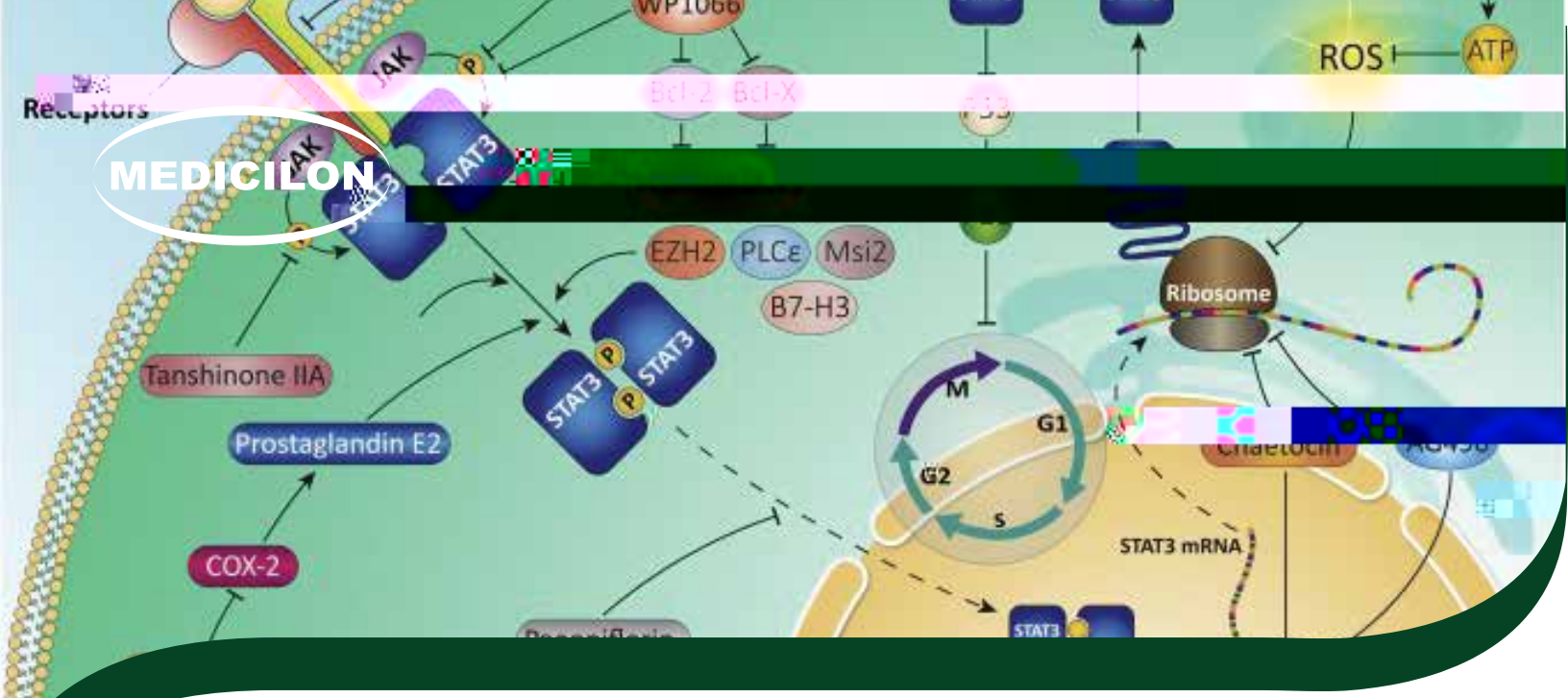


STAT3

STAT3

k

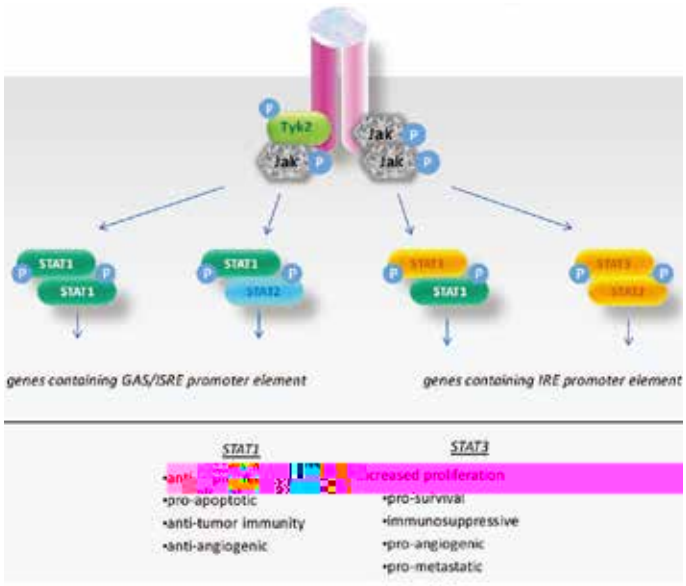
PÈæk[ko}oah] m¸STAT3

STAT3

STAT3

k

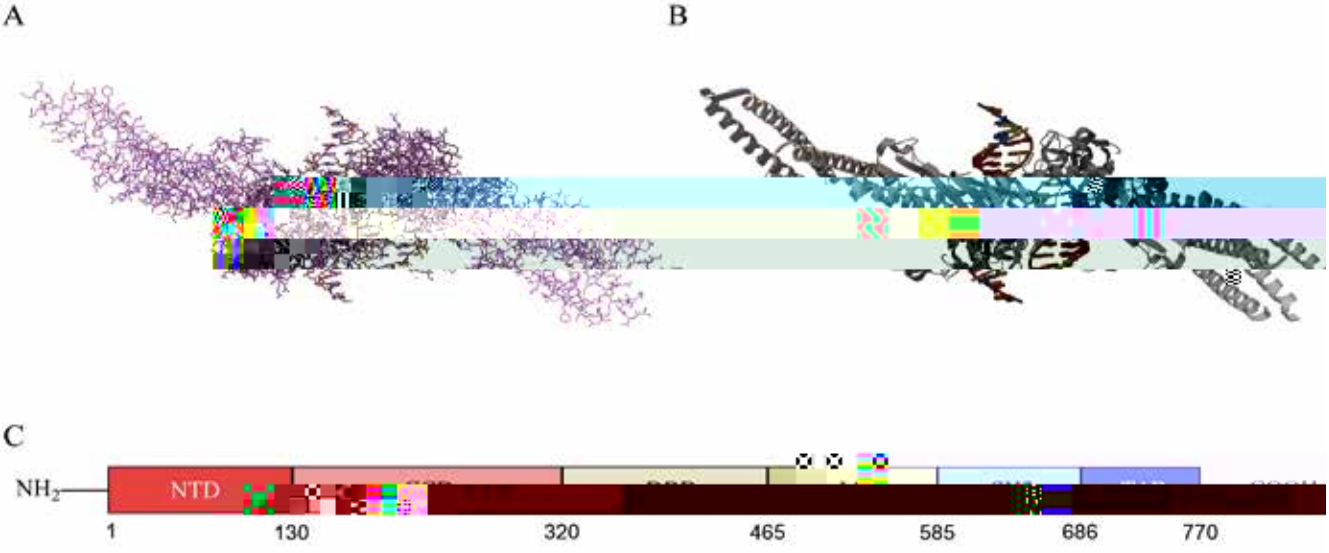
STAT3



STAT3

STAT STAT1 STAT2 STAT3 STAT4 STAT5A STAT5B STAT6 STAT3
STAT3α STAT3β STAT3α STAT3β C 55 STAT3β
STAT3α DNA STAT3 STAT3 17
770

- N (NTD) STAT
- (CCD) STAT3
- DNA (DBD) DNA
- (LD) DBD SH2 DNA
- SRC 2 (SH2) STAT STAT3
  STAT3
- (TAD)



