Design, synthesis and *in-silico* study of 2,4-diphenylquinolines on KDM4B proteins

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Supporting information

1. Chemistry: General information

The reactions were carried out in a 400 W Biotage® Initiator+ microwave and once finished, the formation of the product was confirmed by thin layer chromatography (TLC), using 0.25 mm thick UV silufol chromatoplates, TLC silica gel. The purification of the products present in the reaction crude was done by column chromatography supported on solid silica gel using eluent mixtures of petroleum ether: ethyl acetate, with gradual increase of polarity. All reagents and solvents used in the synthesis of 2,4-diphenylquinolines were purchased from Sigma Aldrich and Merck. **^{1}H NMR** spectra were recorded on a Bruker Avance-400 (400 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm; DMSO-d_6: δ 2.50 ppm). Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, br = broad, m = multiplet), coupling constants (Hz) and integration. **^{13}C NMR** spectra were recorded on a Bruker Avance-400 (400 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from solvent resonance as the internal standard ($CDCl_3$: δ 77.00 ppm). A Bruker spectrophotometer, tensor 27 on KBr pellets was used to record the **IR** spectra.

General procedure for the synthesis of 2,4-diphenylquinoline 11:

In a 5 mL vial, aniline **14a-g** (1 mmol), phenylacetylene **13** (1.5 mmol), benzaldehyde **15a,b** (1 mmol), and iodine (0.4 mmol) in 1.67 mL of glacial CH_3COOH were added. The vial was hermetically sealed, placed in MW apparatus, and irradiated for 30 min at 160 °C. The progress of the reaction was monitored with aid of TLC. The reaction mass was neutralized with sodium bicarbonate ($NaHCO_3$) solution to pH ≅ 9, which was washed with a saturated $Na_2S_2O_3$ and brine solution. The crude was extracted with dichloromethane. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure by solvent evaporation. The products **11** was purified by column supported on silica gel using petroleum ether: ethyl acetate; with a 30:1 polarity.

Procedure for the synthesis of 6-methyl-4-phenyl-2-(pyridin-2-yl)quinoline (**12**):

In a 5 mL vial, aldimine **17** (0.66 g, 3.37 mmol), previously synthesized, phenylacetylene **13** (0.52 g, 555.1 µL, 5.06 mmol), and iodine (0.34 g, 1.3 mmol) in 1.67 mL of glacial CH_3COOH were added. The vial was hermetically sealed, placed in MW apparatus, and irradiated for 30 min at 160 °C. The progress of the reaction was monitored with aid of TLC. The reaction mass was neutralized with sodium bicarbonate ($NaHCO_3$) solution to pH ≅ 9, which was washed with a saturated $Na_2S_2O_3$ and brine solution. The crude was extracted with dichloromethane. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure by solvent evaporation. The product was purified by column supported on silica gel using petroleum ether: ethyl acetate; with a 10:1 polarity

*1.1. Compound spectrum **11a-h** and **12.***

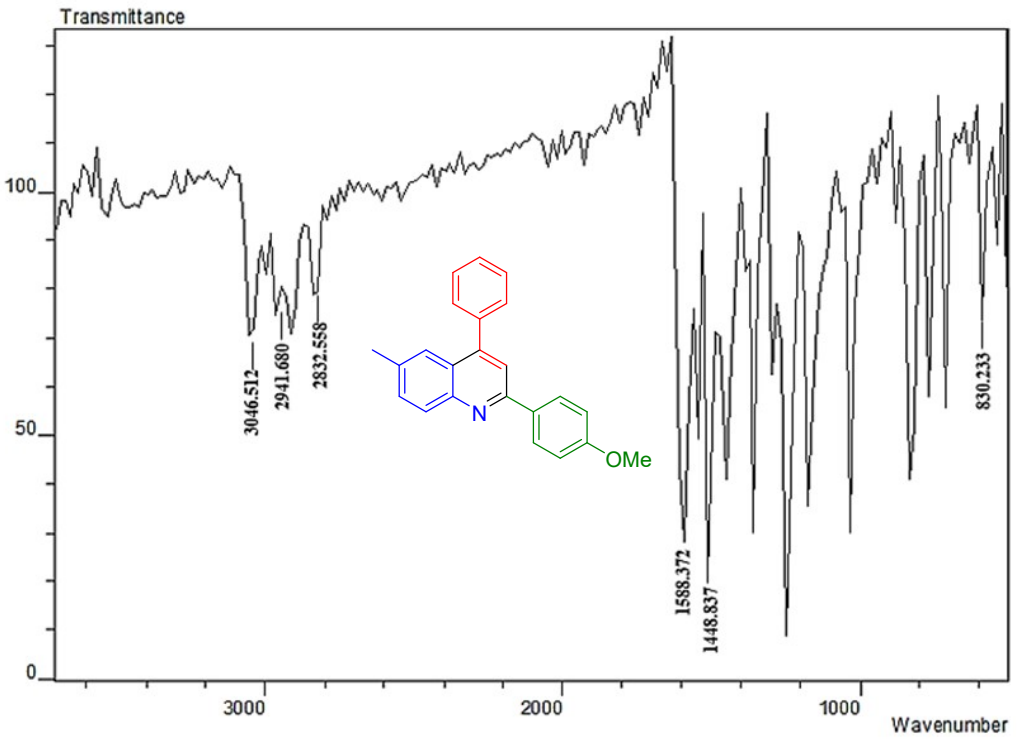

Figure S1. IR spectrum of 2-(4-methoxyphenyl)-6-methyl-4-phenylquinoline (**11a**)

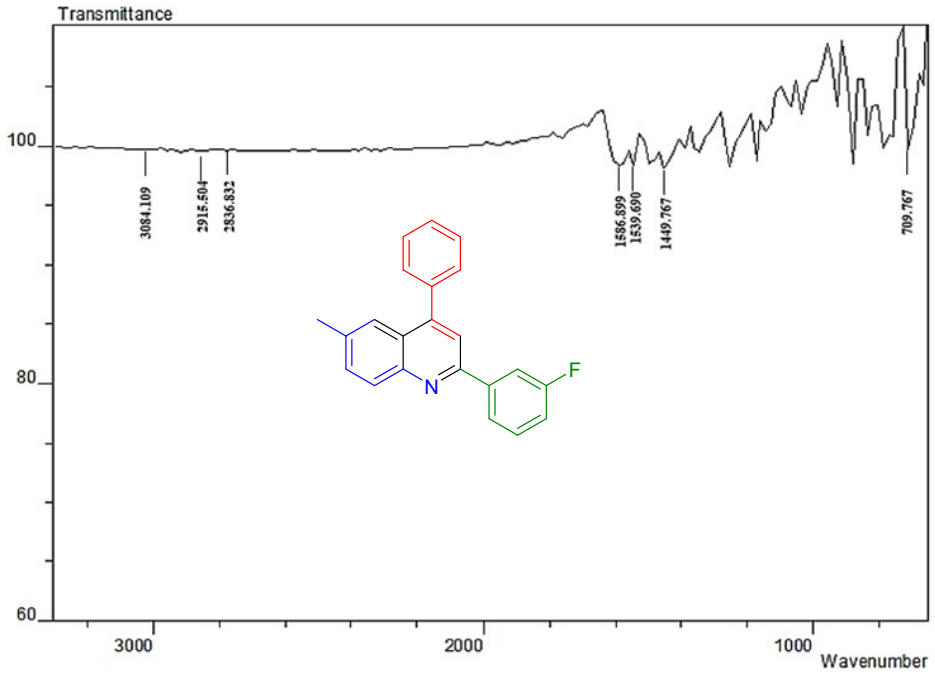

Figure S2. IR spectrum of 2-(3-fluorophenyl)-6-methyl-4-phenylquinoline (**11b**)

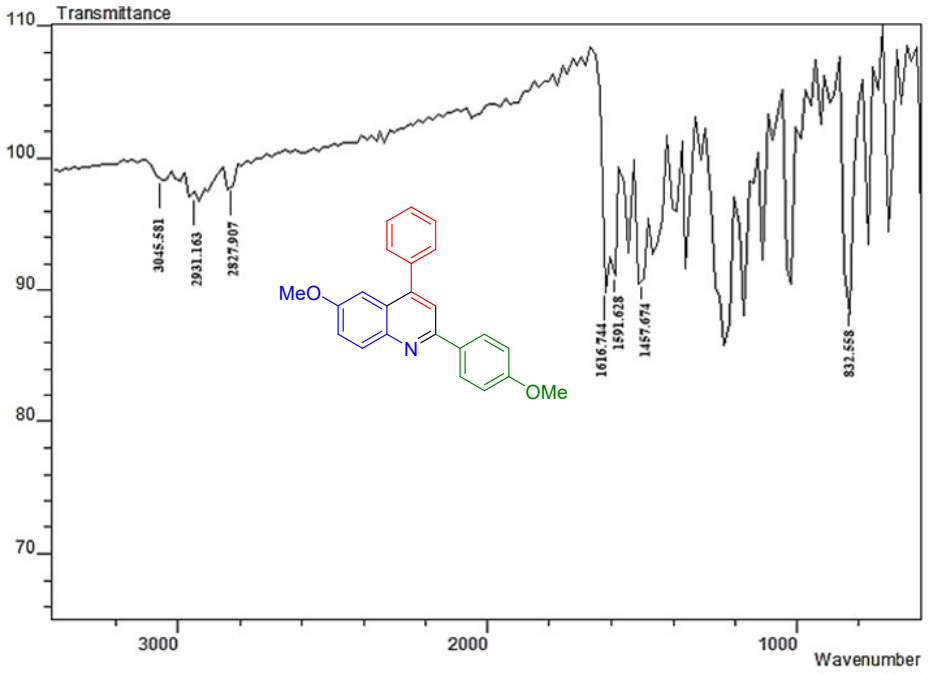

Figure S3. IR spectrum of 6-methoxy-2-(4-methoxyphenyl)-4-phenylquinoline (**11c**)

