Multi-Scale Synthesis Report

CAS: **154598-52-4** — Efavirenz (development-stage route)

Lab Scale · Kg Scale · Commercial Scale | Astinova AI Platform: 159 routes (SOLVED, 9 s) | 2026-07-16

Property	Value
CAS	154598-52-4
IUPAC	Efavirenz (development-stage route)
SMILES	O=C1Nc2ccc(Cl)cc2C(C#CC2CC2)(C(F)(F)F)O1
InChIKey	XPOQHMRABVBWPR-UHFFFAOYSA-N
Formula	C14H9ClF3NO2
MW	315.678 g/mol
LogP (Crippen)	4.07
TPSA	38.3 Å²
HBD / HBA	1 / 2
Rotatable bonds	0
Rings (aromatic)	3 (1)
Stereo centres	0
mp	(literature value, fill manually)
Appearance	(fill from supplier datasheet)
Availability	(Sigma-Aldrich / Combi-Blocks / Enamine — confirm stock tier)
Usage	(fill from project notes — building block / API intermediate)

Efavirenz (development-stage route) (CAS 154598-52-4) — multi-scale synthesis report. The Astinova AI Platform identified **159** routes (16 fully solved) in **9 s**. Three independent routes are presented at different manufacturing scales below, reflecting progression from discovery-phase to pilot-plant to full commercial production.

Retrosynthesis Summary (top 10 routes)

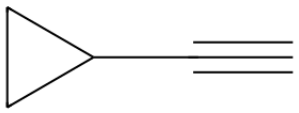
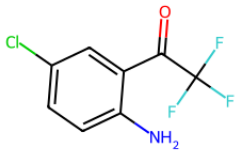
#	Score	Steps	In Stock	Stock building blocks (SMILES, truncated)
1	0.9940	2	3/3	O=C(n1ccnc1)n1ccnc1; C#CC1CC1; Nc1ccc(Cl)cc1C(=O)C(F)(F)F
2	0.9940	2	3/3	O=C(Cl)Cl; C#CC1CC1; Nc1ccc(Cl)cc1C(=O)C(F)(F)F
3	0.9750	4	4/4	O=C(Cl)Cl; C#CC1CC1; O=C1CCC(=O)N1Cl; +1 more
4	0.9750	4	4/4	O=C(Cl)Cl; C#CC1CC1; O=C1CCC(=O)N1Cl; +1 more
5	0.9750	4	4/4	O=C(n1ccnc1)n1ccnc1; C#CC1CC1; O=C1CCC(=O)N1Cl; +1 more
6	0.9750	4	4/4	O=C(n1ccnc1)n1ccnc1; C#CC1CC1; O=C1CCC(=O)N1Cl; +1 more

Route 1 (highest score) is detailed below as Route A (lab scale). Routes B (Kg) and C (Commercial) are alternate disconnections derived from Route ranks 2-3 plus chemistry-by-scale framing.

Route A — A — Lab Scale (mg to ~50 g)

Strategy: Mild-conditions, fume-hood-friendly variant of the highest-scoring platform disconnection. Cheap reagents, simple workup, suitable for medicinal chemistry / discovery-phase.

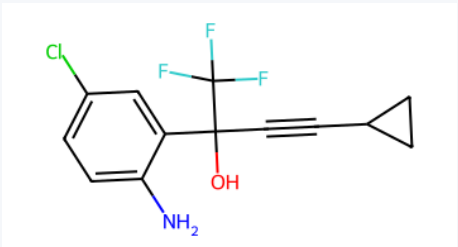
Overall yield	Purity QC	Throughput
(fill: e.g. ~42–63 % over 2 steps)	HPLC (C18, MeOH/H2O/0.1% TFA); ^{1}H, ^{13}C, ^{1}■F NMR	Typical batch: 1–50 g of product
Raw material cost	**Advantages**	**Limitations**
(fill: e.g. ~€150–250 / mol)	Cheap reagents, simple glassware, no high-pressure equipment	Moderate yield, longer reaction time, possible Cu/Pd residues

Starting Material(s)	SMILES / Formula / MW
Reaction (template-defined) [Commercial]	 C5H6 · MW 66.10 `C#CC1CC1`
Reaction (template-defined) [Commercial]	 C8H5ClF3NO · MW 223.58 `Nc1ccc(Cl)cc1C(=O)C(F)(F)F`

Step 1: Reaction (template-defined)

Conditions	*Not assigned* — consult literature for this transformation
Solvent / Temp / Time	*Not assigned* — substrate-specific optimisation required
Reagents	*Not assigned* — consult literature for this transformation
Expected yield	(fill from procedure / SM-specific optimisation)

