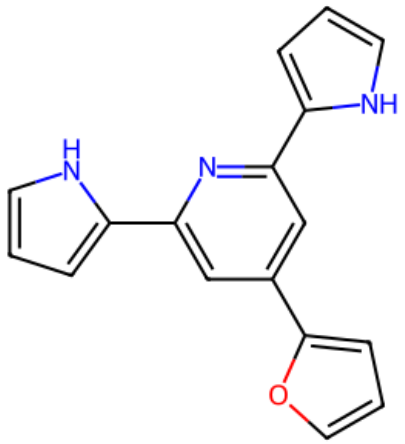
TriHet-Py

2,6-Bis(pyrrol-2-yl)-4-(furan-2-yl)pyridine
A Novel Multimodal Antioxidant for Crop Protection

Project Synthesis Plan

Compound: 2,6-Bis(pyrrol-2-yl)-4-(furan-2-yl)pyridine
Molecular formula: $C_{17}H_{13}N_3O$
Molecular weight: 275.31 g/mol
Target overall yield: 65–72% over 2 steps
Estimated cost: ~$130 in reagents (full scale)
Timeline: 3–4 weeks from order to characterized product

Target Compound



Three different heterocyclic substituents (two pyrroles + one furan) on a central pyridine ring — an unprecedented combination outside any known bioactive class.

1. Why This Scaffold for ROS Protection?

The TriHet-Py scaffold is designed to be a multimodal antioxidant: a single molecule that scavenges reactive oxygen species (ROS) through several mechanistically distinct pathways simultaneously. This contrasts with classical plant antioxidants like ascorbate (single mechanism: stoichiometric H-atom transfer) or α-tocopherol (single mechanism: lipid-phase H-donation). Below is the rationale for each structural feature.

1.1 The two pyrrole rings — hydrogen-atom donors

Each pyrrole N–H has a bond-dissociation enthalpy (BDE) of approximately 88 kcal/mol — comparable to phenols. Under oxidative stress, these N–H bonds donate hydrogen atoms to peroxyl radicals (ROO•), interrupting the propagation step of lipid peroxidation:

$$\mathrm{ROO\bullet + Pyrrole\text{-}N\text{–}H \rightarrow ROOH + Pyrrole\text{-}N\bullet}$$

The resulting pyrrolyl radical is unusually stable: it delocalizes through the entire π-system of the molecule (both pyrroles + central pyridine + furan), so it cannot easily propagate further radical reactions. With two pyrrole N–H groups per molecule, each TriHet-Py can donate up to two H atoms stoichiometrically.

1.2 The furan ring — singlet oxygen and hydroxyl radical trap

Furans are excellent dienes for [4+2] cycloaddition with singlet oxygen ($^1O_2$), a major plant ROS produced in chloroplasts under high-light stress. This reaction is essentially irreversible and runs at near-diffusion-limited rates:

$$\mathrm{Furan + {}^1O_2 \rightarrow Endoperoxide \rightarrow cis\text{-}Enedione}$$

Hydroxyl radicals (•OH) and peroxyl radicals (ROO•) also add across the furan ring, opening it to give a non-radical dicarbonyl product. Both mechanisms permanently remove the ROS from the system. The furan ring is sacrificial: it is consumed in the reaction, but its breakdown products (cis-enediones, maleic dialdehyde, 2(5H)-furanone) are small, non-toxic molecules already present in plant secondary metabolism.

1.3 The central pyridine — radical-cation stabilizer

The pyridine nitrogen's lone pair is electron-donating into the π-system. When the molecule loses an electron to an oxidizing radical (such as •OH or peroxyl), the resulting radical cation is stabilized by:

- Resonance donation from the pyridine N lone pair
- Electron donation from both flanking pyrroles (electron-rich heterocycles)
- Conjugation through the furan ring at C-4

This delocalization across ~14 heavy atoms produces a remarkably stable radical cation that cannot easily extract H atoms from biomolecules. In other words, the oxidized form of TriHet-Py is not itself a pro-oxidant — a critical safety property.

