

Agricultural University of Georgia

School of Natural Sciences and biotechnology



Challenges in the Nitration of Quercetin: An Investigation of Reaction Conditions

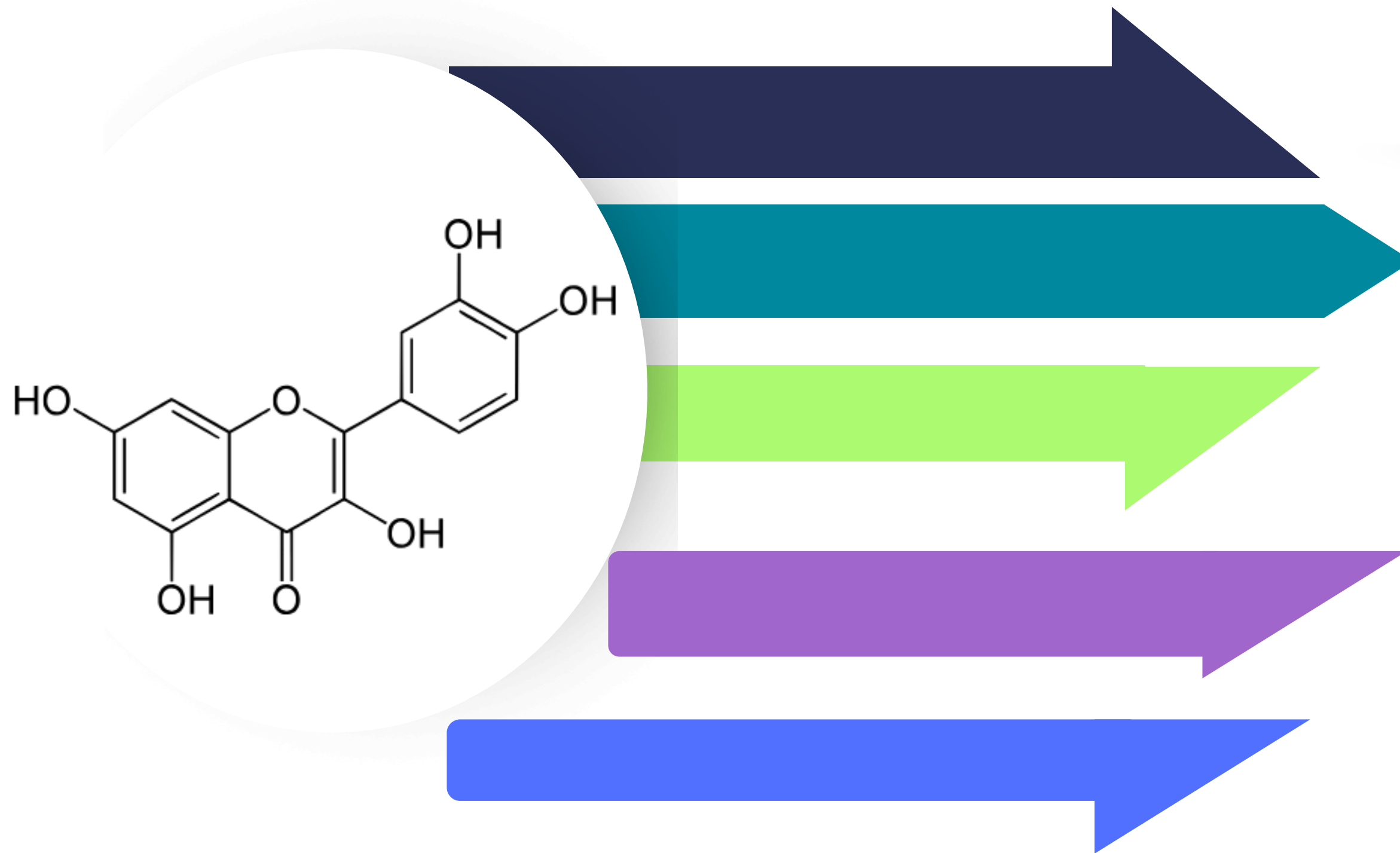
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Quercetin: A Bioactive Flavonoid



01

A naturally occurring and widely distributed compound

02

Antioxidant

03

Chemically reactive

04

Chromophore high λ_{max}

05

Metal chelator

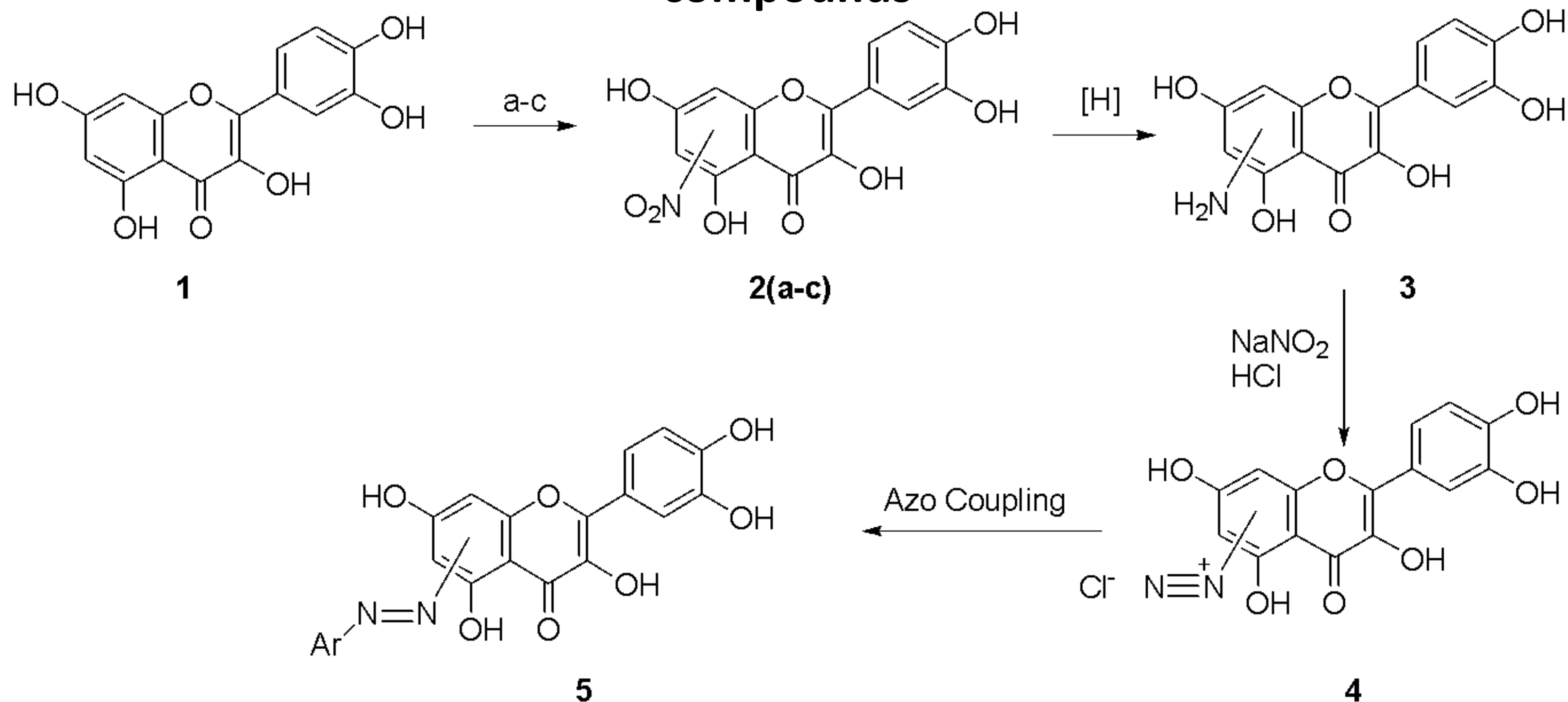
Why nitration?

