

4H-Pyran-4-One (γ -Pyrone): Structure, Electronic Character, Spectrochemical Signature, and Pharmaceutical Relevance of a Privileged Heterocyclic Scaffold

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ABSTRACT

4H-Pyran-4-one (γ -pyrone, CAS 108-97-4) is the parent six-membered oxygen heterocycle underlying the Pyranone (4-pyrone) family, a scaffold that recurs throughout natural-product and drug-like chemistry - from simple metal chelators such as maltol and kojic acid to complex chromone- and flavone-based pharmacophores. This dissertation consolidates four literature-based reference reports into a single account of the molecule's identity, bonding and hybridization, aromaticity, spectrochemical fingerprint (UV-vis, FT-IR, ¹H/¹³C NMR, EI-MS), physicochemical behaviour, chemical reactivity, and pharmaceutical relevance, with emphasis on its use as a validated core scaffold in molecular docking studies (ScienceDirect Topics, n.d.; MacDonald *et al.*, 1981; Wikipedia contributors, 2024). The synthesis presented here shows that although the ring is fully planar and conjugated, with every heavy atom sp²-hybridized, structural and magnetic-susceptibility evidence favours a cross-conjugated, non-classically-aromatic description over true benzenoid aromaticity. This electronic duality - partial charge separation between a neutral dienone and a zwitterionic aromatic-like resonance form - is shown to explain essentially all of the compound's diagnostic spectral and chemical behaviour, and underlies the therapeutic versatility of its many substituted descendants.

Keywords: 4H-pyran-4-one, Aromaticity, Kojic acid, Maltol, Molecular docking, γ -pyrone.

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INTRODUCTION AND COMPOUND IDENTITY

4H-Pyran-4-one, also known as γ -pyrone or 4-pyranone (CAS 108-97-4, C₅H₄O₂, MW 96.08 g/mol), is a six-membered oxygen heterocycle consisting of a ring ether oxygen and a conjugated C4 carbonyl flanked by two symmetric enol-ether double bonds (C2=C3 and C5=C6) (ScienceDirect Topics, n.d.; National Institute of Standards and Technology, n.d.; Wikipedia contributors, 2024). Its SMILES representation is O=c1ccoccl, and it forms the central pharmacophoric core of an entire family of natural products and drug-like scaffolds, including maltol, kojic acid, meconic acid, and the chromone/flavone class of plant pigments.

Because this core recurs so frequently as the central fragment in docking studies of pyranone-based drug candidates, its

spectrochemical and electronic fingerprint is routinely used as the reference baseline against which substituted analogues are compared (ScienceDirect Topics, n.d.; Palmer *et al.*, 2024; Chromanone - A prerogative therapeutic scaffold, 2021). This dissertation brings together four previously separate reference reports - covering hybridization, aromaticity, spectrochemistry, and general chemical character - into one coherent structure-property-activity narrative.

Nomenclature and Identifiers

IUPAC name: 4H-Pyran-4-one. Common synonyms: γ -pyrone (gamma-pyrone), 4-pyranone, 4-pyrone, pyrocoman. InChIKey: CVQUWLDCFXOXEN-UHFFFAOYSA-N.

Molecular Structure

The skeletal (line-angle) structure (Figure 1) shows the ring ether oxygen (O1), the two cross-conjugated enol-ether double bonds (C2=C3 and C5=C6), and the C4 carbonyl that together define the molecule's cross-conjugated dienone system discussed throughout this dissertation.



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Electronic Structure and Atom-by-Atom Hybridization

Hybridization states were assigned to every heavy atom using the standard steric-number (electron-domain) method, in which Steric Number (SN) equals the number of σ -bonds plus the number of lone pairs, giving sp^3 (SN=4, tetrahedral), sp^2 (SN=3, trigonal planar), or sp (SN=2, linear) as the result (General valence-bond / hybridization theory, n.d.)