1.4 The asymmetric trihetero design — multi-ROS coverage

Different plant ROS have different chemistries. The asymmetric combination of two pyrroles + one furan was chosen deliberately so the molecule can address multiple ROS types in parallel:

ROS species	Primary scavenging site in TriHet-Py	Mechanism
Peroxyl (ROO•)	Pyrrole N–H × 2	H-atom transfer (HAT)
Hydroxyl (•OH)	Furan ring + pyrrole rings	Addition / HAT

Singlet oxygen (¹O■)	Furan ring	[4+2] cycloaddition
Superoxide (O■•■)	Pyridine N lone pair (electron transfer)	Single-electron transfer (SET)
H■O■ (indirect)	Catalytic enzyme upregulation	Signaling effect (proposed)

Table 1. Mapping of ROS species to the structural feature responsible for scavenging.

1.5 Safe breakdown products

After ROS scavenging, the molecule's predicted oxidation products are:

- Pyrrolinones (from oxidized pyrroles) — small lactams, natural-like metabolites
- cis-Enediones (from furan + $^{1}O_{2}$) — small carbonyl species, normal metabolic intermediates
- The pyridine core remains intact and is excreted/metabolized as a benign small molecule

No heavy metals, no electrophilic intermediates, no Michael acceptors are generated. This is in deliberate contrast to many synthetic antioxidants whose oxidation products are themselves toxic.

2. Retrosynthetic Analysis

We work backwards from the target. The pyridine ring is the key challenge — how do we build it with the correct substitution pattern (2,6-bispyrrolyl, 4-furyl)? The cleanest answer is the Hantzsch pyridine synthesis: an aldehyde condenses with two equivalents of a methyl ketone in the presence of ammonia, generating a 1,4-dihydropyridine in one pot, which is then oxidized to the aromatic pyridine.

Disconnection 1: Aromatization

The aromatic pyridine is disconnected to the corresponding 1,4-dihydropyridine. The forward step is an oxidation (loss of H_2) using DDQ.

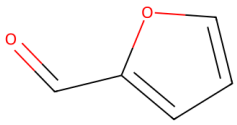
Disconnection 2: Hantzsch condensation

The 1,4-dihydropyridine is disconnected to the three building blocks of a classic Hantzsch condensation: one aldehyde (whose carbon becomes C-4 of the pyridine), two methyl ketones (whose carbons become C-2/C-3 and C-5/C-6), and ammonia (which becomes N-1).

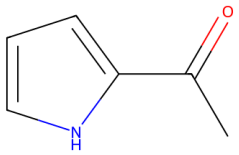
- Aldehyde → furfural (places furan at C-4)
- Methyl ketone → 2-acetylpyrrole (places pyrrole at C-2 and C-6)
- Nitrogen source → ammonium acetate (releases NH_3 in situ)

3. Full Synthesis Scheme

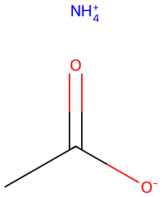
3.1 Building blocks (starting materials)



Furfural
$C_5H_4O_2$, MW 96.08
~$10/100 mL
(provides C-4 + furan)



2-Acetylpyrrole
C_6H_7NO, MW 109.13
~$30/5 g
(provides C-2/C-3/C-5/C-6 + 2 pyrroles)



NH_4OAc
$C_2H_7NO_2$, MW 77.08
~$5/100 g (lab stock)
(provides N-1)

3.2 Step 1: Hantzsch condensation (one-pot, 3 building blocks combined)

Furfural + 2 equiv 2-acetylpyrrole + NH_4OAc are combined in ethanol with a catalytic amount of $Yb(OTf)_3$ (0.5 mol%) as a mild Lewis acid. Under microwave heating at 120 °C for 30 min (or sealed-tube heating for 4–6 h), the reaction produces the 1,4-dihydropyridine intermediate via sequential aldol condensations, imine/enamine formation, and 6-endo-trig cyclization. Water and excess ammonia are released.