Nitro groups provide a versatile handle for further chemical transformation

Reduction to amines enables subsequent functionalization.

Diazotization opens access to diverse aromatic derivatives.

Strategy of the synthesis of quercetin containing azo compounds

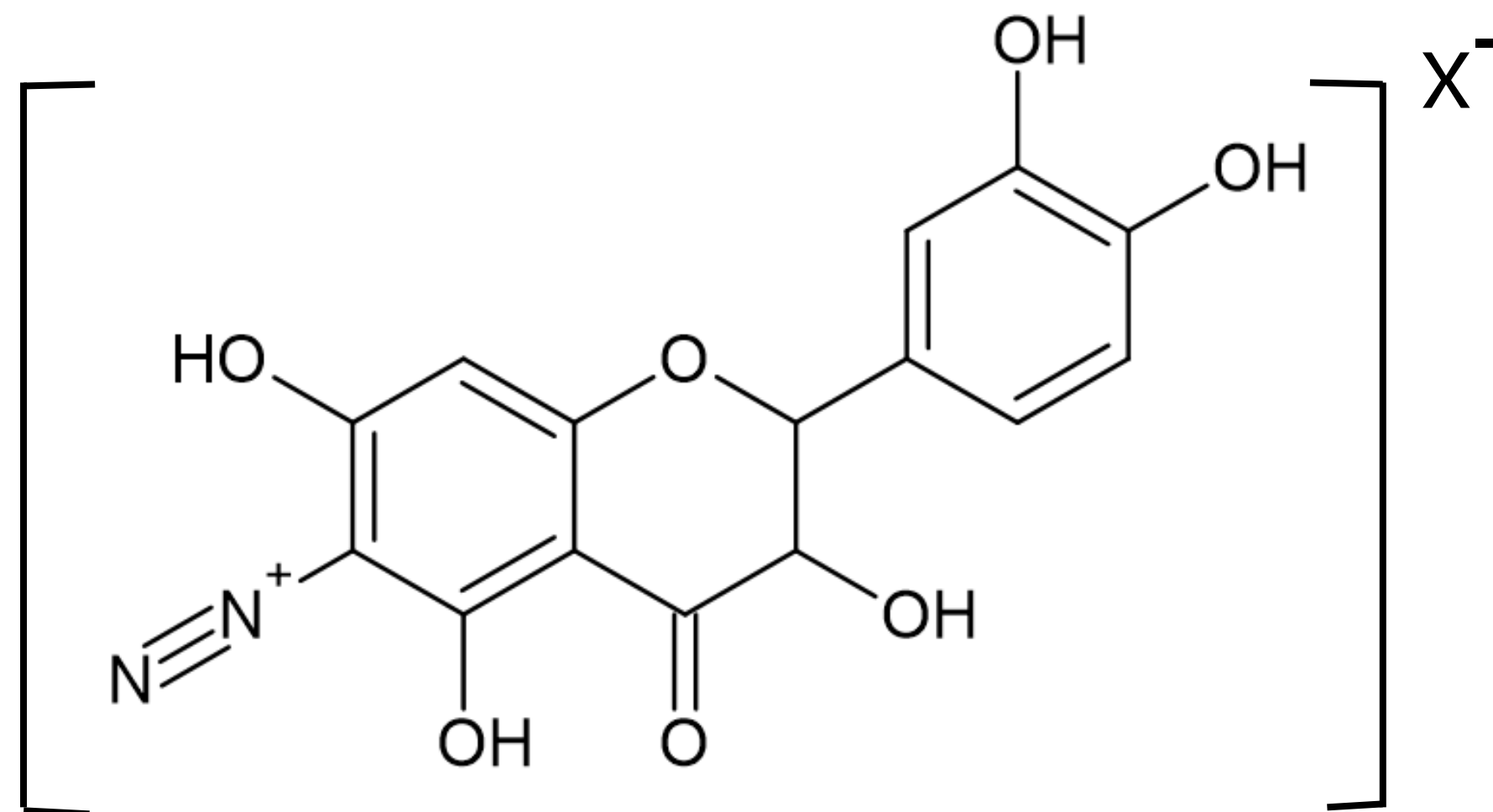


where: Ar - moiety of biological active aromatic compound

(a) $\text{KNO}_3/\text{H}_2\text{SO}_4$; (b) $\text{NH}_4\text{NO}_3/\text{TCA}/\text{MeCN}$; (c) $\text{KNO}_3/\text{TCA}/\text{MeCN}$.

