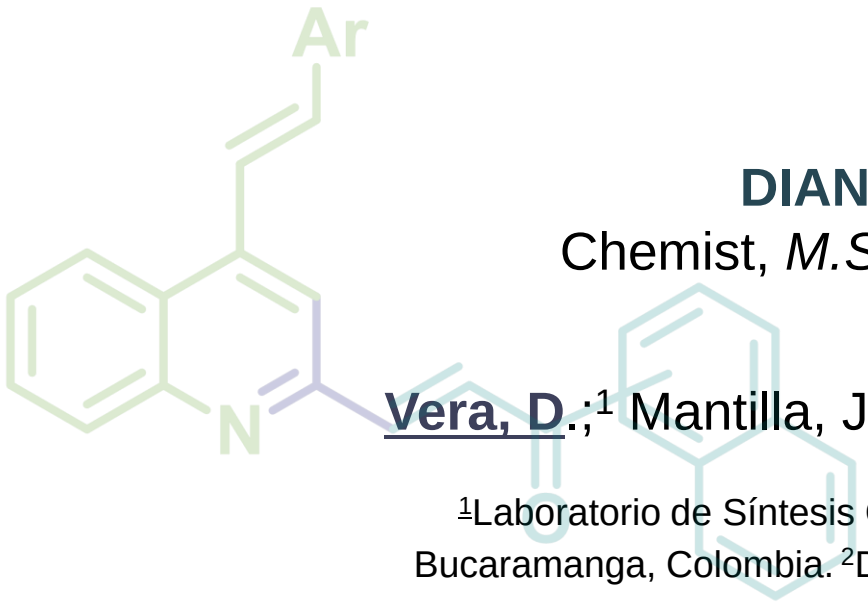
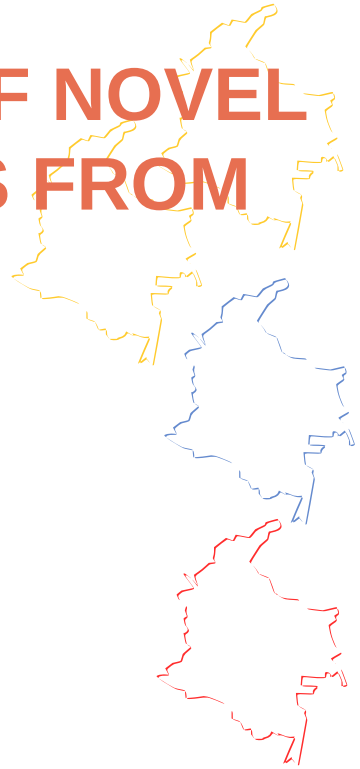
A FACILE AND CONVENIENT THREE-STEP SYNTHESIS OF NOVEL STYRYLQUINOLINE-CHALCONE MOLECULAR HYBRIDS FROM 2'-AMINOPHENYLCHALCONES





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Rio de Janeiro, Brasil. 14-18 Noviembre/2022

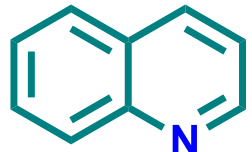
Universidad Industrial de Santander UIS LSO

INTRODUCTION

LSO

Design and development of novel methodologies of synthesis

Quinoline based molecular hybrid



(1)

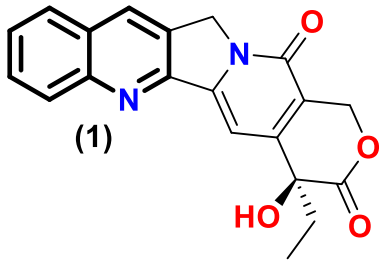
Privileged scaffolds and Bioactive moieties

Design strategy

MOLECULAR HYBRIDIZATION

Synthesis. **2020**, *52*, 1804-1822; Acta Cryst., **2022,** C78, 671-680

QUINOLINES AS PRIVILEGED SCAFFOLDS



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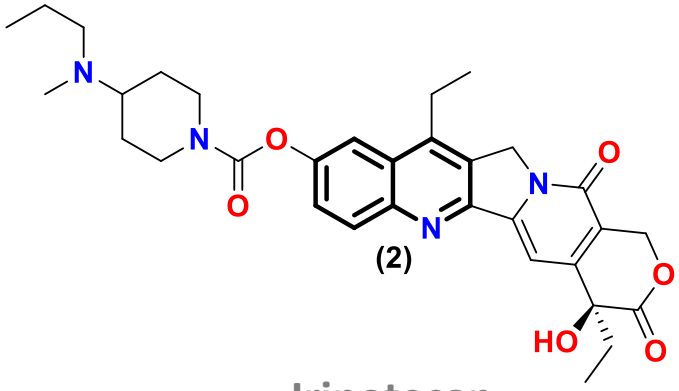

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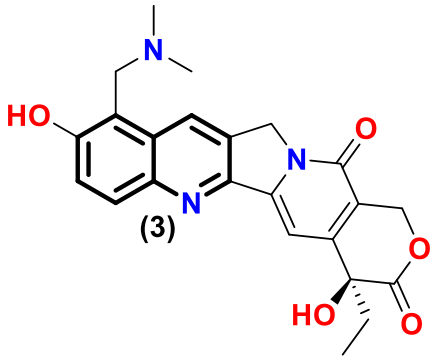

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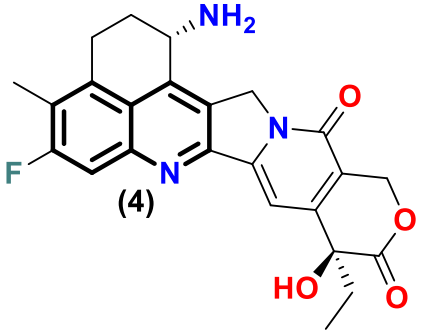

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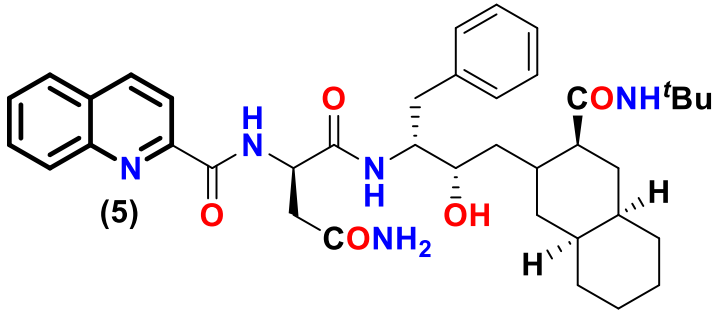

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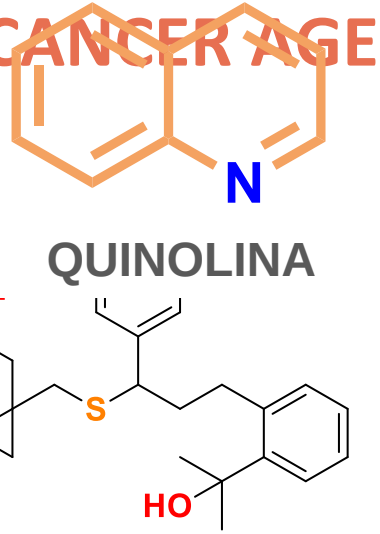
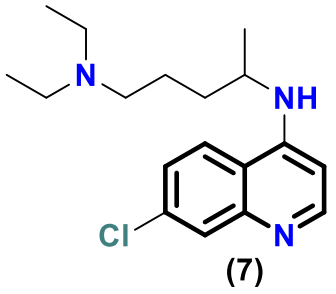


Montelukast

ANTIASTHMATIC

QUINOLINA



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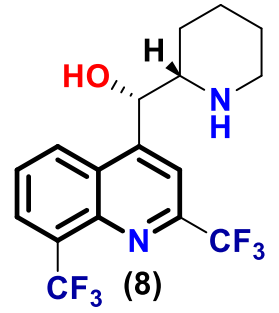

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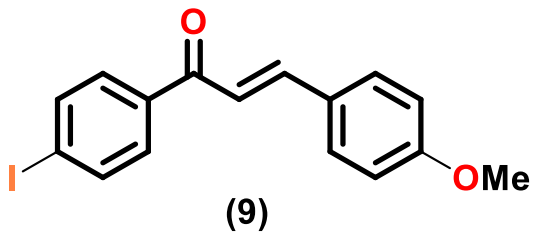
ANTIMALARIAL

Biomed. Pharmacother., **2014**, *68*, 1161–1175.; *Eur. J. Med. Chem.*, **2010**, *45*, 3245–3264.**;** *Eur. J. Med. Chem.*, **2015**, *97*, 871–910.