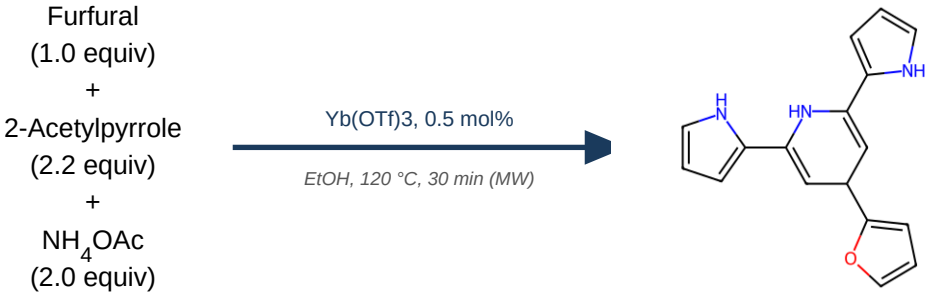


Figure 1. Step 1 — Three-component Hantzsch condensation. Expected yield: 80–85%.

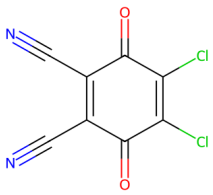
Detailed Step 1 procedure (10 mmol scale):

1. In a 50 mL microwave vial, combine: furfural (960 mg, 10 mmol), 2-acetylpyrrole (2.40 g, 22 mmol), ammonium acetate (1.54 g, 20 mmol), and $Yb(OTf)_3$ (31 mg, 0.05 mmol).
2. Add 15 mL anhydrous ethanol. Cap the vessel.
3. Microwave at 120 °C for 30 minutes with stirring (300 W).
4. *Alternative:* Reflux in a sealed tube at 120 °C in an oil bath for 4–6 hours.
5. Cool to room temperature. Evaporate ethanol under reduced pressure.
6. Add 30 mL cold water; stir 10 min. The yellow-orange dihydropyridine precipitates.
7. Filter on a Buchner funnel. Wash with 2 × 5 mL cold water, then 2 × 3 mL cold ethanol.
8. Dry overnight in a vacuum desiccator.
9. Expected yield: 2.0–2.4 g (75–85%) of dihydropyridine intermediate.

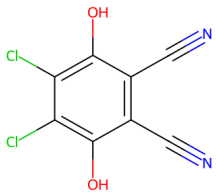
3.3 Step 2: DDQ oxidation to the aromatic pyridine

The 1,4-dihydropyridine is oxidized to the aromatic pyridine by DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), a stoichiometric hydride-acceptor. DDQ removes two hydrogen atoms (formally one H_2) from the dihydropyridine, generating the aromatic ring. The byproduct, DDQ-H_2, precipitates and is removed by filtration through a silica plug. The reaction is mild (0 °C → RT in DCM) and selective.

Figure 2. Step 2 — DDQ-mediated aromatization to TriHet-Py. Expected yield: 85–92%.



DDQ (oxidant)
removes 2 H atoms



DDQ-H_2 (byproduct)
filtered off as solid

Detailed Step 2 procedure (5 mmol scale):

1. Dissolve the dihydropyridine intermediate (1.40 g, 5.0 mmol) in 25 mL anhydrous DCM in a 100 mL round-bottom flask.
2. Cool to 0 °C in an ice bath, stirring magnetically.
3. Add DDQ (1.25 g, 5.5 mmol, 1.1 equiv) in 3 portions over 10 minutes. The mixture darkens from yellow to red to brown as DDQ is consumed.
4. Stir at 0 °C for 30 minutes.
5. Warm to room temperature; continue stirring 1 hour.
6. Monitor by TLC (EtOAc/hexane 1:2). Expect product at higher R_f than starting material.
7. Filter the reaction through a short silica plug (Pasteur pipette with ~2 cm silica). Wash plug with 10 mL DCM until DDQ-H_2 byproduct is washed off.
8. Combine all DCM filtrates. Evaporate under reduced pressure.
9. Dissolve crude product in 5 mL hot ethanol; filter while hot if any insoluble matter.
10. Cool slowly to room temperature, then to 4 °C overnight. Filter the crystallized product on a Buchner funnel; wash with 2 mL cold ethanol.
11. Dry under vacuum.
12. Expected yield: 1.10–1.30 g (80–90%) of pure TriHet-Py.