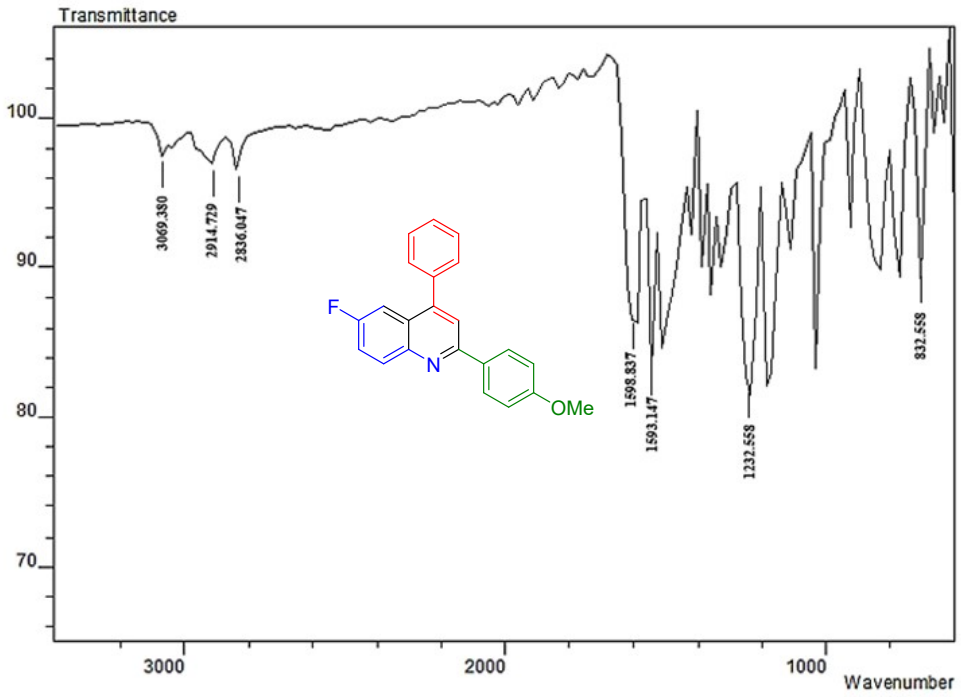

Figure S4. IR spectrum of 6-fluoro-2-(4-methoxyphenyl)-4-phenylquinoline (**11d**)

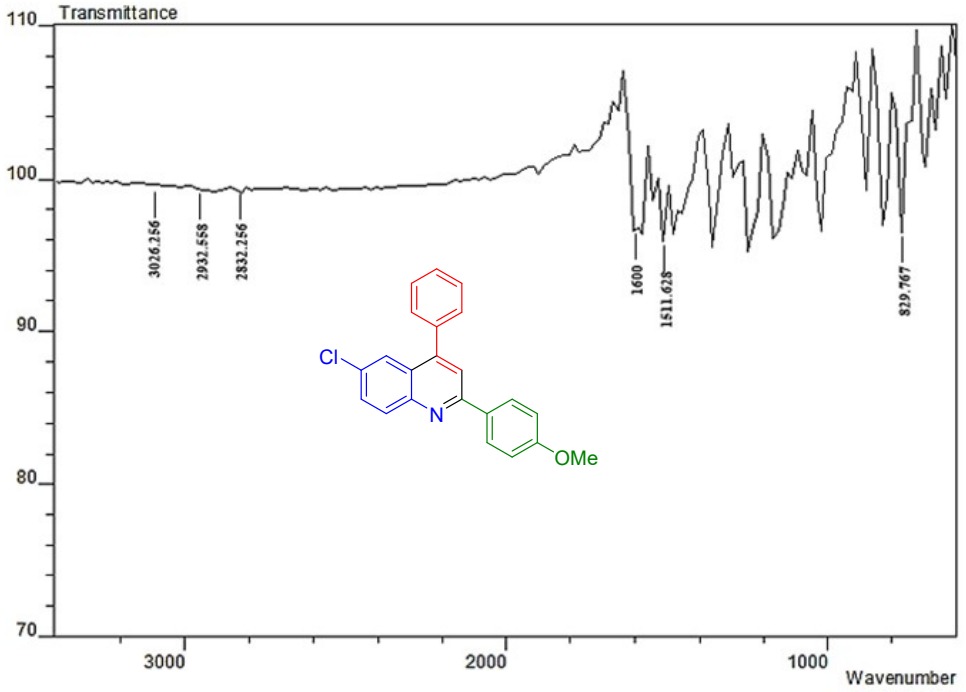

Figure S5. IR spectrum of 6-chloro-2-(4-methoxyphenyl)-4-phenylquinoline (**11e**)

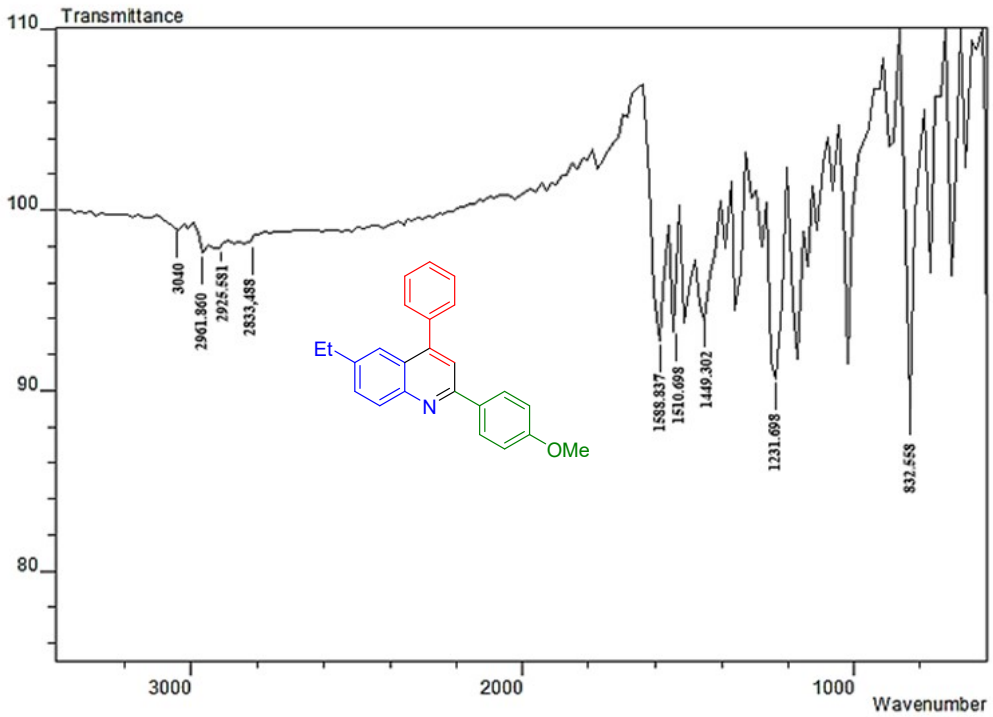

Figure S6. IR spectrum of 6-ethyl-2-(4-methoxyphenyl)-4-phenylquinoline (**11f**)

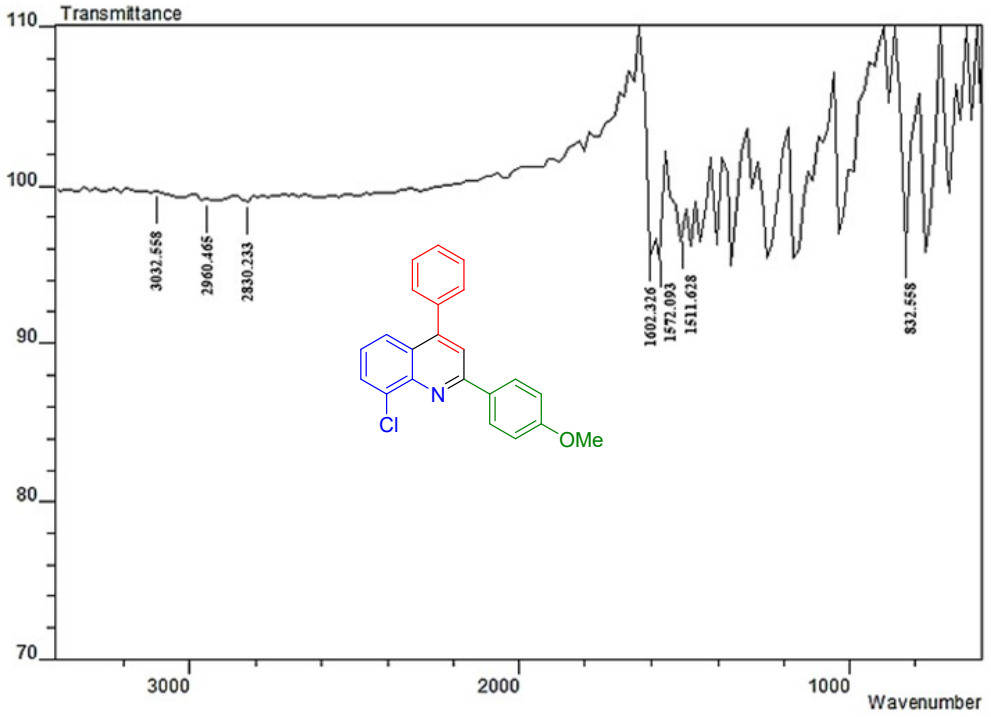

Figure S7. IR spectrum of 8-chloro-2-(4-methoxyphenyl)-4-phenylquinoline (**11g**).