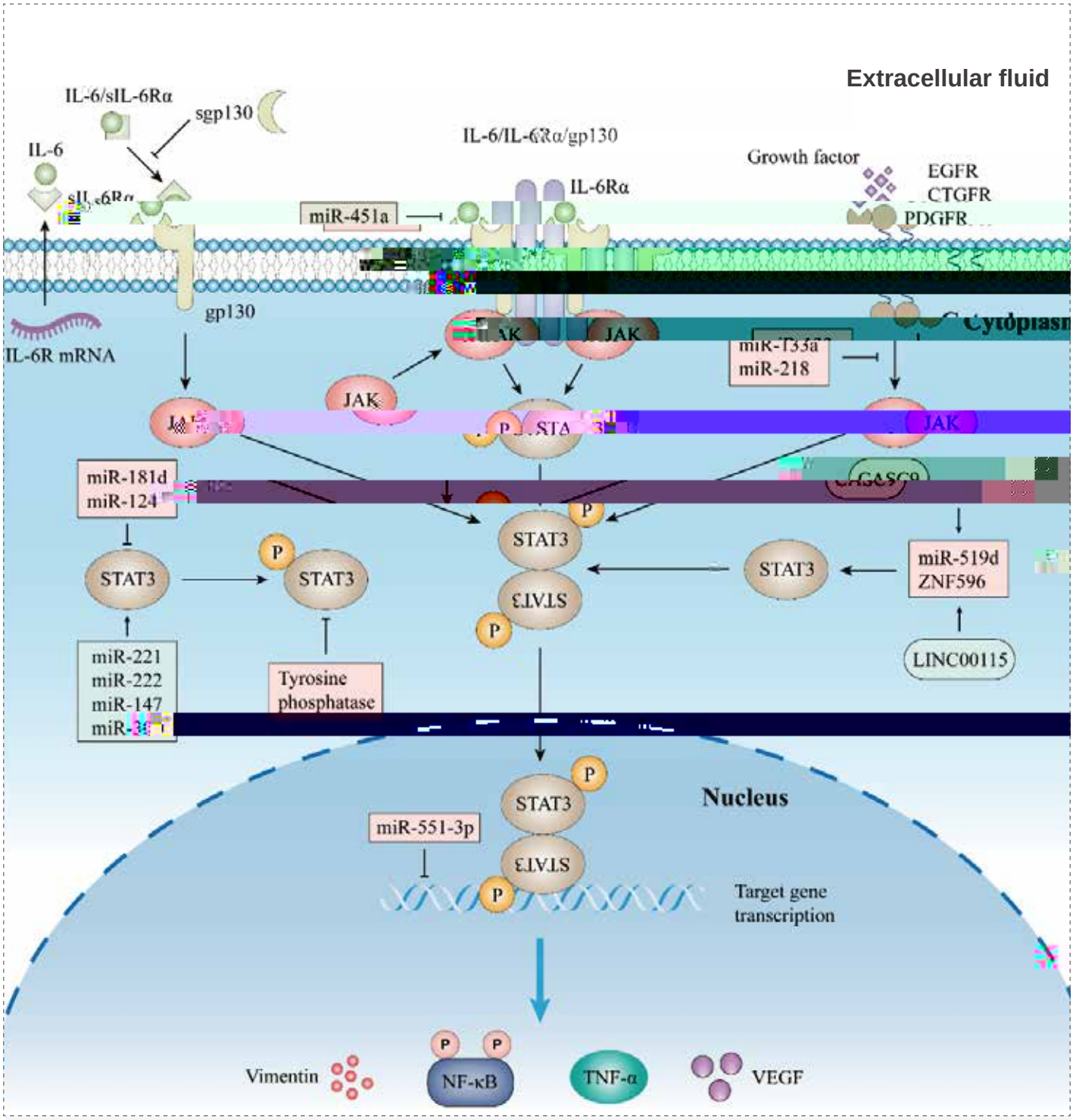
STAT3 [2]

STAT3

JAK/STAT
(IL) IL-6 TME IL-6
IL-6 TME
IL-6 IL-6 JAK/STAT3
IL-6/JAK/STAT3 JAK
JAK1 JAK2 JAK3 TYK2 JAK3 JAK

(JH1-7) JH1 JH2 SH2 FERM

IL-6 IL-6 IL-6 α (IL-6Rα) gp130 IL-6/IL-6R/gp130
JAK JAK gp130 gp130 STAT3 STAT3
JAK STAT3 705 STAT3
, ,



IL-6/JAK/STAT3 [2]

