https://doi.org/10.3311/PPch.23808

Periodica Polytechnica Chemical Engineering, 68(3), pp. 277–286, 2024

Synthesis and Studies of 9-Activated 4,5-Dimethoxyacridine Multifunctionalizable Building Blocks

Panna Vezse[1], Ádám Golcs[1,2,3*], Péter Huszthy[1], Tünde Tóth[1,4]

[1] Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Szent Gellért tér 4., H-1111 Budapest, Hungary
[2] Department of Pharmaceutical Chemistry, Semmelweis University, Hőgyes Endre utca 9., H-1092 Budapest, Hungary
[3] Center for Pharmacology and Drug Research & Development, Department of Pharmaceutical Chemistry, Semmelweis University, Hőgyes Endre utca 9., H-1092 Budapest, Hungary
[4] Centre for Energy Research, Konkoly-Thege Miklós út 29-33., H-1121 Budapest, Hungary
* Corresponding author, e-mail: golcs.adam@edu.bme.hu

Received: 07 November 2023, Accepted: 04 April 2024, Published online: 27 June 2024

Abstract

9-Substituted-4,5-bifunctionalized acridines are common subunits of numerous drugs and fluorescent dyes, thus studies were carried out on a series of their potential precursors from the aspect of preparation, reactivity, chemical stability and potential applications. The syntheses of the new 9-fluoro-, 9-triflate and 9-lithiated derivatives of 4,5-dimethoxyacridine were reported. All the new intermediates supplemented with the recently synthetized 9-haloacridine analogues were compared and their applicability was discussed. The reactivity of the studied acridino-precursors was tested by using them as starting materials in Suzuki-Miyaura and Kharasch type cross-couplings as well as in Li-organic reactions.

Keywords

acridine, cross-coupling, lithiation, reactivity, stability

1 Introduction

Acridines are one of the most widely used heteroaromatic building blocks. Their derivatives are frequently applied as antibiotics [1], antimalarials [2], cytostatics [3] or as a signaling unit of various optochemically active agents [4–7].

Synthetic modifications of acridines usually focus on the substitution at position 9, which is generally carried out *via* a 9-haloacridine precursor, especially 9-chloroacridine, while the subsequent step is typically a C-C cross-coupling, like Suzuki-Miyaura- or Kharasch-reaction [8–10]. Moreover, acridines can also be modified at other positions to obtain a multifunctionalizable scaffold or to provide the desired chemical or photophysical properties. Since the 1950s compounds containing a 9-modified acridine or a 4,5-bifunctionalized acridine substructure have been successfully used as precursors of pharmaceutics in oncology [11–19] and infectiology [20], while some of them also proved to be effective as anti-inflammatory- [21] or antifungal [22] drugs. The value of 9-substituted as well as 4,5-bifunctionalized acridines is also demonstrated by numerous industrial patents in the recent decades [23–28]. Nowadays, these acridine-scaffolds are still the bases of a wide range of applications in coordination chemistry [29], optochemistry [30], corrosion inhibition [31], and also in pharmaceutical industry as precursors for a great variety of anticancer agents [32–34] and drugs against Alzheimer's disease [35].

Furthermore, the modified acridine-diols are not only valuable precursors, but the analogues of these heterocyclic key intermediates also exhibit a broad-range of pharmaceutical and chemotherapeutic activities, including anticancer, antiviral, anti-inflammatory, antimalarial and antimicrobial effects [36–39].

Recently, we successfully accomplished the transformations of 4,5-dimethoxyacridone to 9-haloacridines (Scheme 1), and used them for modified and thoroughly optimized Kharasch type cross-coupling reactions [5, 40]. Furthermore, we extended the synthetic possibilities by applying the recently reported highly reactive 9-bromo-4,5-dimethoxyacridine in Suzuki-reaction [40]. It was also showed, that the reported 4,5,9-trisubstituted acridines

Cite this article as: Vezse, P., Golcs, Á., Huszthy, P., Tóth, T. "Synthesis and Studies of 9-Activated 4,5-Dimethoxyacridine Multifunctionalizable Building Blocks", Periodica Polytechnica Chemical Engineering, 68(3), pp. 277–286, 2024. https://doi.org/10.3311/PPch.23808

had an increased reactivity and decreased stability compared to those of the corresponding unsubstituted ones [40]. These highly reactive multifunctionalizable intermediates open new ways for diverse post-synthetic modifications of the acridine backbone in contrast to the majority of conventional multistep synthetic procedures, which functionalize the acridine scaffold using ring closure steps [8, 41, 42].