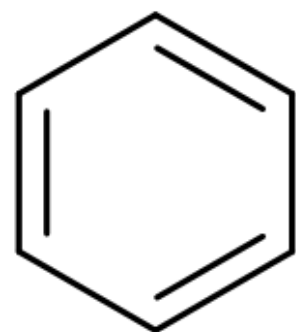
Diazonium Salts: Versatile Synthetic Intermediates

- Azo coupling
- Sandmeyer reactions
- Balz–Schiemann reaction
- Cyanation

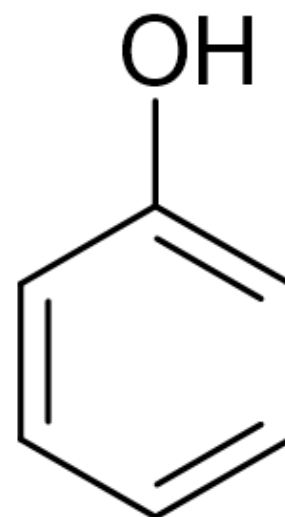


- Radical arylation
- Boronate synthesis

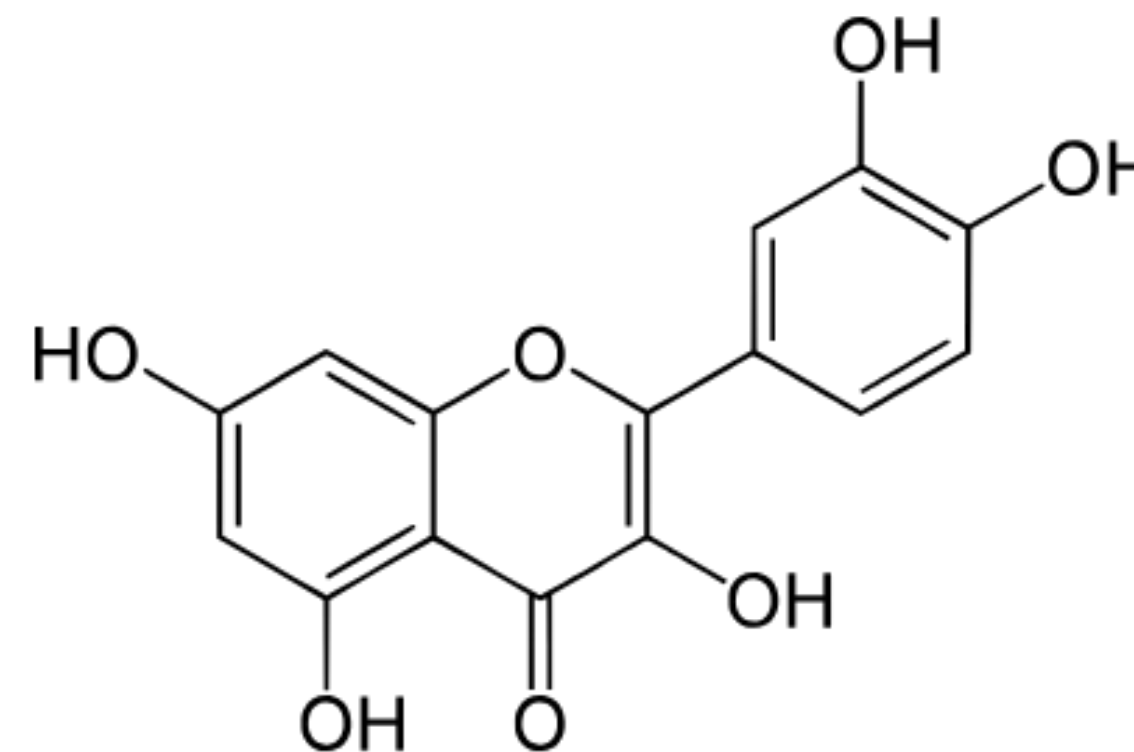
Electrophilic Aromatic Nitration



Reference substrate



Electron-rich
aromatic ring



Polyhydroxylated aromatic
system
Multiple activating –OH groups

Increasing electronic
activation

The central chemical problem

Why is quercetin difficult to nitrate?