Applying this method atom-by-atom shows that every ring atom - the ring Oxygen (O1), all four ring carbons (C2, C3, C5, C6), the central carbonyl Carbon (C4) - and the exocyclic carbonyl oxygen are sp^2 hybridized. For the two oxygens, one lone pair occupies an in-plane sp^2 orbital while the second sits in a pure, unhybridized 2p orbital perpendicular to the ring, available for conjugative donation into the π -system; treating either oxygen as sp^3 (as in a simple ether) would misrepresent this conjugative donation and the planar geometry actually observed.

This uniform sp^2 hybridization forces the entire six-membered ring into a single plane, a constraint independently confirmed by microwave and X-ray structural studies that find the ring atoms essentially coplanar (MacDonald *et al.*, 1981; Lumbroso *et al.*, 1986; Chemistry of isolated 4-pyranones, n.d.).

The π -System and Cross-Conjugation

Six unhybridized 2p orbitals, one per ring atom, overlap side-by-side to form an extended π -system that is best described as cross-conjugated rather than a single delocalized Hückel loop: independent C2=C3 and C5=C6 “enol-ether” alkenes each conjugate toward the central C4=O carbonyl, which simultaneously accepts donation from the O1 ring-oxygen lone pair (ScienceDirect Topics, n.d.; MacDonald *et al.*, 1981; Ligabue and Lazzeretti, 1999).

This three-branch convergence onto a single sp^2 acceptor carbon is the structural definition of cross-conjugation, and is captured by two resonance contributors: a neutral cross-conjugated dienone (structure 1a) and a charge-separated, aromatic-like oxocarbenium/enolate form (structure 1b) in which the O1 lone pair has fully donated into the ring and negative charge localizes on the carbonyl oxygen.

Aromaticity of the γ -Pyrone Ring

Whether 4H-pyran-4-one should be regarded as aromatic has been examined by several independent physical methods, and the consensus across this literature is that the ring shows only partial, non-classical aromatic character rather than true benzenoid aromaticity (MacDonald *et al.*, 1981; Lumbroso *et al.*, 1986; Chemistry of isolated 4-pyranones, n.d.; Ligabue and Lazzeretti, 1999; Zarycz *et al.*, 2025).

Microwave-spectroscopic structural studies find the ring planar with a dipole moment close to 4 D, but report little structural

evidence for enhanced aromaticity (MacDonald *et al.*, 1981; Lumbroso *et al.*, 1986; Chemistry of isolated 4-pyranones, n.d.); a molecular magnetic-susceptibility anisotropy analysis independently classifies both 2- and 4-pyrone as nonaromatic on physical grounds (Ligabue and Lazzeretti, 1999), while more recent NMR-based aromaticity indices continue to probe this question with modern computational tools (Zarycz *et al.*, 2025).

Chemical reactivity provides converging, if softer, evidence for partial aromatic contribution: the carbonyl oxygen is markedly more basic than in a simple ketone because protonation is stabilized by donation of the ring-oxygen lone pair, generating an aromatic-like 4-hydroxypyrylium cation, and electrophilic substitution preferentially occurs at the 3- and 5-positions while nucleophiles attack at 2- and 6-positions - a pattern more consistent with a partially delocalized ring than with a simple cyclic dienone.

For a dissertation or thesis context, the most defensible position - and the one adopted throughout this work - is that γ -pyrone is a conjugated, resonance-stabilized heterocycle with partial, non-classical aromatic character, not a fully aromatic benzenoid ring (MacDonald *et al.*, 1981; Lumbroso *et al.*, 1986; Chemistry of isolated 4-pyranones, n.d.; Ligabue and Lazzeretti, 1999).

Spectrochemical Characterization

UV-Visible (Electronic) Spectroscopy

Vacuum-UV/UV absorption and photoionization studies on the parent compound resolve two principal singlet transitions (Table 1) (ScienceDirect Topics, n.d.; Palmer *et al.*, 2024; Parsons *et al.*, 2023).

For 2,6-disubstituted derivatives relevant to most drug-like analogues, reported UV maxima in ethanol/methanol typically cluster in two envelopes, roughly 225-260 nm and 285-325 nm, reflecting the same $n \rightarrow \pi^*$ / $\pi \rightarrow \pi^*$ pair red-shifted and intensified by conjugating substituents at C2/C6 (ScienceDirect Topics, n.d.; Representative synthetic and spectroscopic studies, n.d.).