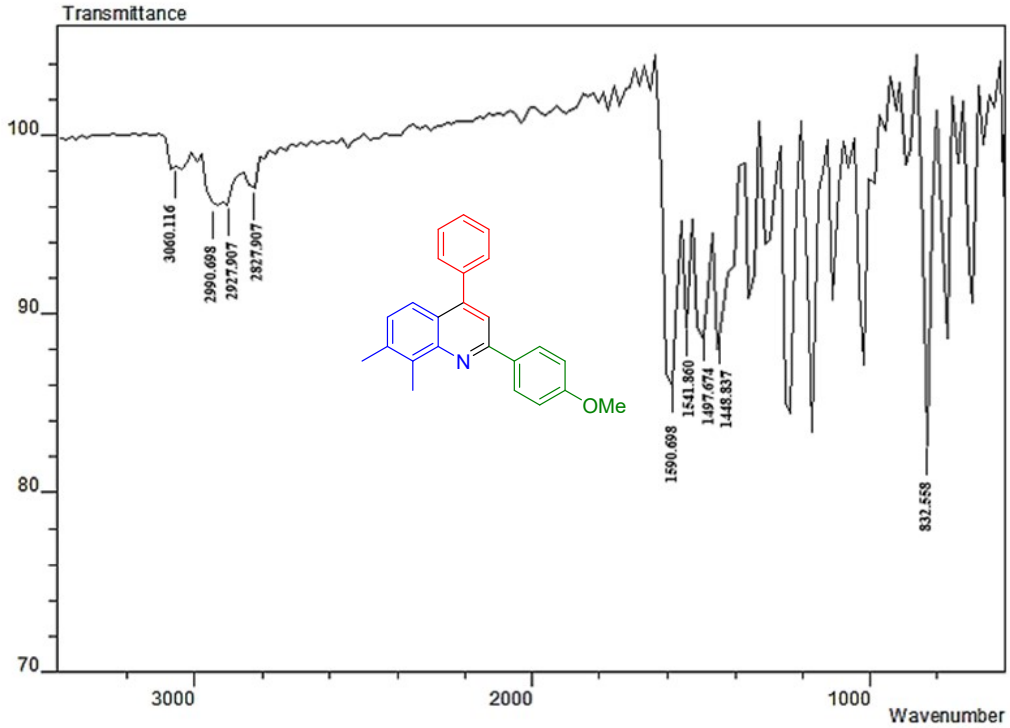

Figure S8. IR spectrum of 2-(4-methoxyphenyl)-7,8-dimethyl-4-phenylquinoline (**11h**)

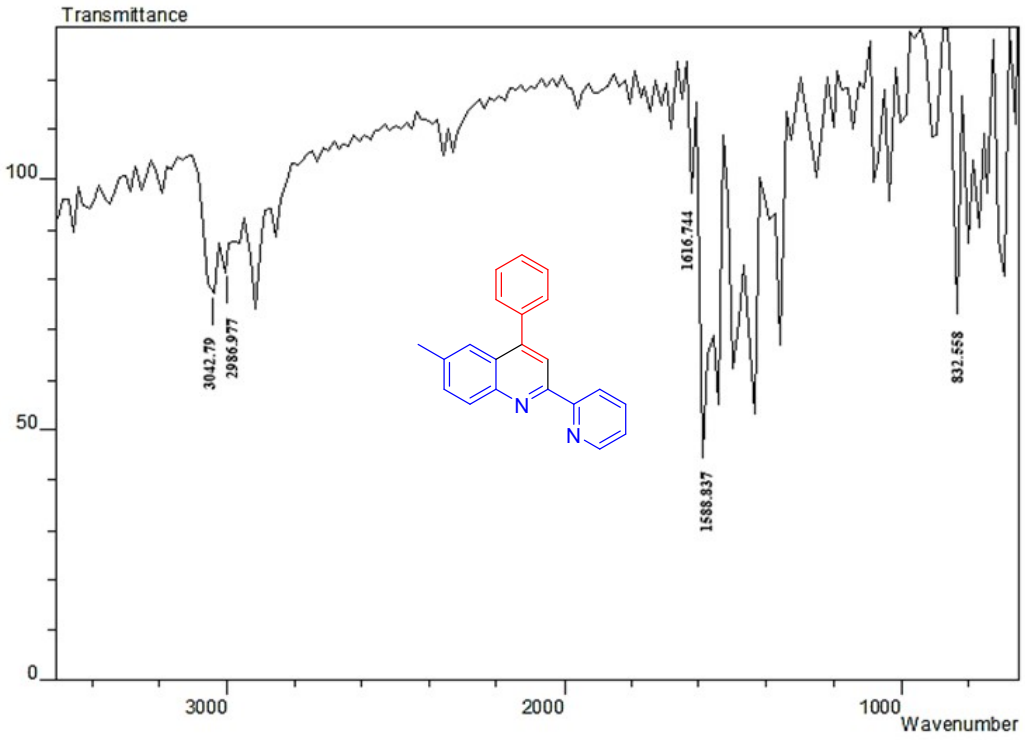

Figure S9 IR spectrum of 6-methyl-4-phenyl-2-(pyridin-2-yl)quinoline (**12**)

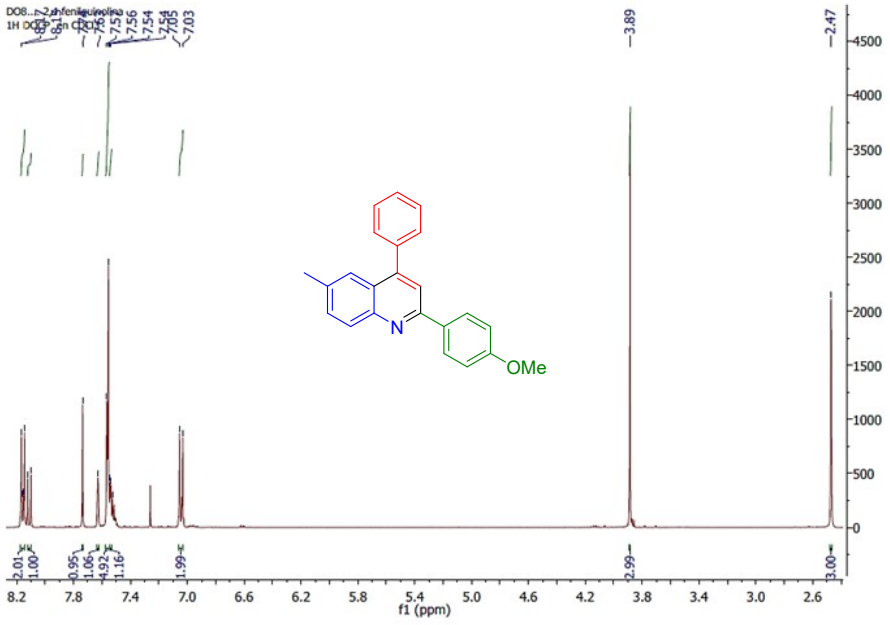

Figure S10. ^{1}H NMR spectrum of 2-(4-methoxyphenyl)-6-methyl-4-phenylquinoline (**11a**)

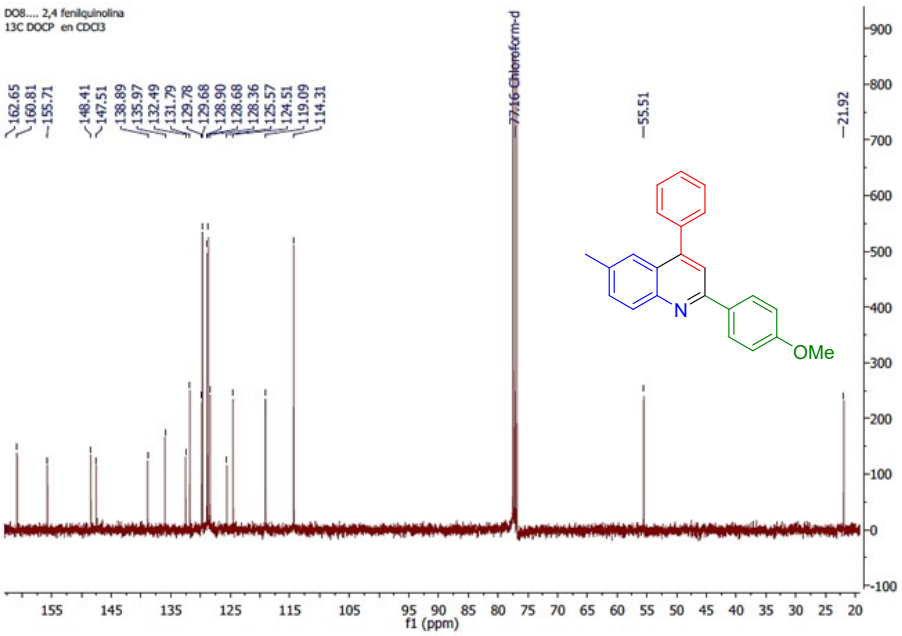

Figure S11. ^{13}C NMR spectrum of 2-(4-methoxyphenyl)-6-methyl-4-phenylquinoline (**11a**)