01

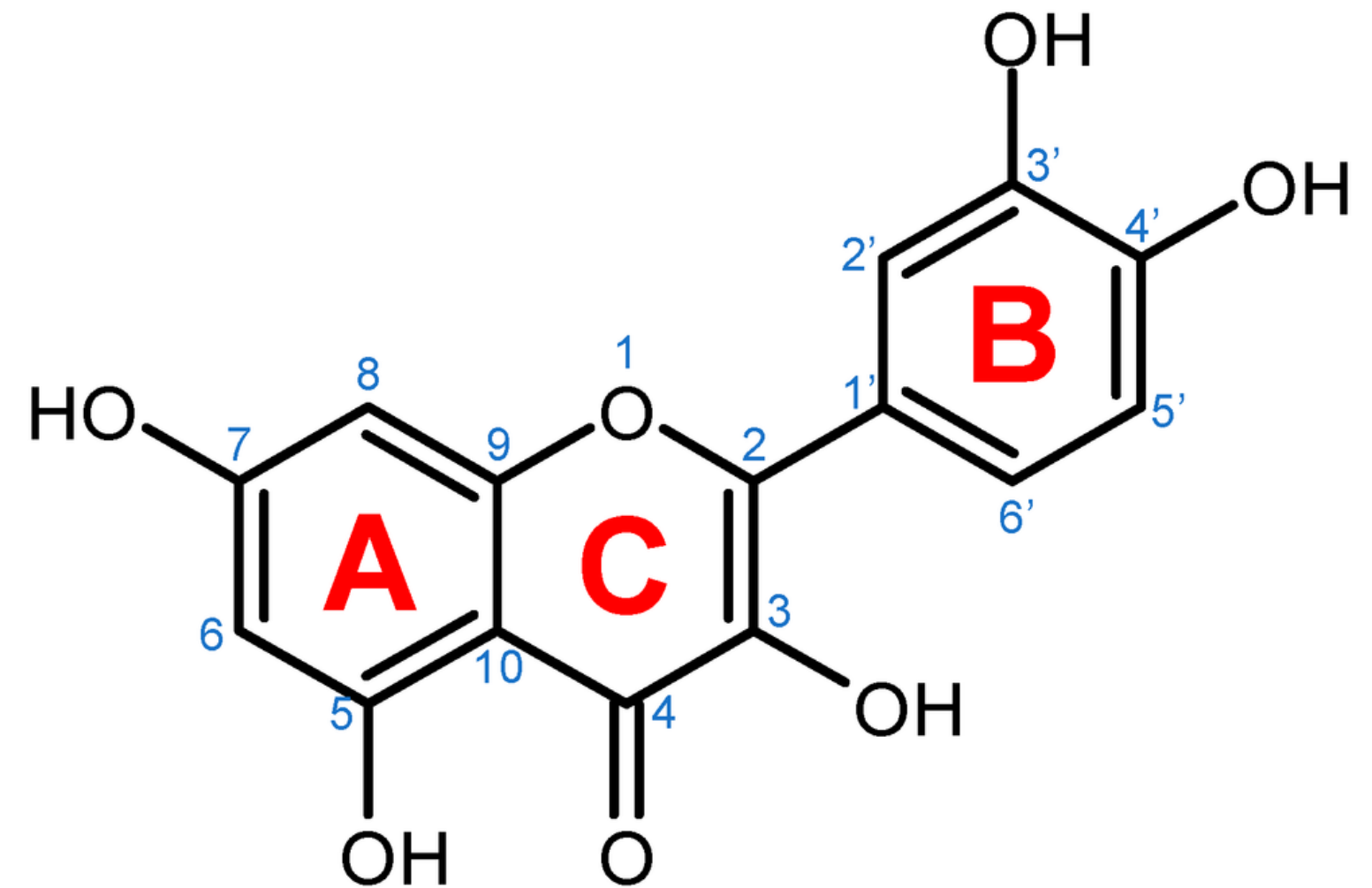
Highly activated aromatic system

02

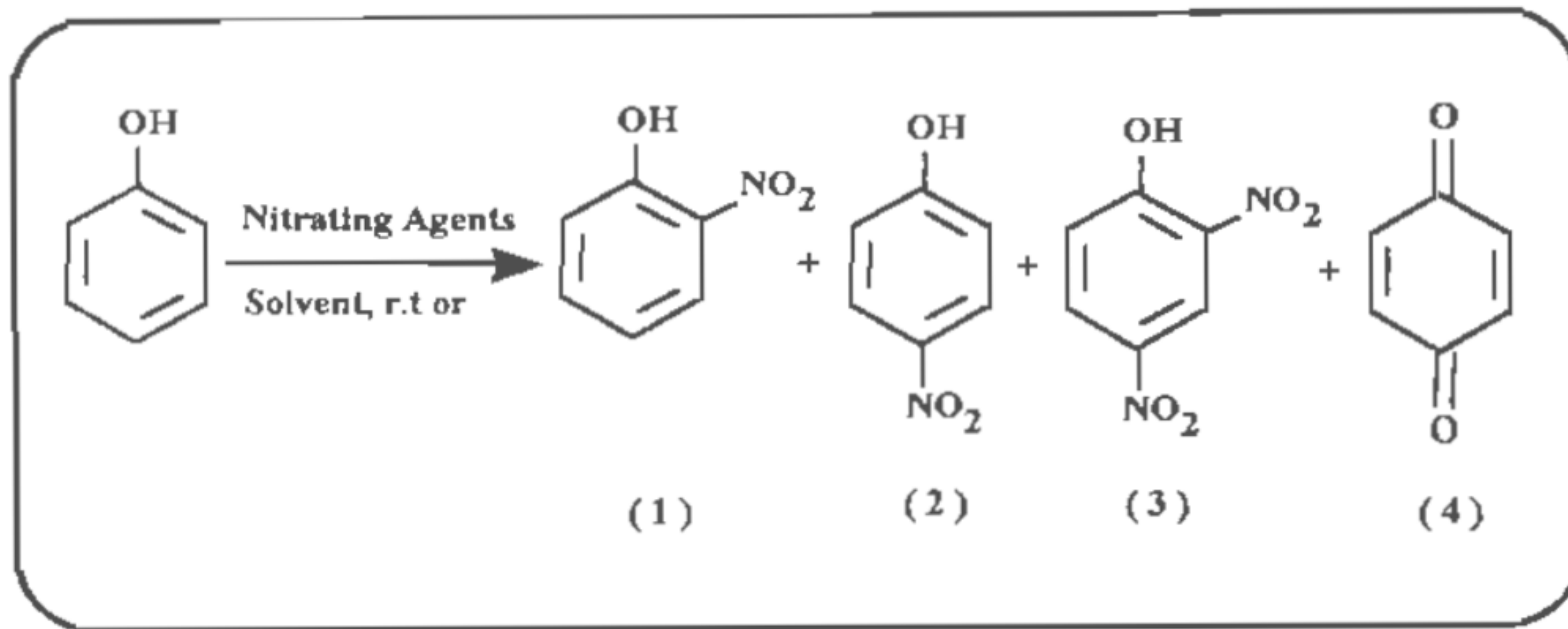
Multiple competing positions

03

High oxidation susceptibility



Nitration of Phenols Using Nitrate Salts



Examples: $\text{Cu}(\text{NO}_3)_2$; $\text{Fe}(\text{NO}_3)_3$; $\text{Cr}(\text{NO}_3)_3$; NaNO_3