STAT3

STAT3-HDAC

k

k k

k k

histone deacetylase HDAC

! k HDAC HDACi

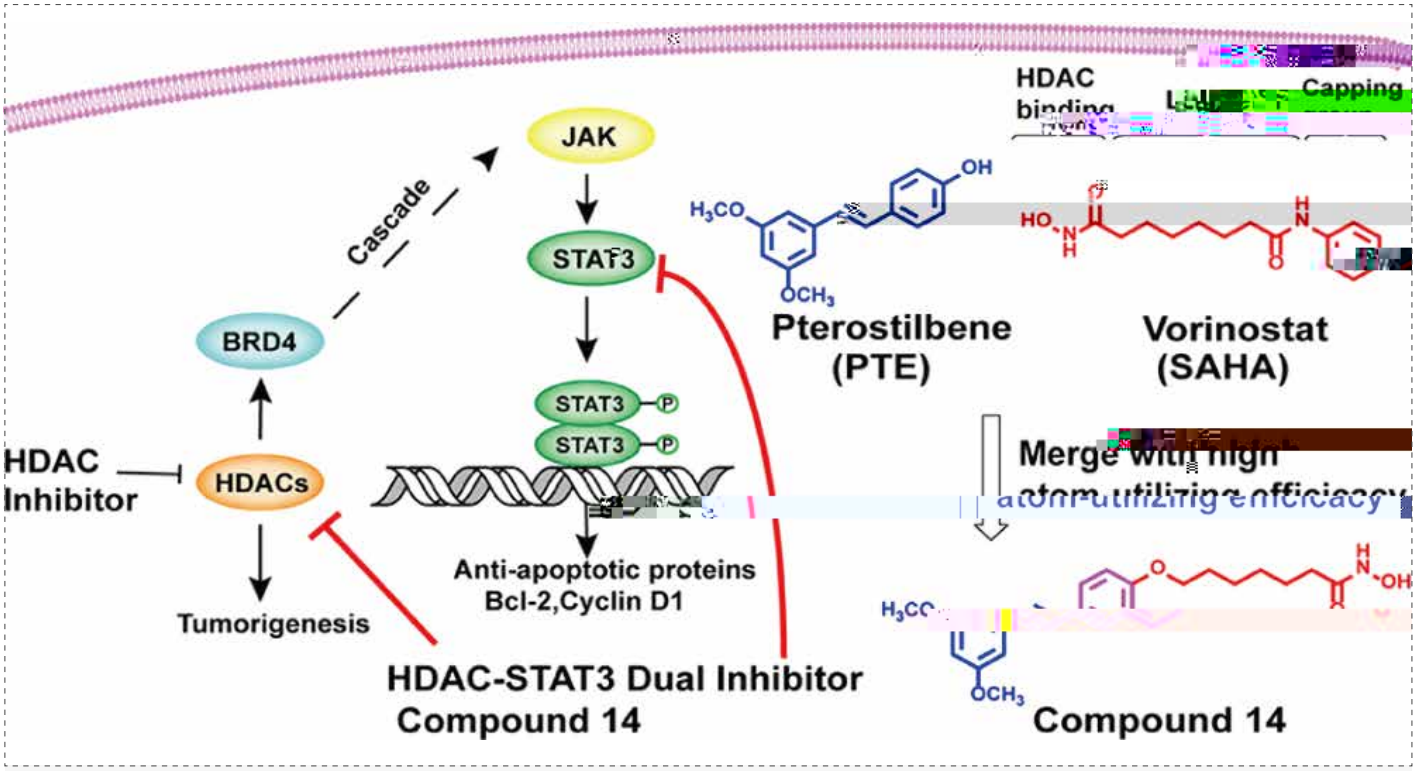
! k HDACi

k HDACi k

HDAC STAT3 HDAC

k HDACi STAT3-HDAC

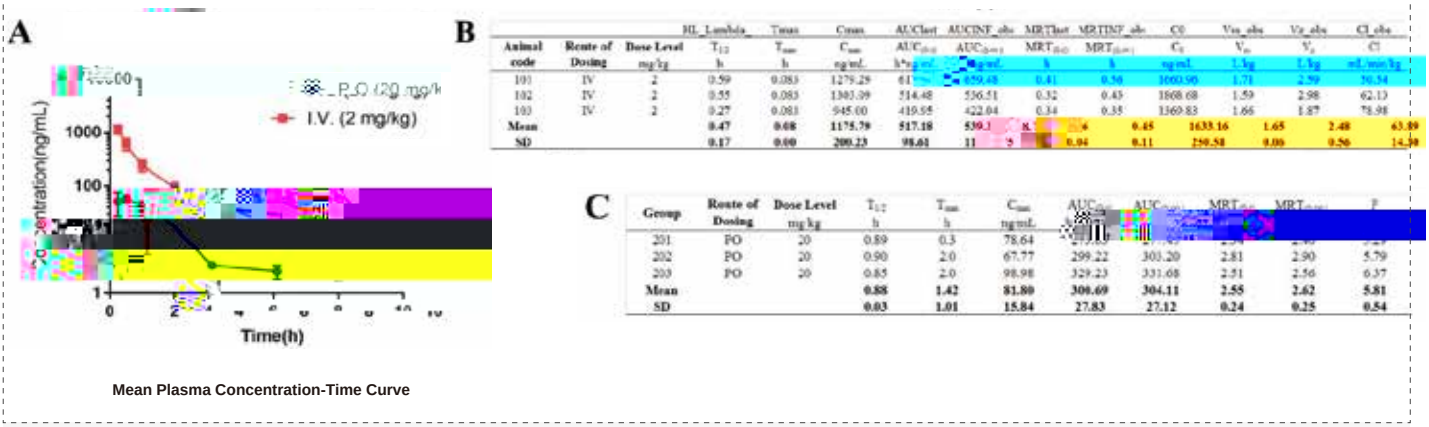
k BRD4-HDAC JAK1-HDAC S0 Td[37700B4AR-11 0056F5001 1 }TJ0.008 T