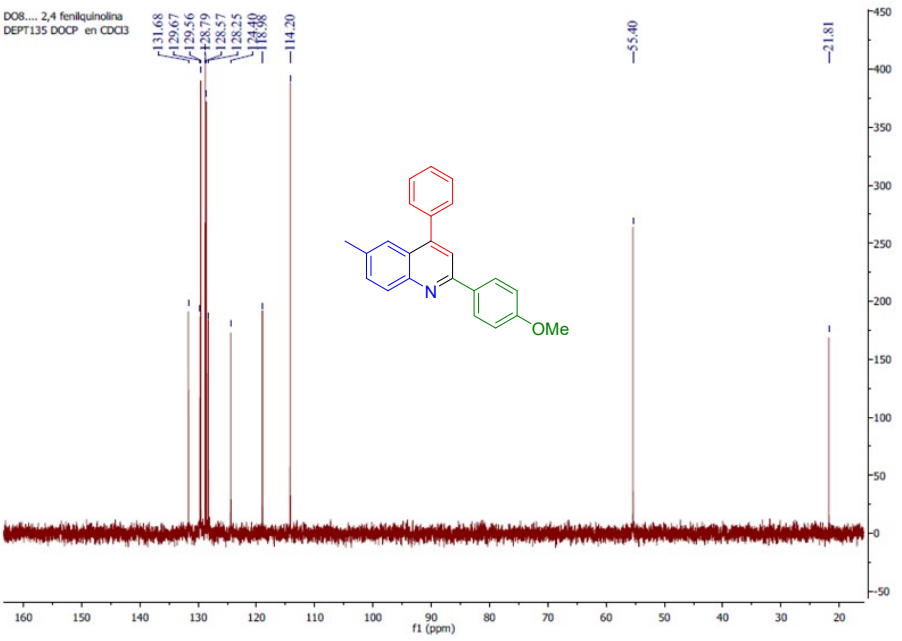

Figure S12. DEPT spectrum of 2-(4-methoxyphenyl)-6-methyl-4-phenylquinoline (**11a**)

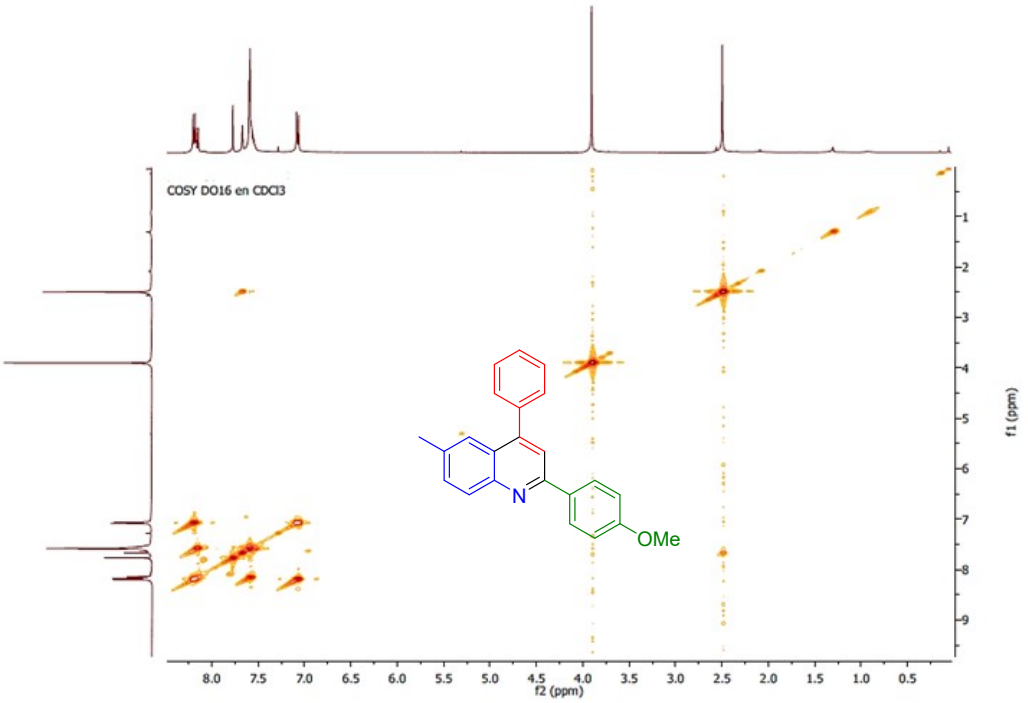

Figure S13. COSY spectrum of 2-(4-methoxyphenyl)-6-methyl-4-phenylquinoline (**11a**).

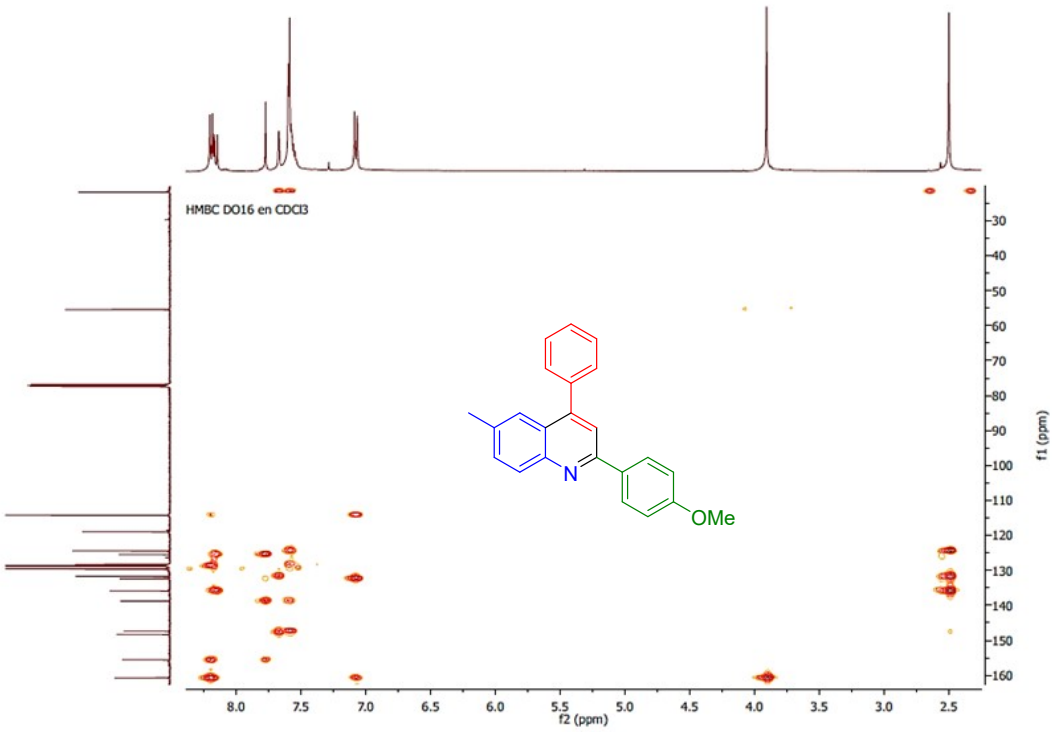

Figure S11. HMBC spectrum of 2-(4-methoxyphenyl)-6-methyl-4-phenylquinoline (**11a**).

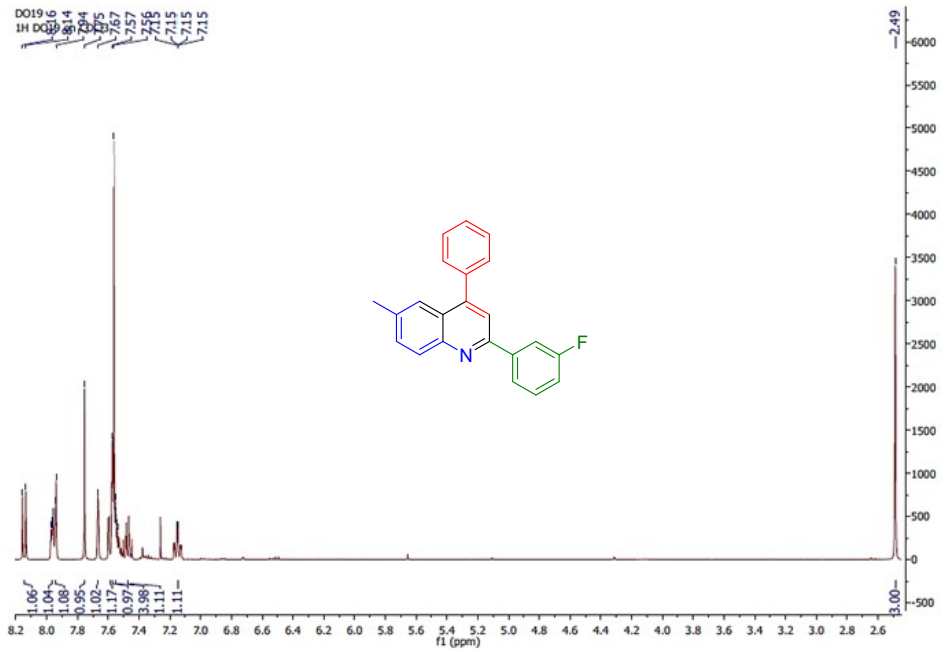

Figure S15. ^{1}H NMR spectrum of 2-(3-fluorophenyl)-6-methyl-4-phenylquinoline (**11b**).