BIOLOGICAL ACTIVITY OF CHALCONES



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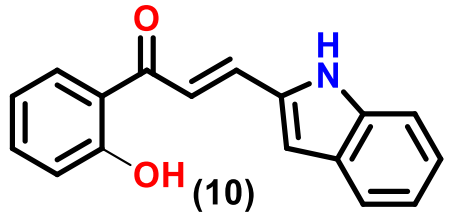

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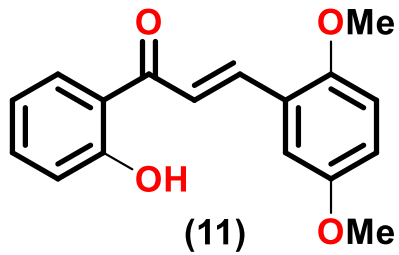

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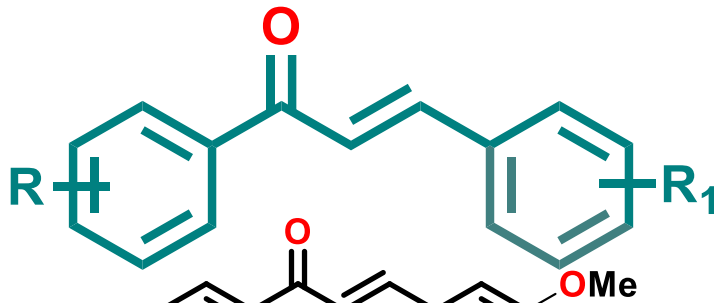

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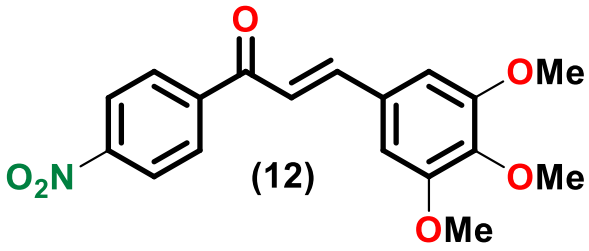

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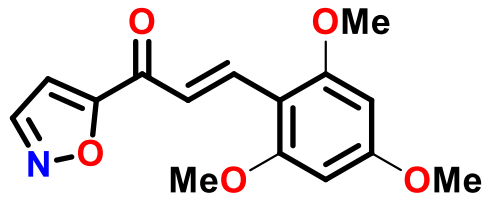

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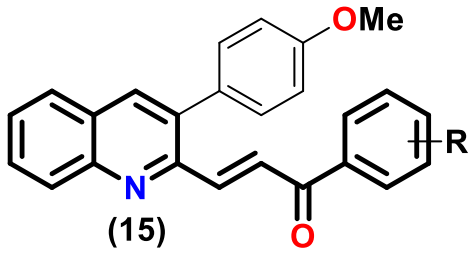
ANTIBACTERIAL AND ANTIOXIDANT

Eur J Med Chem., 2014, 85, 758–777.; *J Med Chem.*, **2009**, *52*, 7228–7235 (2009).; *J Photochem Photobiol B.*, **2011**, *102*, 200–208 (2011).; *Int J Pharm Pharm Sci.*, **2011**, *3*, 125–128.

BIOLOGICALLY ACTIVE QUINOLINE-CHALCONE HYBRID



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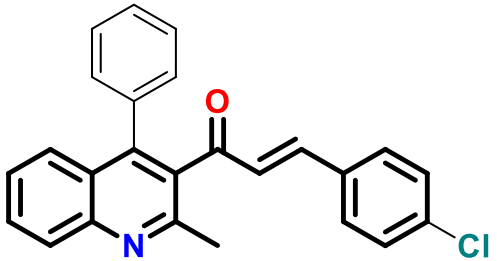
R = 3,4,5-triOMe



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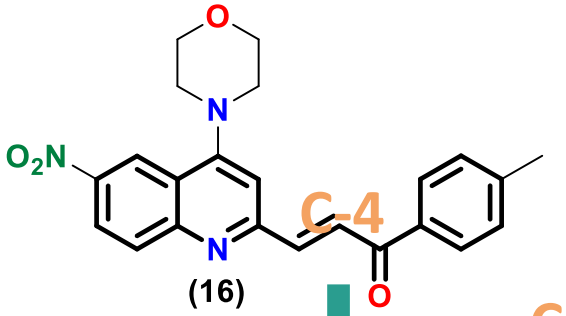

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C-4

C-3

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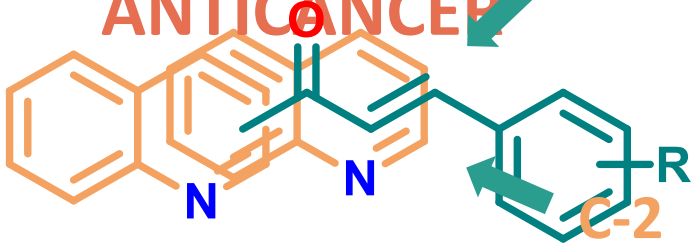
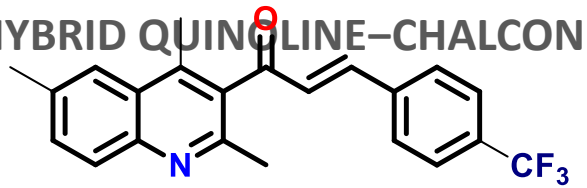


C-2

HYBRID QUINOLINE–CHALCONE



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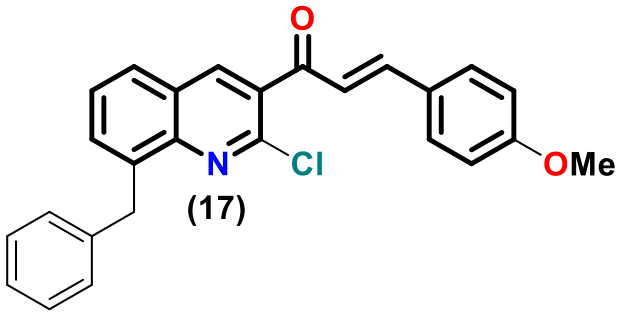

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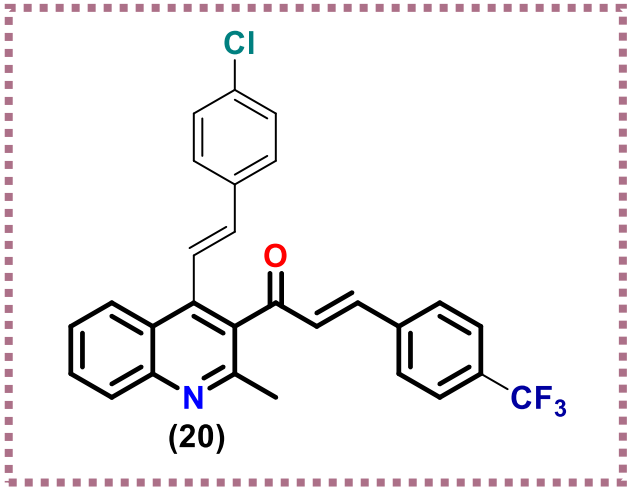