Infrared (FT-IR) Vibrational Spectroscopy

The carbonyl stretch is the most diagnostic IR band for this scaffold (Table 2); because C4 is cross-conjugated with both ring alkenes through the flanking ring oxygen, its stretching frequency is significantly lowered relative to a simple dialkyl ketone (ScienceDirect Topics, n.d.; Representative synthetic and spectroscopic studies, n.d.).

When a 2,6-disubstituted analogue is prepared for docking studies, the carbonyl band typically shifts modestly (roughly 1630-1660 cm^{-1} depending on substitution and conjugation length), and this shift is routinely cross-checked against DFT-predicted (B3LYP/6-31G(d,p) or similar) harmonic frequencies before docking (ScienceDirect Topics, n.d.; Representative synthetic and spectroscopic studies, n.d.).

Nuclear Magnetic Resonance (NMR) Spectroscopy

The pronounced upfield shift of the carbonyl carbon, together with the strongly deshielded C-2/C-6 signals, is the classic NMR fingerprint used to argue for significant charge delocalization in this ring system (Table 3), and is closely reproduced by DFT-computed shieldings (B3LYP/6-31G* and related basis sets) (ScienceDirect Topics, n.d.; Parsons *et al.*, 2023; Representative synthetic and spectroscopic studies, n.d.).

Mass Spectrometric Fragmentation (EI-MS)

Electron-impact mass spectra show the molecular ion at m/z 96 ($C_5H_4O_2$, base peak) undergoing sequential losses characteristic of the pyranone ring (Table 4) (ScienceDirect Topics, n.d.; Wikipedia contributors, 2024; ChemicalBook, n.d.-a).

The sequential CO-loss pathway is a signature of the ring oxygen/carbonyl system and is routinely checked against a newly docked or synthesized analogue's mass spectrum to confirm that the pyranone core survived the synthetic route unchanged.

Physicochemical Properties

4H-Pyran-4-one is a low-melting, hygroscopic crystalline solid (mp $\approx$ 32-34°C, bp $\approx$ 210-215°C, density $\approx$ 1.19 g/cm³) with a mild logP ($\approx$ 0.64) and a polar surface area of $\approx$ 30.2 Å² reflecting its two oxygen-based hydrogen-bond acceptors (ScienceDirect Topics, n.d.; ChemicalBook, n.d.-a; ChemSrc, n.d.).

Its ground-state dipole moment, 3.79 $\pm$ 0.02-0.03 D in the gas phase, is notably larger than simple ketones such as acetone ($\approx$ 2.9 D), a direct manifestation of the charge separation created when the ring-oxygen p-lone-pair donates into the conjugated π -system (ScienceDirect Topics, n.d.; MacDonald *et al.*, 1981; Lumbruso *et al.*, 1986).

The compound is miscible with water and most polar organic solvents; this distinctly greater water-compatibility relative to a simple cyclohexanone reflects the same unsaturated, dipolar ring-oxygen/carbonyl electronics. Recommended storage is 2-8°C, as the compound is hygroscopic and can degrade on prolonged exposure to heat, light, or oxidizing agents; standard laboratory handling precautions apply, as it is classified as a mild irritant.

Chemical Reactivity

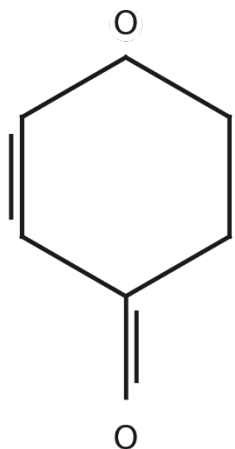
Reactivity is governed by the interplay of a conjugated, weakly Lewis-basic ring oxygen and a cross-conjugated, vinylogously activated carbonyl, which together make the molecule considerably more reactive and more basic than a simple aliphatic ketone (ScienceDirect Topics, n.d.; Wikipedia contributors, 2024).

