Synthesis and Optimization of Di-Substituted Acridine Photo-organocatalysts

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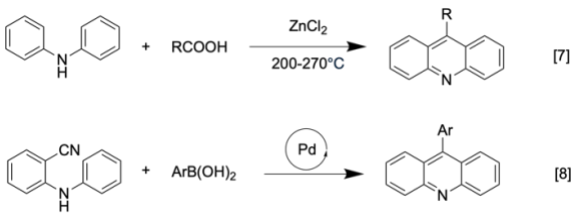
ABSTRACT: Acridine photo-organocatalysts have shown great promise in a multitude of chemical reactions, but the main obstacle with acridine lies in their harsh synthesis conditions. This investigation employed a method of synthesis consisting of a 3-step process, namely an Ullmann reaction, cyclization and Boc addition. Using this, it aimed to synthesize dimethyl-9(10H)-acridone Boc compounds, as well as optimize their synthesis. Furthermore, conditions were screened for synthesis of the starting material of 2,7-diphenyl-9(10H)-acridone Boc, namely for 4-bromo-[1,1'-biphenyl]-3-carboxylic acid using Suzuki-Miyaura reaction. The synthesis was optimized by increasing the pH after cyclization to enable Boc addition, by decreasing reaction time for Boc addition from 18 hours to 4 hours, and upon finding two di-methylacridin-9(10H)-one compounds formed during the cyclization step their separation was optimized by being performed after Boc addition. Furthermore, a total of 5 distinct dimethyl-9(10H)-acridone Boc compounds were synthesized in scaled-up conditions with yields of 51-74%, each making at least 0.750 g of compound. Screening conditions for 4-bromo-[1,1'-biphenyl]-3-carboxylic acid did not succeed in synthesizing the compound of interest.

Photocatalysts are compounds whose absorption of light, namely photon energy, allows them to initiate and catalyze a multitude of chemical reactions [1]. This process is known as photocatalysis, and it has garnered an abundance of interest, as light is a renewable resource and as such is environmentally friendly [2]. Furthermore, photocatalysis has numerous applications, namely in medicinal chemistry, organic synthesis and water purification [3]. Commonly used photocatalysts include iridium and ruthenium, and as precious metals they are both regarded as devastating to the environment and also high in cost [4]. In order to tackle both the cost and environmental devastation of these photocatalysts, more interest has been placed on photo-organocatalysts, which are synthesized entirely from organic materials [5]. Acridine is an example of a photo-organocatalyst that has shown promise in various chemical reactions [6]. The main problem with acridine photocatalysts is their synthesis.

Scheme 1: Showing the common synthetic pathways for acridine



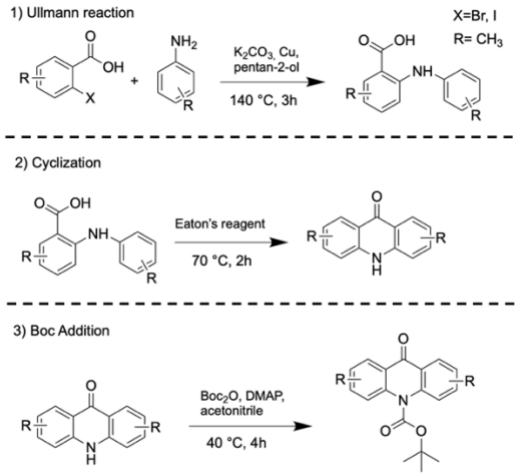
As seen in figure 1, synthetic pathways for acridine often involve harsh conditions, such as high temperatures of 200-270°C required in Bernthsen synthesis, or they require costly catalysts, such as palladium noted above [7][8].

In this project a simple synthetic pathway that does not require harsh temperatures of 200-270°C or usage of catalysts is employed to obtain acridine photocatalysts. The main aim of this project is to utilize and optimize this proposed synthetic pathway in order to obtain dimethyl-9(10H)-acridone Boc. A sub-aim is to screen for conditions of Suzuki-Miyaura reaction to obtain one of the starting materials necessary for the synthesis of 2,7-diphenyl-9(10H)-acridone Boc. The importance of the addition of substituents onto the acridine core lies in their expected ability to stabilize the radical formed during photocatalysis. This increased stability was showcased in a recent study where acridine was used as a photocatalyst in achieving anti-Markovnikov addition of water, in which the acridine that resulted in the highest product yield had two methyl groups substituted onto its core [9]. This highlights the importance of improving the synthesis of acridine photocatalysts with substituents attached onto their core.

The synthetic pathway of acridines used consists of a 3-step process, as shown in scheme 2 below, starting with an Ullmann reaction where an aniline derivative - toluidine, and 2-halo-methylbenzoic acid react to form di-methyl 2-(phenylamino)benzoic acid. Following this, cyclization of the product results in di-methylacridin-

9(10H)-one. Lastly, the addition of Boc protection group is performed, and this forms dimethyl-9(10H) acridone Boc.

Scheme 2: Showing the 3-step synthesis pathway for acridine photo-organocatalysts utilized



During the Ullmann reaction, following the procedure from Roda et al., as the first step in the synthesis, a solution of 2-halo-methylbenzoic acid (1.00 eq), toluidine (1.38 eq), anhydrous K2CO3 (1.38 eq) and copper (0.20 eq) in solvent pentan-2-ol (1.00 eq) was heated and stirred for 3 h under reflux. Following full conversion, the solvent was evaporated under reduced pressure using a rotary evaporator and the residue was dissolved using 100 mL of hot water and filtered through Celite. This Celite was thoroughly washed with 300 mL of water, and the solution obtained was acidified to a pH 6, as checked with pH paper. This resulted in formation of precipitate which was filtered and washed with water [10].

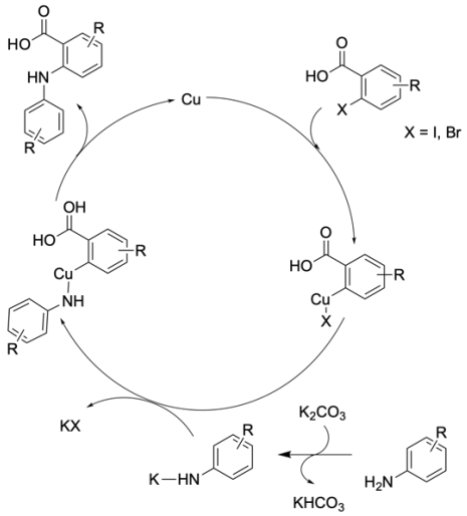


Figure 1: Mechanism of Ullmann reaction to synthesize di-methyl 2-(phenylamino)benzoic acid [11]

During the Ullmann reaction, as seen in the mechanism depicted in figure 1, copper acts as a catalyst and inserts into the halogen-carbon bond. Potassium carbonate acts as a base and allows for the exchange of a hydrogen attached onto the nitrogen on toluidine for a potassium. This process paves the way for oxidative addition of 2-methylbenzoic acid and toluidine, as potassium removes the halogen attached to the 2-methylbenzoic acid. Lastly, in order to remove copper from the compound, reductive elimination takes place, resulting in the synthesis of di-methyl 2-(phenylamino)benzoic acid [11].

The next step in the reaction, according to the procedure from Chamberlain et al. and Li et al., is the cyclization reaction where the product from the previous reaction, di-methyl 2-(phenylamino)benzoic acid (1.00 eq) and Eaton's reagent (7.70%) were heated and stirred for 2 h at 70 °C [12]. After full conversion is confirmed by UPLC, the solution is poured into hot water (200 mL) and subsequently neutralized to a pH of 7 using aqueous ammonia. The precipitate is filtered off, washed with water and left to dry [13].

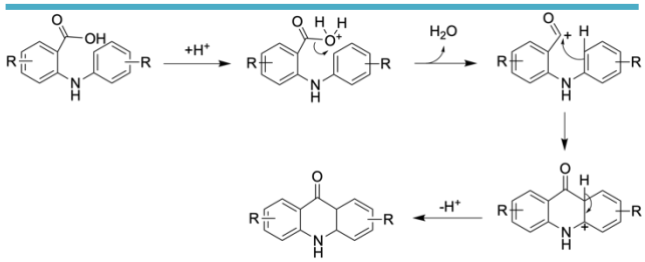


Figure 2: Mechanism of cyclization in order to synthesize di-methylacridin-9(10H)-one

The cyclization reaction is enabled by Eaton's reagent which consists of methanesulfonic acid which functions as a catalyst, whilst phosphorus pentoxide functions as a water scavenger. This property as a water scavenger allows for the reactant to form di-methylacridin-9(10H)-one, as seen in figure 2.

The last step during the synthesis scheme is the addition of Boc protection group onto the previously formed di-methylacridin-9(10H)-one. During this reaction DMAP (0.50 eq), di-methylacridin-9(10H)-one (1.00 eq) and acetonitrile were stirred for 4 h at 40 °C, while a solution of Boc_2O (2.50 eq), and acetonitrile was added through a syringe into the solution during this time. After full conversion, in order to remove impurities, the sample synthesized was columned using silica gel as the stationary phase and

the desired compound evaporated under reduced pressure. Each compound was characterized using both a proton and carbon NMR.

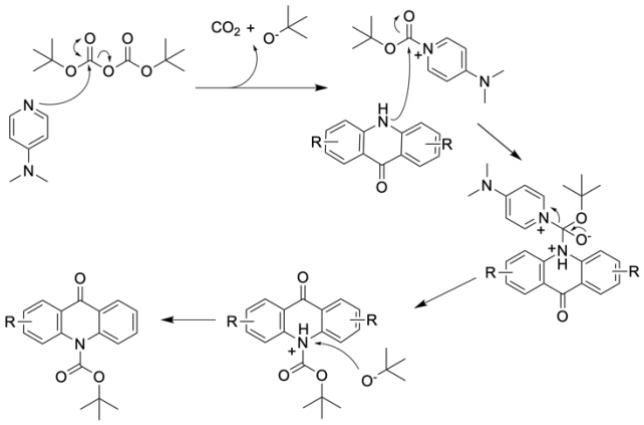
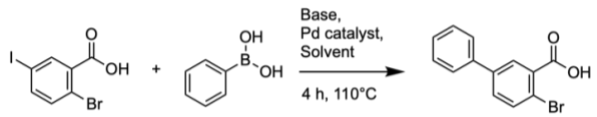


Figure 3: Mechanism of Boc addition to synthesize di-methyl-9(10H) acridone Boc [14]

Addition of a Boc protection group is achieved using the attack of DMAP onto the carbonyl group on Boc_2O, resulting in tert-butyl carbonate as the leaving group. This then enables di-methylacridin-9(10H)-one to attach onto the carbonyl site, resulting in a negatively charged oxygen. DMAP as the better leaving group is removed and the leftover proton on the nitrogen is removed by tert-butyl carbonate resulting in the product di-methyl-9(10H) acridone Boc [14].