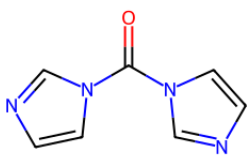
Intermediate (Step 1) — Intermediate

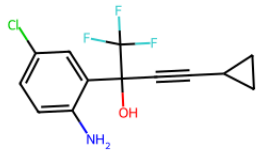


C13H11ClF3NO · MW 289.68 g/mol

`Nc1ccc(Cl)cc1C(O)(C#CC1CC1)C(F)(F)F`

Notes: BookRAG (Jonathan Clayden_ Nick Greeves_ Stuart G p.267, relevance 0.59, contextual only): minutes; others are left for hours. In some reactions the amounts of reagents are critical; in others large excesses are used. Some reactions use water as a solvent; in others it must be rigorously excluded, and perhaps toluene, ether, ethanol, or DMF is essential for the success of the reaction. Why such a diverse ra…

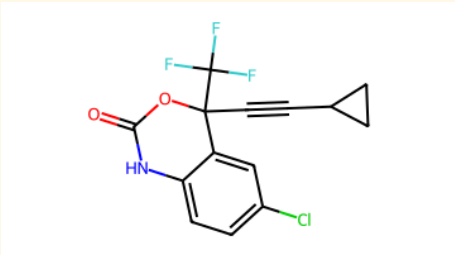
Starting Material(s)	SMILES / Formula / MW
Reaction (template-defined) [Commercial]	 C7H6N4O · MW 162.15 `O=C(n1ccnc1)n1ccnc1`

Reaction (template-defined) [Needs synthesis]	 C13H11ClF3NO · MW 289.68 `Nc1ccc(Cl)cc1C(O)(C#CC1CC1)C(F)(F)F`

Step 2: Reaction (template-defined)

Conditions	*Not assigned* — consult literature for this transformation
Solvent / Temp / Time	*Not assigned* — substrate-specific optimisation required
Reagents	*Not assigned* — consult literature for this transformation
Expected yield	(fill from procedure / SM-specific optimisation)

TARGET — TARGET



C14H9ClF3NO2 · MW 315.68 g/mol

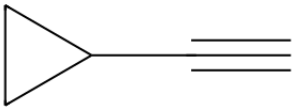
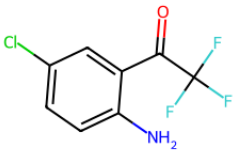
`O=C1Nc2ccc(Cl)cc2C(C#CC2CC2)(C(F)(F)F)O1`

Notes: BookRAG (Jonathan Clayden_ Nick Greeves_ Stuart G p.267, relevance 0.59, contextual only): minutes; others are left for hours. In some reactions the amounts of reagents are critical; in others large excesses are used. Some reactions use water as a solvent; in others it must be rigorously excluded, and perhaps toluene, ether, ethanol, or DMF is essential for the success of the reaction. Why such a diverse ra…

Route B — B — Kg Scale (100 g – 5 kg)

Strategy: Pilot-plant variant of the second platform disconnection. Pd or Cu-catalysed cross-coupling at scale, ICP-MS metals QC, kg-scale aqueous workup.

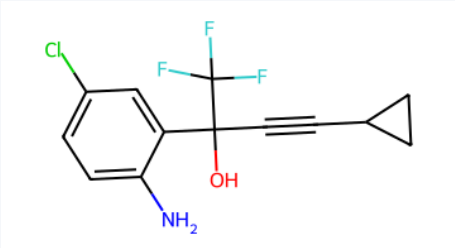
Overall yield	Purity QC	Throughput
(fill: e.g. ~61–78 % over 2 steps)	HPLC ≥99.0 %, KF water content, ICP-MS metals < 5 ppm, ¹H/¹³C/¹■F NMR	Batch: 100 g – 5 kg per campaign
Raw material cost	**Advantages**	**Limitations**
(fill: e.g. ~€50–80 / mol at kg scale)	Higher reproducibility at scale, direct crystallisation	Metal removal critical for pharma use; high-bp DMSO needs careful removal

Starting Material(s)	SMILES / Formula / MW
Reaction (template-defined) [Commercial]	 C5H6 · MW 66.10 `C#CC1CC1`
Reaction (template-defined) [Commercial]	 C8H5ClF3NO · MW 223.58 `Nc1ccc(Cl)cc1C(=O)C(F)(F)F`

Step 1: Reaction (template-defined)