Enhanced Basicity and Electrophilic Character

The carbonyl oxygen is unusually basic because protonation is stabilized by ring-oxygen lone-pair donation, generating an aromatic-like 4-hydroxypyrylium cation. The ring undergoes 1,2-nucleophilic addition at C4 as in a normal ketone (attenuated by conjugation), 1,6-/vinylogous conjugate addition at C2 or C6 (Michael-acceptor-like behaviour), and, under certain conditions, electrophilic aromatic-type substitution at ring carbons.

The Signature Ring-Transformation Reaction

The most characteristic transformation of 4H-pyran-4-one is its reaction with primary amines in protic solvents, converting the ring oxygen into a ring nitrogen via an addition-ring-opening-recyclization sequence to give the corresponding 4-pyridone - a transformation widely exploited to convert



4H-Pyran-4-one (γ -pyrone)
 $C_5H_4O_2$ · CAS 108-97-4

Figure 1: Skeletal structure of 4H-pyran-4-one (γ -pyrone), $C_5H_4O_2$, CAS 108-97-4.

Table 1: Principal electronic transitions of the parent 4H-pyran-4-one.

Band	Position	Assignment	Character
Broad, intense band	$\approx$ 5.38 eV ($\approx$ 230 nm)	Allowed $\pi \rightarrow \pi^*$ transition(s) ($^1A_1$ -type, overlapping states)	High absorption cross-section ($\sim$ 30 Mb); dominates the near-UV/UV spectrum, reflecting the conjugated dienone π -system
Weak, vibronically structured onset	$\approx$ 3.56 eV ($\approx$ 348 nm)	Symmetry-forbidden $n \rightarrow \pi^*$ ($^1A_2$ excited state)	Very low intensity; eight resolved vibrational sub-bands built on the carbonyl excitation

Table 2: Diagnostic FT-IR vibrational bands of 4H-pyran-4-one.

Vibrational Mode	Region (cm ⁻¹)	Comment
$\nu(\text{C=O})$, ring carbonyl	≈ 1660	Lower than typical saturated/aryl ketones ($\sim 1715 \text{ cm}^{-1}$); reflects charge-separated character from conjugation with the ring-oxygen lone pair - direct vibrational evidence for resonance structure 1b
$\nu(\text{C=C})$, ring	$\approx 1590\text{-}1610$	Coupled ring stretching of the two enol-ether double bonds; often overlaps with ring-breathing modes
$\nu(\text{C-O-C})$, asym./sym. ring ether	$\approx 1150\text{-}1200 / 1000\text{-}1030$	Characteristic of the endocyclic vinyl-ether linkage; confirms ring closure in synthesized analogues
$=\text{C-H}$ stretch (ring vinylic H)	$\approx 3060\text{-}3130$	Weak-to-medium bands; $\text{sp}^2 \text{ C-H}$, above the aliphatic C-H envelope
Ring deformation / out-of-plane C-H bend	$\approx 820\text{-}900$	Fingerprint-region bands used with the carbonyl band to confirm the intact pyranone ring

Table 3: ¹H and ¹³C NMR chemical shifts of the parent compound.

Nucleus / Position	δ (ppm, CDCl ₃)	Assignment Note
¹ H, H-2/H-6	7.88	α to ring oxygen; deshielded by adjacent O and by conjugation with the carbonyl (³ J(H2-H3) $\approx 6.0 \text{ Hz}$)
¹ H, H-3/H-5	6.38	β to ring oxygen, adjacent to carbonyl carbon; more shielded, vinyl-ether-like environment
¹³ C, C-4 (carbonyl)	179.9	Notably upfield of a normal ketone carbonyl ($\sim 200\text{-}210 \text{ ppm}$); consistent with the charge-separated resonance contributor 1b
¹³ C, C-2/C-6	155.6	Strongly deshielded ring carbons attached to the ether oxygen
¹³ C, C-3/C-5	118.3	Shielded α, β -unsaturated ring carbons, consistent with vinylogous enol-ether character

pyranone natural products into pharmacologically important pyridinone analogues (Wikipedia contributors, 2024, Deferiprone and iron-maltol, 2023).