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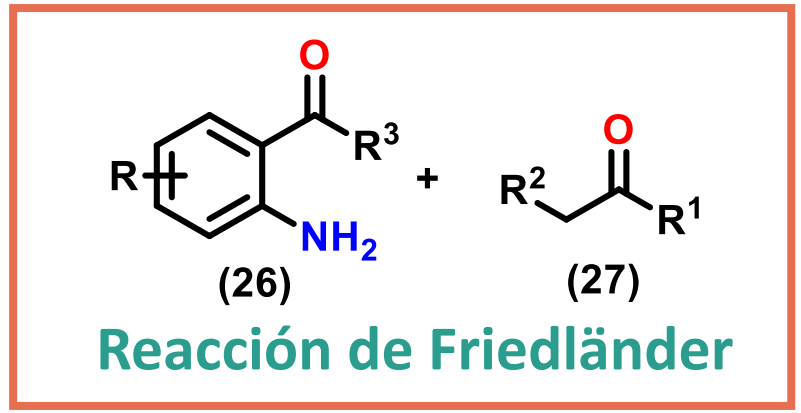
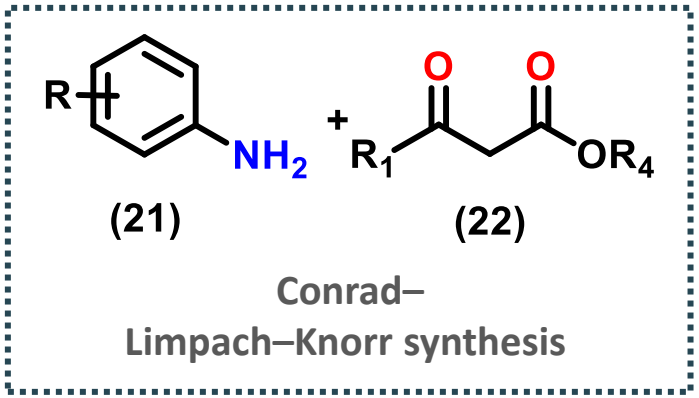
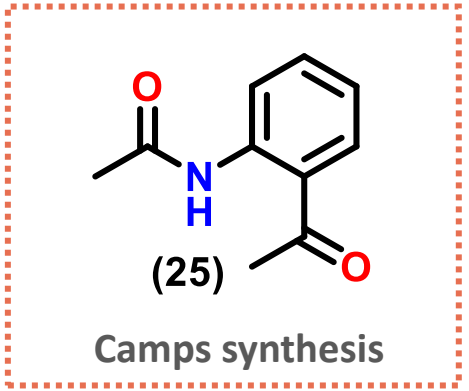
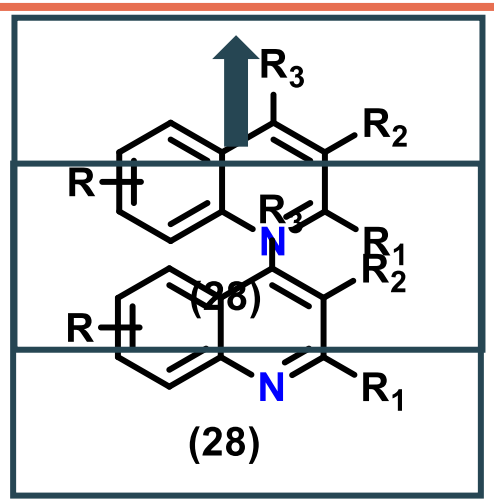
J Mol Struct., **2020**, *1202*, 127310.; *Eur J Med Chem.*, **2015**, *97*, 306–319.; *J Med Chem.*, **2019**, *62*, 993–1013.; *Bioorg Chem.*, **2019**, *85*, 1–17.; *Indian Journal of Chemistry - Section B Organic and Medicinal Chemistry.*, **2010**, *49*, 1109–1116.; *Synthesis.* **2020**, *52*, 1804-1822

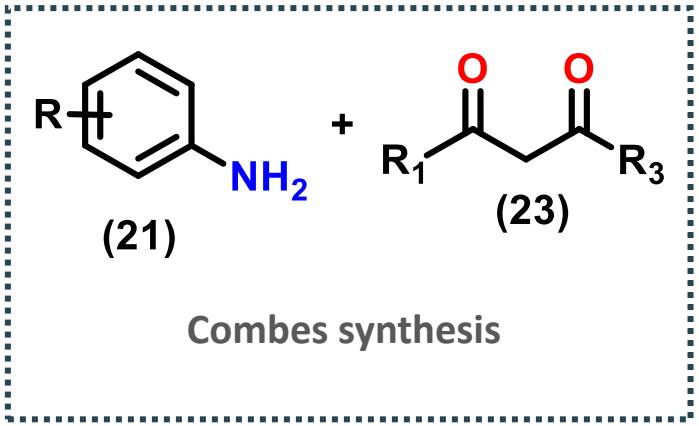
METHODOLOGIES FOR QUINOLINE SYNTHESIS

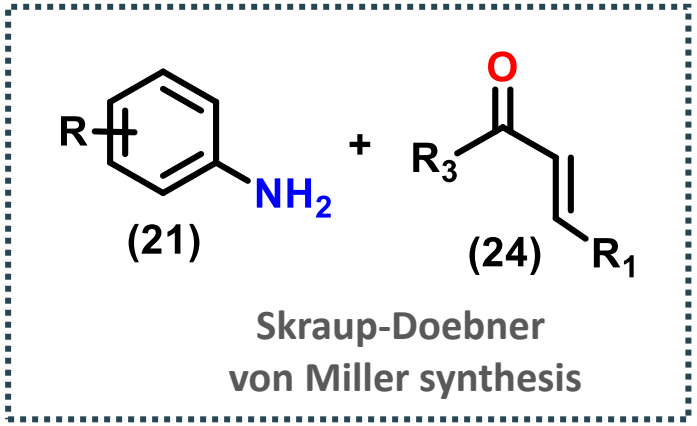










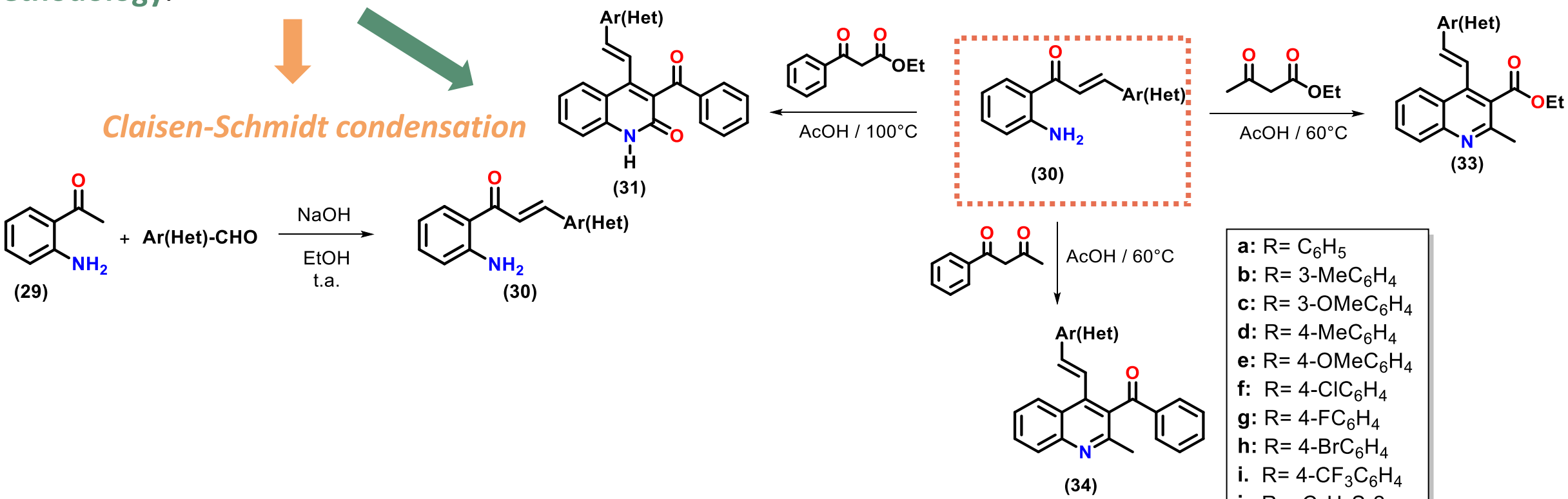


J. Org. Chem., **2006**, *71*, 6592–6595.; *Chem. Rev.*, **1947**, *43*, 43–68.

STYRYLQUINOLINE SYNTHESIS: FRIEDLÄNDER REACTION

PREVIOUS WORKS IN LSO

Synthesis of **4-estirilquinolones (31)** and **4-styrylquinolines (32)-(34)** starting from **2-aminoarylchalcones (30)**, using the ***Friedländer*** **methodology**.