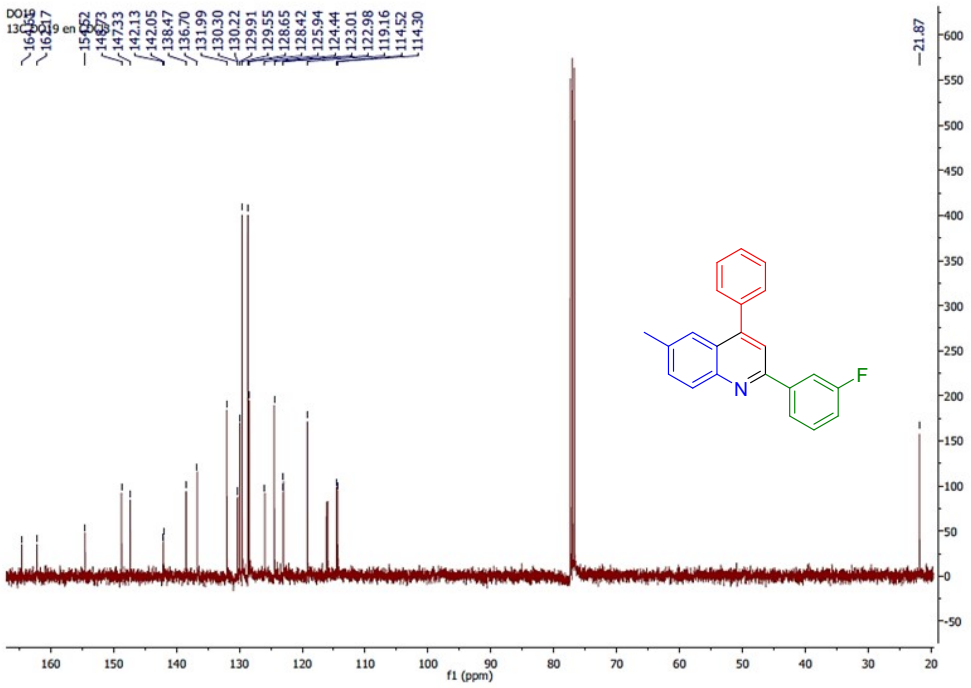

Figure S12. ^{13}C NMR spectrum of 2-(3-fluorophenyl)-6-methyl-4-phenylquinoline (**11b**).

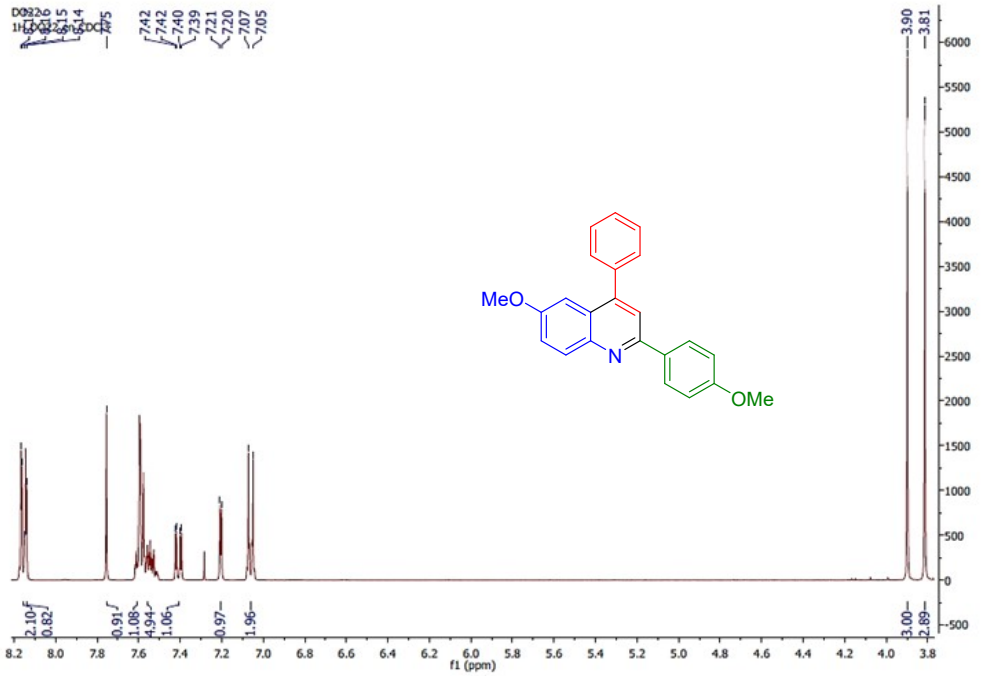

Figure S17. ^{1}H NMR spectrum of 6-methoxy-2-(4-methoxyphenyl)-4-phenylquinoline (**11c**)

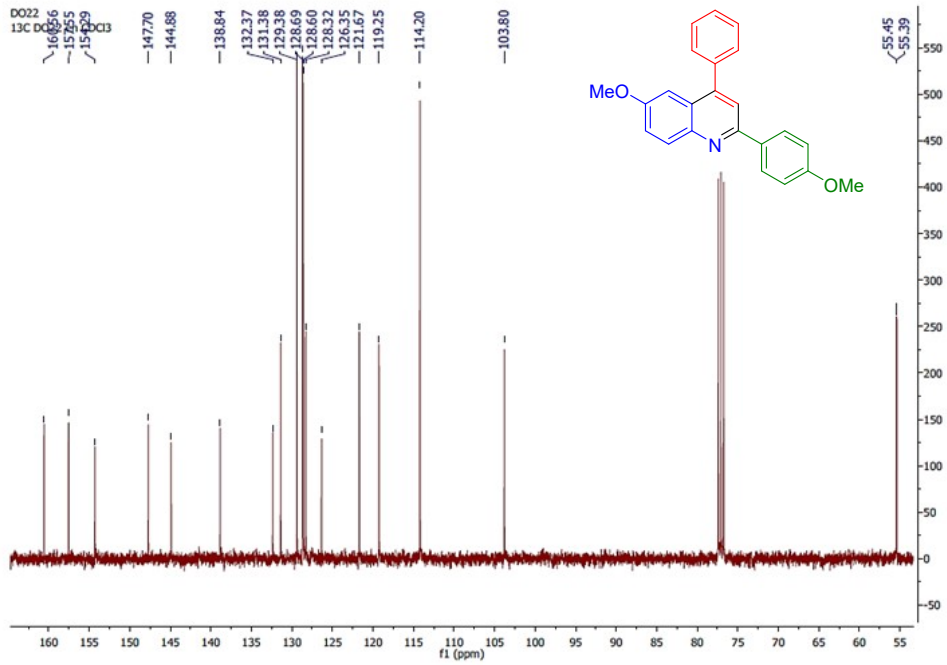

Figure S18. ^{13}C NMR spectrum of 6-methoxy-2-(4-methoxyphenyl)-4-phenylquinoline (**11c**)

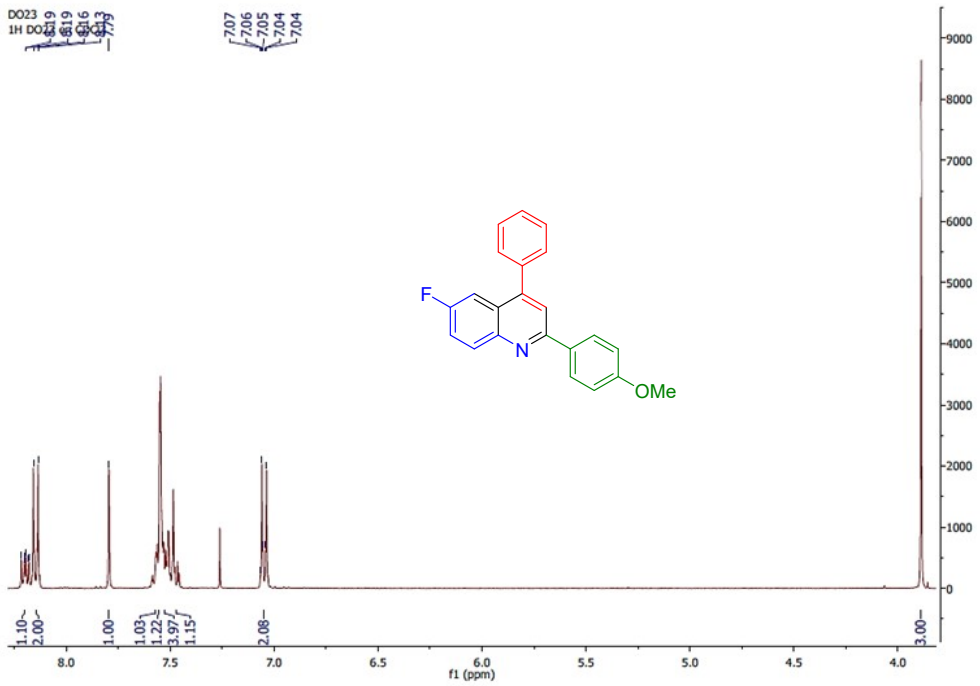

Figure S19. ^{1}H NMR spectrum of 6-fluoro-2-(4-methoxyphenyl)-4-phenylquinoline (**11d**)