As a sub-aim, the synthesis scheme to obtain 2,7-diphenyl-9(10H)-acridone Boc was started, with initial focus on obtaining the starting material needed for the reaction to proceed using the already developed synthesis scheme mentioned in scheme 2. The starting product whose synthesis was planned is 4-bromo-[1,1'-biphenyl]-3-carboxylic acid, using the proposed synthesis scheme 3 below.

Scheme 3: Proposed synthesis scheme for 4-bromo-[1,1'-biphenyl]-3-carboxylic acid, Suzuki-Miyaura reaction



For the proposed synthesis scheme of Suzuki-Miyaura, first a screening for optimal conditions in order to synthesize the starting material as shown in scheme 3 was performed. The reaction was set up in 24 vials in a metal heating plate, with each vial containing 2-bromo-5-iodobenzoic acid (1.00 eq) and boronic acid (1.20 eq). Half of the vials were placed in a toluene solvent and the other half in a THF/water (1:1) solvent. There were 4 bases (2.00 eq) tested including $NaCO_3$, K_2CO_3, K_3PO_4 and CsF. As well as this, 3 catalysts were tested, namely XPhos, XantPhos and tBuBrettPhos. All of the reactions ran for 4 h at 110 °C on the heating plate.

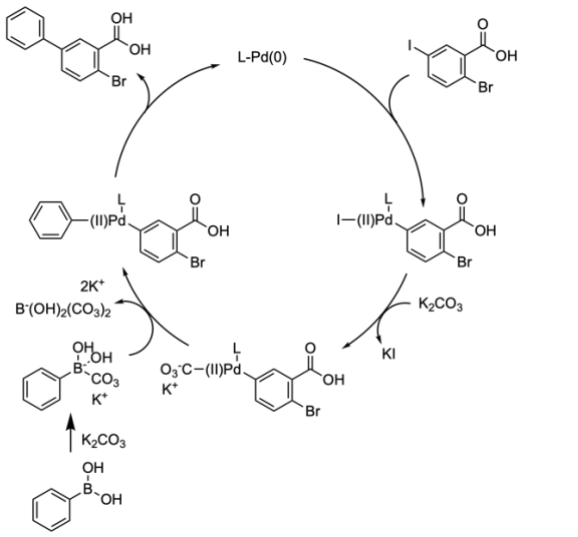


Figure 4: Proposed mechanism of Suzuki-Miyaura reaction to obtain 4-bromo-[1,1'-biphenyl]-3-carboxylic acid [15]

The proposed mechanism of Suzuki-Miyaura to obtain the starting product 4-bromo-[1,1'-biphenyl]-3-carboxylic acid can be found in figure 4. As can be seen, firstly oxidative addition occurs where the palladium catalyst inserts itself between the iodine-carbon bond in 2-bromo-5-iodobenzoic acid. The base, namely as an example K_2CO_3, removes the halogen from its bond to palladium, and also simultaneous activates boronic acid which allows for phenyl addition onto 2-bromo-5-iodobenzoic acid. Lastly, palladium is removed via reductive elimination [15].

Optimization of the synthesis scheme for dimethyl-9(10H)-acridone Boc consisted of tackling problems during their synthesis. The first problem encountered involved that the insufficiently basic pH of 7 during the workup after the cyclization reaction resulted in formation of the acridine salt base. This did not allow for Boc protection to take place on the nitrogen of di-methylacridin-9(10H)-one. Hence, the pH was increased to 10, and as the environment was more basic the salt base of acridine was freed and the addition of the Boc protection group was made possible.

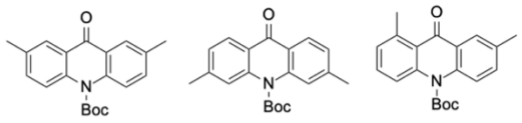
Another improvement to the previous method is the optimization of reaction time needed for the Boc addition step of the synthesis pathway. Initially, the solvent used was valerolactone and the reaction of Boc addition occurred dropwise over 18 hours. The solvent was changed to acetonitrile and this decreased the reaction time to only 4 hours. This is a very considerable decrease in time which improves overall time efficiency of the synthesis pathway.

During the cyclization step in the synthesis of two of the di-methylacridin-9(10H)-one compounds, it was determined that for each reaction 2 compounds formed instead of the one desired. Namely, in the synthesis of 3,6-dimethylacridin-9(10H)-one additionally 1,6-dimethylacridin-9(10H)-one was formed, and in the synthesis of 2,6-dimethylacridin-9(10H)-one an additional product as 1,7-dimethylacridin-9(10H)-one formed. This was made possible due to the spin of the benzene ring as the methyl groups are located in ortho and para positions respectively to the carboxylic acid group.

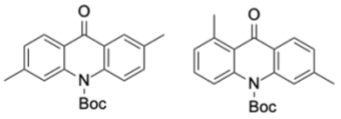
Whilst this finding did allow for the synthesis of more products at once, it led to a very difficult problem of separating the two compounds. At first, the separation of the two compounds was attempted after the cyclization step and this was done using a column with 1% methanol in DCM as the most successful combination. However, even with this combination many subsequent chromatography columns were required to separate the two compounds and this resulted in very low yields. Thus, in order to tackle this problem, the approach was changed, such that the compounds were no longer separated after cyclization but instead after the Boc addition was complete. This allowed for a much better separation of the two compounds, using 10% MTBE in pentane as the eluent of the mobile phase. Resulting as well in much higher yields.

Each of the dimethyl-9(10H) acridone Boc compounds synthesized where characterized using ^{1}H NMR and ^{13}C NMR, these can be found in the supporting information in figures S1-10. As can be seen in table 1, the strides made in optimization of the synthesis increased the low initial yields that span from 0-55%, into the much higher yields of 51-74% after the optimization and scale-up of the reactions were performed. Another note is that within the initial synthesis 3,6-dimethylacridin-9(10H)-one and 1,6-dimethylacridin-9(10H)-one were not successfully made as their separation after cyclization could not be achieved. However, having separated them after the Boc addition they resulted in a 74% yield, which showcases the importance of this optimization step.

Table 1: Showing the initial and final yield of dimethyl-9(10H) acridone Boc compounds synthesized



Initial*	0.159 g	0.000 g	0.000 g
Yield	26%	0%	0%
Final**	1.459 g	1.537 g	1.004 g
Yield	51%	74%	



Initial*	0.080 g	0.117 g
Yield	20%	55%
Final**	0.778 g	1.512 g
Yield	70%	

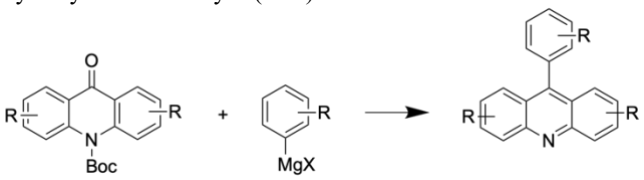
* Initial yield refers to starting material 1.00-1.18 g
**Final yield refers to scale-up in starting material to 3.00-4.00 g

The screening of conditions for Suzuki-Miyaura to obtain 4-bromo-[1,1'-biphenyl]-3-carboxylic acid resulted in inconclusive results. To start, the reactions that ran in water/THF (1:1) as a solvent largely evaporated due to 110 °C temperature of the heating plate. This was unexpected as the vials were properly closed, but a possible improvement would be to utilize vials with metal caps instead of plastic caps as this could be the reason that water was able to evaporate. Likely due to the majority of the solvent evaporating all the vials with water/THF (1:1) as solvent did not show the formation of any product using UPLC analysis. Out of 12 vials with the solvent toluene, a total of 10 showed a formation of a product using UPLC analysis, however, the mass present was 282 m/z and this does not correspond to 4-bromo-[1,1'-biphenyl]-3-carboxylic acid with a molecular weight of 277. As this is not the desired product, the contents of the toluene vials were added together and extracted, which allowed for the 100 mg of product retrieved to be columned. Unfortunately, the product was not successfully retrieved using the column either, the only compound successfully retrieved from the column and confirmed by NMR was diphenyl.

The unsuccessful column can be attributed in part to only 100 mg retrieved from the screening process. Thus, in the future the Suzuki-Miyaura reaction in toluene can be scaled-up and repeated in order to isolate the identity of the product with mass 282 m/z seen on the UPLC. Furthermore, if this is not the starting product new conditions for the reaction can be screened as well.

A future outlook from this project is that the synthesized and characterized dimethyl-9(10H) acridone Boc compounds will undergo Grignard addition and hydrolysis to form the final acridine photo-organocatalysts, as seen in scheme 4. Following this, their photocatalytic ability will be tested in a specific photochemical reaction that is selected.

Scheme 4: Synthesis scheme for Grignard addition and hydrolysis of dimethyl-9(10H) acridone Boc



In conclusion, during this investigation the synthesis pathway was successfully utilized to synthesize 5 different dimethyl-9(10H) acridone Boc compounds. Furthermore, their synthesis was optimized, as achieved by adjusting the pH of solution to allow for Boc addition, decreasing the reaction time for Boc addition to 4 hours and optimizing the separation of 2 di-methylacridin-9(10H)-one when formed together by separating them after Boc addition. The screening of conditions for Suzuki-Miyaura reaction to obtain 4-bromo-[1,1'-biphenyl]-3-carboxylic acid, as the starting material for 2,7-diphenyl-9(10H)-acridone Boc did not yield the desired results as there is no evidence the reactions were successful in yielding the product. The synthesis and optimization to obtain dimethyl-9(10H) acridone Boc are crucial as the compounds will become photocatalyst and will be tested for their ability in photocatalysis of a given chemical reaction.

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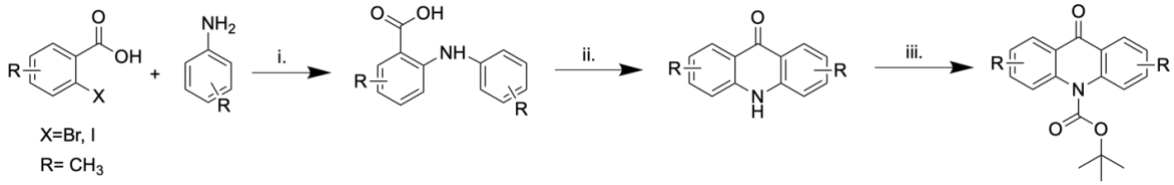
Supporting Information

Experimental Procedure and Materials

Scheme 1: Synthesis route of Di-methyl substituted Acridone Boc



Procedure for Ullmann reaction in synthesis step i.