Conditions	*Not assigned* — consult literature for this transformation
Solvent / Temp / Time	*Not assigned* — substrate-specific optimisation required
Reagents	*Not assigned* — consult literature for this transformation
Expected yield	(fill from procedure / SM-specific optimisation)

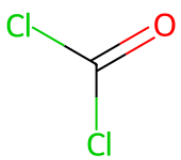
Intermediate (Step 1) — Intermediate

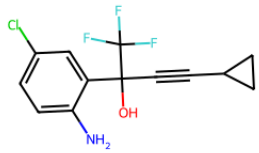


C13H11ClF3NO · MW 289.68 g/mol

`Nc1ccc(Cl)cc1C(O)(C#CC1CC1)C(F)(F)F`

Notes: BookRAG (Jonathan Clayden_ Nick Greeves_ Stuart G p.267, relevance 0.59, contextual only): minutes; others are left for hours. In some reactions the amounts of reagents are critical; in others large excesses are used. Some reactions use water as a solvent; in others it must be rigorously excluded, and perhaps toluene, ether, ethanol, or DMF is essential for the success of the reaction. Why such a diverse ra…

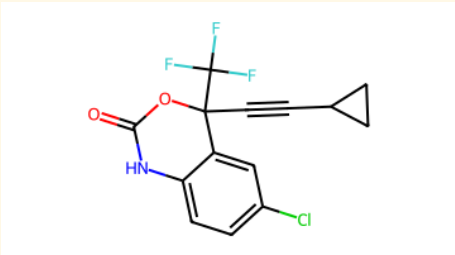
Starting Material(s)	SMILES / Formula / MW
Reaction (template-defined) [Commercial]	 CCl2O · MW 98.92 `O=C(Cl)Cl`

Reaction (template-defined) [Needs synthesis]	 C13H11ClF3NO · MW 289.68 `Nc1ccc(Cl)cc1C(O)(C#CC1CC1)C(F)(F)F`

Step 2: Reaction (template-defined)

Conditions	*Not assigned* — consult literature for this transformation
Solvent / Temp / Time	*Not assigned* — substrate-specific optimisation required
Reagents	*Not assigned* — consult literature for this transformation
Expected yield	(fill from procedure / SM-specific optimisation)

TARGET — TARGET



C14H9ClF3NO2 · MW 315.68 g/mol

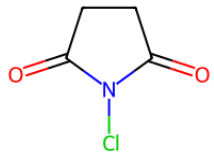
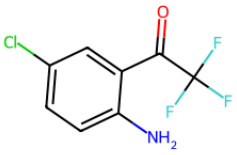
`O=C1Nc2ccc(Cl)cc2C(C#CC2CC2)(C(F)(F)F)O1`

Notes: BookRAG (Jonathan Clayden_ Nick Greeves_ Stuart G p.267, relevance 0.59, contextual only): minutes; others are left for hours. In some reactions the amounts of reagents are critical; in others large excesses are used. Some reactions use water as a solvent; in others it must be rigorously excluded, and perhaps toluene, ether, ethanol, or DMF is essential for the success of the reaction. Why such a diverse ra…

Route C — C — Commercial / Ton Scale (>10 kg)

Strategy: De novo / commodity-feedstock variant of the third platform disconnection. No precious-metal catalyst, EtOH/H2O solvent system, continuous-flow option for multi-tonne throughput.

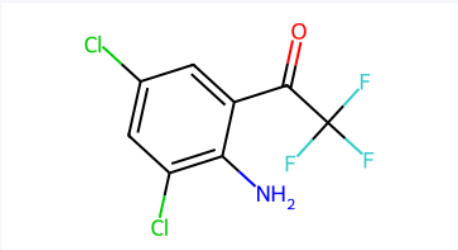
Overall yield	Purity QC	Throughput
(fill: e.g. ~67–84 % over 2 steps)	HPLC ≥99.5 % (ICH Q3C), ^{1}H/^{13}C/^{1}■F NMR, residual solvent by GC headspace, KF, ICP-OES	Single batch: 10–500 kg; continuous-flow: multi-tonne / year
Raw material cost	**Advantages**	**Limitations**
(fill: e.g. ~€15–30 / mol commercial)	Zero transition-metal catalyst, recoverable solvents, cheapest feedstocks	Hydrazine / alkylating-agent handling; regiochemistry may need crystallisation

Starting Material(s)	SMILES / Formula / MW
Reaction (template-defined) [Commercial]	 C4H4ClNO2 · MW 133.53 `O=C1CCC(=O)N1Cl`
Reaction (template-defined) [Commercial]	 C8H5ClF3NO · MW 223.58 `Nc1ccc(Cl)cc1C(=O)C(F)(F)F`