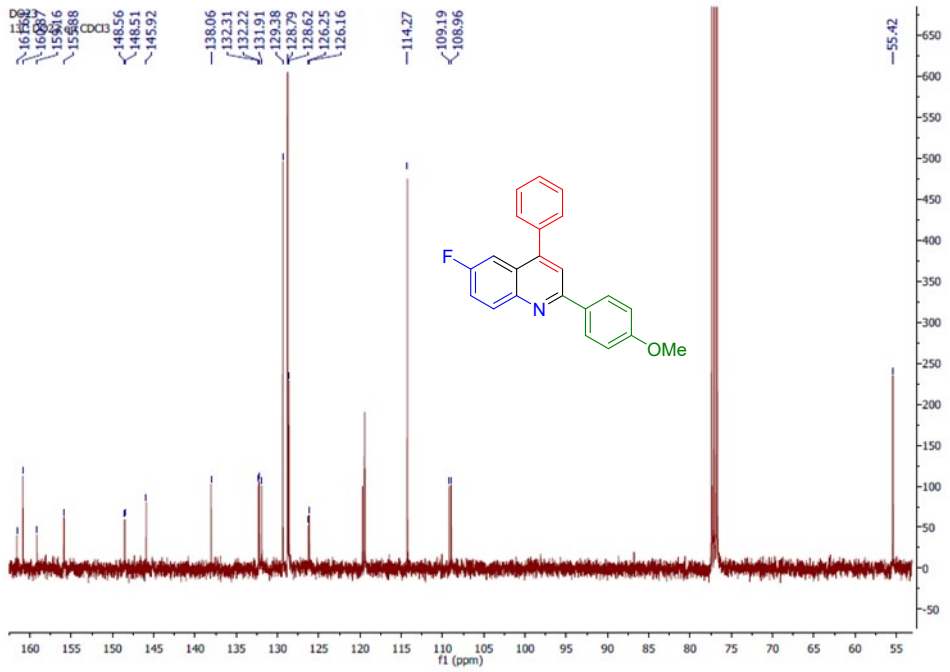

Figure S20. ^{13}C NMR spectrum of 6-fluoro-2-(4-methoxyphenyl)-4-phenylquinoline (**11d**)

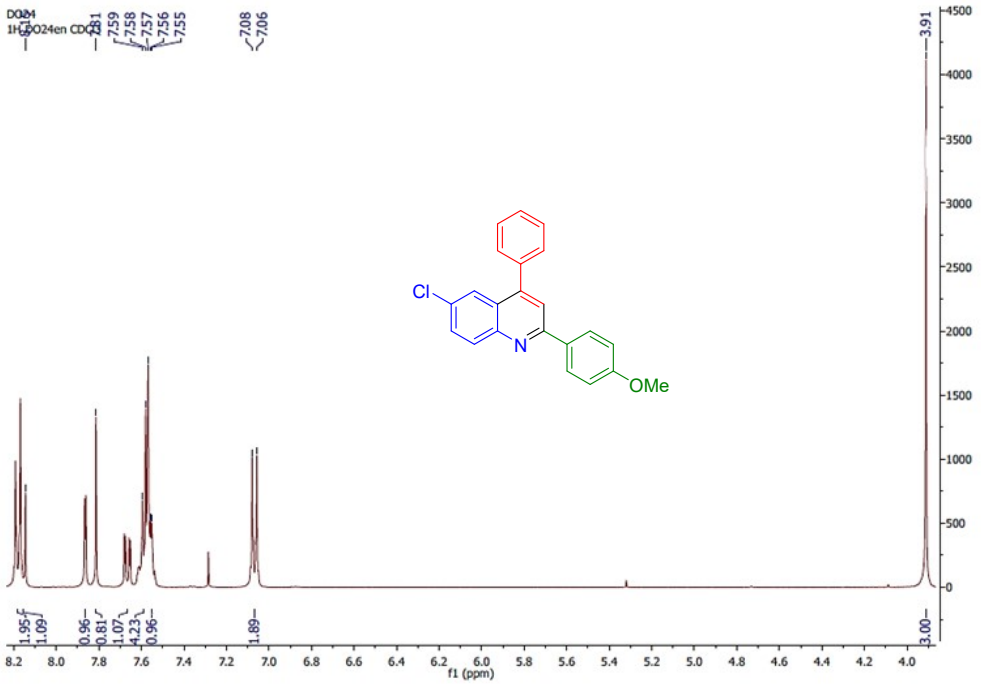

Figure S21. ^{1}H NMR spectrum of 6-chloro-2-(4-methoxyphenyl)-4-phenylquinoline (**11e**).

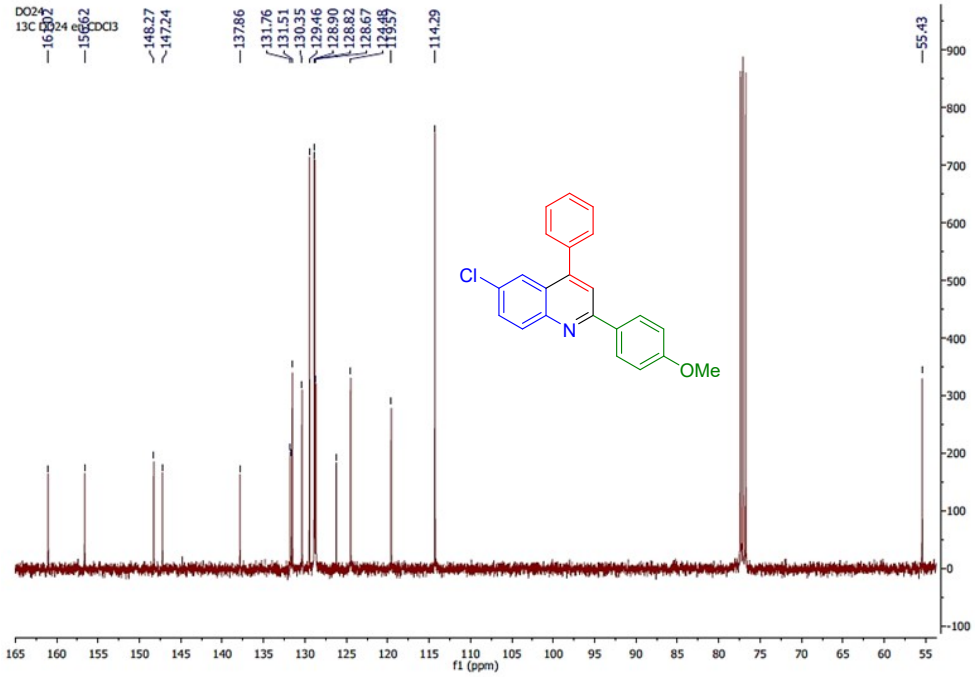

Figure S22. ^{13}C NMR spectrum of 6-chloro-2-(4-methoxyphenyl)-4-phenylquinoline (**11e**).

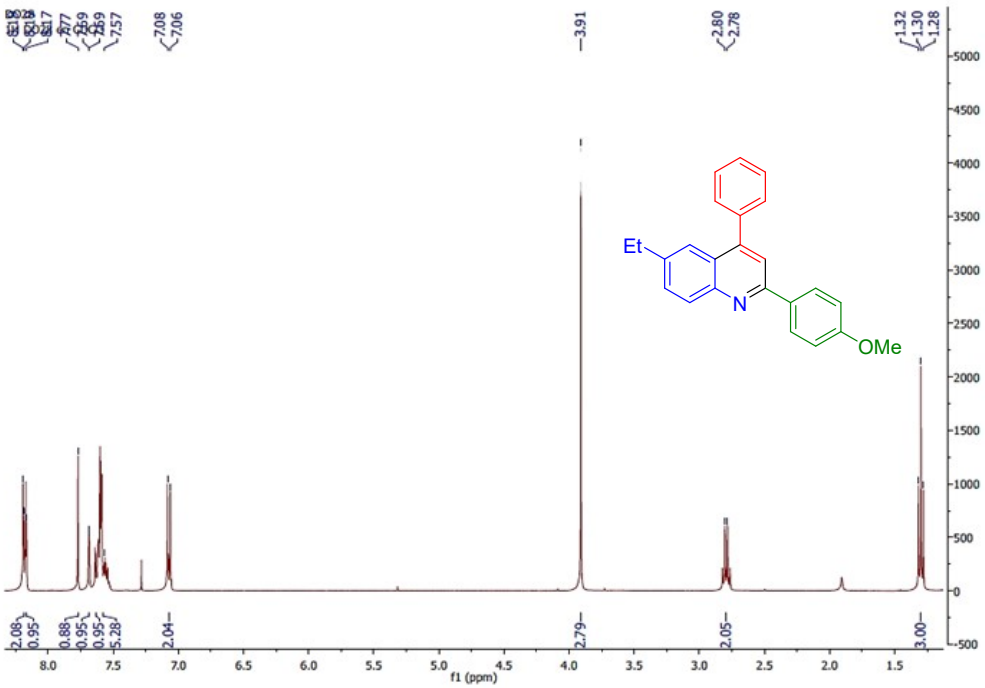

Figure S23. ^{1}H NMR spectrum of 6-ethyl-2-(4-methoxyphenyl)-4-phenylquinoline (**11f**)

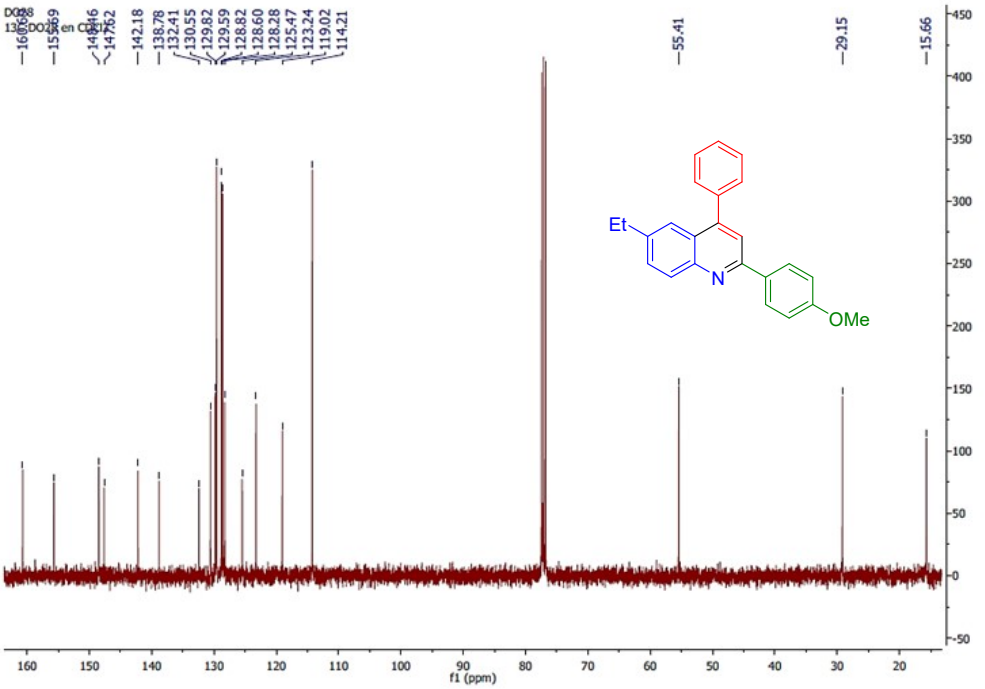

Figure S24. ^{13}C NMR spectrum of 6-ethyl-2-(4-methoxyphenyl)-4-phenylquinoline (**11f**)

