	1.7305
Hydroxyphenyllactic acid	1.7143
(-)-Aspartic acid	1.7143
Prednisolone	1.6821
Spermidine	1.6724
Palmitic acid	1.6628
Benzamide	1.6306
Nicotinamide riboside (chloride)	1.6177
Glycocholic acid	1.6177
2'-O-Methyladenosine	1.6080
Folinic acid	1.5951
Sucralose	1.5854
Cortodoxone	1.5822
Taurochenodeoxycholic acid (sodium salt)	1.5822
Benzophenone	1.5726
1-Hexadecanol	1.5726
N-Acetyl-L-tryptophan	1.5564
N-Acetyl-D-glucosamine	1.5468
Methyl 3-phenylpropanoate	1.5436
3-Hydroxybenzoic acid	1.5403
Royal Jelly acid	1.5242
2-Phenylpropionic acid	1.5178
D-Cysteine	1.5178

L-Homocitrulline	1.5178
Coniferyl alcohol	1.5017
2',4'-Dimethylacetophenone	1.4888
2-(4-Methoxyphenyl)acetic acid	1.4823
3,3'-Diiodo-L-thyronine	1.4791
Raffinose	1.4791
Menaquinone-4	1.4727
Levulinic acid	1.4694
N4-Acetylcytidine	1.4662
Sucrose	1.4630
Taurocholic acid	1.4630
Octopamine (hydrochloride)	1.4565
Hydroxyacetone	1.4533
Docosapentaenoic acid (22n-3)	1.4469
Vanillic acid	1.4469
N-Acetyl-L-methionine	1.4437
2-Furoic acid	1.4404
1-Hydroxypyrene	1.4243
Glyoxalic acid	1.4211
NADPH (tetrasodium salt)	1.4211
3-(3-Hydroxyphenyl)propionic acid	1.4179
7-Ketolithocholic acid	1.4147
5-Methoxyindole-3-acetic acid	1.4114
Fumaric acid	1.4114
Malic acid	1.4082
Desloratadine	1.4050
(S)-b-aminoisobutyric acid	1.4050
Nerol	1.4018
p-Toluic acid	1.3985
4,6-Dioxoheptanoic acid	1.3985
Dihydrocaffeic acid	1.3921
Arachidonic acid	1.3921
Oglufanide	1.3857
Vanillylmandelic acid	1.3857
4-Methylbiphenyl	1.3824
Dulcite	1.3792
L-Pipecolic acid	1.3792
α-Lipoic Acid	1.3760
Melatonin	1.3695
Hippuric acid	1.3663
Sulcatone	1.3631
Erucic acid	1.3566
L-Tartaric acid	1.3534

L-Carnitine	1.3502
Azelaic acid	1.3470
Ac-Ala-OH	1.3341
2-Methylbenzoxazole	1.3341
α-D-Glucose-1-phosphate (disodium hydrate)	1.3341
Lactose	1.3309
2-Acetonaphthone	1.3244
Liothyronine	1.3212
(-)-(S)-Equol	1.3148
4-Methoxycinnamic acid	1.3148
N-Acetyl-5-hydroxytryptamine	1.3115
Lornoxicam	1.3083
4-Pyridoxic acid	1.3051
Pentadecanoic acid	1.3019
2-Hydroxyhexanoic acid	1.2986
2,4-Dihydroxybenzaldehyde	1.2954
Biocytin	1.2922
2,4-Dihydroxybenzoic acid	1.2858
Spinacine	1.2793
Cyclo(his-pro) (TFA)	1.2729
Acetylcysteine	1.2729
SDMA	1.2632
Mevalonic acid (lithium salt)	1.2632
DL-Homocysteine thiolactone (hydrochloride)	1.2600
2,6-Dimethoxybenzoic acid	1.2600
DL-O-Phosphoserine	1.2600
Isorhamnetin	1.2568
N-Oleoyl glycine	1.2535
Corticosterone	1.2535
L-Arabinitol	1.2471
5-Hydroxyindole-3-acetic acid	1.2406
Creosol	1.2342
3-Methyl-L-histidine	1.2342
L-Azetidine-2-carboxylic acid	1.2310
1-Methyluric acid	1.2310
Methyl p-tert-butylphenylacetate	1.2278
5-Hydroxymethyluracil	1.2245
Cinnamic acid	1.2245
1,3-Dimethyluric acid	1.2213
Guanosine 5'-triphosphate (trisodium salt)	1.2213
Trimethylamine N-oxide	1.2149
D-(-)-Lactic acid	1.2149
2-Methoxybenzoic acid	1.2116