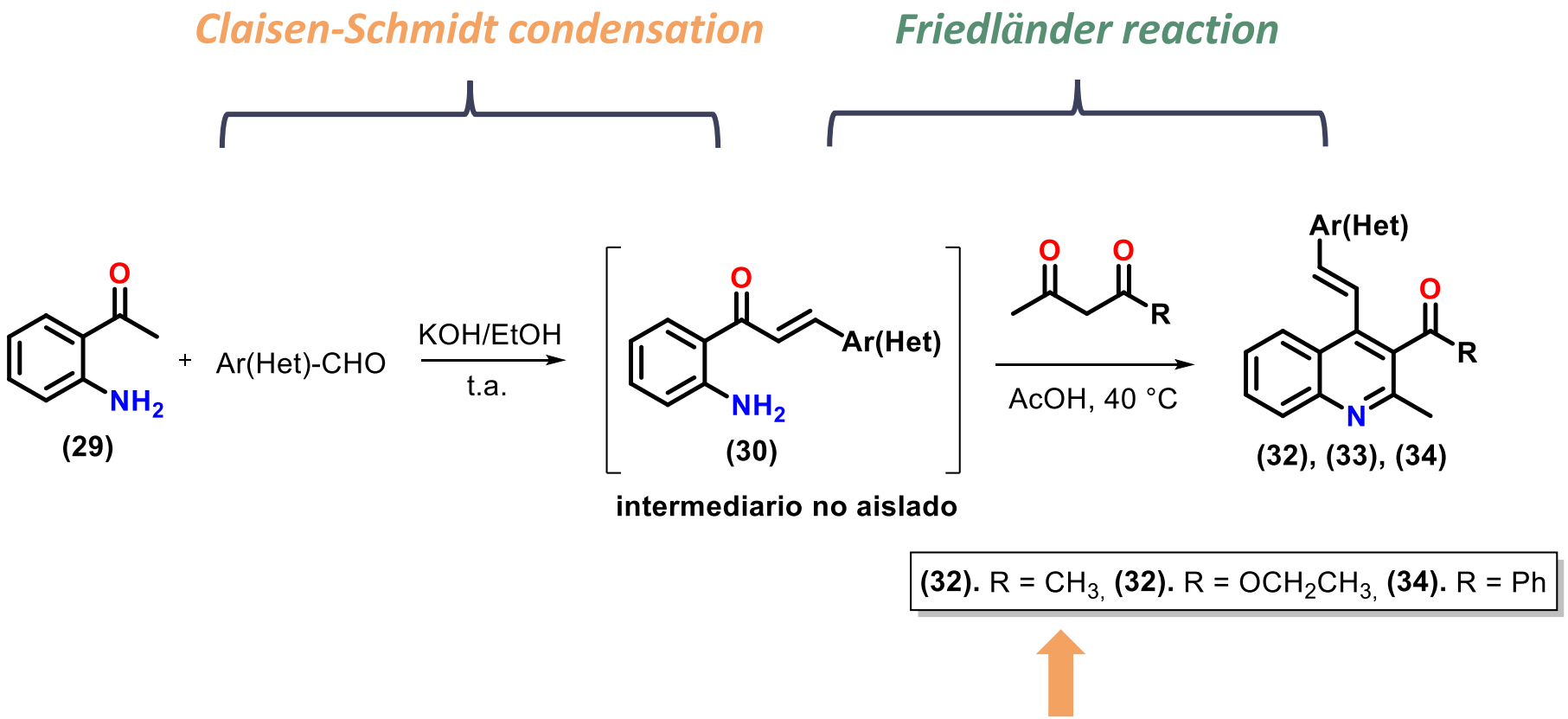


Synthesis. **2020**, *52*, 1804-1822

ESTYRYLQUINOLINES SYNTHESIS: FRIEDLÄNDER REACTION

PREVIOUS WORKS IN LSO

Development of a one-pot two-step methodology, for the **4-styrylquinolines (38)**, **(39)** y **(40)** preparation.



Synthesis. **2020**, *52*, 1804-1822.; Ardila Rodríguez, D. M. *Trabajo de Investigación.* **2020**. UIS; Lipez, K. J. *Tesis de Pregrado*. **2020**. UIS.; Vera Alarcón, D. R. *Tesis de Pregrado*. **2020**. UIS

SYNTHESIS OF STYRYLQUINOLINE-CHALCONE HYBRID

PREVIOUS WORKS IN LSO

Synthesis of novel molecular hybrid **styrylquinoline-chalcone (35)**, using the ***Claisen-Schmidt condensation***

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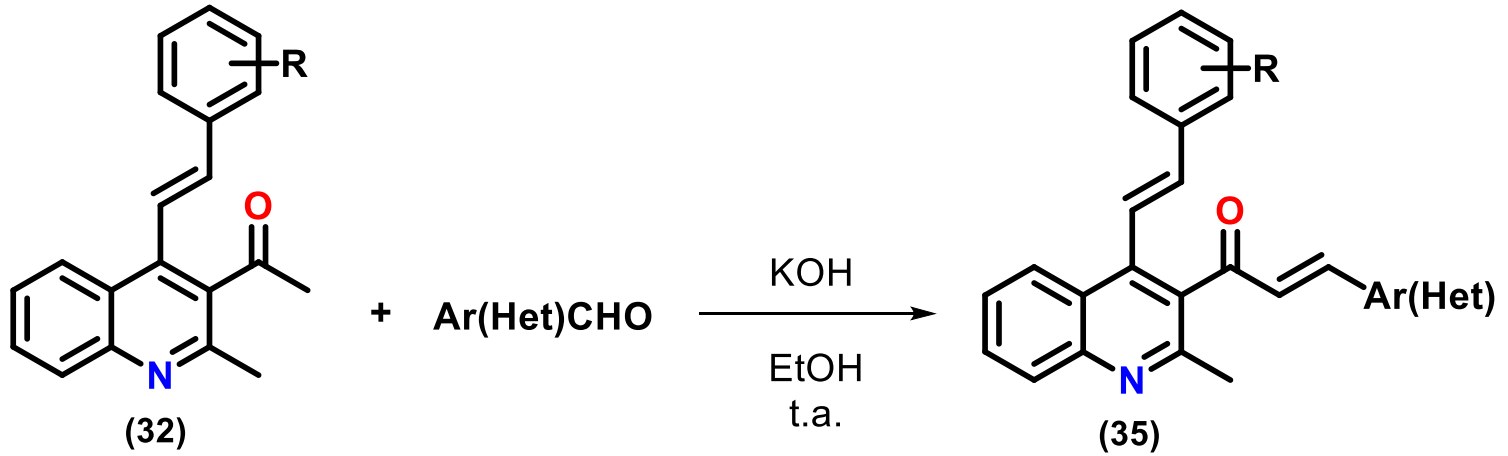