Preparation of 5-methyl-2-(p-tolyamino) benzoic acid
A solution of p-toluidine (6.21 mmol, 665.44 mg, 1.38 eq), 2-iodo-5-methylbenzoic acid (4.50 mmol, 1.18 g, 1.00 eq), anhydrous K2CO3 (6.21 mmol, 858.25 mg, 1.38 eq), and copper (0.90 mmol, 57.19 mg, 0.20 eq) in pentan-2-ol (5 mL) was heated under reflux for 3 h. The presence of a full conversion of reactants to the product was confirmed by UPLC analysis. The solvent was evaporated under reduced pressure, and the residue was dissolved in hot H2O (100 mL) and then filtered through Celite. The Celite was washed with H2O (300 mL), and the filtrate was acidified with concentrated HCl to pH 6. The precipitate was isolated by filtration and washed with H2O. The reaction was successful in obtaining 5-methyl-2-(p-tolylamino)benzoic acid, with a total of 0.914g and this is a yield of 83.85%.
1H NMR (400 MHz, DMSO-D6) δ 9.38 (s, 1H), 7.67 (s, 1H), 2.27 (s, 3H), 2.20 (s, 3H).

Preparation of 4-methyl-2-(m-tolyamino) benzoic acid
A solution of m-toluidine (5.27 mmol, 5.6 mL, 1.38 eq), 2-iodo-5-methylbenzoic acid (3.82 mmol, 1.00 g, 1.00 eq), anhydrous K2CO3 (5.27 mmol, 727.82 mg, 1.38 eq), and copper (0.76 mmol, 48.50 mg, 0.20 eq) in pent-2-ol (5 mL) was heated under reflux for 3 h. The presence of a full conversion of reactants to the product was confirmed by UPLC analysis. The solvent was evaporated under reduced pressure, and the residue was dissolved in hot H2O (100 mL) and then filtered through Celite. The Celite was washed with H2O (300 mL), and the filtrate was acidified with concentrated HCl to pH 6. The precipitate was isolated by filtration and washed with H2O. The product was obtained as 4-methyl-2-(m-tolyamino)benzoic acid, weighing 959 mg, with a yield of 104.15%.
1H NMR (400 MHz, DMSO-D6) δ 9.60 (s, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.09 – 7.00 (m, 3H), 6.90 (d, J = 7.5 Hz, 1H), 6.59 (dd, J = 8.3, 1.6 Hz, 1H), 2.30 (s, 3H), 2.23 (s, 3H).

Preparation of 5-methyl-2-(m-tolyamino) benzoic acid
A solution of m-toluidine (6.21 mmol, 0.6 mL, 1.38 eq), 2-iodo-5-methylbenzoic acid (4.50 mmol, 1.18 g, 1.00 eq), anhydrous K2CO3 (6.21 mmol, 858.25 mg, 1.38 eq), and copper (0.90 mmol, 57.19 mg, 0.2 eq) in pentan-2-ol (5 mL) was heated under reflux for 3 h. The presence of a full conversion of reactants to the product was confirmed by UPLC analysis. The solvent was evaporated under reduced pressure, and the residue was dissolved in hot H2O (100 mL) and then filtered through Celite. The Celite was washed with H2O (300 mL), and the filtrate was acidified with concentrated HCl to pH 6. The precipitate was isolated by filtration and washed with H2O. A total amount of product obtained is 592 mg, this is a yield of 54.31%.
1H NMR (400 MHz, DMSO-D6) δ 7.69 (s, 1H), 7.21 (dt, J = 10.7, 5.5 Hz, 3H), 6.99 (d, J = 7.1 Hz, 2H), 6.83 (d, J = 7.4 Hz, 1H), 2.24 (d, J = 23.7 Hz, 6H).

Preparation of 4-methyl-2-(m-tolyamino) benzoic acid

A solution of m-toluidine (25.67 mmol, 16 mL, 1.38 eq), 2-bromo-4-methylbenzoic acid (18.60 mmol, 4.00 g, 1.00 eq), anhydrous K2CO3 (25.67 mmol, 3.55 mg, 1.38 eq), and copper (3.72 mmol, 236.4 mg, 0.2 eq) in pentan-2-ol (16.0 mL) was heated under reflux for 3 h. The presence of a full conversion of reactants to the product was confirmed by UPLC analysis. The solvent was evaporated under reduced pressure, and the residue was dissolved in hot H2O (100 mL) and then filtered through Celite. The Celite was washed with H2O (300 mL), and the filtrate was acidified with concentrated HCl to pH 6. The precipitate was isolated by filtration and washed with H2O. The weight of the compound is 2.885 g, and this is a yield of 64.25%.
1H NMR (400 MHz, DMSO-D6) δ 7.73 (s, 1H), 7.24 (s, 1H), 7.01 (s, 2H), 6.83 (s, 1H), 6.61 (s, 1H), 6.32 (s, 0H), 2.29 (s, 3H), 2.13 (d, J = 10.8 Hz, 3H).

Preparation of 5-methyl-2-(p-tolyamino) benzoic acid
A solution of p-toluidine (15.80 mmol, 1.69 g, 1.38 eq), 2-iodo-5-methylbenzoic acid (11.45 mmol, 3.00 g, 1.00 eq), anhydrous K2CO3 (15.80 mmol, 2.18 g, 1.38 eq), and copper (2.29 mmol, 145.50 mg, 0.2 eq) in pentan-2-ol (12.70 mL) was heated under reflux for 3 h. The presence of a full conversion of reactants to the product was confirmed by UPLC analysis. The solvent was evaporated under reduced pressure, and the residue was dissolved in hot H2O (100 mL) and then filtered through Celite. The Celite was washed with H2O (300 mL), and the filtrate was acidified with concentrated HCl to pH 6. The precipitate was isolated by filtration and washed with H2O. The total weight of the product measured is 2.174 g, this is a yield of 78.77%.
1H NMR (400 MHz, DMSO-D6) δ 7.67 (s, 0H), 7.19 (s, 1H), 7.15 (d, J = 7.7 Hz, 3H), 7.08 (s, 2H), 2.29 (s, 3H), 2.20 (s, 3H).

Preparation of 5-methyl-2-(m-tolyamino) benzoic acid
A solution of m-toluidine (21.06 mmol, 2.6 mL, 1.38 eq), 2-iodo-5-methylbenzoic acid (15,26 mmol, 4.00 g, 1.00 eq), anhydrous K2CO3 (21.06 mmol, 2.91 g, 1.38 eq), and copper (3.05 mmol, 194 mg, 0.2 eq) in pentan-2-ol (17.0 mL) was heated under reflux for 3 h. The presence of a full conversion of reactants to the product was confirmed by UPLC analysis. The solvent was evaporated under reduced pressure, and the residue was dissolved in hot H2O (100 mL) and then filtered through Celite. The Celite was washed with H2O (300 mL), and the filtrate was acidified with concentrated HCl to pH 6. The precipitate was isolated by filtration and washed with H2O. A total amount of product 2.470 g was weighed, this is a yield of 67.12%.
1H NMR (400 MHz, DMSO-D6) δ 7.64 (s, 0H), 7.19 (s, 2H), 6.95 (s, 1H), 6.77 (s, 1H), 2.24 (s, 4H), 2.17 (s, 3H).

Procedure for Cyclization reaction in synthesis step ii.

Preparation of 2,7-dimethylacridin-9(10H)-one
A mixture of 5-methyl-2-(p-tolylamino)benzoic acid (3.79 mmol, 0.914 g) in Eaton's reagent (10 mL, 7.70%) was stirred at 70 °C for 2 h. The presence of a full conversion of reactants to the product was confirmed by UPLC analysis. The mixture was poured into ice-water (50 g), and extracted with EtOAc (50 mL x 2). The combined organic layers were dried using filter paper. NMR analysis was preformed of the dried mass obtained on the filter paper and of the liquid from the extractions that was dried using rotary evaporator.
The weighed amount of solid precipitate is 886 mg, this a yield of 104.76%.
The NMR results of liquid from extractions only showed the results of ethyl acetate, and the product was not present.
NMR of solid precipitate: 1H NMR (400 MHz, DMSO-D6) δ 11.61 (s, 1H), 7.97 – 7.91 (m, 2H), 7.48 (dd, J = 8.5, 2.1 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 2.34 (d, J = 0.9 Hz, 6H)

Preparation of 3,6-dimethylacridin-9(10H)-one
A mixture of 4-methyl-2-(m-tolylamino)benzoic acid (3.97 mmol, 0.959 g) in Eaton's reagent (11 mL, 7.70%) was stirred at 70 °C for 2 h. Then, it was poured into hot water (200 ml), which was neutralized by aq. ammonia to PH = 7. The obtained precipitate was filtered off, washed with hot water, and dried in air overnight to give acridone as a powder. UPLC results showed that a new compound was formed, however, there were two peaks very close to one another and the compounds also exhibited the same weight. The mass weighed was 877 mg of compound, with the yield as 98.83%. Using NMR analysis, we could see that 2 compounds were present, and then we preformed a TLC where we could see 2 spots. After this, a column was preformed with 15% ethyl acetate

in pentane. However, we were unable to isolate the compound of interest after 2 columns preformed, and only 19 mg of the compound remained so this experiment will need to be repeated.

Preparation of 2,6-dimethylacridin-9(10H)-one

A mixture of 5-methyl-2-(m-tolylamino)benzoic acid (2.45 mmol, 0.592 g) in Eaton's reagent (6.5 mL, 7.70%) was stirred at 70 °C for 2 h. In order to find out if the product was formed we used UPLC analysis, the UPLC analysis showed conversion but there are 2 peaks present. Then, the solution was poured into hot water (200 ml), which was neutralized by aq. ammonia to PH = 10. The obtained precipitate was filtered off, washed with hot water, and dried in air overnight to give acridone as a powder.

On the TLC there are 2 dots present (Rf values of 0.32 and 0.48 respectively). We did 2 columns and still could not separate the compounds fully, but we managed to isolate the first dot, the column was first run with 3% methanol in DCM and then 1% methanol in DCM.

NMR of the first dot on TLC (corresponding to 1,7-dimethylacridin-9(10H)-one):

1H NMR (400 MHz, DMSO-D6) δ 11.44 (s, 1H), 7.95 (s, 1H), 7.54 – 7.45 (m, 2H), 7.34 (dd, J = 23.9, 8.3 Hz, 2H), 6.92 (d, J = 7.2 Hz, 1H), 2.85 (s, 3H), 2.39 (s, 3H)

The next day, we managed to preform a column to fully separate the 2 compounds, this was done using 1% methanol in DCM.