Pyridoxylamine	1.2116
Taurine	1.2116
Tyramine	1.1987
6-Biopterin	1.1987
PCL 016	1.1891
2',4'-Dihydroxyacetophenone	1.1891
α-Pyridone	1.1859
4-Aminobenzoic acid	1.1826
3-Amino-4-methylpentanoic acid	1.1826
(2-Aminoethyl)phosphonic acid	1.1730
1-Dodecanol	1.1665
L-Lactic acid	1.1665
D-Leucine	1.1665
Oleoylethanolamide	1.1665
Eicosapentaenoic Acid	1.1633
Pregnenolone	1.1633
2,6-Dibromophenol	1.1569
Phenylpropiolic acid	1.1536
Paraxanthine	1.1504
Methyl anisate	1.1375
Arachidic acid	1.1375
(S)-Malic acid	1.1311
3-Methyl-2-oxobutanoic acid	1.1311
(S)-(+)-1,2-Propanediol	1.1311
Methyl Paraben	1.1311
1,2-Cyclohexanedione	1.1279
Chenodeoxycholic Acid	1.1279
LysoPC(14:0/0:0)	1.1279
H-D-Trp-OH	1.1214
Mesitaldehyde	1.1214
N-Acetyl-L-leucine	1.1117
L-SelenoMethionine	1.1117
(R)-pyrrolidine-2-carboxylic acid	1.1085
Lauric acid	1.1053
2,4-Di-tert-butylphenol	1.1021
γ-Cyclodextrin	1.1021
Linoleic acid	1.0956
Elaidic acid	1.0924
4-Pentenoic acid	1.0924
Glycyl-L-valine	1.0892
Estradiol	1.0892
Pregnenolone monosulfate	1.0892
Androsterone	1.0795

Adipic acid	1.0795
Diethyl phosphate	1.0731
2-Methylsuccinic acid	1.0699
Docosahexaenoic Acid	1.0699
2-Hydroxyphenylacetic acid	1.0602
Uracil	1.0602
3-Hydroxypicolinic acid	1.0602
Cysteamine (hydrochloride)	1.0570
Diphenyl disulfide	1.0570
Eriodictyol	1.0570
2-Hydroxy-4-methylbenzaldehyde	1.0505
SY-640	1.0473
3-Methyladipic acid	1.0441
2-O-Methylcytosine	1.0408
7-Methylxanthine	1.0408
Cholestenone	1.0408
11-Beta-hydroxyandrostenedione	1.0408
Bisphenol A	1.0408
2-Hydroxy-2-methylbutanoic acid	1.0376
Cyclohexaneacetic acid	1.0312
Tetrahydrobiopterin	1.0247
Medroxyprogesterone acetate	1.0247
Imidazol-1-yl-acetic acid	1.0247
4-Methoxybenzaldehyde	1.0215
2-Methylbenzaldehyde	1.0215
N-Acetylputrescine hydrochloride	1.0183
Nudifloramide	1.0183
D-Alanine	1.0183
2-Oxovaleric acid	1.0151
3-Methyl-2-oxovaleric acid	1.0151
1-Hydroxyoctadecane	1.0086
Oxalic Acid	1.0054
Orotic acid	1.0054
3-Methylxanthine	1.0054
5'-Guanylic acid (disodium salt)	1.0022
Dinoprost	1.0022
Ara-C	1.0000
2,6-Dihydroxyacetophenone	0.9990
Crustecdysone	0.9893
5,6-Dihydroxyindole	0.9893
alpha-D-glucose	0.9893
D-Sorbitol	0.9893
Histamine	0.9893