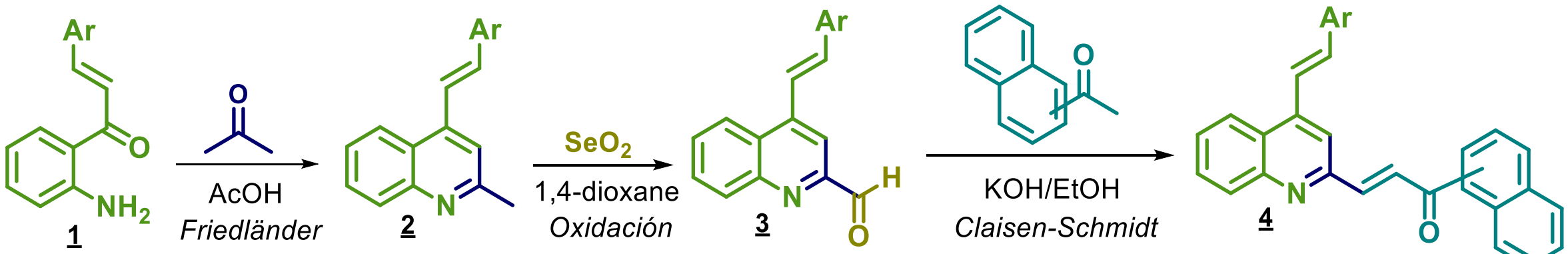
Ar = 4-$(OCH_3)C_6H_4$; 2,3-di$(OCH_3)C_6H_4$; 2,4-di$(OCH_3)C_6H_4$; 2,5-di$(OCH_3)C_6H_4$; 3,4-di$(OCH_3)C_6H_4$; 3,4,5-tri$(OCH_3)C_6H_4$;4-Cl; 4-F; 4-CF_3; 3-OH-4-OCH_3. **Het =** 1,3-benzodioxol-5-yl; C_4H_3S-2; C_5H_4N-3

Synthesis. **2020**, *52*, 1804-1822.; Ardila Rodríguez, D. M. *Trabajo de Investigación.* **2020**. UIS.; Rodríguez Ibañez, D. F. Tesis de Pregrado. **2019**. UIS.

CURRENT WORK

LSO

Synthetic route designed and developed for the new **hybrids of styrylquinoline-chalcone** **4** type.



Ar = C_6H_5; 2-ClC_6H_4; 2,3-ClC_6H_3; 2,6-ClC_6H_3; 2-Cl-6-FC_6H_3; 3-ClC_6H_4; 3,4-ClC_6H_3; 4-ClC_6H_4; 4-BrC_6H_4; 4'-FC6H4.

CHARACTERIZED BY:

IR, HRMS (Q-TOF-ESI), RMN ^{1}H,^{13}C, HMBC

RESULTS

STEP 1

Strategic precursor synthesis:
4-styryl-2-methylquinolines 2.

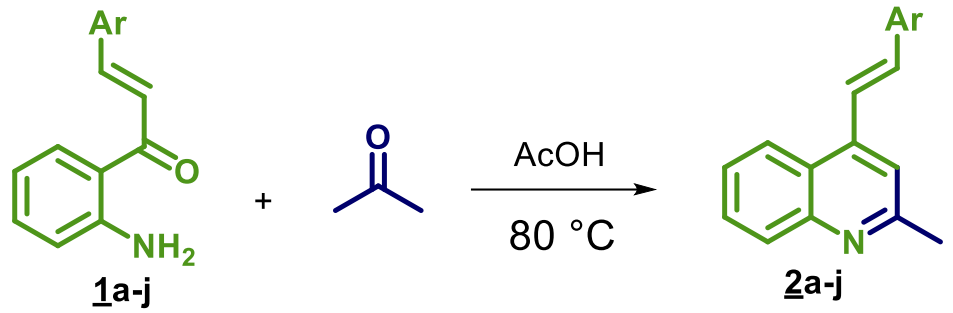
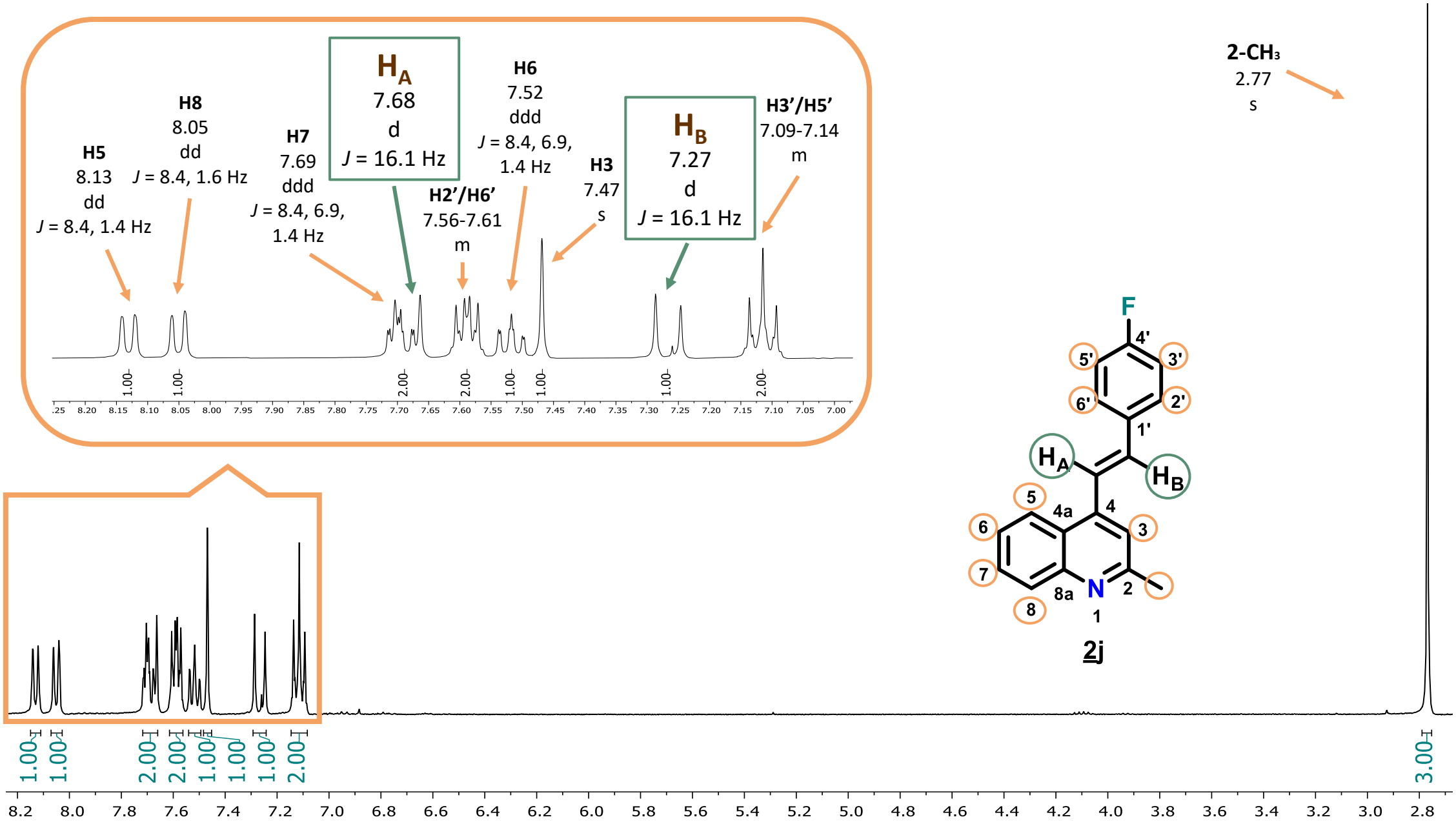


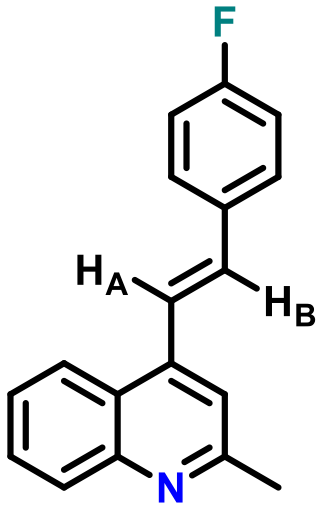
Table 1. Yields, m.p., and reaction time for compounds **2a-j**.