Literature Precedent: Nitration of Quercetin

Bi(NO₃)₃-based nitration → unsuccessful

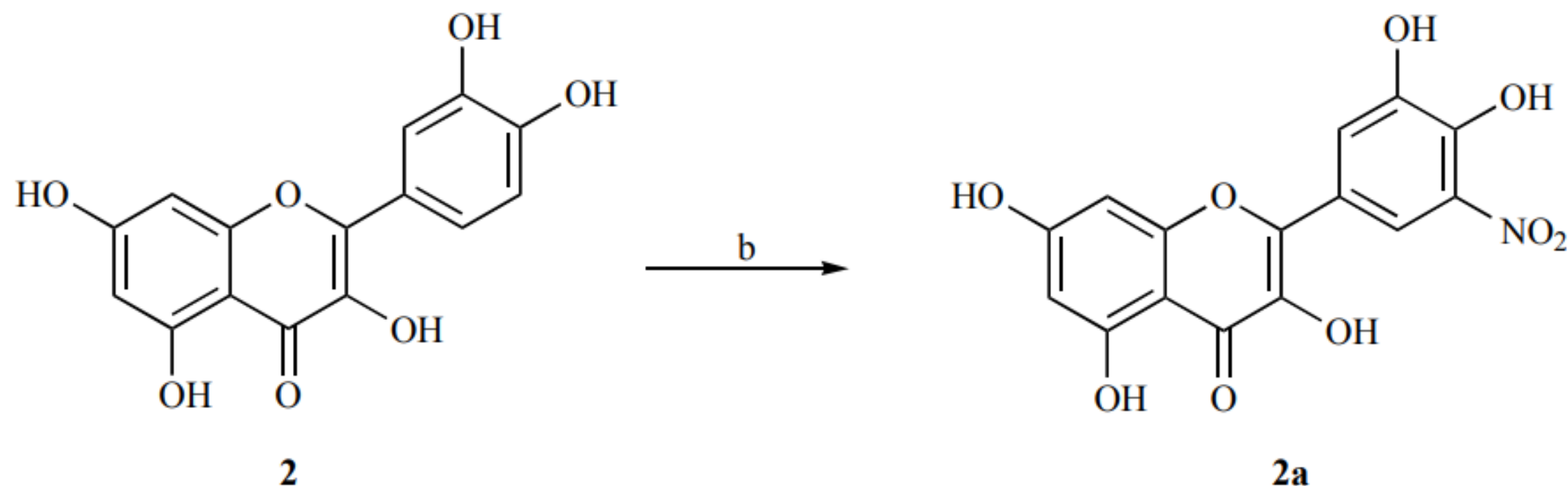
NO_x system → successful nitration

5'-Nitroquercetin → isolated product

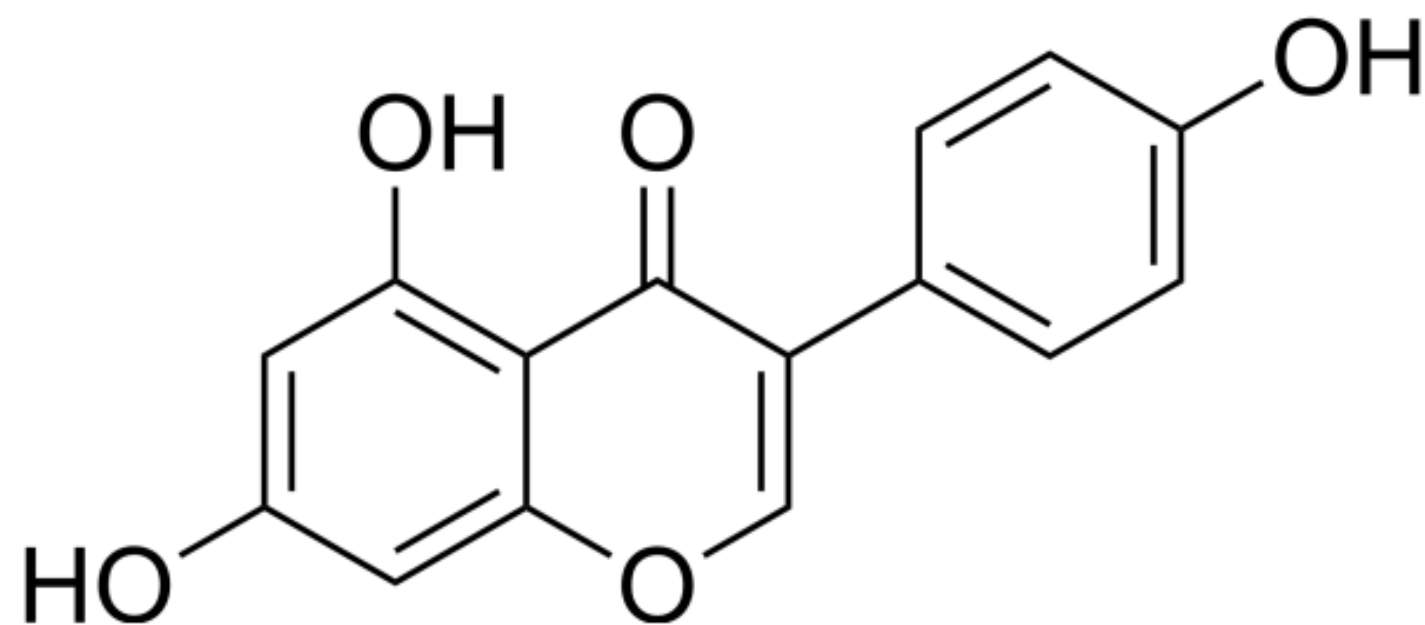
Yield: 20%

Appearance: orange powder

Main issue: competing side reactions



Nitration of Genistein



Trifluoroacetic anhydride + ammonium
nitrate

Solvent: acetonitrile

Experimental Strategy

- Investigation of different nitrating systems
- Variation of acidic medium
- Variation of temperature
- Time-dependent monitoring by TLC
- Comparison of reaction mixtures with quercetin reference
- Evaluation of color changes and chromatographic behavior

Experimental Section



1

KNO₃/H₂SO₄ Nitration System

- Quercetin: 0.14 g (0.0014 mol)
- KNO₃: 0.17 g (0.005 mol)
- H₂SO₄: 10 mL (conc.)

2

NH₄NO₃/TCA/ACN Nitration System

- Quercetin: 0.42 g (0.0014 mol)
- NH₄NO₃: 0.112 g (1 equiv.) + 0.24 g (excess)
- TCA: 0.5 mL (0.0056 mol)
 - ACN: 4 mL

3

NH₄NO₃/HCOOH Nitration System

- Quercetin: 0.42 g (0.0014 mol)
- NH₄NO₃: 0.112 g (0.0014 mol)
- HCOOH: 0.212 mL (0.0056 mol)