Aminomalonic acid	0.9893
Isethionic acid	0.9861
2-Acetyl-3-ethylpyrazine	0.9861
C16-PAF	0.9861
Uridine 5'-monophosphate	0.9828
2-Ethylpyrazine	0.9828
8-Hydroxy-2'-deoxyguanosine	0.9828
D-Glucuronic acid	0.9828
D-Arabitol	0.9828
Cytidine	0.9828
Oxytetracycline	0.9796
Xanthine	0.9796
L-Hydroxyproline	0.9796
N-Acetyl-L-phenylalanine	0.9764
Uridine	0.9732
L-Citrulline	0.9732
Lithocholic acid	0.9700
Phenoxyacetic acid	0.9700
2-Phenylacetamide	0.9667
D-(+)-Phenyllactic acid	0.9667
Valdecoxib	0.9667
Dimethylmalonic acid	0.9635
DL-Mevalonolactone	0.9635
Methoxyacetic acid	0.9603
DL-Asparagine	0.9603
H-Phe-Phe-OH	0.9603
1-Octanol	0.9571
DPPC	0.9571
Dichlorisone acetate	0.9571
Citicoline	0.9506
Xylose	0.9506
Phosphocreatine (disodium)	0.9474
4-Hydroxycoumarin	0.9410
Isoprenaline (hydrochloride)	0.9377
D-Pipecolinic acid	0.9377
1,4-Dimethoxybenzene	0.9377
4-Hydroxybenzyl cyanide	0.9377
12-Hydroxydodecanoic acid	0.9345
Melanin	0.9345
17α-Hydroxyprogesterone	0.9313
(R,R)-(+)-Hydrobenzoin	0.9313
Dodecanedioic acid	0.9313
L-Tryptophan	0.9313

Oxoadipic acid	0.9313
D-Panthenol	0.9281
Guanidine (hydrochloride)	0.9281
TRIA-662	0.9281
Genistein	0.9248
(E)-Ferulic acid	0.9248
L-Alanyl-L-leucine	0.9248
Adrenosterone	0.9155
Nervonic acid	0.9152
Cyclic AMP	0.9152
FAPy-adenine	0.9152
Indolelactic acid	0.9152
Octadecanal	0.9120
Gamma-Linolenic acid	0.9087
Quinolinic acid	0.9087
10-Undecenoic acid	0.9087
N-Acetyl-L-arginine	0.9055
2-Naphthol	0.9055
3,5-Dihydroxyacetophenone	0.9055
7-Methylguanosine	0.9023
L-Glutamic acid	0.9000
3-Hydroxyphenylacetic acid	0.8991
2-(1H-Indol-3-yl)ethan-1-ol	0.8991
N-Acetyl-L-tyrosine	0.8991
2'-Deoxyguanosine	0.8991
Prostaglandin E2	0.8991
Undecanedioic acid	0.8958
Kinetensin	0.8926
D-Mannose	0.8926
Palmitoleic acid	0.8926
3-Methylbut-2-enoic acid	0.8926
6-Hydroxynicotinic acid	0.8926
Triolein	0.8894
3-Indolepropionic acid	0.8894
6-Thioguanine	0.8894
Thyminose	0.8894
3-Hydroxyhippuric acid	0.8894
Phthalic acid mono-2-ethylhexyl ester	0.8862
Phenylephrine (hydrochloride)	0.8733
2-hydroxymethyl benzoic acid	0.8733
p-Synephrine	0.8701
D-(+)-Cellobiose	0.8668
L-Methionine sulfoxide	0.8668

Suberic acid	0.8604
3-Methoxytyramine	0.8604
N-Acetylglycine	0.8604
3-Hydroxyvaleric acid	0.8604
Purine	0.8572
Homovanillic acid	0.8572
Isomaltose	0.8572
Pantethine	0.8539
H-Gly-Pro-OH	0.8539
5-Aminosalicylic Acid	0.8456
Pyruvic acid	0.8449
Uric acid	0.8443
(-)-Menthol	0.8443
Delta-Tocopherol	0.8411
Tetrahydrothiophen-3-one	0.8411
Terephthalic acid	0.8378
Caffeic acid	0.8378
i-Inositol	0.8378
L-Palmitoylcarnitine (chloride)	0.8378
1-Methyl-L-histidine	0.8378
Cholic acid	0.8346
5-Hydroxytryptophan	0.8317
O-Acetylserine	0.8314
2(5H)-Furanone	0.8282
H-Val-Tyr-OH	0.8282
L-Gulono-1,4-lactone	0.8282
Phosphorylethanolamine	0.8249
Cytosine	0.8217
Alanylphenylalanine	0.8217
L-Valyl-L-phenylalanine	0.8185
Isovaleric acid	0.8185
5-Methyltetrahydrofolic acid	0.8153
L-Methionine	0.8088
Kynurenic acid	0.8056
Nepsilon-Acetyl-L-lysine	0.8056
3-Methoxybenzoic acid	0.8024
N-Methylnicotinamide	0.8024
Sphingomyelin	0.8024
p-Tolualdehyde	0.7992
Cysteinylglycine (TFA)	0.7992
Desaminotyrosine	0.7959
Daidzein	0.7959
Phenylpyruvic acid	0.7959