Compound	Ar	[%] Yield	m.p. [°C]	t [h]
3a	C_6H_5	86	94-96	15
3b	2-ClC_6H_4	79	115-117	14
3c	3-ClC_6H_4	87	72-74	12
3d	4-ClC_6H_4	85	126-128	14
3e	2,3-$Cl_2C_6H_3$	84	136-138	13
3f	3,4-$Cl_2C_6H_3$	72	133-135	14
3g	2,6-$Cl_2C_6H_3$	94	137-139	14
3h	2–Cl,6-FC_6H_3	74	102-104	17
3i	4–BrC_6H_4	81	119-121	13
3j	4-FC_6H_4	84	122-124	15

^{1}H NMR SPECTRUM OF 2j ($CDCl_3$)



STRUCTURAL CORROBORATION OF 2j



2j

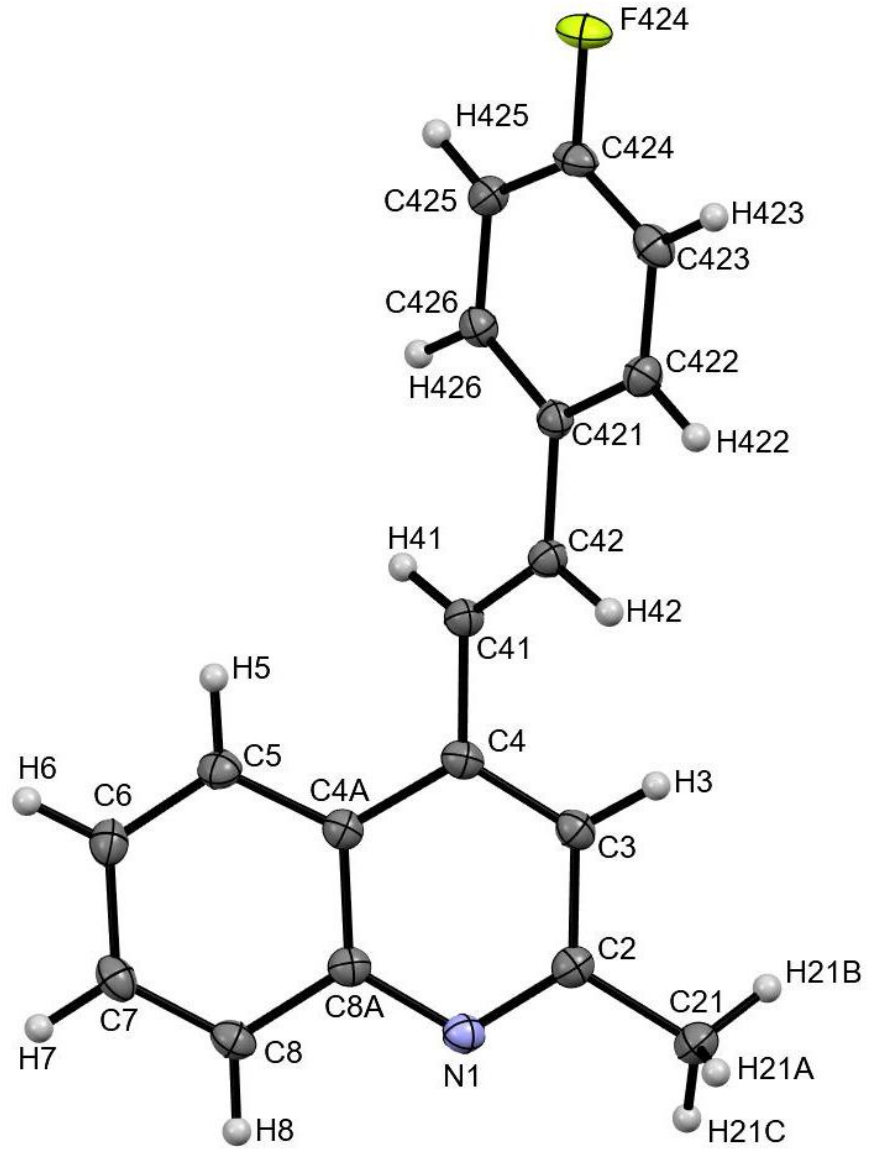


Figure 1. ORTEP diagram of **2j**.

Molecular formula	**$C_{18}H_{14}FN$**
Spatial group	P 2_1/c
Cell lenght	**a** 13.5921(7) **b** 12.7103(6) **c** 7.6215(3)
Cell angles	**α** 90 **β** 103.133(2) **ɤ** 90
Cell volume	1282.25
Z, Z’	**Z**: 4 **Z’**: 1
Factor-R	4.20

STEP 2

Synthesis of the intermediates:
4-styryl-2-formylquinolines 3.

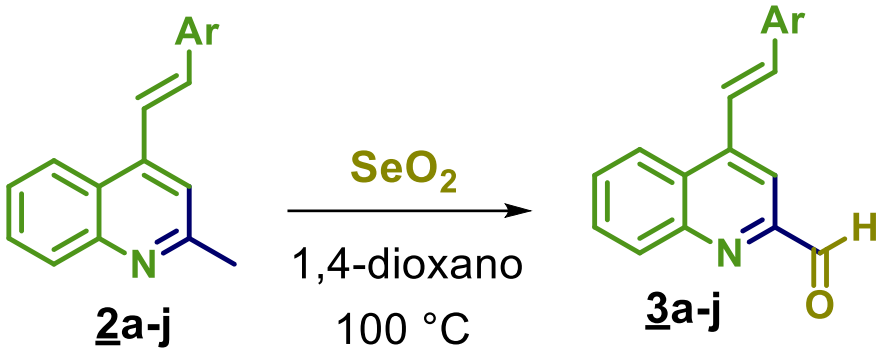
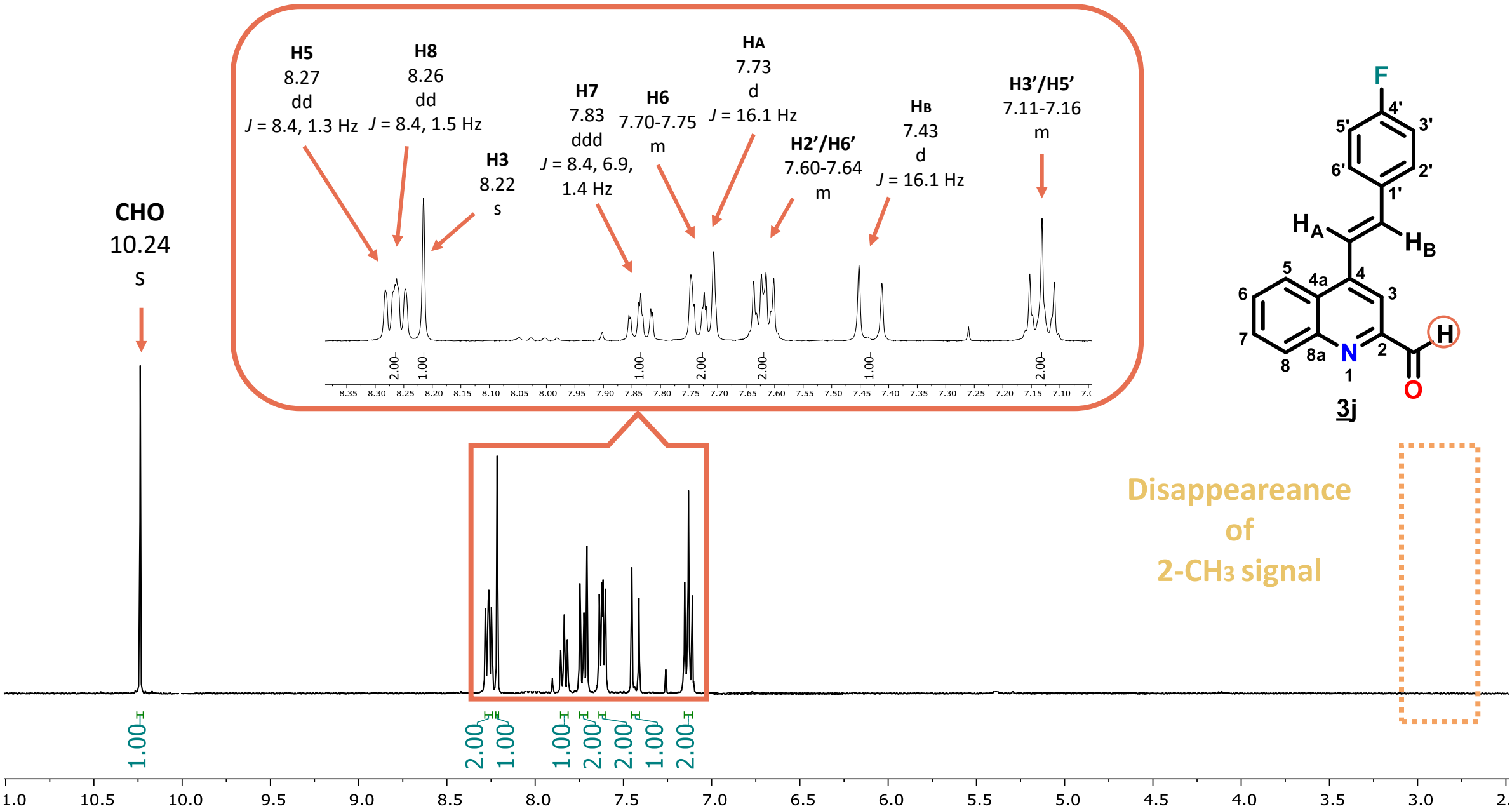