The NMR of the second dot on TLC is (corresponding to 2,6-dimethylacridin-9(10H)-one):

1H NMR (400 MHz, DMSO-D6) δ 8.10 (d, J = 8.2 Hz, 1H), 7.99 (dd, J = 2.4, 1.1 Hz, 1H), 7.54 (dd, J = 8.7, 2.1 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.05 (dd, J = 8.4, 1.5 Hz, 1H), 2.44 (s, 3H), 2.42 – 2.40 (m, 3H).

From the first compound formed 1,7-dimethylacridin-9(10H)-one we obtained 146 mg and from the second compound formed 2,6-dimethylacridin-9(10H)-one we obtained 264 mg. Overall when both products are added, the products have a 71.56% yield compared to expected.

Preparation of 3,6-dimethylacridin-9(10H)-one

A mixture of 4-methyl-2-(m-tolylamino)benzoic acid (11.94 mmol, 2.885 g) in Eaton's reagent (31.68 mL, 7.70%) was stirred at 70 °C for 2 h. In order to find out if the product was formed we used UPLC analysis, and as there were 2 peaks present on the UPLC we can see that two products were formed. Then, we poured the product into hot water (200 ml), and then neutralized using aq. ammonia to PH = 10. The obtained precipitate was filtered off, washed with hot water, and dried in air overnight to give acridone as a powder. After the workup, a UPLC of the water left after precipitate was filtered off showed presence of both compounds, thus the organic layer was extracted using DCM 3 times, and then once with ethyl acetate. The water left after this part of the workup was again run through UPLC and no presence of the product could be noted.

The crude NMR: 1H NMR (400 MHz, DMSO-D6) δ 8.07 (dd, J = 15.3, 8.2 Hz, 2H), 7.50 (dd, J = 8.4, 7.2 Hz, 1H), 7.28 (s, 1H), 7.22 (s, 1H), 7.04 (ddd, J = 13.7, 8.3, 1.6 Hz, 2H), 6.93 (d, J = 7.2 Hz, 1H), 2.85 (s, 3H), 2.44 (d, J = 5.9 Hz, 7H).

As there were two retention times on the UPLC, indicative of 2 compounds, a column was preformed in order to separate them. Using TLC plate we saw good separation at 1% methanol in DCM, and thus this was used to preform the first column, with around 400 ml of silica gel. During this first run of the column we managed to separate the first dot on the TLC in part but for the majority the flasks all still showed to contain both compounds on the TLC plates. Thus, we will need to re-run the column.

NMR of 1st dot: (indicative of 1,6-dimethylacridin-9(10H)-one)

1H NMR (400 MHz, DMSO-D6) δ 8.06 (d, J = 8.2 Hz, 1H), 7.51 (dd, J = 8.4, 7.1 Hz, 1H), 7.33 (d, J = 8.3 Hz, 1H), 7.23 (s, 1H), 7.03 (dd, J = 8.3, 1.6 Hz, 1H), 6.94 (d, J = 7.2 Hz, 1H), 2.86 (s, 3H), 2.44 (s, 3H).

We decided to continue with the boc addition step for the mixture of both compounds, and then after this is completed we will separate them using a column. This is because on the TLC a mixture of the acridone Boc compounds showed a better separation (using previously obtained compounds). The yield of the mixtred fractions is 2.357 g, which is a 88.28% yield.

Preparation of 2,7-dimethylacridin-9(10H)-one

A mixture of 5-methyl-2-(p-tolylamino)benzoic acid (9.01 mmol, 2.174 g) in Eaton's reagent (24 mL, 7.70%) was stirred at 70 °C for 2 h. UPLC analysis showed that full conversion to product happened. Then, it was poured into hot water (200 ml), which was neutralized by aq. ammonia to PH = 10. The obtained precipitate was filtered off, washed with hot water, and dried in air overnight to give acridone as a powder. The UPLC of the water after filtration showed no presence of the compound so it did not need to be re-filtered. The weighed amount of solid

precipitate is 1.958 g, this is a yield of 97.41%.
1H NMR (400 MHz, DMSO-D6) δ 11.59 (s, 1H), 8.01 (s, 2H), 7.54 (dd, J = 8.5, 2.1 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 2.41 (s, 6H).

Preparation of 2,6-dimethylacridin-9(10H)-one
A mixture of 5-methyl-2-(m-tolylamino)benzoic acid (10.24 mmol, 2.470 g) in Eaton's reagent (29.5 mL, 7.70%) was stirred at 70 °C for 2 h. In order to find out if the product was formed, we used UPLC analysis, and after about an hour and a half there was full conversion to the product. There were 2 peaks present, indicative of the two formed compounds. Then, the solution was poured into hot water (200 ml), which was neutralized by aq. ammonia to PH = 10. The obtained precipitate was filtered off, washed with hot water, and dried in air overnight to give acridone as a powder. The filtration water showed the presence of the compounds still on the UPLC, so it was re-filtered.
NMR: 1H NMR (400 MHz, DMSO-D6) δ 11.54 (s, 1H), 11.45 (s, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 16.4 Hz, 2H), 7.58 – 7.30 (m, 6H), 7.27 (s, 1H), 7.08 – 7.01 (m, 1H), 6.92 (d, J = 7.1 Hz, 1H), 2.50 (p, J = 1.8 Hz, 4H), 2.44 (s, 2H), 2.40 (d, J = 4.6 Hz, 5H).
Characterization of NMR is hard as there are 2 compounds present, thus it is difficult to analyze. A total of 2.253 g, this is a yield of 98%.

Procedure for Boc addition in synthesis step iii.

Preparation of tert-butyl 2,7-dimethyl-9-oxoacridine-10(9H)-carboxylate
Compounds 2,7-dimethylacridin-9(10H)-one (886.0 mg, 3.97 mmol, 1.00 eq.) and N,N-dimethylpyridin-4-amine (242.4 mg, 396.82 umol, 0.5 eq.) were both weighed and added to a round-bottom flask, where the solvent acetonitrile (36.98 mL) was also added, on a heat plate with a stirring bar. A portion of the acetonitrile solvent and (BOC)2O were added (2.19 mL, 9.52 mmol, 2.50 eq.) using a syringe over the course of 18 hours at 40°C. After this, an additional 16 hours was added to the time as the syringe was not done with the addition of solvent and boc. The first UPLC after about half of the addition, showed no new product. Another UPLC was repeated after full addition of solvent and boc and yet again no new product could be noted.
Thus, the initial compound of 2,7-dimethylacridin-9(10H)-one was retrieved by filtering under vacuum. The weight of compound retrieved was measured as 416 mg, thus we retrieved 46.95% of the original compound that we started out with.
Using 1HNMR the results showed that the inital compound was retrieved as the results allign with the literature.
1H NMR (400 MHz, DMSO-D6) δ 8.03 – 7.98 (m, 2H), 7.54 (dd, J = 8.5, 2.1 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 2.41 (d, J = 0.9 Hz, 6H).

Preparation of tert-butyl 2,7-dimethyl-9-oxoacridine-10(9H)-carboxylate
After the initial compound of 2,7-dimethylacridin-9(10H)-one was retrieved the experiment was repeated. The compound 2,7-dimethylacridin-9(10H)-one (416.0 mg, 1.86 mmol, 1.00 eq) and N,N-dimethylpyridin-4-amine (113.81 mg, 931.59 umol, 0.5 eq.), were both weighed and added to a round-bottom flask, together with a stirring bar. After this, a portion of the solvent acetonitrile (17 mL) and the (BOC)2O (1.07 mL, 4.66 mmol, 2.50 eq.) were combined into a syringe, the remained of the solvent was added to the flask.
The reaction was put on a hot plate where it was heated and stirred for 18 hours at a temperature of 40°C, during this time the syringe added the boc and solvent over time into the mixture. The first UPLC after about 3 hours showed some conversion to tert-butyl 2,7-dimethyl-9-oxoacridine-10(9H)-carboxylate. Another UPLC was repeated after full addition of solvent and boc and the starting materials were no longer present, as conversion to product occured. After this, the organic layer was extracted using ethyl acetate, done 3 times with ethyl acetate and then the organic layer was washed once with brine. After this, the solution was evaporated under vaccum, the weight of compound was measured as 1.610 g, this is a yield of 267% and as such it is clear that there are impurities present in the sample.
Using 1HNMR we can see the final product was produced.
1H NMR (400 MHz, DMSO-D6) δ 7.64 (ddd, J = 8.7, 2.3, 0.7 Hz, 2H), 7.52 (d, J = 8.7 Hz, 2H), 2.42 (s, 6H), 1.63 (s, 9H).
However, many peaks in the NMR also showcase the impurities present, this is the crude NMR.
After column, a total of 159 mg of the product was obtained, this is a yield of 26.39%.

After it was columned another NMR was preformed
1H NMR (400 MHz, DMSO-D6) δ 8.08 – 8.02 (m, 2H), 7.65 (ddd, J = 8.7, 2.3, 0.7 Hz, 2H), 7.53 (d, J = 8.7 Hz, 2H), 2.43 (s, 6H), 1.64 (s, 9H).
13C NMR (101 MHz, DMSO-D6) δ 177.27, 151.76, 137.19, 135.71, 133.19, 126.14, 122.05, 117.92, 87.19, 27.61, 20.72.

Preparation of tert-butyl 2,6-dimethyl-9-oxoacridine-10(9H)-carboxylate
The compound 2,6-dimethylacridin-9(10H)-one (264.0 mg, 1.18 mmol, 1.00 eq) and N,N-dimethylpyridin-4-amine (72.23 mg, 591.20 umol, 0.5 eq.), were both weighed and added to a round-bottom flask, together with a stirring bar. After this, a portion of the solvent acetonitrile (10 mL) was also added to the flask, and the rest was combined with (BOC)2O (0.679 mL, 2.96 mmol, 2.50 eq.) into a syringe.
The reaction was put on a hot plate where it was heated and stirred for 4 hours at temperature of 40°C, during this time the syringe added the boc and solvent over time into the mixture. The first UPLC showed some conversion to the product, and the second UPLC comfirmed that the product was formed. However, there were 2 peaks present instead of one, thus we opted to NMR the sample.
1H NMR (400 MHz, DMSO-D6) δ 7.66 (dd, J = 8.7, 2.2 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.34 (s, 1H), 7.29 – 7.23 (m, 1H), 2.44 (s, 3H), 1.67 (s, 9H).