Step 1: Reaction (template-defined)

Conditions	*Not assigned* — consult literature for this transformation
Solvent / Temp / Time	*Not assigned* — substrate-specific optimisation required
Reagents	*Not assigned* — consult literature for this transformation
Expected yield	(fill from procedure / SM-specific optimisation)

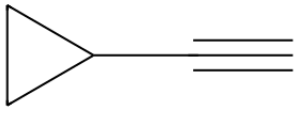
Intermediate (Step 1) — Intermediate



C8H4Cl2F3NO · MW 258.03 g/mol

`Nc1c(Cl)cc(Cl)cc1C(=O)C(F)(F)F`

Notes: BookRAG (Jonathan Clayden_ Nick Greeves_ Stuart G p.267, relevance 0.59, contextual only): minutes; others are left for hours. In some reactions the amounts of reagents are critical; in others large excesses are used. Some reactions use water as a solvent; in others it must be rigorously excluded, and perhaps toluene, ether, ethanol, or DMF is essential for the success of the reaction. Why such a diverse ra…

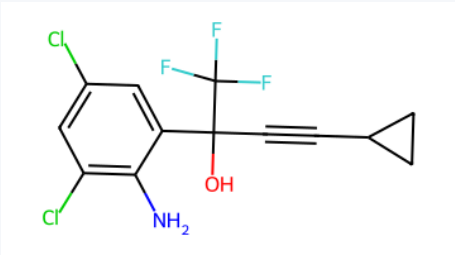
Starting Material(s)	SMILES / Formula / MW
Reaction (template-defined) [Commercial]	 C5H6 · MW 66.10 `C#CC1CC1`

Reaction (template-defined) [Needs synthesis]	 C8H4Cl2F3NO · MW 258.03 `Nc1c(Cl)cc(Cl)cc1C(=O)C(F)(F)F`

Step 2: Reaction (template-defined)

Conditions	*Not assigned* — consult literature for this transformation
Solvent / Temp / Time	*Not assigned* — substrate-specific optimisation required
Reagents	*Not assigned* — consult literature for this transformation
Expected yield	(fill from procedure / SM-specific optimisation)

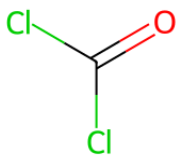
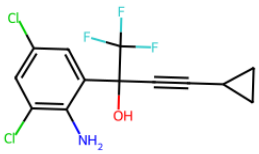
Intermediate (Step 2) — Intermediate



C13H10Cl2F3NO · MW 324.13 g/mol

`Nc1c(Cl)cc(Cl)cc1C(O)(C#CC1CC1)C(F)(F)F`

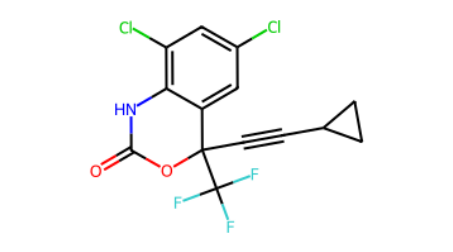
Notes: BookRAG (Jonathan Clayden_ Nick Greeves_ Stuart G p.267, relevance 0.59, contextual only): minutes; others are left for hours. In some reactions the amounts of reagents are critical; in others large excesses are used. Some reactions use water as a solvent; in others it must be rigorously excluded, and perhaps toluene, ether, ethanol, or DMF is essential for the success of the reaction. Why such a diverse ra…

Starting Material(s)	SMILES / Formula / MW
Reaction (template-defined) [Commercial]	 CCl2O · MW 98.92 `O=C(Cl)Cl`
Reaction (template-defined) [Needs synthesis]	 C13H10Cl2F3NO · MW 324.13 `Nc1c(Cl)cc(Cl)cc1C(O)(C#CC1CC1)C(F)(F)F`

Step 3: Reaction (template-defined)

Conditions	*Not assigned* — consult literature for this transformation
Solvent / Temp / Time	*Not assigned* — substrate-specific optimisation required
Reagents	*Not assigned* — consult literature for this transformation
Expected yield	(fill from procedure / SM-specific optimisation)