4

KNO₃/TCA/ACN Nitration System

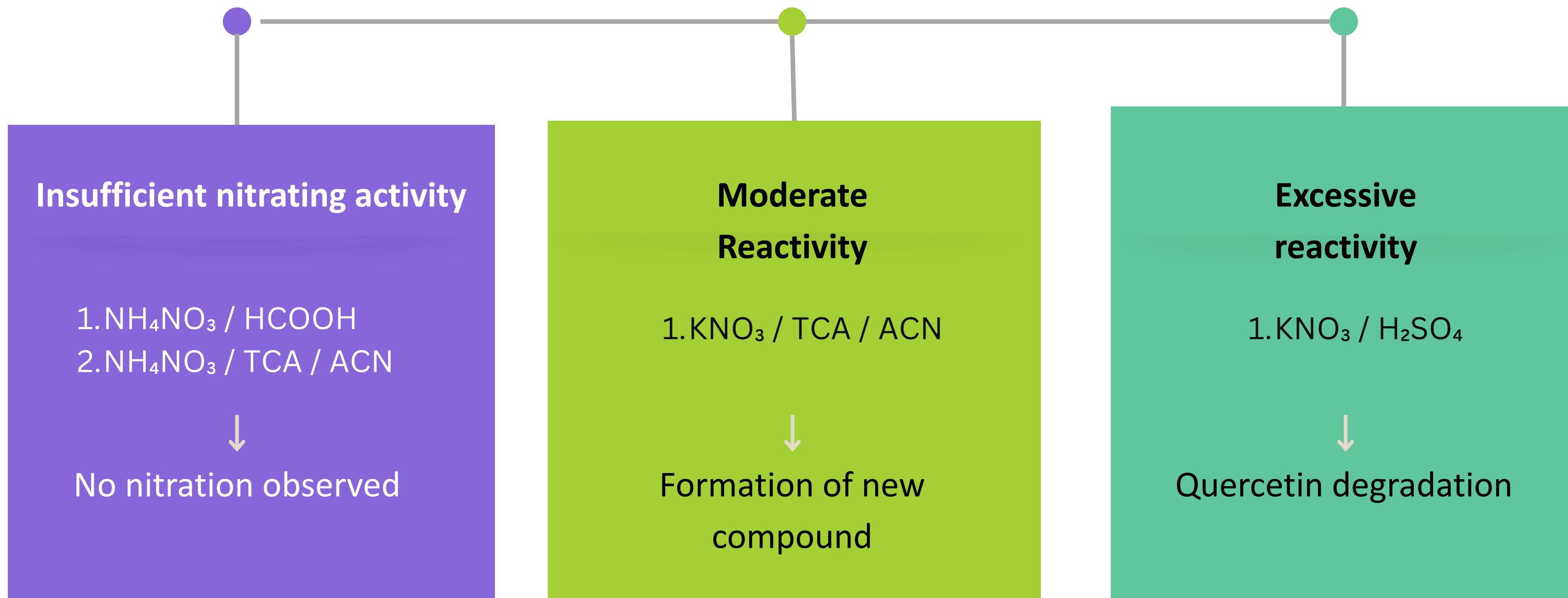
- Quercetin: 0.42 g (0.0014 mol)
- KNO₃: 0.1415 g (0.0014 mol, 1 equiv.)
- TCA: 0.5 mL
- ACN: 3 mL

Experimental conditions

Run	Source of NO ₂ ⁺	Acid	Solvent	Temperature (°C)
2a	KNO ₃	H ₂ SO ₄	-	0-5
2b	NH ₄ NO ₃	TCA	MeCN	rt-35
2c	NH ₄ NO ₃	HCOOH	MeCN	rt-reflux
2d	KNO ₃	TCA	MeCN	rt-35

Optimization of Nitration Conditions

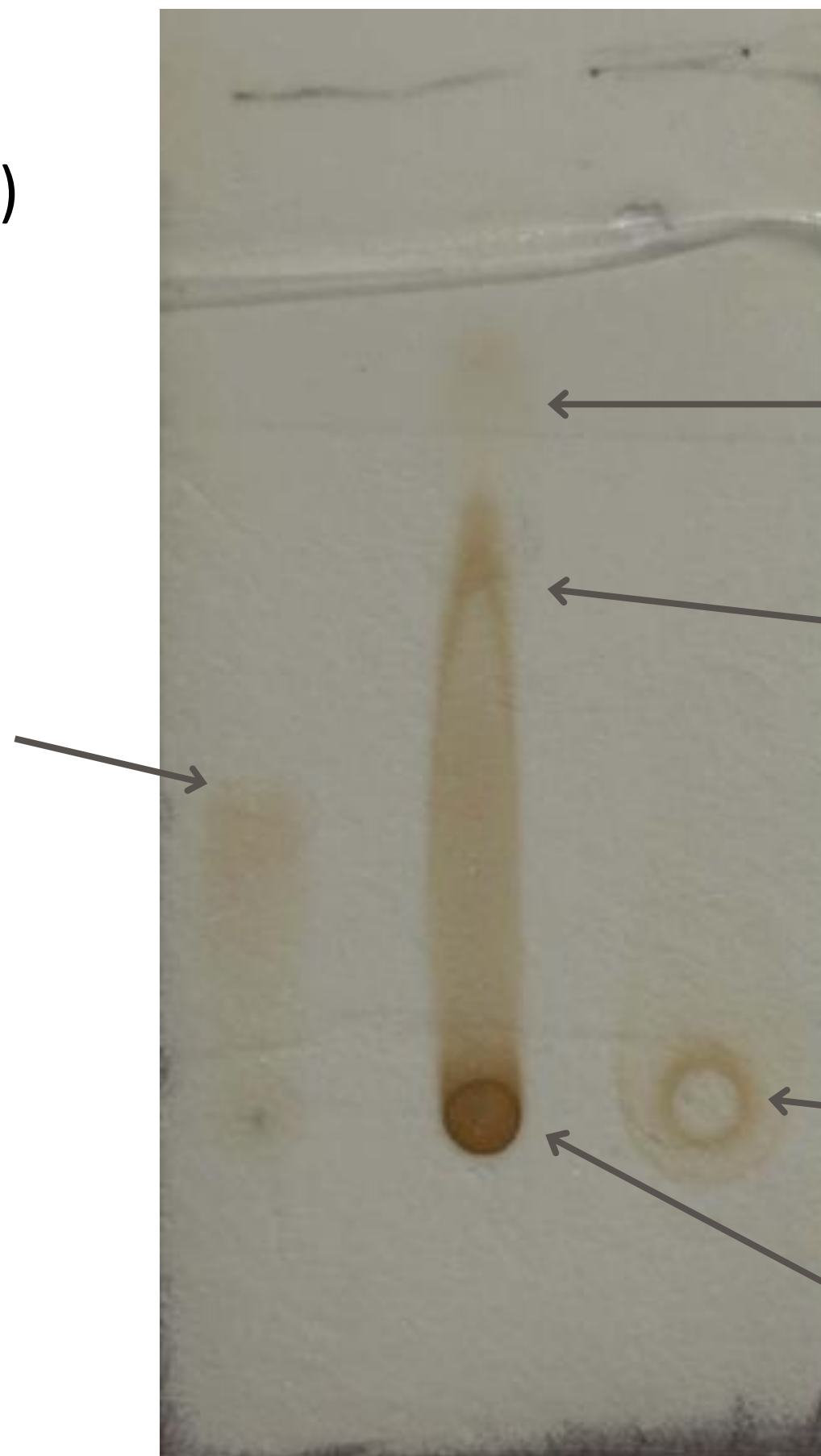
Effect of nitrating system and acidic medium on quercetin reactivity



TLC Sample 1

Eluent — EtOAc:Chloroform (2:1)