The sample was columned, and then evaporated under rotary evaporator. The final weight of the product is 80 mg of product, the yield is 20.92%.
Using 1HNMR we can see the final product was produced.
1H NMR (400 MHz, DMSO-D6) δ 7.66 (dd, J = 8.8, 2.2 Hz, 1H), 7.48 (d, J = 8.5 Hz, 1H), 7.33 (s, 1H), 7.24 (s, 0H), 2.43 (s, 6H), 1.10 (d, J = 1.7 Hz, 9H).
13C NMR (101 MHz, DMSO-D6) δ 176.90, 151.70, 145.22, 139.14, 137.13, 135.73, 133.22, 126.95, 126.14, 125.22, 121.96, 119.97, 117.59, 117.00, 87.41, 27.61, 22.25, 20.72.

Preparation of tert-butyl 1,7-dimethyl-9-oxoacridine-10(9H)-carboxylate
The compound 1,7-dimethylacridin-9(10*H*)-one (146.0 mg, 653.90 mmol, 1.00 eq) and N,N-dimethylpyridin-4-amine (39.94 mg, 326.95 mmol, 0.5 eq.), were both weighed and added to a round-bottom flask, together with a stirring bar. After this, the solvent acetonitrile (6 mL) was added in part to the same flask, and the rest of the solvent was combined with (BOC)2O (0.375 mL, 1.36 mmol, 2.50 eq.) and added into a syringe.
The reaction was put on a hot plate where it was heated and stirred for 4 hours at temperature of 40°C, during this time the syringe added the boc and solvent over time into the mixture. The first UPLC showed conversion to the product, as did the second but the presence of 2 peaks means we opted to do an NMR first before the workup step.
1H NMR (400 MHz, DMSO-D6) δ 7.98 – 7.90 (m, 1H), 7.68 – 7.56 (m, 3H), 7.49 (t, J = 7.8 Hz, 1H), 7.19 (dt, J = 7.3, 1.0 Hz, 1H), 2.79 (s, 3H), 2.42 (s, 3H), 1.61 (s, 9H).

A column was preformed to purify the sample, final mass obtained is 117 mg of tert-butyl 1,7-dimethyl-9-oxoacridine-10(9H)-carboxylate, this is a 55% yield. Using 1HNMR we can see the final product was produced.
1H NMR (400 MHz, DMSO-D6) δ 7.93 (dt, J = 1.8, 0.8 Hz, 1H), 7.64 – 7.60 (m, 1H), 7.60 – 7.58 (m, 1H), 7.57 (d, J = 0.7 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.19 (dt, J = 7.4, 1.0 Hz, 1H), 2.79 (s, 3H), 2.42 (s, 3H), 1.60 (s, 9H).
13C NMR (101 MHz, DMSO-D6) δ 180.28, 151.87, 140.87, 140.64, 136.65, 134.84, 133.48, 132.95, 127.11, 126.10, 124.94, 122.13, 118.82, 117.83, 86.38, 27.64, 23.42, 20.77.

Preparation of tert-butyl 1,6-dimethyl-9-oxoacridine-10(9H)-carboxylate and tert-butyl 3,6-dimethyl-9-oxoacridine-10(9H)-carboxylate
The compounds 1,6-dimethylacridin-9(10H)-one and 3,6-dimethylacridin-9(10H)-one (2.457 g, 10.56 mmol, 1.00 eq) and N,N-dimethylpyridin-4-amine (644.85 mg, 5.28 mmol, 0.5 eq.), were both weighed and added to a round-bottom flask, together with a stirring bar. After this, the solvent acetonitrile (100 mL) was used to dissolve the mixture, but about 10 mL of acetonitrile was added together with (BOC)2O (6 mL, 26.39 mmol, 2.50 eq.) into a syringe with 16 mL. The 16 mL of acetonitrile and boc were added over a period of 4 hours. The reaction was put on a hot plate where it was heated and stirred for 4 hours at temperature of 40°C, during this time the syringe added the boc and solvent over time into the mixture. The UPLC showed conversion to the product, of both reactants, shown as two peaks.

A column was preformed to separate the two compounds, and this was preformed with 10% MTB in methanol, which showed good sepeartion on the TLC prior to column. Using the column, tert-butyl 1,6-dimethyl-9-oxoacridine-10(9H)-carboxylate and tert-butyl 3,6-dimethyl-9-oxoacridine-10(9H)-carboxylate were separated successfully. The weighed total of tert-butyl 1,6-dimethyl-9-oxoacridine-10(9H)-carboxylate is 1.004g and of tert-butyl 3,6-dimethyl-9-oxoacridine-10(9H)-carboxylate is 1.537g. This means there is a total yield of 74.52%.

Proton NMR of tert-butyl 1,6-dimethyl-9-oxoacridine-10(9H)-carboxylate:
1H NMR (400 MHz, DMSO-D6) δ 8.05 (d, J = 8.1 Hz, 1H), 7.62 (dd, J = 8.6, 7.3 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 7.36 (s, 1H), 7.23 (dd, J = 8.1, 1.5 Hz, 1H), 7.18 (d, J = 7.4 Hz, 1H), 2.80 (s, 3H), 2.47 (s, 3H), 1.63 (s, 9H).
13C NMR (101 MHz, DMSO-D6) δ 178.86, 151.00, 143.70, 140.08, 139.92, 137.77, 132.28, 126.23, 126.05, 124.53, 121.62, 120.79, 116.81, 116.23, 85.98, 26.77, 22.76, 21.30.

Proton NMR of tert-butyl 3,6-dimethyl-9-oxoacridine-10(9H)-carboxylate:
1H NMR (400 MHz, DMSO-D6) δ 8.16 (d, J = 8.1 Hz, 2H), 7.30 – 7.23 (m, 4H), 2.49 (s, 6H), 1.69 (s, 9H).
13C NMR (101 MHz, DMSO-D6) δ 176.13, 151.23, 144.82, 138.68, 126.52, 124.81, 119.46, 116.29, 87.20, 27.18, 21.80.

Preparation of tert-butyl 2,7-dimethyl-9-oxoacridine-10(9H)-carboxylate
The compound 2,7-dimethylacridin-9(10H)-one (1.958 g, 8.77 mmol, 1.00 eq) and N,N-dimethylpyridin-4-amine (535.69 mg, 4.38 mmol, 0.5 eq.), were both weighed and added to a round-bottom flask, together with a stirring bar. After this, the solvent acetonitrile (83 mL) was added, but only 70 mL of solvent was added initially to the flask. The remaining solvent was combined with (BOC)2O (5 mL, 21.92 mmol, 2.50 eq.) into a syringe with 18 mL, which was added over the course of 4 hours using a syringe pump. The flask was kept at 40°C on a hot plate for 4 h. The first UPLC after about 3 h showed some conversion to tert-butyl 2,7-dimethyl-9-oxoacridine-10(9H)-carboxylate. Another UPLC was repeated after full addition of solvent and boc and the starting materials were no longer present, as conversion to product occured.
Using 1HNMR (crude) we can see the final product was produced, however many impurities remain in the crude NMR.
1H NMR (400 MHz, DMSO-D6) δ 8.13 – 8.04 (m, 2H), 8.01 (s, 2H), 7.54 (d, J = 8.5 Hz, 3H), 7.44 (d, J = 8.5 Hz, 2H), 2.50 (q, J = 2.0 Hz, 6H), 2.42 (d, J = 9.0 Hz, 9H), 1.99 (s, 9H).
Peaks attributed to ethyl acetate: quartet at 4 ppm, singlet at 2 ppm and triplet around 1.2 ppm. Some impurties remain, one of them is DMAP.

It will be columned. In order to rid it of impurities, it was columned in 5% ethyl acetate in pentane. After it was columned another NMR was preformed, The final weight of the product is 1.459 g, this is a yield of 51%.
1H NMR (400 MHz, DMSO-D6) δ 8.06 (d, J = 2.3 Hz, 2H), 7.65 (dd, J = 8.7, 2.3 Hz, 2H), 7.53 (d, J = 8.6 Hz, 2H), 2.43 (s, 6H), 1.65 (s, 9H).

Preparation of tert-butyl 2,6-dimethyl-9-oxoacridine-10(9H)-carboxylate and tert-butyl 1,7-dimethyl-9-oxoacridine-10(9H)-carboxylate
The compounds 2,6-dimethylacridin-9(10H)-one and 1,7-dimethylacridin-9(10H)-one (2.253 g, 10.09 mmol, 1.00 eq) and N,N-dimethylpyridin-4-amine (616.40 mg, 5.05 mmol, 0.5 eq.), were both weighed and added to a round-bottom flask, together with a stirring bar. After this, a portion of the solvent acetonitrile (94 mL) was added into the mixture and the rest was combined with (BOC)2O (5.7 mL, 25.23 mmol, 2.50 eq.) into a syringe and was added using a syringe pump over the course of 4 h. The reaction was put on a hot plate where it was heated and stirred for 4 h at temperature of 40°C. The first UPLC and the second UPLC did not show full conversion, as there were peaks present both from the new compounds and from the starting compounds. This was further checked by TLC as well where it was clear that the starting compounds remained. Thus, in order to push the reaction forward we added 3 mL (BOC)2O with 6 mL acetonitrile. Then the UPLC showed full conversion to the product, and 2 peaks were present as there are two compounds present.

The sample was columned with 10% MTBE in pentane to separate the two compounds, during the 1st column we retrieved the majority of the tert-butyl 1,7-dimethyl-9-oxoacridine-10(9H)-carboxylate, but the majority of tert-

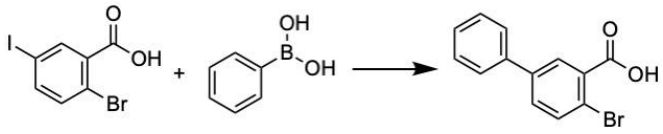
butyl 2,6-dimethyl-9-oxoacridine-10(9H)-carboxylate still came out together with the other compound.

Tert-butyl 1,7-dimethyl-9-oxoacridine-10(9H)-carboxylate
1H NMR (400 MHz, DMSO-D6) δ 7.91 (dt, J = 1.8, 0.9 Hz, 1H), 7.64 – 7.51 (m, 3H), 7.46 (dt, J = 8.5, 0.9 Hz, 1H), 7.17 (dt, J = 7.4, 1.0 Hz, 1H), 2.78 (s, 3H), 2.40 (d, J = 0.9 Hz, 3H), 1.59 (s, 9H).
As there was a peak at about 1.5 ppm that we could associate with any impurity we preformed a CNMR.
13C NMR (101 MHz, DMSO-D6) δ 180.28, 151.87, 140.87, 140.64, 136.65, 134.84, 133.48, 132.96, 127.12, 126.11, 124.95, 122.13, 118.83, 117.84, 86.38, 27.64, 23.44, 20.78.
As the CNMR came out clean this means that the compound is not tainted.