4-Aminohippuric acid	0.7927
Maltotetraose	0.7927
L-Kynurenine	0.7895
D-Desthiobiotin	0.7872
L-Isoleucine	0.7863
Perillartine	0.7798
3-Chloro-L-tyrosine	0.7798
Phloretin	0.7776
L-Dihydroorotic acid	0.7766
2-Piperidone	0.7766
Sarcosine	0.7734
Decanedioic acid	0.7702
2,5-Furandicarboxylic acid	0.7702
Lecithin	0.7669
2-Methylcitric acid	0.7669
DL-3-Phenyllactic acid	0.7669
4-Amino-L-phenylalanine	0.7669
H-HoArg-OH	0.7669
Indole-3-acetamide	0.7628
Methylmalonic acid	0.7605
D(-)-2-Aminobutyric acid	0.7605
Ergothioneine	0.7602
meso-Erythritol	0.7576
(Ethoxymethyl)benzene	0.7573
Taurolithocholic acid (sodium salt)	0.7573
Hydrocinnamic acid	0.7573
Octanoic acid	0.7547
Triacetin	0.7541
Nicotinuric acid	0.7541
Cholesterol	0.7541
L-Thyroxine	0.7508
Pyrocatechuic acid	0.7508
Citraconic acid	0.7476
(Z)-Aconitic acid	0.7476
L-Histidine	0.7476
2'-Deoxyinosine	0.7476
Scyllo-Inositol	0.7463
DL-Norvaline	0.7444
Gamma-glutamylcysteine	0.7444
Ascorbyl palmitate	0.7412
3-Hydroxyisobutyric acid	0.7399
L-DABA	0.7376
Deoxycholic acid sodium salt	0.7354

3,5-Dihydroxybenzoic acid	0.7299
Nicotinamide N-oxide	0.7270
(S)-3-Hydroxybutanoic acid	0.7254
5-Hydroxytryptophol	0.7250
L-Homocysteine	0.7250
D-Ribose(mixture of isomers)	0.7231
Dihydrodaidzein	0.7218
3-Hydroxyisovaleric acid	0.7218
2,3,5-Trimethylpyrazine	0.7218
4-Ethylphenol	0.7218
N-Acetylornithine	0.7212
Pyridoxal phosphate	0.7196
Ellagic acid	0.7186
L-Arginine	0.7186
Glycolic acid	0.7154
4-Hydroxy-3-methylbenzoic acid	0.7122
3-Indoleacetonitrile	0.7086
3,4-Dimethoxyphenylacetic acid	0.7070
D-Mannitol	0.7067
4-Hydroxyphenylacetic acid	0.7064
γ-Aminobutyric acid	0.7057
Ethyl glucuronide	0.7057
Beta-Cortol	0.7025
L-Glutamine	0.7025
Glycylglycine	0.7025
4-Hydroxymethylpyrazole	0.7012
p-Anisic acid	0.7006
trans-Vaccenic acid	0.6993
Butylparaben	0.6993
Urocanic acid	0.6960
Spaglumic Acid	0.6931
3-Nitro-L-tyrosine	0.6928
Thiamine (hydrochloride)	0.6919
L-Cystathionine	0.6915
Ethoxyacetic acid	0.6915
TFAP	0.6893
Anserine	0.6880
N-Acetylhistamine	0.6864
L-Homoserine	0.6864
3-Indoleacetic acid	0.6848
Isovalerylcarnitine	0.6838
Ethylmalonic acid	0.6799
Urea	0.6793

