《Fmoc Solid-Phase Peptide Synthesis and Common Fmoc-Protected Amino Acids》

Introduction to Fmoc Solid-Phase Synthesis

Fmoc solid-phase synthesis was pioneered by Eric Atherton and Bob Sheppard at the University of Cambridge in the late 1970s (systematically refined by Chan and White). Its core methodology employs the Fmoc (9-fluorenylmethoxycarbonyl) group as the α-amino protecting group for amino acids. Peptide chains are stepwise assembled on an insoluble resin through gentle piperidine deprotection (avoiding acid-induced damage to the peptide chain) and activated carboxyl-group coupling. Key advantages include:

1. Mildness and Safety:

The Fmoc group exhibits strong resistance to acids (e.g., TFA), while side-chain protecting groups (such as Boc) require acid-mediated cleavage

Only a single TFA cleavage step is required to simultaneously release the peptide from the resin and remove side-chain protections, eliminating the side-reaction risks associated with repeated strong-acid treatments in Boc chemistry.

2. Efficiency and Control:

Byproducts are rapidly removed via stepwise washing;

The characteristic UV absorption of the Fmoc group enables real-time reaction monitoring.

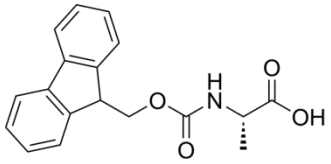
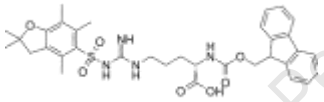
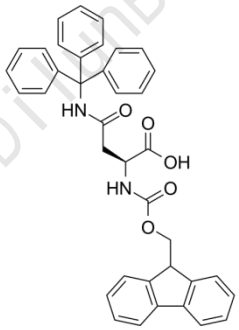
3. Versatile Application Compatibility:

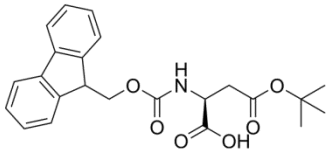
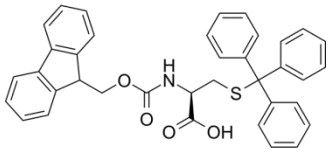
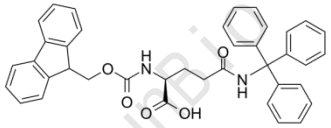
Compatible with acid-sensitive amino acids (e.g., tryptophan/methionine) and complex modified peptides.

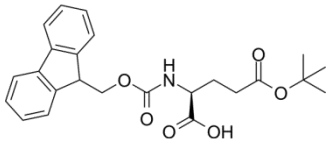
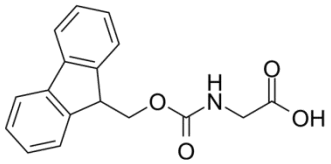
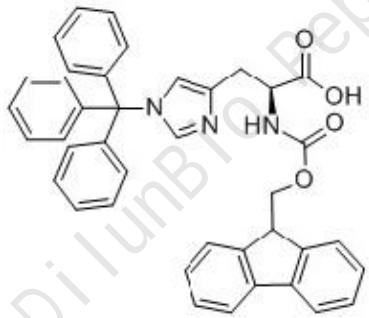
Serves as the foundational technology for automated peptide synthesizers (e.g., Dilunbio 386 Pro) and industrial peptide drug production, progressively replacing traditional Boc synthesis.

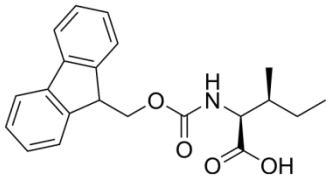
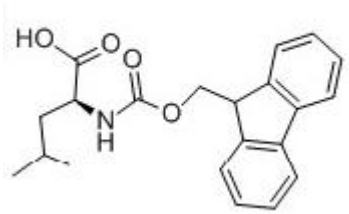
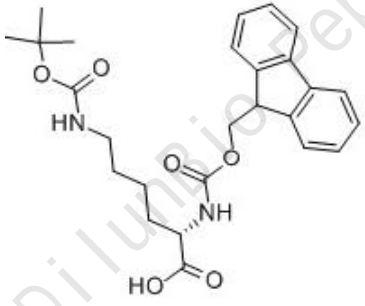
❖ **The following table compiles common Fmoc-amino acids used in solid-phase peptide synthesis.**

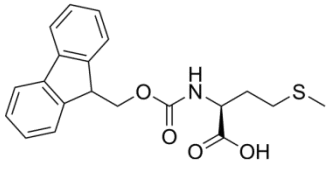
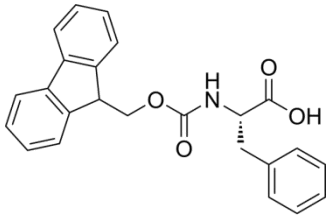
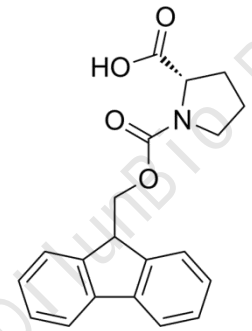
Common Fmoc-Protected Amino Acids for Solid-Phase Peptide Synthesis