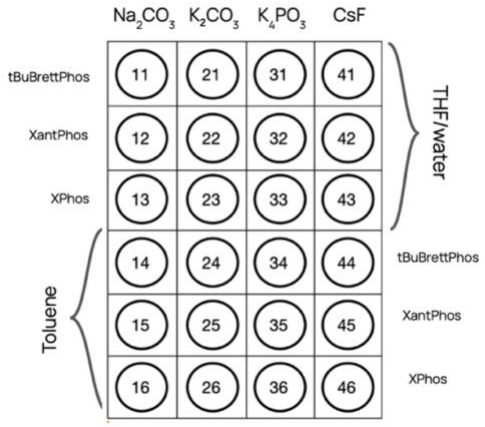
As only about 500 mg of tert-butyl 2,6-dimethyl-9-oxoacridine-10(9H)-carboxylate was retrieved with the first column, another column of the mixed fractions was preformed, yet again with 10% MTBE in pentane.
Tert-butyl 1,7-dimethyl-9-oxoacridine-10(9H)-carboxylate
1H NMR (400 MHz, DMSO-D6) δ 8.16 (d, J = 8.1 Hz, 1H), 8.06 (dd, J = 2.2, 1.1 Hz, 1H), 7.66 (dd, J = 8.7, 2.3 Hz, 1H), 7.48 (d, J = 8.7 Hz, 1H), 7.33 (t, J = 1.1 Hz, 1H), 7.25 (dd, J = 8.3, 1.4 Hz, 1H), 2.49 (d, J = 1.0 Hz, 3H), 2.43 (s, 3H), 1.67 (s, 9H).

From 2,6-dimethyl-9-oxoacridine-10(9H)-carboxylate a total of 778 mg was obtained and 1.512 g of 1,7-dimethyl-9-oxoacridine-10(9H)-carboxylate. This means the yield is 70.55%.

Scheme 2: Synthesis route for 4-bromo-[1,1'-biphenyl]-3-carboxylic acid



Screening for conditions:
In order to screen for the conditions to obtain 4-bromo-[1,1'-biphenyl]-3-carboxylic acid from 2-bromo-5-iodobenzoic acid and boronic acid, a total of 24 vials (4 rows and 6 columns) were set up in a metal heating plate, such that each vial had 21.79 mg of 2-bromo-5-iodobenzoic acid (1.00 eq) and also contained 9.75 mg of boronic acid (1.20 eq), as these are the starting materials. The two solvents that will be tested include toluene and THF/water (1:1), such that the first 3 columns (columns 1,2 and 3) contained toluene and the last 3 (columns 4,5 and 6) contained THF/water (1:1) as the solvent, total amount of solvent added to each vial is 2 mL. A total of 4 different bases (2.00 eq) will be tested, such that the first row will have 14.13 mg of NaCO3 in each vial, in row two a total of 18.43 mg of K2CO3 is added, row three will have 28.30 mg of K3PO4 and lastly row 4 has vials with 10.25 mg of CsF in them. A total of 3 different catalysts were used, in suvh a way that rows one and four contained tBuBrettPhos, columns two and five had XantPhos and columns three and six had XPhos. After setting up the reactions they ran for 4 hours at 110°C.
The first observation made after the experiment ran was that the majority of the water had evaporated from all the vials with THF/water solvent. The contents of each vial were analyzed using UPLC. As expected from the majority of the solvent evaporating, vials of THF/water did not yield any majory product as shown by UPLC results. However, for toluene a product could be seen using UPLC analysis, with a mass of 282 m/z, but unfortunately this was neither our desired mass, nor could we gauge what the mass could be attributed to. Thus, a workup was preformed by combining the contents of all the vials that contained toluene as a solvent, except 2 which did not yield the mass (vials 14 and 34), this included extraction using ethyl acetate a total of 3 times to extract the organic layer, and this layer was then washed with brine once. After this, the organic layer was filtered through phase separation paper and evaporated under reduced pressure. A NMR of the compound was taken, using DMSO, but as the NMR was unclear and contained a lot of impurities a column was preformed to attempt to isolate the compound. The column ran with 10% MTBE in pentane, but the desired product was not isolated. The only product that was isolated and confirmed by NMR is diphenyl, but this was not the desired product.



^{1}H NMR for Compound Characterization

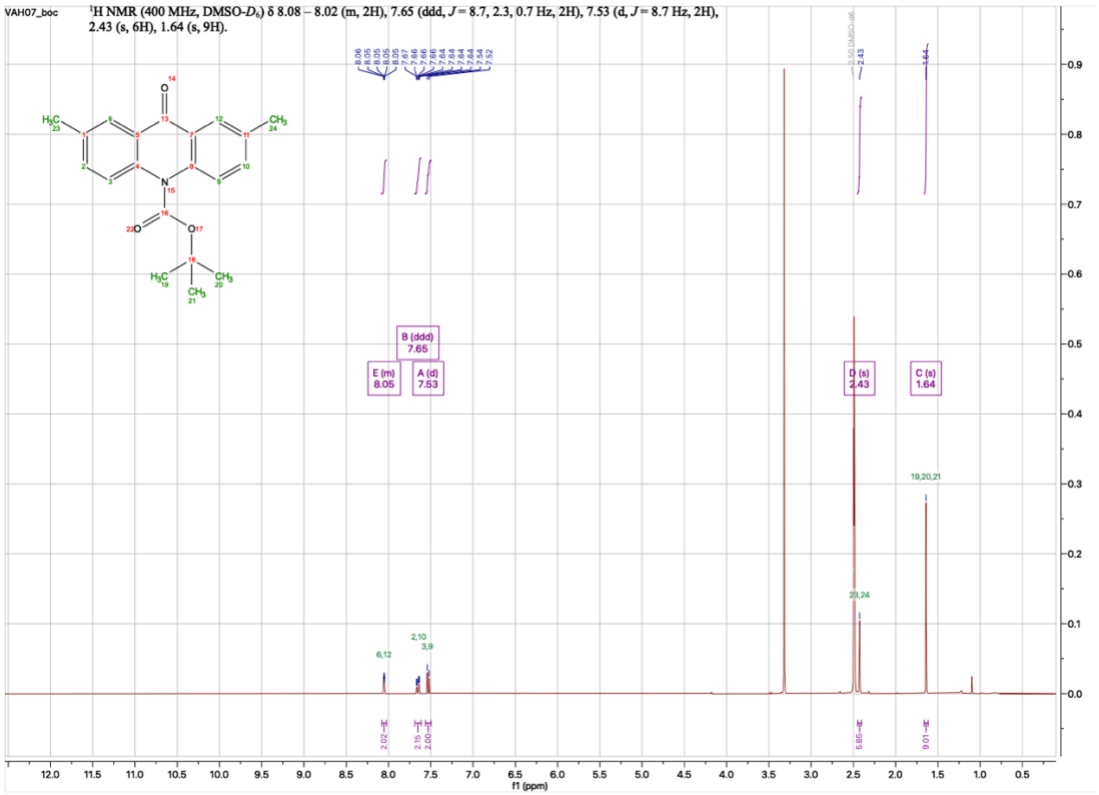


Figure S1: *^{1}H NMR of tert-butyl 2,7-dimethyl-9-oxoacridine-10(9H)-carboxylate*

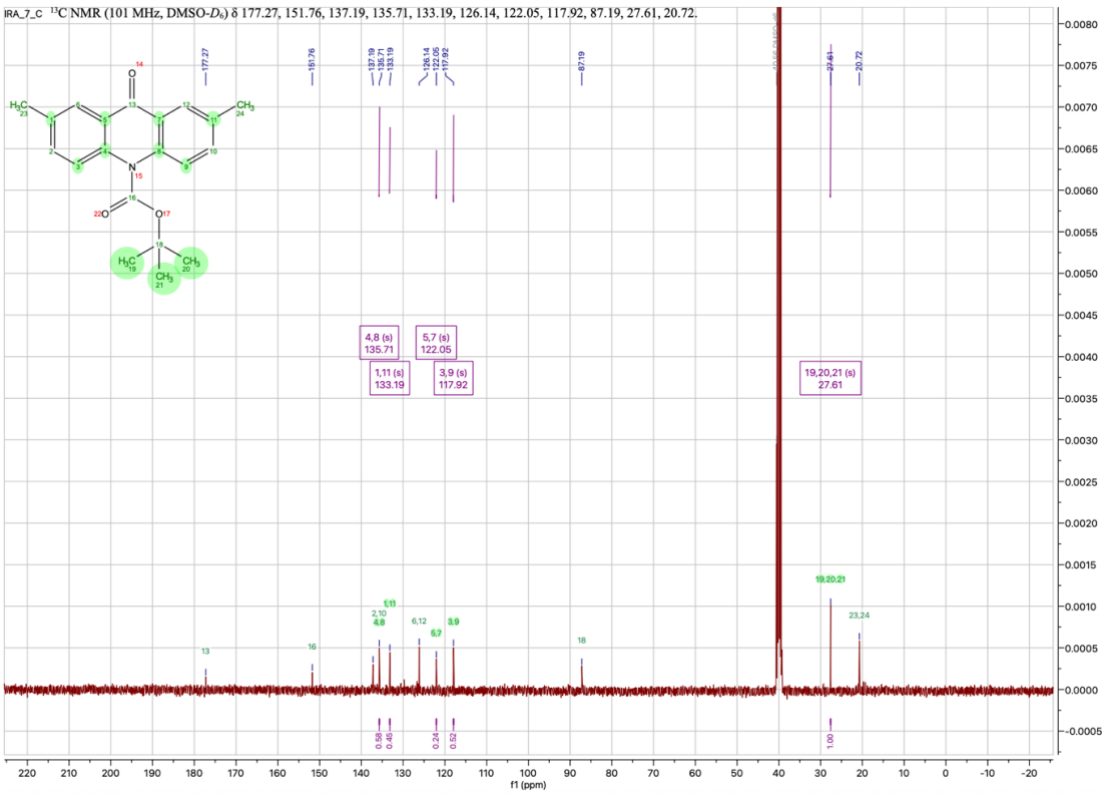


Figure S2: *^{13}C NMR of tert-butyl 2,7-dimethyl-9-oxoacridine-10(9H)-carboxylate*