Quercetin
 $R_f=0.50$



Reaction
 $R_f=0.84$

Reaction
 $R_f=0.7$

Reaction $R_f=0$

Reaction $R_f=0$

Time-Dependent Monitoring

Reaction system: KNO_3 / Quercetin / TCA / ACN

Monitoring interval: 10 min

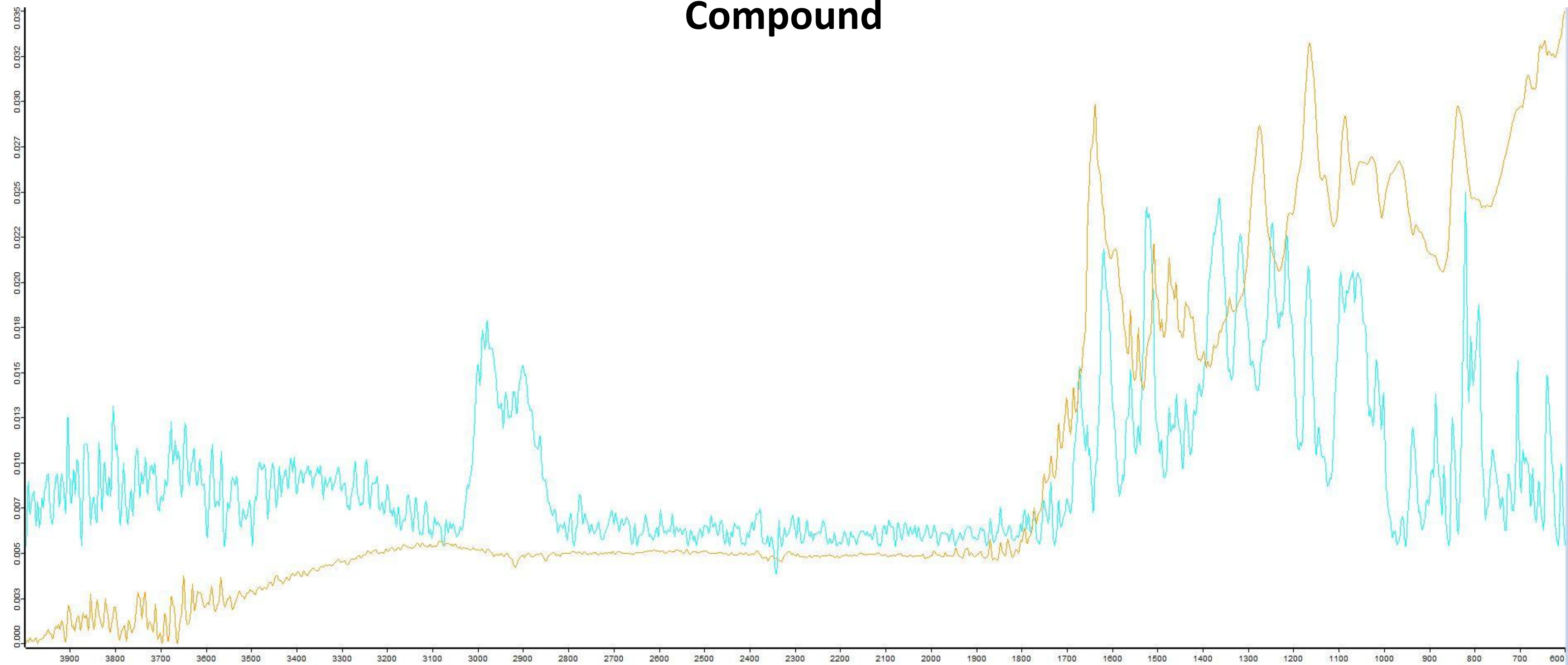
Observations

- Rapid appearance of new TLC components after the color change
- Progressive decrease in R_f of the higher- R_f component
- Material increasingly observed at the origin
- Reaction transformation occurred rapidly relative to the sampling interval