Metal-Chelation and Cycloaddition Behaviour

Hydroxylated ring relatives such as kojic acid and maltol present an adjacent carbonyl-enolate (O,O') donor pair that chelates hard metal ions (Fe^{3+} , Al^{3+} , Ga^{3+}) with high affinity, a property directly traceable to the conjugated carbonyl/ring-oxygen electronics described above (Arshad and Hanif, 2022; Metal complexes of maltol, 2006; Bernstein *et al.*, 2000); the cross-conjugated diene system can also act as a diene, or less commonly as an electron-poor dienophile, in Diels-Alder-type cycloadditions.

Pharmaceutical and Therapeutic Relevance

4H-Pyran-4-one itself functions mainly as a synthetic building block, but its ring system is the core pharmacophore of an entire family of biologically active natural products and drugs (ScienceDirect Topics, n.d.; Rehuman *et al.*, 2022; γ -Pyrone natural products, n.d.).

Kojic Acid and Tyrosinase Inhibition

Kojic acid (5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one) (Figure 2) is a well-established tyrosinase inhibitor used clinically as a skin-depigmenting agent, acting through copper-chelation at the enzyme active site, and is the parent scaffold for numerous antibacterial, antifungal, anticancer, and anti-Alzheimer's analogues (Rehuman *et al.*, 2022; Synthesis, biological evaluation, 2022; Zilles *et al.*, 2022).

Because unmodified kojic acid has limited potency and stability, extensive medicinal-chemistry effort has focused on kojic acid-amino acid, kojic acid-triazole, and kojic acid-quinolone hybrids as improved tyrosinase inhibitors and antibrowning or antibacterial agents (Kojic acid-derived tyrosinase inhibitors, n.d.; New kojic acid-amino acid hybrids, 2015; Design, synthesis and biological evaluation, 2025; Kojic acid-amino acid conjugates, 2009).

Maltol, Deferiprone, and Metal-Based Therapeutics

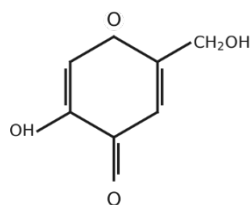
Maltol and ethyl maltol (Figure 3), 3-hydroxy-4-pyranones bearing a methyl substituent, are widely used as O,O'-chelating ligands for medicinal and diagnostic metal complexes,

including orally bioavailable gallium maltolate investigated in oncology and gallium/iron-maltol complexes used in iron-deficiency and antimicrobial applications (Arshad and Hanif, 2022; Bernstein *et al.*, 2000; Pharmaceutical compositions of gallium complexes, n.d.; Pharmaceutical compositions, n.d.). The related hydroxypyridinone class, produced by the pyranone-to-pyridinone ring-transformation reaction described above, includes deferiprone, a clinically used iron chelator for transfusion-related iron overload with an expanding investigational role in neurodegenerative and infectious disease (Deferiprone and iron-maltol, 2023; Metal complexes of maltol, 2006).

Chromones, Flavones, and Kinase Inhibition

Benzo-fused 4-pyranones - the chromone and flavone classes - display broad antioxidant, anti-inflammatory, antiviral, antimicrobial, and anticancer activity, and remain a highly active area of synthetic medicinal chemistry (ScienceDirect Topics, n.d.; Synthesis of chromones, 2023; Bhatt *et al.*, 2016; One-pot synthesis, 2023; Synthesis and antioxidant properties, 2009; Synthesis and investigation of flavanone derivatives, 2022; Flavones and related compounds, 2023).

The clinically investigated chromone alkaloid flavopiridol, derived from the natural product rohitukine, is a potent Cyclin-Dependent Kinase (CDK) inhibitor that induces cell-cycle arrest and apoptosis across multiple tumour types and was among the first CDK inhibitors tested in clinical oncology trials (Flavopiridol as cyclin dependent kinases, n.d.; Review of flavopiridol, 2005; Flavopiridol: A promising cyclin-dependent kinase inhibitor, 2024; Flavopiridol as cyclin dependent kinase, 2018; Flavopiridol, a novel cyclin-dependent kinase inhibitor, n.d.).



Kojic acid
5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one

Figure 2: Kojic acid, 5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one.