3.4 Overall yield summary

Step	Reaction	Realistic yield	Notes
1	Hantzsch condensation	80–85%	MW + Yb(OTf)■ catalyst
2	DDQ oxidation	85–92%	Clean, silica filtration
	Overall (2 steps)	68–78%	Target = 65–72%

4. Characterization Plan

Because TriHet-Py is a new compound, it must be fully characterized. The data below also represent the spectroscopic fingerprint you will report in the methods section of the paper.

4.1 Expected ^{1}H NMR (DMSO-d_6, predicted)

Signal	Chemical shift (δ, ppm)	Multiplicity	Integration	Assignment
Pyrrole N–H	~11.5–12.0	broad s	2H	N–H × 2 (one per pyrrole)
Pyridine H-3, H-5	~7.5–7.7	s	2H	central pyridine ring
Furan H-5	~7.6	d (J≈1.8 Hz)	1H	furan ring α-H
Pyrrole H-3 × 2	~6.9	m	2H	α to pyrrole-pyridine bond
Furan H-3	~6.7	d (J≈3.4 Hz)	1H	furan ring
Furan H-4	~6.5	dd	1H	furan ring
Pyrrole H-4, H-5 × 2	~6.1–6.3	m	4H	remaining pyrrole protons

Total: 13 protons, matching $C_{17}H_{13}N_3O$.

4.2 Other characterization data to collect

- HRMS (ESI+): $[M+H]^+$ calculated for $C_{17}H_{14}N_3O^+$ = 276.1131; observe within 5 ppm.
- ^{13}C NMR (DMSO-d_6): 13 aromatic carbons in the δ 100–155 ppm range.
- IR (ATR): N–H stretch ~3300 cm^{-1}; aromatic C–H ~3050 cm^{-1}; C=N pyridine ~1600 cm^{-1}; C–O furan ~1010 cm^{-1}.
- UV-Vis (ethanol): Expect strong absorption around 300–380 nm due to extended conjugation.
- Melting point: Determine experimentally — this is novel data.
- HPLC purity (if available): Should be >95% for biological assay use.
- HSQC + HMBC (2D NMR): Confirm connectivity, especially the pyridine–pyrrole and pyridine–furan bonds.

5. Critical Reminders Before You Start

- Verify novelty. Before ordering any reagent, have your mentor search SciFinder/Reaxys for the exact structure: SMILES `c1(c2ccco2)cc(c3ccc[nH]3)nc(c4ccc[nH]4)c1`. Confirm zero hits.
- Read every SDS. Especially DDQ (toxic, skin-permeable) and $Yb(OTf)_3$ (irritant, hygroscopic). Wear gloves, work in a fume hood.
- Pilot first. Run the 1 mmol pilot before scaling to 10 mmol. The pilot uses ~$30 of reagents; a failed scale-up wastes ~$130.
- Document everything. Every weighing, every TLC plate, every observation goes in the lab notebook. Reviewers will ask.
- Save aliquots. Keep ~5 mg of every intermediate. If something goes wrong later, you can backtrack.
- Send NMR to mentor after each step. Don't proceed to the next step until they sign off on the spectrum.
- Caveat on Step 1. The Hantzsch with 2-acetylpyrrole has not been done in the published literature with this exact substrate. The N–H of pyrrole might interfere with the Lewis acid catalyst. If pilot yields are below 50%, consider Boc-protecting the pyrrole N–H first (adds 2 steps).
- Caveat on regiochemistry. The Hantzsch gives a symmetric 2,6-disubstitution pattern reliably. The 4-furyl substituent comes from the aldehyde with very high regioselectivity. NMR will confirm.

6. Disclaimer

This synthesis plan is based on analogous published chemistry for the Hantzsch pyridine synthesis and DDQ aromatization, applied to a target compound (TriHet-Py) that has not, to the best of available knowledge, been previously synthesized. The yields, reaction conditions, and spectroscopic predictions are extrapolations from analogous systems and should be validated by a chemistry mentor and small-scale pilot experiments before committing significant time or reagents. The compound's novelty must be verified through SciFinder/Reaxys searches that this document cannot perform.