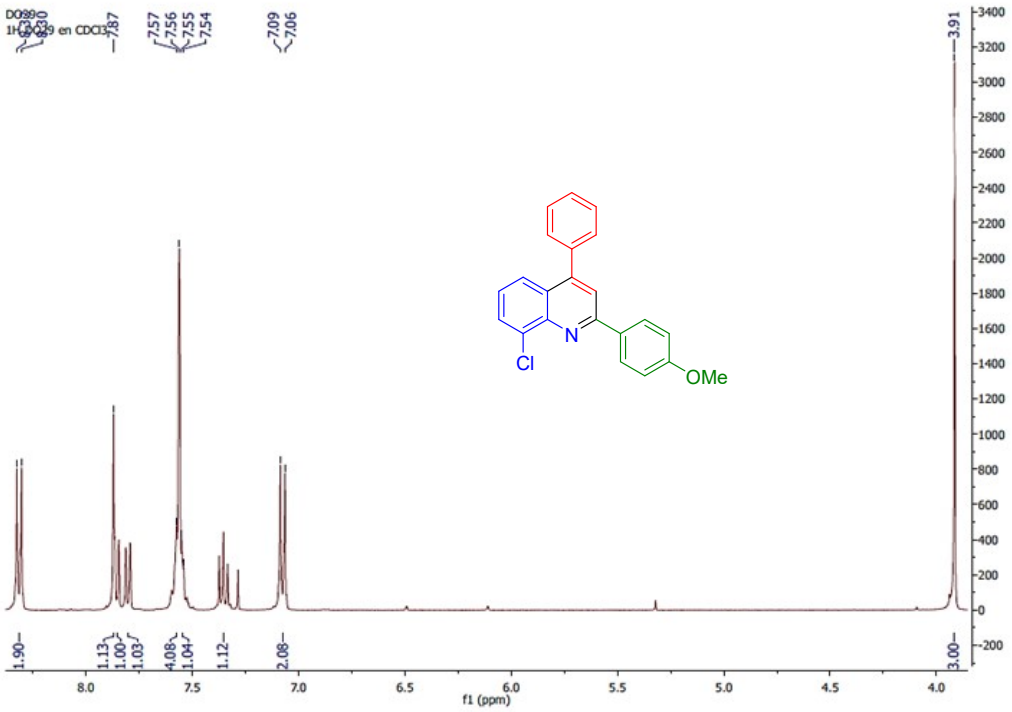

Figure S25. ^{1}H NMR spectrum of 8-chloro-2-(4-methoxyphenyl)-4-phenylquinoline (**11g**)

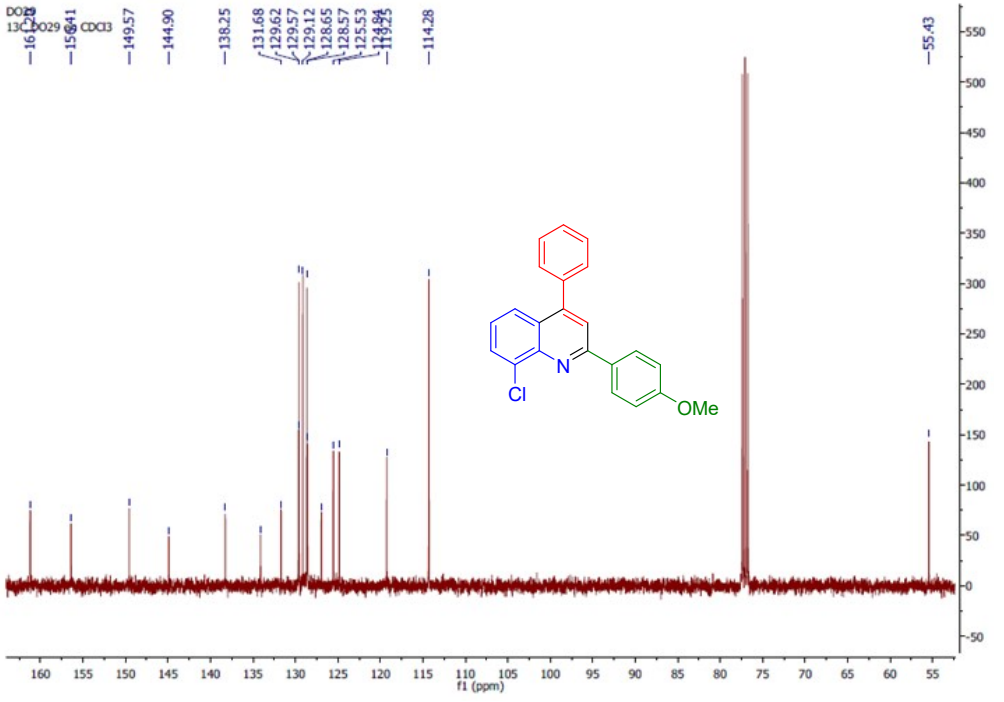

Figure S26. ^{13}C NMR spectrum of 8-chloro-2-(4-methoxyphenyl)-4-phenylquinoline (**11g**)

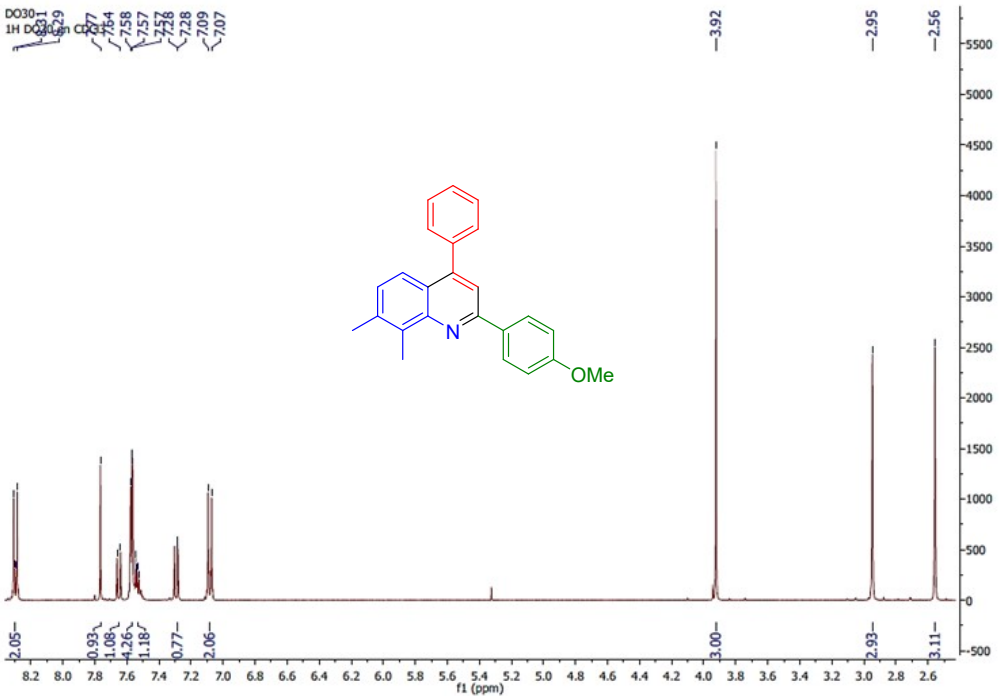

Figure S27. ^{1}H NMR spectrum of 2-(4-methoxyphenyl)-7,8-dimethyl-4-phenylquinoline (**11h**)