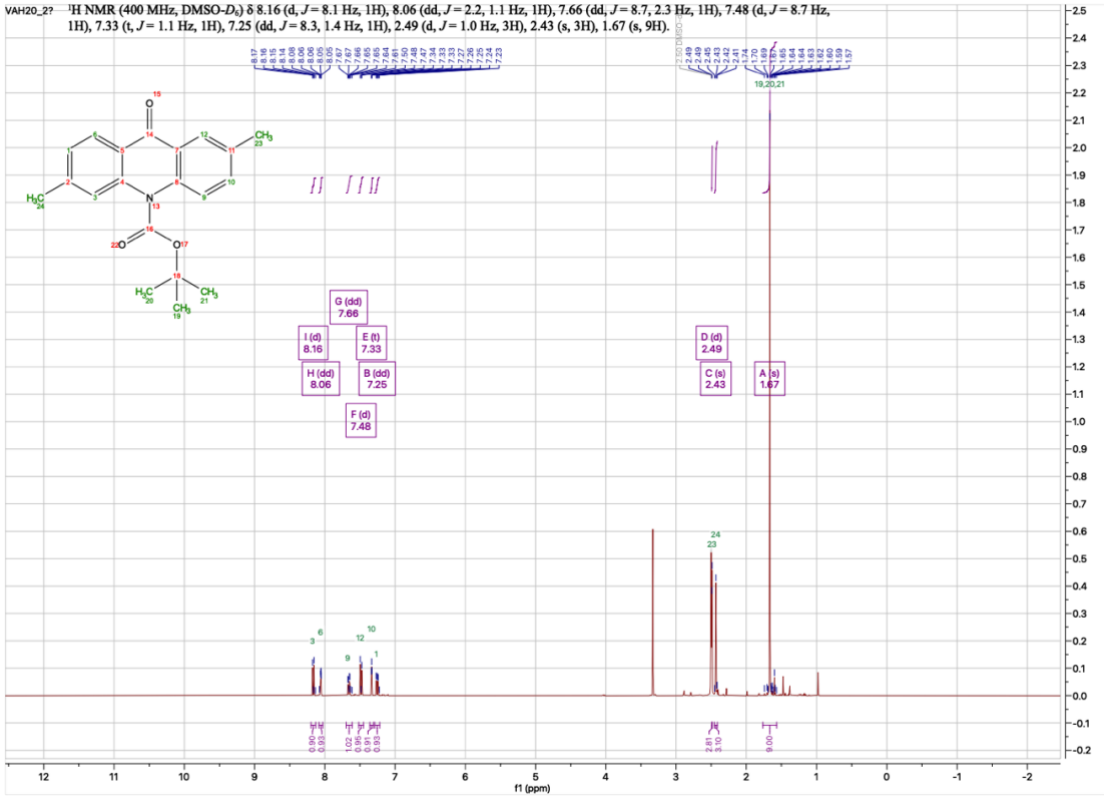


Figure S3: *[1]H NMR of tert-butyl 2,6-dimethyl-9-oxoacridine-10(9H)-carboxylate*

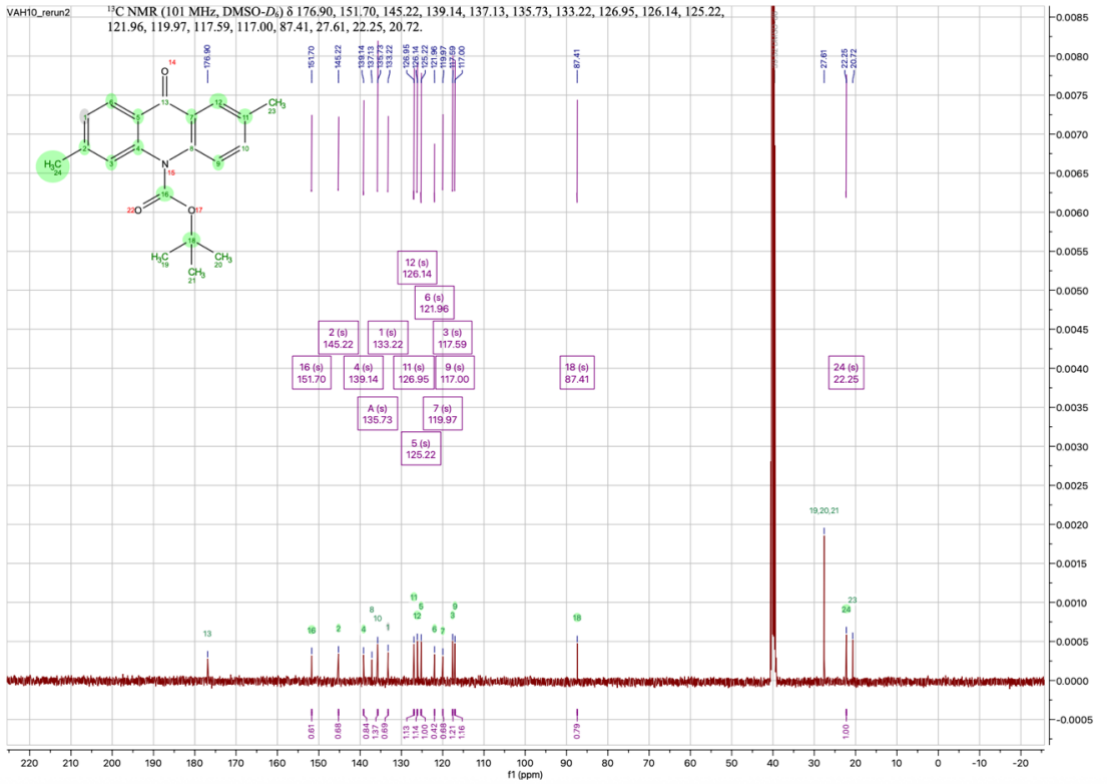


Figure S4: *[13]C NMR of tert-butyl 2,6-dimethyl-9-oxoacridine-10(9H)-carboxylate*

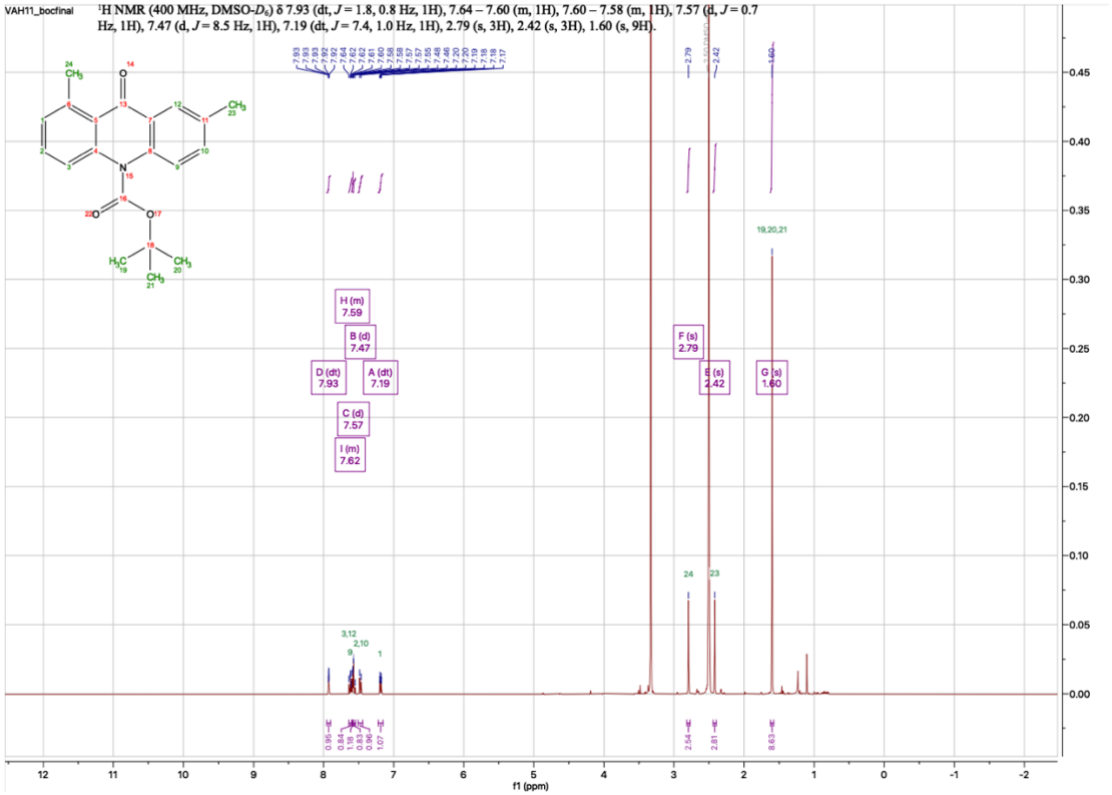


Figure S5: *[1]H NMR of tert-butyl 1,7-dimethyl-9-oxoacridine-10(9H)-carboxylate*

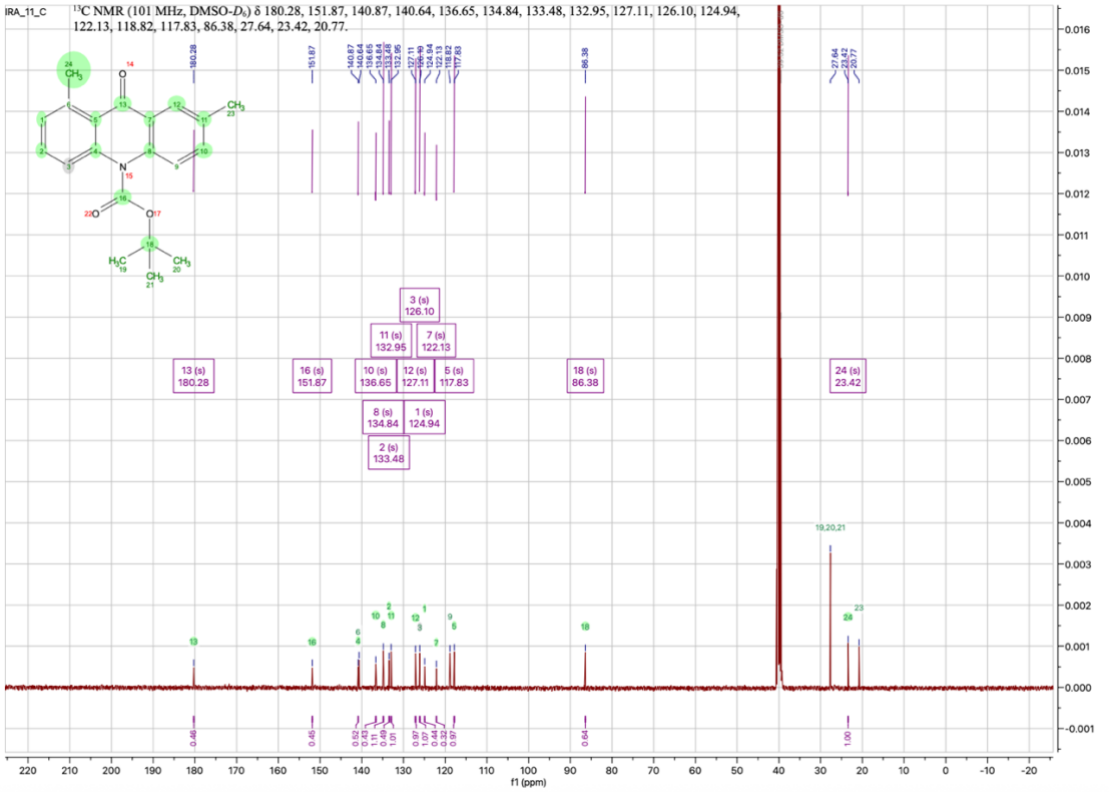


Figure S6: *[13]C NMR of tert-butyl 1,7-dimethyl-9-oxoacridine-10(9H)-carboxylate*