Table 2. Yields, m.p., and reaction time for **3a-j**.

Compound	Ar	[%] Yield	m.p. [°C]	t [h]
3a	C_6H_5	96	148-150	1
3b	2-ClC_6H_4	92	158-160	2
3c	3-ClC_6H_4	92	196-198	2
3d	4-ClC_6H_4	86	184-186	2
3e	2,3-$Cl_2C_6H_3$	91	195-195	1
3f	3,4-$Cl_2C_6H_3$	92	191-193	1
3g	2,6-$Cl_2C_6H_3$	96	179-181	1
3h	2–Cl,6-FC_6H_3	97	192-194	2
3i	4–BrC_6H_4	90	183-185	2
3j	4-FC_6H_4	89	144-146	1

^{1}H NMR SPECTRUM OF 3j ($CDCl_3$)



RESULTS

STEP 3

Synthesis of the new molecular hybrid of type **styrylquinoline-chalcone 4**.

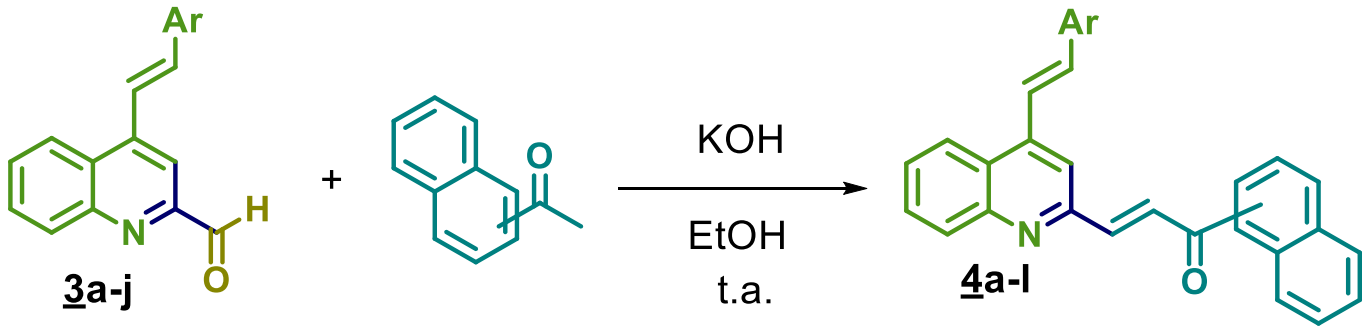
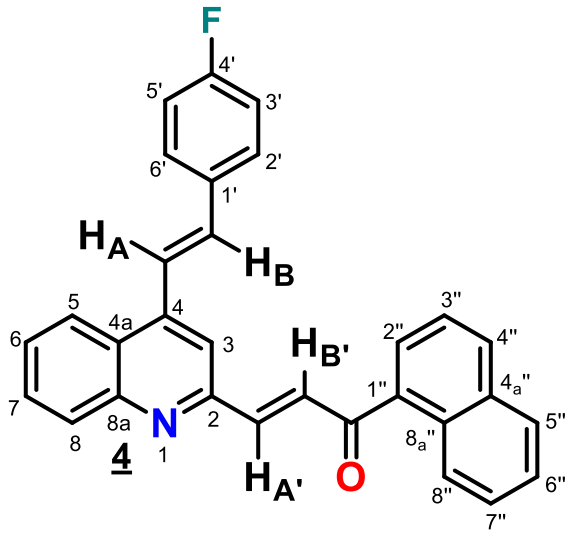


Table 3. Yields, m.p., and reaction time for **4a-l**.

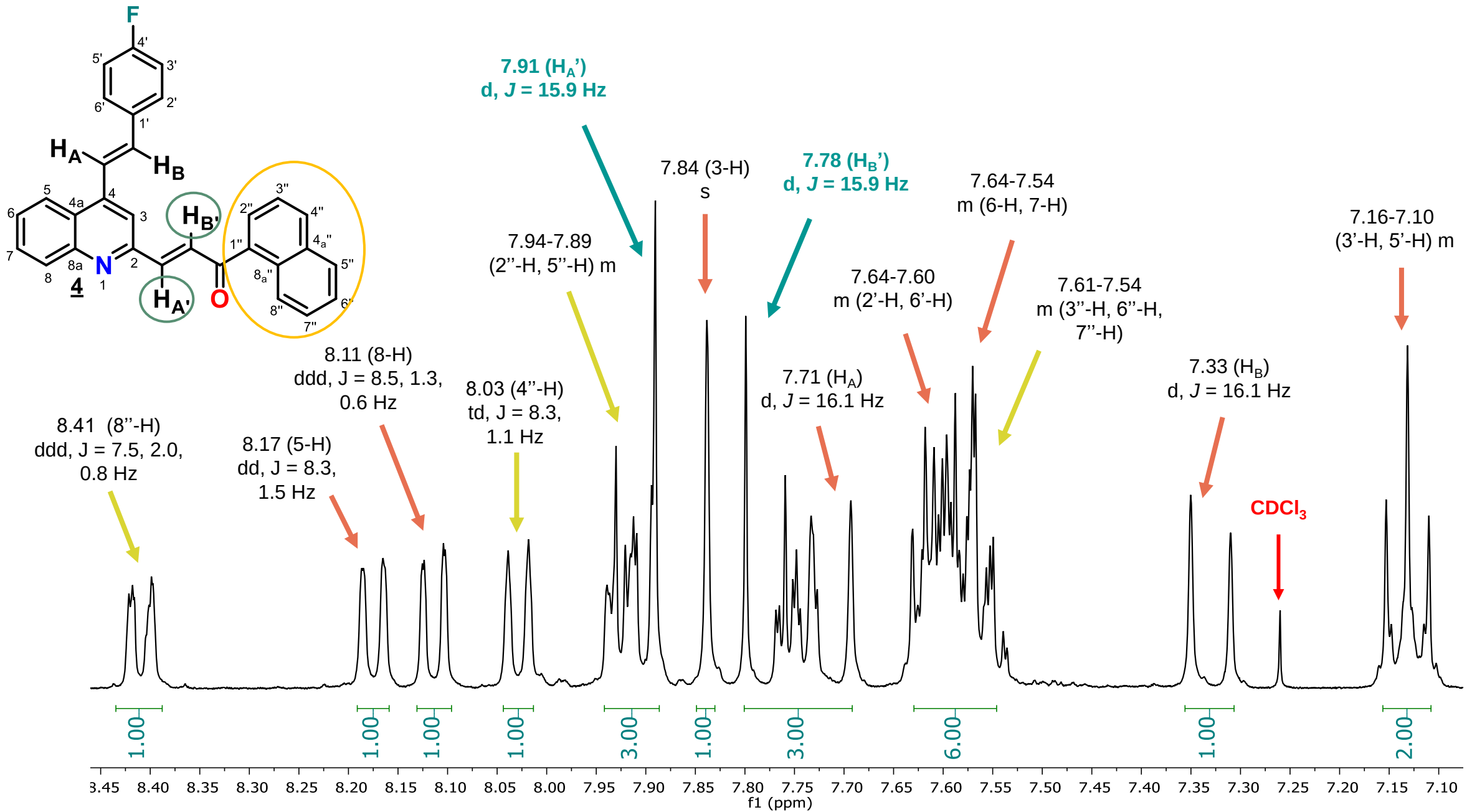
Compound	Ar	Ar'	t [h]	[%] yield	m. p. [°C]
4a	C_6H_5	1-$C_{10}H_7$	4	82	177 – 179
4b	2-ClC_6H_4	1-$C_{10}H_7$	1	95	168 – 170
4c	3-ClC_6H_4	1-$C_{10}H_7$	1	96	139 – 141
4d	4-ClC_6H_4	1-$C_{10}H_7$	2	93	183– 185
4e	2,3-$Cl_2C_6H_3$	1-$C_{10}H_7$	2	94	186 – 188
4f	3,4-$Cl_2C_6H_3$	1-$C_{10}H_7$	2	92	167 – 169
4g	2,6-$Cl_2C_6H_3$	1-$C_{10}H_7$	1	97	181 – 183
4h	2-Cl-6-FC_6H_3	1-$C_{10}H_7$	3	93	185 – 187
4i	4-BrC_6H_4	1-$C_{10}H_7$	2	88	169 – 171
4j	4-FC_6H_4	1-$C_{10}H_7$	2	81	178 – 180
4k	C_6H_5	2-$C_{10}H_7$	4	86	213 – 215
4l	2-Cl-6-FC_6H_3	2-$C_{10}H_7$	3	89	208 – 210