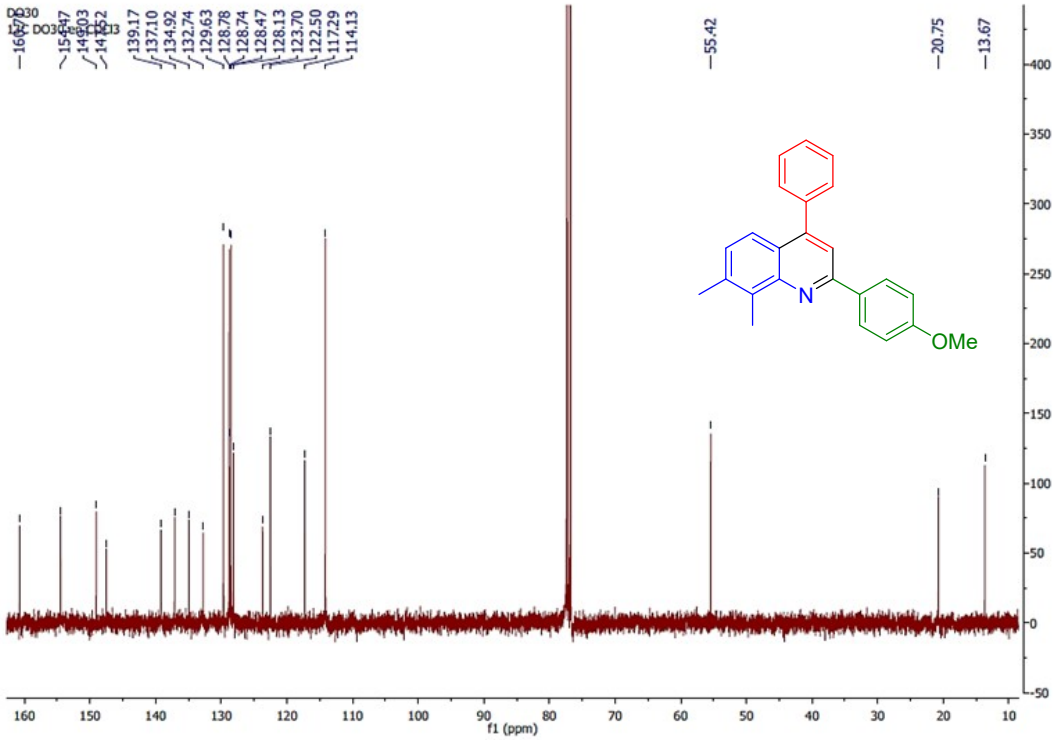

Figure S28. ^{13}C NMR spectrum of 2-(4-methoxyphenyl)-7,8-dimethyl-4-phenylquinoline (**11h**)

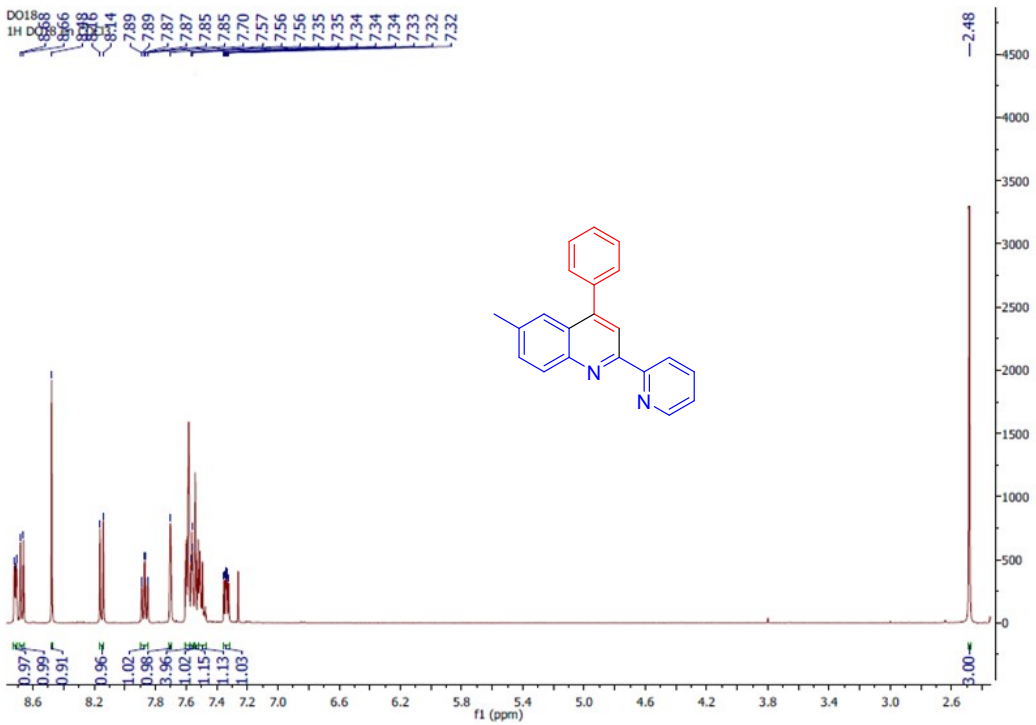

Figure S29. ^{1}H NMR spectrum of 6-methyl-4-phenyl-2-(pyridin-2-yl)quinoline (**12**)

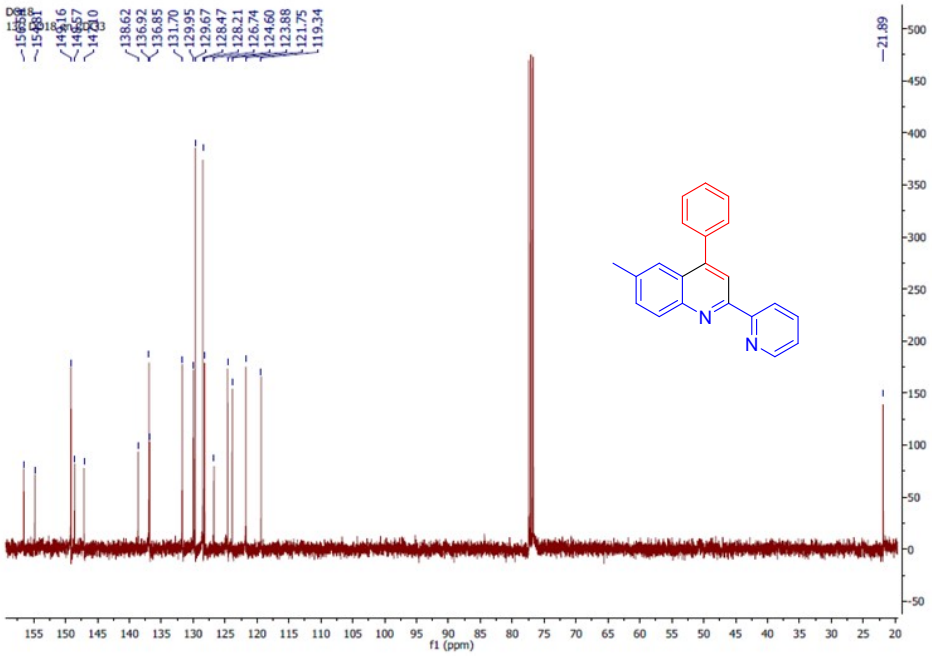

Figure S30. ^{13}C NMR spectrum of 6-methyl-4-phenyl-2-(pyridin-2-yl)quinoline (**12**)

1.2. *Proposed reaction mechanisms for the synthesis of the compounds* ***11a*** *y* ***12****.*

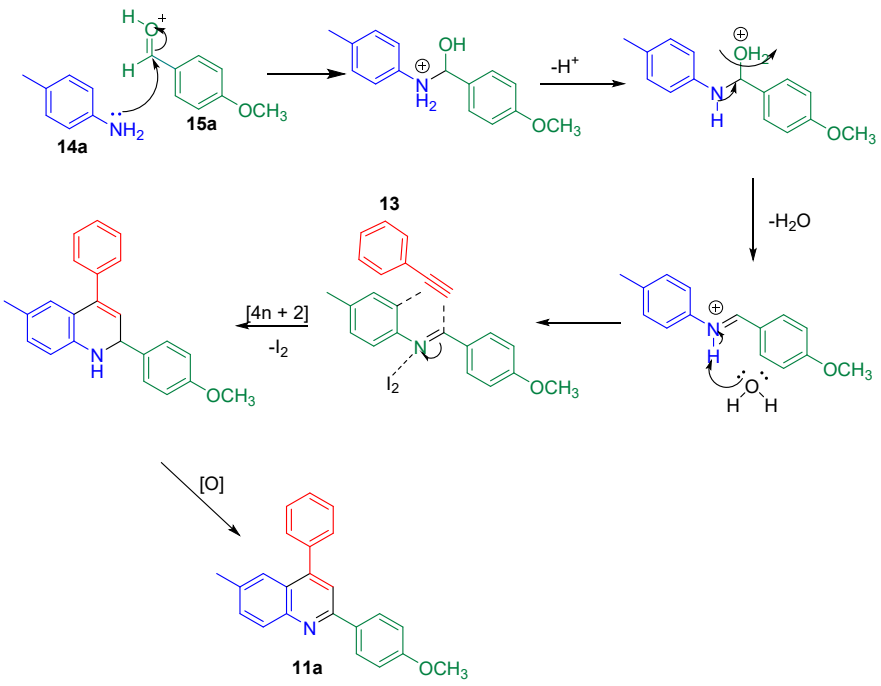

Figure S31. Proposed reaction mechanisms for the synthesis of 2-(4-methoxyphenyl)-6-methyl-4-phenylquinoline **11a**.

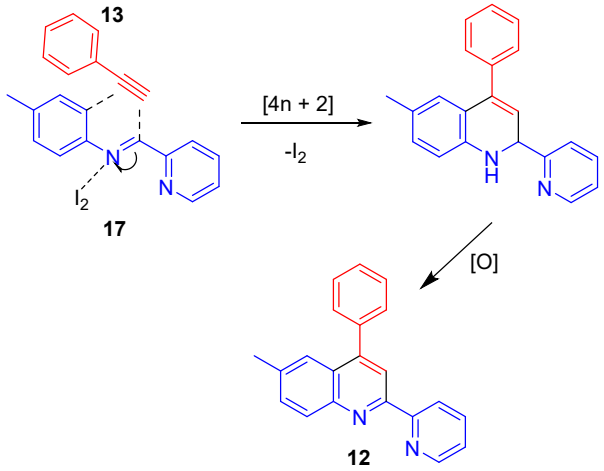

Figure S32. Proposed reaction mechanisms for the synthesis of 6-methyl-4-phenyl-2-(pyridin-2-yl)quinoline (**12**).