Vanilpyruvic acid	0.6790
Glycohyodeoxycholic acid	0.6786
Thyroxine sulfate	0.6761
Hyodeoxycholic acid	0.6761
L-Proline	0.6761
5,6-Dihydro-5-methyluracil	0.6757
5-Amino-3H-imidazole-4-Carboxamide	0.6741
L-Ascorbic acid 2-phosphate (trisodium)	0.6732
4,6-O-Ethylidene-α-D-glucose	0.6728
4-Carboxypyrazole	0.6719
Linalool	0.6706
Theophylline	0.6699
Pseudouridine	0.6696
L-Valine	0.6690
Creatinine	0.6674
3-Methylglutaric acid	0.6670
Cholesteryl palmitate	0.6638
Cholesteryl oleate	0.6622
Pregnanediol	0.6616
4-Methyl-1-phenyl-2-pentanone	0.6603
Folic acid	0.6593
Phosphorylcholine	0.6587
Allantoin	0.6580
5,6-Dihydrouridine	0.6554
Glycochenodeoxycholic acid	0.6532
H-Tyr(3-I)-OH	0.6516
α-Vitamin E	0.6509
Tauroursodeoxycholate	0.6506
Ferulic acid	0.6503
Methyl cyclohexanecarboxylate	0.6467
L-Alloisoleucine	0.6458
2,5-Dihydroxybenzoic acid	0.6448
N6-Methyladenosine	0.6442
4-Methyl-2-oxopentanoic acid	0.6438
3b-Hydroxy-5-cholenoic acid	0.6435
N-Methylhydantoin	0.6390
Nicotinamide	0.6390
Lipoic acid	0.6368
DL-Glutamine	0.6368
1,5-Anhydrosorbitol	0.6342
2'-Deoxyadenosine-5'-triphosphate (trisodium)	0.6329
Nerolidol	0.6313
Glutathione oxidized	0.6293

3,4-Dihydroxybenzeneacetic acid	0.6290
SAH	0.6274
Myristic acid	0.6274
Norharmane	0.6252
1,3-Dithiane	0.6248
L-Aspartic acid	0.6203
Isohomovanillic acid	0.6187
5-Methoxytryptophol	0.6181
Citric acid	0.6181
D-(+)-Glucono-1,5-lactone	0.6136
Deoxycholic acid	0.6129
β-Alanine	0.6074
Cytidine-5'-triphosphate	0.6068
L-Ornithine	0.6065
(S)-2-Hydroxy-3-phenylpropanoic acid	0.6049
3-Hydroxyglutaric acid	0.6049
Pipecolic acid	0.6049
Leucyl-phenylalanine	0.6013
L-Norleucine	0.6000
5-Aminovaleric acid	0.5968
3-Amino-2-piperidinone	0.5955
Maltose	0.5904
N-(5-Aminopentyl)acetamide	0.5897
Succinic acid	0.5894
D-(+)-Trehalose	0.5871
Phenylacetylglutamine	0.5868
L-Cysteine	0.5865
Chondroitin (sulfate)	0.5862
5-Hydroxy-2'-deoxyuridine	0.5817
L-Threonine	0.5813
3,4-Dihydroxymandelic acid	0.5807
Methionine sulfoxide	0.5788
DL-Homocysteine	0.5781
Oleic acid	0.5775
3-Methyluridine	0.5759
4-Hydroxybenzoic acid	0.5759
Coproporphyrin III	0.5710
sn-Glycerol 3-phosphate	0.5678
NSC 16590	0.5659
5-Methylcytosine	0.5655
2-Methylacetophenone	0.5646
Creatine	0.5626
DL-Tryptophan	0.5617