^{1}H NMR SPECTRUM OF 4j ($CDCl_3$)

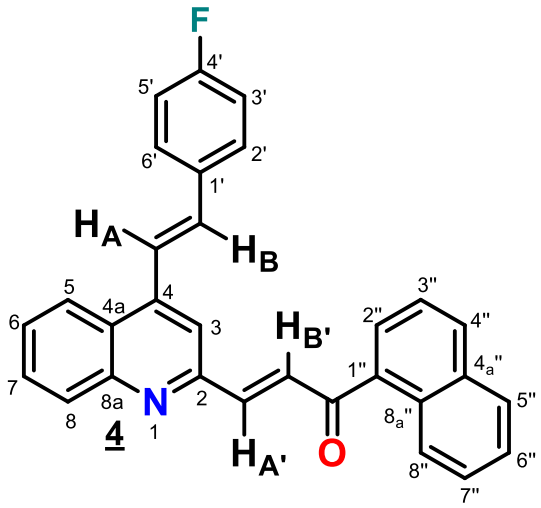


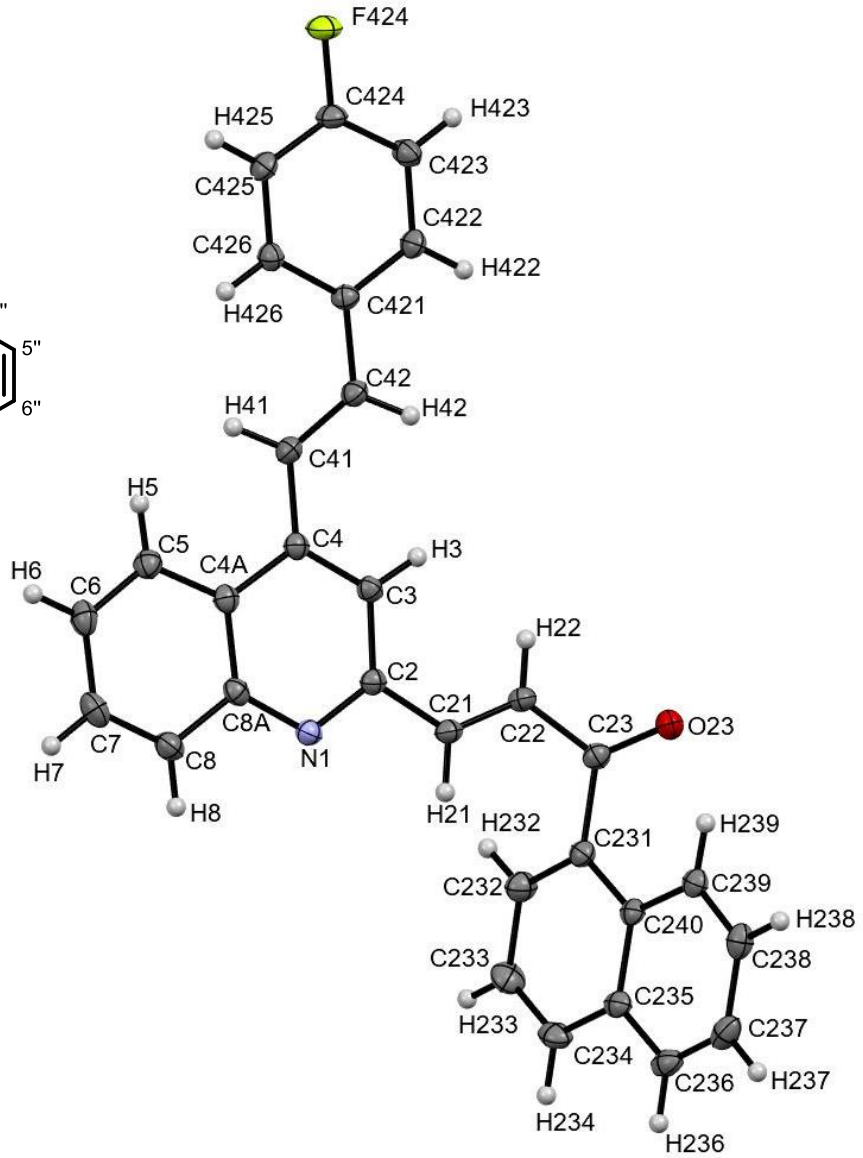
Disappearance of 2-CHO signal

^{1}H NMR SPECTRUM OF 4j ($CDCl_3$)



STRUCTURAL CORROBORATION OF 4j





Molecular formula	**$C_{30}H_{20}FNO$**
Spatial group	P $\bar{1}$ (2)
Cell lenght	**a** 9.6679(12) **b** 10.1279(12) **c** 12.6482(13)
Cell angles	**α** 111.420(4) **β** 103.871(4) **ɤ** 96.632(5)
Cell volume	1090.68
Z, Z’	**Z**: 2 **Z’**: 1
Factor-R	4.44

CONCLUSIONS

- Following the facile synthesis methodology developed in LSO, from **2'-aminoarylchalcones** **1a-j** we reported the synthesis of **(*E*)-2-methyl-4-styrylquinolines** **2a-j** through *Friedländer* reaction.

- **(*E*)-2-methyl-4-styrylquinolines** **2a-j** were transformed into **(*E*)-2-formyl-4-styrylquinolines** **3a-j**, using selenium dioxide as oxidizing agent.

- Finally, by the *Claisen-Schmidt* condensation of the **formyl derivatives** **2a-j** with acetonaphtones, we successfully obtained the novel **quinolinyl-chalcones** **4a-l** hybrid in good yields.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OUR LABORATORY, LSO

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Ph.D. Alirio Palma


M.Sc. Student


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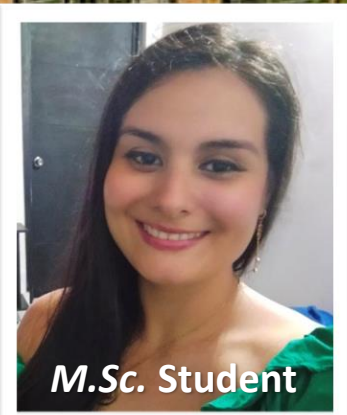
M.Sc. Student

OBRIGADO