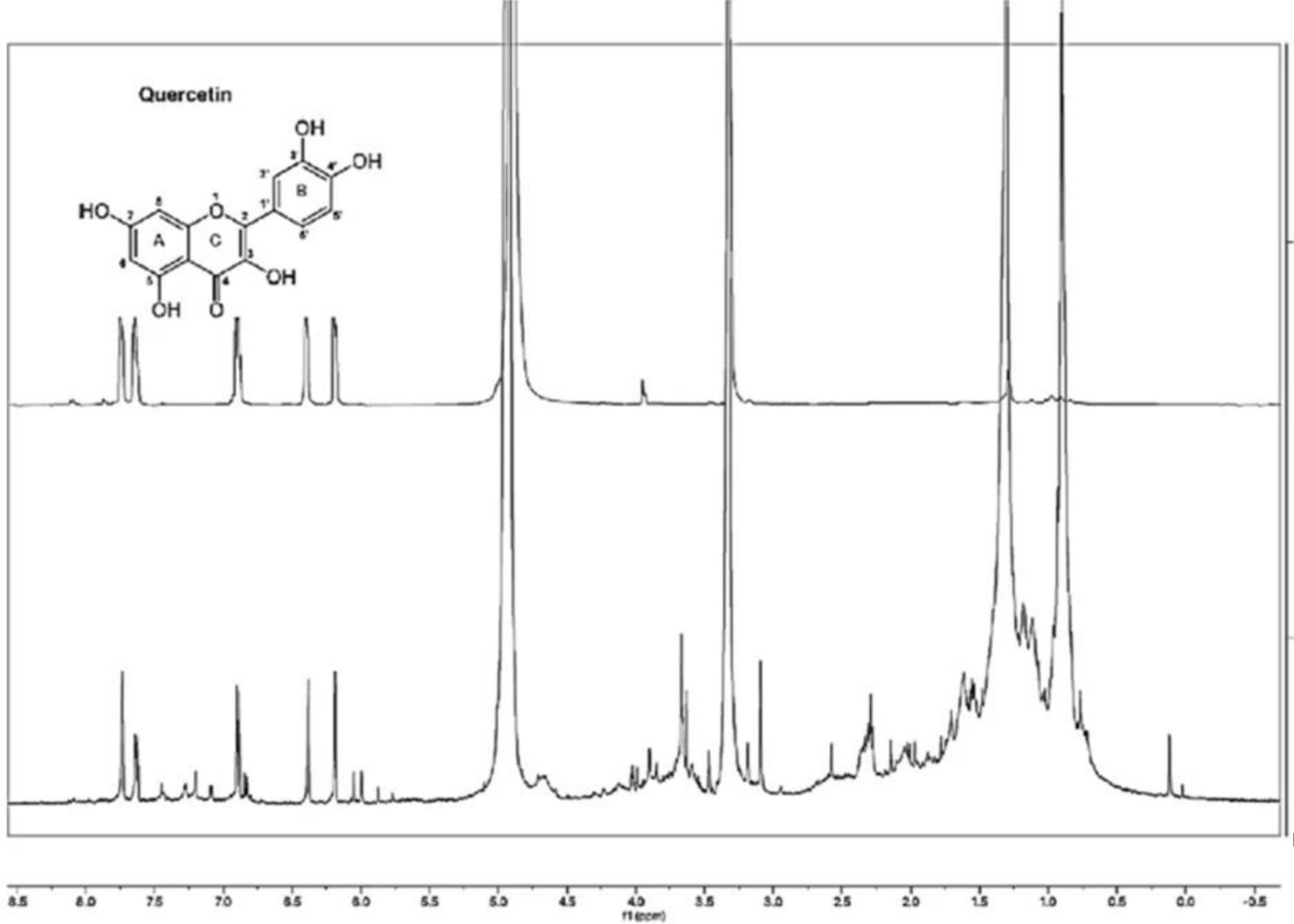


IR Spectra of Quercetin and the Obtained Compound

Quercetin
Compound



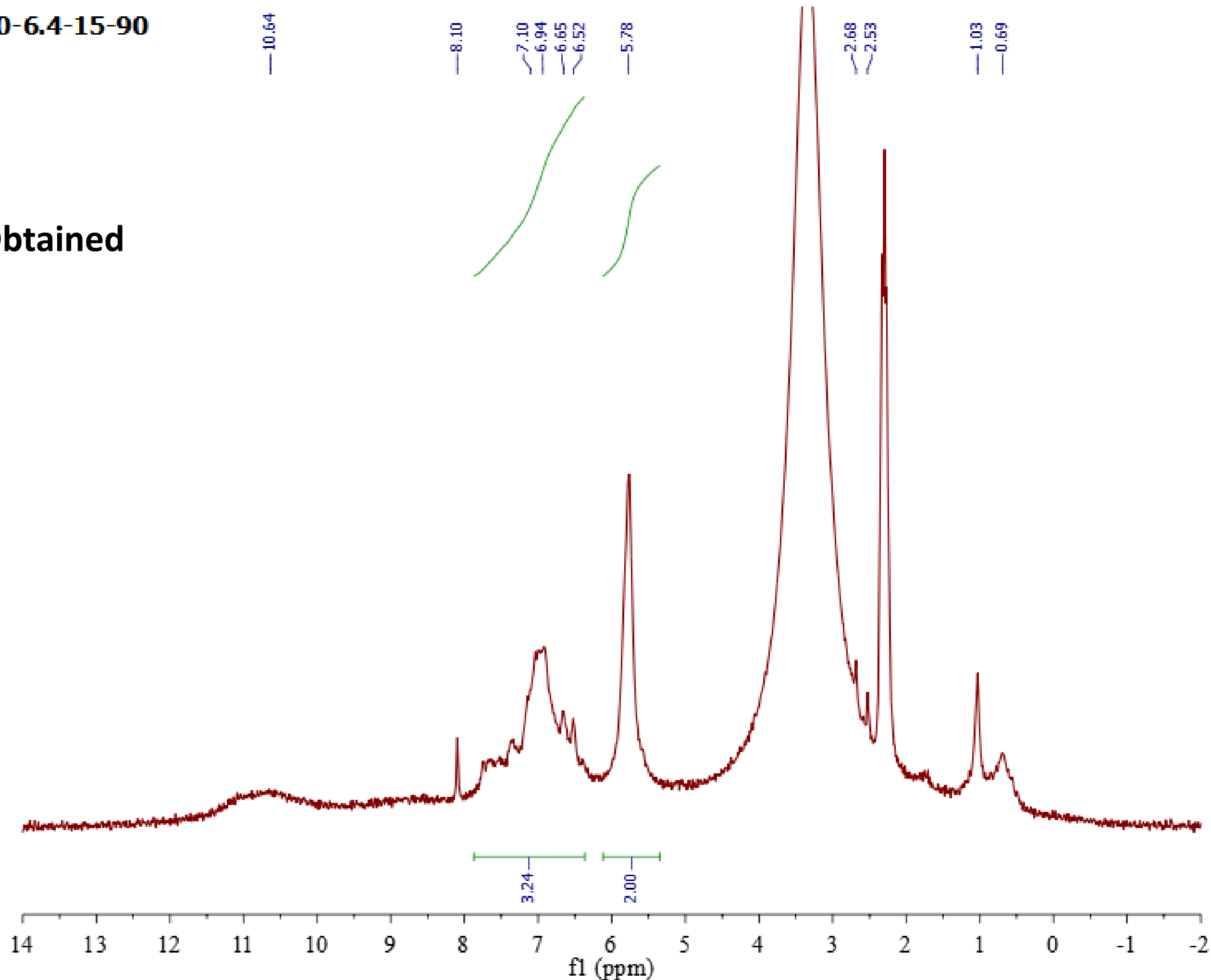
Quercetin ¹H NMR spectrum



[7] R.R Exploring the therapeutic potential of Derris elliptica (Wall.) Benth in Streptozotocin-Induced diabetic Rats: Saudi Pharmaceutical Journal, 2024.

¹H NMR Spectrum of the Obtained Compound

Parameter	Value
1 Data File Name	c:/projects/ data/ 2026/ 06/ 11/ 161428-1D EXTENDED+ Nitroquendine/ Enhanced/ data. 1d
2 Spectrometer	SPINSOLVE 60 CARBON
3 Solvent	DMSO
4 Sample	Nitroquendine
5 Number of Scans	91
6 Acquisition Date	2026-06-11T16:14:28.666
7 Total acquisition time (min)	22.009999999999998
8 Nucleus	1H



Conclusion

S

- Four nitration systems were investigated for the chemical modification of quercetin.
- The reaction outcome was strongly dependent on the nitrating system and reaction medium.
- NH_4NO_3 -based systems did not result in observable nitration under the investigated conditions.
- Strongly acidic $\text{KNO}_3/\text{H}_2\text{SO}_4$ conditions resulted in degradation of quercetin.
- The obtained compound from $\text{KNO}_3/\text{TCA}/\text{ACN}$ was characterized by IR and ^1H NMR spectroscopy; however, nitration could not be conclusively established.
- The findings demonstrate the sensitivity of quercetin to nitration conditions and the challenges associated with achieving controlled chemical modification.

**Thank you for your
attention**