HDAC-BRD4-LIFR-JAK-STAT3 [3]

Compound 14 STAT3 K_D=33 nM HDAC IC_{50} 23.15 nM [k] Compound 14 MDA-MB-231 IC_{50}=0.78 μM HCT116 IC_{50}=1.07 μM [k]Compound 14 Compound 14 [k]Compound 14 15 mg/kg 54% 53% [k] 30 mg/kg 64% 62% [k] Compound 14 [k] Compound 14 [k]

Compound 14 SD (PK) [k] Compound 14 PK Compound 14 2 mg/kg V_{ss} 1.65 L/kg [k] (Cl) 63.89 mL/min/kg [k] $T_{1/2}$ 0.47h [k] Compound 14 20 mg/kg F 5.81% $T_{1/2}$ 0.88h [k]



Animal code	Route of Dosing	Dose Level mg/kg	$T_{1/2}$ h	T_{max} h	C_{max} ng/mL	AUC_{last} h*ng/mL	AUC_{INF_obs} h*ng/mL	MRT_{last} h	MRT_{INF_obs} h	C_0 ng/mL	V_{ss_obs} L/kg	V_{z_obs} L/kg	Cl_{obs} mL/min/kg
101	IV	2	0.59	0.083	1279.29	617	659.48	0.41	0.56	1660.96	1.71	2.59	50.54
102	IV	2	0.55	0.083	1303.09	514.48	536.51	0.32	0.43	1868.68	1.59	2.98	62.13
103	IV	2	0.27	0.083	945.00	419.55	422.04	0.34	0.35	1360.83	1.66	1.87	78.98
Mean			**0.47**	**0.08**	**1175.79**	**517.18**	**539.3**	**K**	**0.45**	**1633.16**	**1.65**	**2.48**	**63.89**
SD			**0.17**	**0.00**	**200.23**	**98.61**	**11**	**5**	**0.11**	**250.58**	**0.06**	**0.56**	**14.30**

Group	Route of Dosing	Dose Level mg/kg	$T_{1/2}$ h	T_{max} h	C_{max} ng/mL	AUC_{last}	AUC_{INF_obs}	MRT_{last}	MRT_{INF_obs}	F
201	PO	20	0.89	0.3	78.64					
202	PO	20	0.90	2.0	67.77	299.22	303.20	2.81	2.90	5.79
203	PO	20	0.85	2.0	98.98	329.23	331.68	2.51	2.56	6.37
Mean			**0.88**	**1.42**	**81.80**	**308.69**	**304.11**	**2.55**	**2.62**	**5.81**
SD			**0.03**	**1.01**	**15.84**	**27.83**	**27.12**	**0.24**	**0.25**	**0.54**

Pharmacokinetics of Compound 14 in SD rats[3]

YY201

2023 7 STAT3 ——YY201 NMPA
k STAT3 AI
STAT3 ! First-in-class “YY201” k
STAT3 STAT3 Tyr705 Ser727 STAT3
k YY201 STAT3 1-10 ! ! !
! 1-10 nM
YY201 k

STAT3 kSTAT3
k
STAT3 k k
STAT3 PROTAC kSTAT3-PROTAC
STAT3 STAT3 k STAT3

[1]Courtney Nicholas and Gregory B. Lesinski. The Jak-STAT Signal Transduction Pathway in Melanoma. Breakthroughs in Melanoma Research.

[2]Xin Li, et al. STAT3 Inhibitors: A Novel Insight for Anticancer Therapy of Pancreatic Cancer. Biomolecules. 2022 Oct 9;12(10):1450. doi: 10.3390/biom12101450.

[3]Yuhao Ren, et al. Discovery of STAT3 and Histone Deacetylase (HDAC) Dual-Pathway Inhibitors for the Treatment of Solid Cancer. J Med Chem. 2021 Jun 10;64(11):7468-7482. doi: 10.1021/acs.jmedchem.1c00136.

[4]Sailan Zou, et al. Targeting STAT3 in Cancer Immunotherapy. Mol Cancer. 2020 Sep 24;19(1):145.DOI: 10.1186/s12943-020-01258-7.