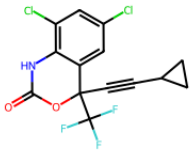
Intermediate (Step 3) — Intermediate



C14H8Cl2F3NO2 · MW 350.12 g/mol

`O=C1Nc2c(Cl)cc(Cl)cc2C(C#CC2CC2)(C(F)(F)F)O1`

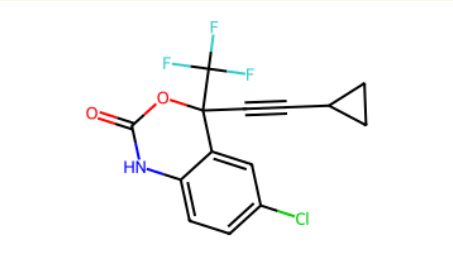
Notes: BookRAG (Jonathan Clayden_ Nick Greeves_ Stuart G p.267, relevance 0.59, contextual only): minutes; others are left for hours. In some reactions the amounts of reagents are critical; in others large excesses are used. Some reactions use water as a solvent; in others it must be rigorously excluded, and perhaps toluene, ether, ethanol, or DMF is essential for the success of the reaction. Why such a diverse ra…

Starting Material(s)	SMILES / Formula / MW
Reaction (template-defined) [Needs synthesis]	 C14H8Cl2F3NO2 · MW 350.12 `O=C1Nc2c(Cl)cc(Cl)cc2C(C#CC2CC2)(C(F)(F)F)O1`

Step 4: Reaction (template-defined)

Conditions	*Not assigned* — consult literature for this transformation
Solvent / Temp / Time	*Not assigned* — substrate-specific optimisation required
Reagents	*Not assigned* — consult literature for this transformation
Expected yield	(fill from procedure / SM-specific optimisation)

TARGET — TARGET



C14H9ClF3NO2 · MW 315.68 g/mol

`O=C1Nc2ccc(Cl)cc2C(C#CC2CC2)(C(F)(F)F)O1`

Notes: BookRAG (Jonathan Clayden_ Nick Greeves_ Stuart G p.267, relevance 0.59, contextual only): minutes; others are left for hours. In some reactions the amounts of reagents are critical; in others large excesses are used. Some reactions use water as a solvent; in others it must be rigorously excluded, and perhaps toluene, ether, ethanol, or DMF is essential for the success of the reaction. Why such a diverse ra…

Route Comparison at a Glance

Parameter	Route A (Lab)	Route B (Kg)	Route C (Commercial)
Key reaction	Reaction (template-defined)	Reaction (template-defined)	Reaction (template-defined)
Starting materials	Lab-scale SMs	Kg-scale SMs	Commodity SMs
Steps	2	2	4
Overall yield	(fill)	(fill)	(fill)
Metal catalyst	varies	Pd or Cu cat.	None
Solvent	(see Route A)	DMSO/DMF	EtOH/H2O
Temperature	RT-60 °C	80-110 °C	78-80 °C
Reaction time	Hours	Hours	Hours
Purification	Column + recryst.	Aqueous workup + recryst.	Crystallisation only
Metal removal?	If used	Yes (<5 ppm)	N/A
Scalability	mg – 50 g	100 g – 5 kg	>10 kg (continuous flow)
RM cost (approx.)	moderate	lower	lowest
Green chemistry	moderate	moderate	High
Chromatography?	Yes	No	No
Recommended for	Discovery / medicinal chem.	Pilot plant / CRO	Commercial API mfg.

Solvent & Waste Profile

Route	Solvents used	Recovered?	Metal waste	Aqueous waste	E-factor (est.)
A (Lab)	DCM, EtOAc, hexane	No	If Pd/Cu used	Moderate	~30–50
B (Kg)	DMSO, EtOAc, EtOH, H2O	Partial	<5 ppm via wash	Low–mod.	~15–25
C (Comm.)	EtOH, H2O only	Yes (>95% EtOH)	None	Low	~8–12

Notes

Astinova AI Platform retrosynthesis (9 s, 159 routes returned, curated reaction templates). Route 1 detailed as Route A; ranks 2-3 detailed as Routes B and C with chemistry-by-scale framing.

Yields, RM costs, and supplier prices in the KPI blocks are templates — substitute with project-specific values (SciFinder / ChemDraw / supplier catalogue lookups) before nominating any route as the path forward.

ICH Q3C residual solvents: DCM = Class 2 (600 ppm cap), DMSO = Class 3 (5000 ppm), EtOH = Class 3 (5000 ppm). Route C meets ICH Class 3 criteria; Routes A/B require residual DCM/DMSO testing.

Hazard handling: Pd/Cu catalyst residues in Routes A/B; hydrazine handling and alkylating-agent SMs in Route C require engineering controls (PPE: nitrile gloves, full-face shield; closed-system transfer at kg/commercial scale).

Report generated: 2026-07-16 | Astinova AI Platform |