Saturated Analogues in CNS Drug Discovery

The saturated ring analogue tetrahydro-4H-pyran-4-one is a documented key intermediate in the synthesis of azaspiro compounds investigated as Histamine H3-Receptor (H3R) antagonists for cognitive and neurological disorders (Chromanone - A prerogative therapeutic scaffold, 2021; ChemicalBook, n.d.-b).

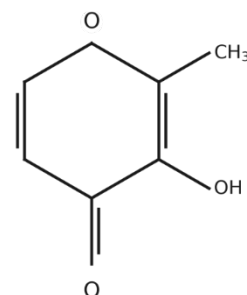
Relevance to Molecular Docking

Planarity from uniform sp^2 hybridization means the core can be treated as a rigid pharmacophore fragment with no ring-pucker conformers to sample during docking, unlike sp^3 -containing saturated rings.

p-orbital donation from the ring oxygen and the polarized C4=O carbonyl define the molecule's hydrogen-bond acceptor sites and electrostatic surface, both direct, predictable consequences of the sp^2 lone-pair placement described in Chapter 2.

Reporting the UV, IR, ^1H NMR, ^{13}C NMR and MS data sets alongside DFT-optimized geometry is the conventional way pharmaceutical-chemistry studies validate a pyranone-core molecule before docking, since it demonstrates that the modelled structure matches the experimentally characterized compound.

Substituents placed on an sp^2 ring carbon (C2, C3, C5, or C6) remain in-plane by construction; substituents that would force pyramidalization at a ring atom should be flagged, since they break the planar conjugation for which this scaffold is typically selected (ScienceDirect Topics, n.d.; MacDonald *et al.*, 1981; Lumbroso *et al.*, 1986; Chemistry of isolated 4-pyranones, n.d.;



Maltol
3-hydroxy-2-methyl-4H-pyran-4-one

Figure 3: Maltol, 3-hydroxy-2-methyl-4H-pyran-4-one.

Table 4: EI-MS fragmentation pattern of the parent compound.

m/z	Relative Intensity	Proposed Process
96	100 ($M^{+\bullet}$)	Molecular ion, $C_5H_4O_2$
69-70	~38-51	Loss of $\bullet CHO$ / HCO (ring-opening)
68	~28	Loss of CO (28 amu) from $M^{+\bullet}$ - diagnostic retro-ring loss for the pyranone carbonyl
42	~32	Further fragmentation to a $C_2H_2O^+$ (ketene-type) fragment
39-41	~6-10 each	Small conjugated/cyclopropenyl-type hydrocarbon fragments

Ligabue and Lazzeretti, 1999; Representative synthetic and spectroscopic studies, n.d.).

CONCLUSION

4H-Pyran-4-one is best understood as a planar, fully sp^2 -hybridized, cross-conjugated heterocycle whose electronic structure sits between a neutral dienone and a charge-separated, partially aromatic resonance. Every diagnostic spectroscopic signature discussed in this dissertation - the red-shifted UV transitions, the lowered carbonyl IR stretch, the anomalously upfield carbonyl ^{13}C shift, and the characteristic sequential CO-loss in EI-MS - converges on this same electronic picture. That picture, in turn, explains both the compound's distinctive reactivity (enhanced basicity, vinylogous electrophilicity, and the signature $O \rightarrow N$ ring-exchange reaction) and the remarkable pharmaceutical breadth of its substituted descendants, from kojic acid and maltol-type metal chelators to chromone- and flavone-based kinase inhibitors, making the unsubstituted ring a scientifically well-justified and thoroughly characterized reference scaffold for pyranone-based drug-discovery and docking programs.

ABBREVIATIONS

CAS: Chemical Abstracts Service; **CDK:** Cyclin-Dependent Kinase; **DFT:** Density Functional Theory; **EI-MS:** Electron-Impact Mass Spectrometry; **FT-IR:** Fourier-Transform Infrared Spectroscopy; **H3R:** Histamine H3 Receptor; **MW:** Molecular Weight; **NMR:** Nuclear Magnetic Resonance; **SN:** Steric Number; **UV-vis:** Ultraviolet-Visible Spectroscopy.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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