Dehydrocholate (sodium)	0.5601
4-Acetamidobutanoic acid	0.5581
Natamycin	0.5575
3-Methylcrotonylglycine	0.5552
Pyrogallol	0.5549
Aminoadipic acid	0.5539
Homogentisic acid	0.5504
Myricetin	0.5488
3-Hydroxyanthranilic acid	0.5485
Glutaric acid	0.5481
Thiamine pyrophosphate	0.5468
Maleic Acid	0.5462
Indole	0.5452
5-Aminolevulinic acid (hydrochloride)	0.5436
Dihydrouracil	0.5427
Xanthosine	0.5420
H-Abu-OH	0.5388
Guanosine 5'-diphosphate (disodium salt)	0.5365
Maltotriose	0.5362
Butyrylcarnitine	0.5349
Propofol	0.5311
7,8-Dihydro-L-biopterin	0.5291
Dimethyl fumarate	0.5285
6-Mercaptopurine	0.5272
1-Methyladenosine	0.5265
Heparan Sulfate	0.5230
Benzylideneacetone	0.5224
D-Serine	0.5220
2,6-Diaminoheptanedioic acid	0.5220
Maltohexaose	0.5195
Hypotaurine	0.5156
Stearic acid	0.5117
Dimethyl sulfone	0.5117
5-Methyluridine	0.5114
Glycodeoxycholic Acid	0.5114
Dehydroepiandrosterone sulfate (sodium salt)	0.5095
3-(Methylthio)propionic acid	0.5091
(R)-3-Hydroxybutanoic acid	0.5066
Ergosterol	0.5040
Acetyl-L-carnitine (hydrochloride)	0.5040
2-Methylpentanedioic acid	0.5014
L-Alanyl-L-glutamine	0.4963
L-Carnosine	0.4956

8-Hydroxyguanosine	0.4937
D-Glutamine	0.4924
L-Asparagine	0.4921
3-Hydroxybutyric acid	0.4905
Riboflavin (phosphate sodium)	0.4898
β-Nicotinamide mononucleotide	0.4872
N2,N2-Dimethylguanosine	0.4866
Selenomethionine	0.4863
Glycine	0.4859
Niacin	0.4837
trans-Aconitic acid	0.4824
DL-Homocystine	0.4795
(-)-Fucose	0.4756
Xylitol	0.4750
2-Hydroxyadipic acid	0.4747
Meglutol	0.4743
2'-Deoxyuridine	0.4743
Phosphonoacetic acid	0.4718
Substance P	0.4692
L-Alanine	0.4682
L-Prolylglycine	0.4640
Benzoic acid	0.4602
L-Lysine	0.4563
Ribitol	0.4550
Galactose 1-phosphate Potassium salt	0.4531
Glucosamine	0.4518
2-Hydroxy-3-methylbutanoic acid	0.4508
γ-L-Glutamyl-L-alanine	0.4492
Thymidine	0.4489
D-α-Hydroxyglutaric acid (disodium)	0.4479
4-Hydroxybenzyl alcohol	0.4473
L-Phenylalanine	0.4460
Thymidine-5'-monophosphate (disodium) salt	0.4434
L-(+)-Arabinose	0.4408
trans-trans-Muconic acid	0.4379
Agmatine (sulfate)	0.4305
Hexadecanedioic acid	0.4296
3-Amino-2-methylpropanoic acid	0.4292
[Leu5]-Enkephalin	0.4205
N-Acetyl-L-aspartic acid	0.4202
p-Coumaric acid	0.4202
L-Homocystine	0.4180
2-Methoxyestrone	0.4163

Hydrocortisone acetate	0.4157
Guanosine	0.4144
D-Allothreonine	0.4031
N4-Acetylcytidine triphosphate (sodium)	0.4022
Dimethyl trisulfide	0.4012
γ-Glu-Phe	0.3983
N-Methylsarcosine	0.3947
Uridine-5'-diphosphate disodium salt	0.3906
D-Ribonolactone	0.3815
D-(-)-Quinic acid	0.3809
Guanidinosuccinic acid	0.3802
Coenzyme A	0.3786
Norepinephrine	0.3728
Antineoplaston A10	0.3657
N2-Methylguanosine	0.3654
Aceglutamide	0.3596
D-Kynurenine	0.3587
1-Methylinosine	0.3467
Urolithin B	0.3422
β-cyano-L-Alanine	0.3387
Pyrroloquinoline quinone	0.3384
1-Methylguanosine	0.3271
N1,N8-Diacetylspermidine (hydrochloride)	0.3219
Dodecanoylcarnitine	0.3190
4-Methylcatechol	0.3155
Coenzyme Q9	0.3090
Ursocholic acid	0.3055
Maltopentaose	0.2952
17a-Hydroxypregnenolone	0.2775
Docosanoic acid	0.2681
Dehydroascorbic acid	0.2671
1-Naphthol	0.2194
5α-Cholestan-3β-ol	0.2156