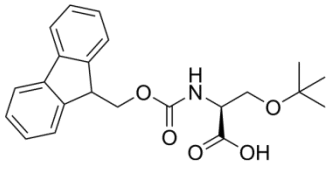
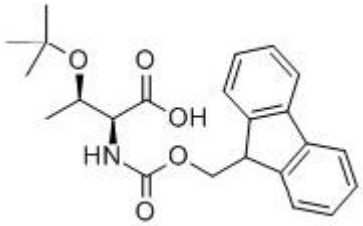
Code	Name	MW	Structural Formula	Molecular Formula	CAS	Properties
A	Fmoc-Ala-OH	311.33		$C_{18}H_{17}NO_4$	35661-39-3	Aliphatic hydrophobic amino acid with neutral charge
R	Fmoc-Arg(Pbf)-OH	648.77		$C_{34}H_{40}N_4O_7S$	154445-77-9	Basic polar amino acid with Pbf-protected guanidyl group blocking side reactions
N	Fmoc-Asn(Trt)-OH	596.67		$C_{38}H_{32}N_2O_5$	132388-59-1	Polar charge-neutral amino acid containing Trt-protected amide moiety resisting hydrolysis

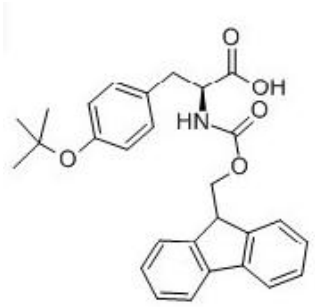
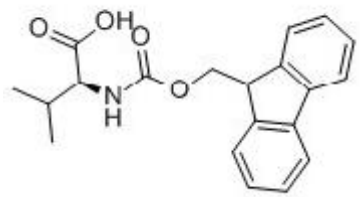
D	Fmoc-Asp(OtBu)-OH	411.45		$C_{23}H_{25}NO_6$	71989-14-5	Acidic polar amino acid with OtBu-protected β-carboxyl group suppressing unintended conjugation
C	Fmoc-Cys(Trt)-OH	585.71		$C_{37}H_{31}NO_4S$	103213-32-7	Sulfur-containing polar neutral amino acid with Trt-protected thiol group preventing oxidation
Q	Fmoc-Gln(Trt)-OH	610.70		$C_{39}H_{34}N_2O_5$	132327-80-1	Polar charge-neutral amino acid containing Trt-protected carboxamide group

E	Fmoc-Glu(OtBu)-OH	425.47		$C_{24}H_{27}NO_6$	71989-18-9	Acidic polar amino acid with OtBu-protected γ-carboxyl group
G	Fmoc-Gly-OH	297.31		$C_{17}H_{15}NO_4$	29022-11-5	Simplest aliphatic hydrophobic amino acid with neutral charge and non-chiral structure
H	Fmoc-His(Trt)-OH	619.71		$C_{40}H_{33}N_3O_4$	109425-51-6	Basic polar amino acid containing Trt-protected imidazolyl group

I	Fmoc-Ile-OH	353.41		$C_{21}H_{23}NO_4$	71989-23-6	Branched-chain aliphatic hydrophobic amino acid with neutral charge
L	Fmoc-Leu-OH	353.42		$C_{21}H_{23}NO_4$	35661-60-0	Branched-chain aliphatic hydrophobic amino acid with neutral charge
K	Fmoc-Lys(Boc)-OH	468.54		$C_{26}H_{32}N_2O_6$	71989-26-9	Basic polar amino acid with Boc-protected ε-amino group

M	Fmoc-Met-OH	371.45		$C_{20}H_{21}NO_4S$	71989-28-1	Thioether-containing hydrophobic amino acid, neutral charge with oxidizable methylthio moiety
F	Fmoc-Phe-OH	387.43		$C_{24}H_{21}NO_4$	35661-40-6	Aromatic hydrophobic amino acid with neutral charge containing phenyl ring
P	Fmoc-Pro-OH	337.37		$C_{20}H_{19}NO_4$	71989-31-6	Heterocyclic secondary amino acid with unique constrained-ring structure and hydrophobic character

S	Fmoc-Ser(tBu)-OH	383.44		$C_{22}H_{25}NO_5$	71989-33-8	Hydroxyl-containing polar residue, neutral charge/tBu-ether protected suppressing ether cleavage
T	Fmoc-Thr(tBu)-OH	397.46		$C_{23}H_{27}NO_5$	71989-35-0	Polar hydroxylic amino acid, neutral charge/tBu-protected
W	Fmoc-Trp(Boc)-OH	526.58		$C_{31}H_{30}N_2O_6$	143824-78-6	Indole-containing aromatic residue, polar neutral/Boc-protected pyrrole nitrogen

Y	Fmoc-Tyr(tBu)-OH	459.53		$C_{28}H_{29}NO_5$	71989-38-3	Phenolic hydroxyl-containing aromatic amino acid, polar neutral/tBu-ester protected preventing O-acylation
V	Fmoc-Val-OH	339.39		$C_{20}H_{21}NO_4$	68858-20-8	Branched-chain aliphatic hydrophobic amino acid with neutral charge