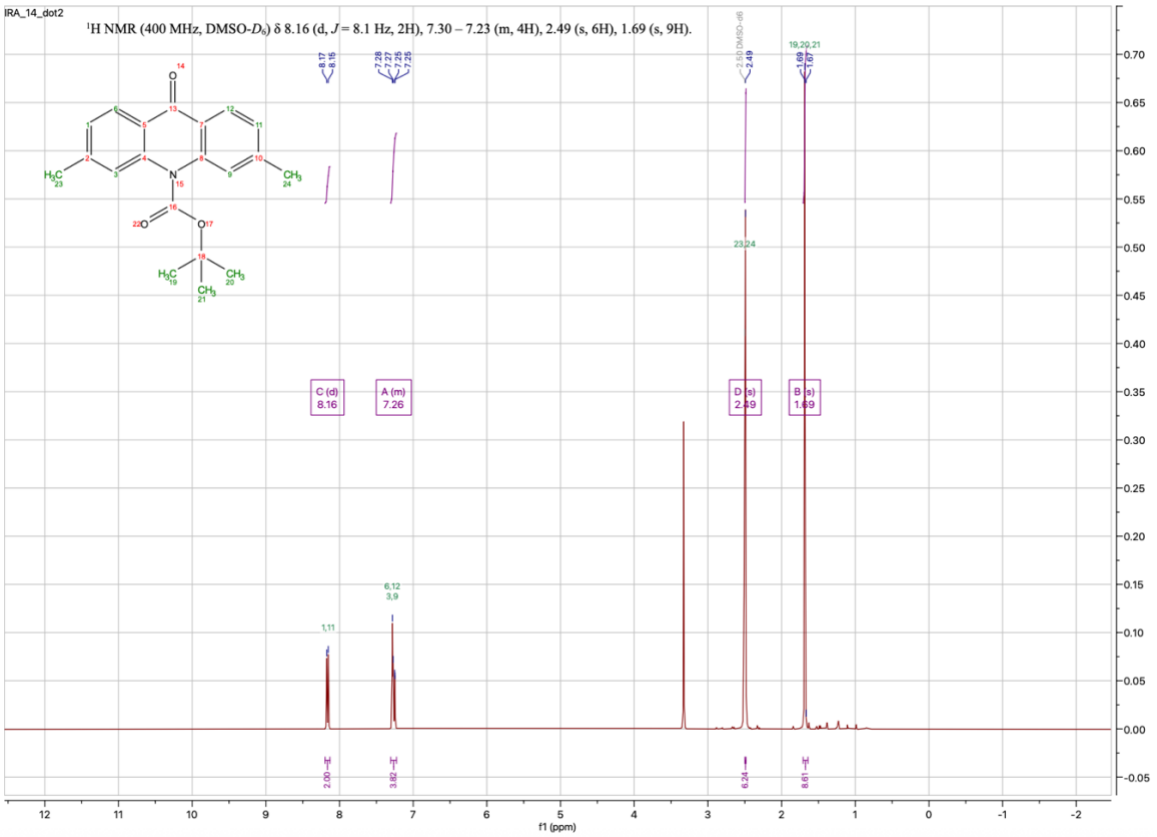


Figure S7: *[1]H NMR of tert-butyl 3,6-dimethyl-9-oxoacridine-10(9H)-carboxylate*

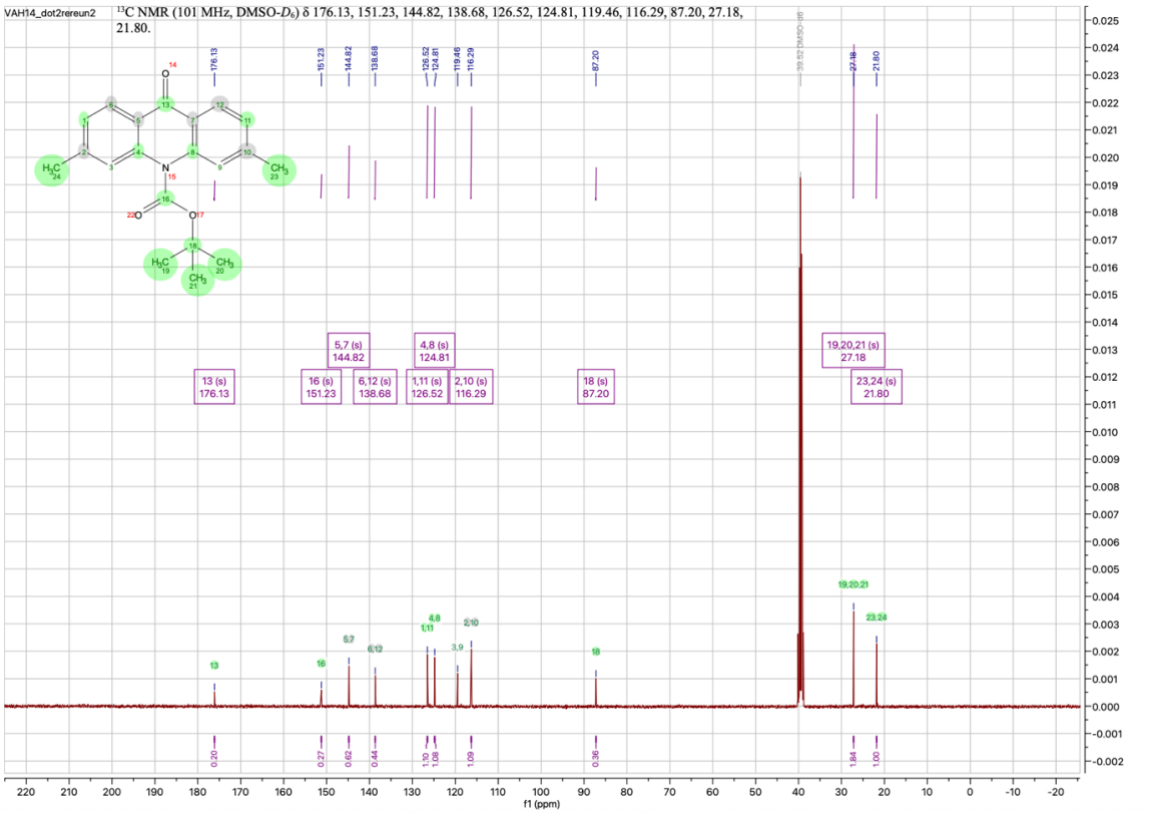


Figure S8: *[13]C NMR of tert-butyl 3,6-dimethyl-9-oxoacridine-10(9H)-carboxylate*

Figure S9: *[1]H NMR of tert-butyl 1,6-dimethyl-9-oxoacridine-10(9H)-carboxylate*

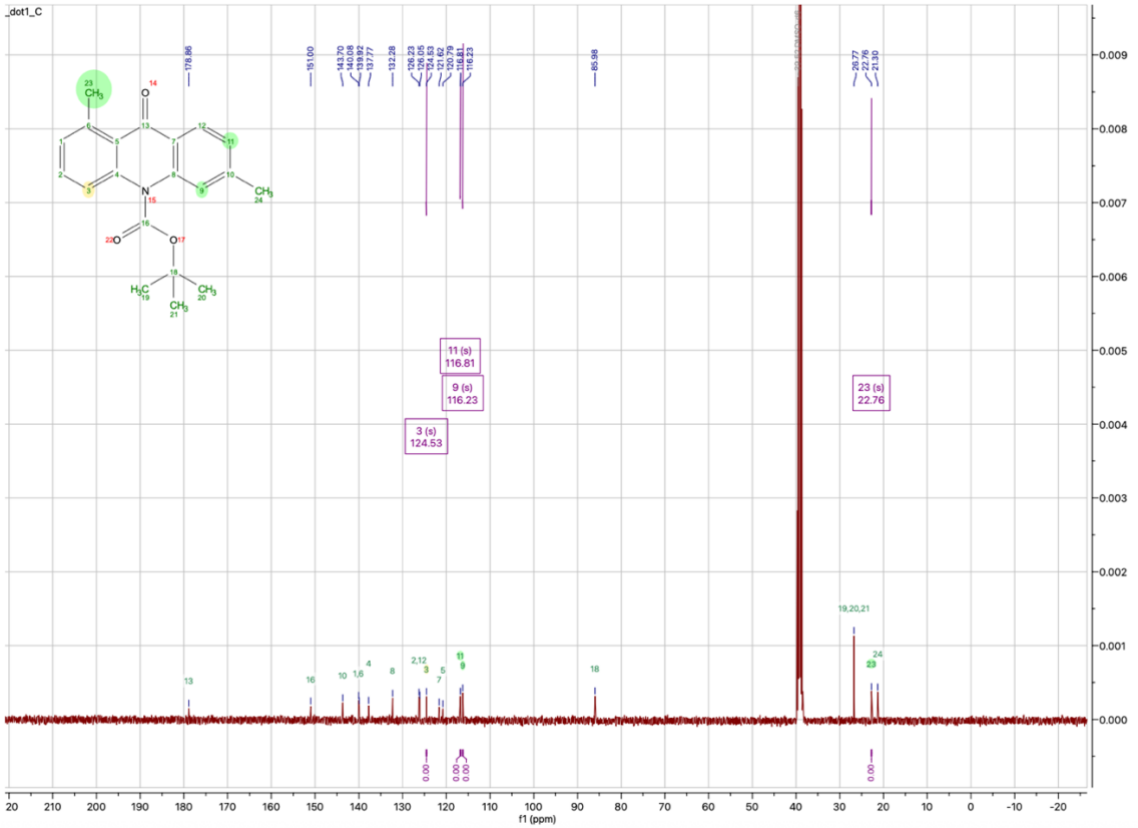


Figure S10: *[13]C NMR of tert-butyl 1,6-dimethyl-9-oxoacridine-10(9H)-carboxylate*