The large number of industrially important analogues and the limitations of using the recently reported 4,5-bifunctionalized-9-chloroacridine intermediates motivated us to extend these studies. Thus, we report herein the synthesis and comparison study of a series of new 9-activated 4,5-dimethoxyacridines as multifunctionalizable synthetic building blocks. All reported compounds were prepared from 4,5-dimethoxyacridone, which was initially synthesized as a precursor for macrocyclic sensor molecules [43]. Reactivity, chemical stability, possible limitations are discussed, and suggestions are made regarding the subsequent modifications of these valuable intermediates.

2 Results and discussion

2.1 Scaffold design and synthetic modifiability

Synthesis of the reactive 4,5,9-trisubstituted acridino-intermediates (**2**) was carried out starting from 4,5-dimethoxyacridone (**1**), which enables a highly diverse assembly of a great variety of potential drug-subunits or fluorescent dyes (Scheme 1) [43].

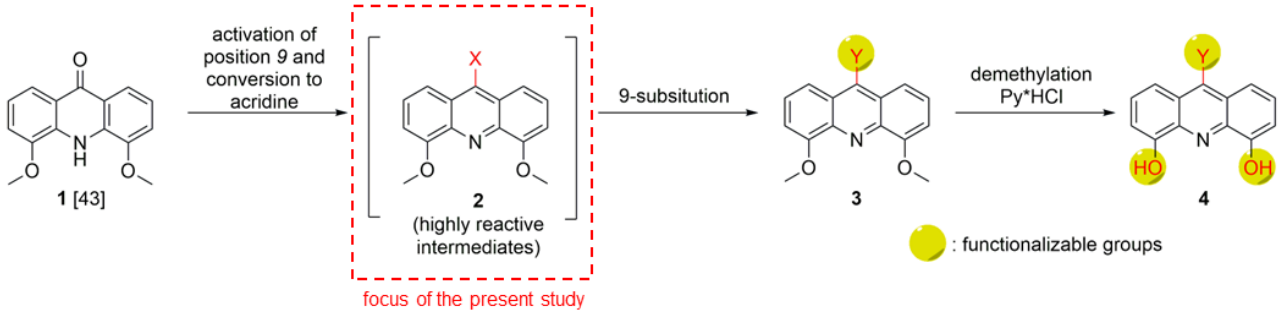
The starting acridone **1** contains methoxy groups at positions 4 and 5, which remain intact in any transformations, which aim to modify the other positions of the acridine moiety. The methyl protective groups can be easily and effectively removed with pyridinium chloride (2 h reaction time, >90% yield [5]) to gain widely modifiable hydroxy groups after incorporating the other desired functions.

The substitution at position 9 of acridines is the other option in focus. Since the most electrophilic center of acridines and acridones is the carbon atom at position 9, functionalization can be carried out regioselectively. Moreover, the introduction of substituents at position 9 opens ways for a sensitive fine-tuning of the building blocks. As the transformation of acridones to acridines extends the aromatic delocalization to the entire tricyclic system, the directly attached 9-subunits of different electronic nature or lipophilicity provide a versatile opportunity for tailoring both physico- and photochemical properties. Although the partial reconversion of acridines to acridones often takes place attributed to their relative stabilities, the 9-substituent can also stabilize the acridine form unless containing an α-H atom [40]. On the other hand, the electron donating methoxy groups at positions 4 and 5 of the acridino-building blocks decrease the chemical stabilities besides their reactivity- and basicity-enhancing effects compared to the unsubstituted 9-acridino-analogues [40]. Thus, applying inert and proton source-free reaction conditions is suggested.

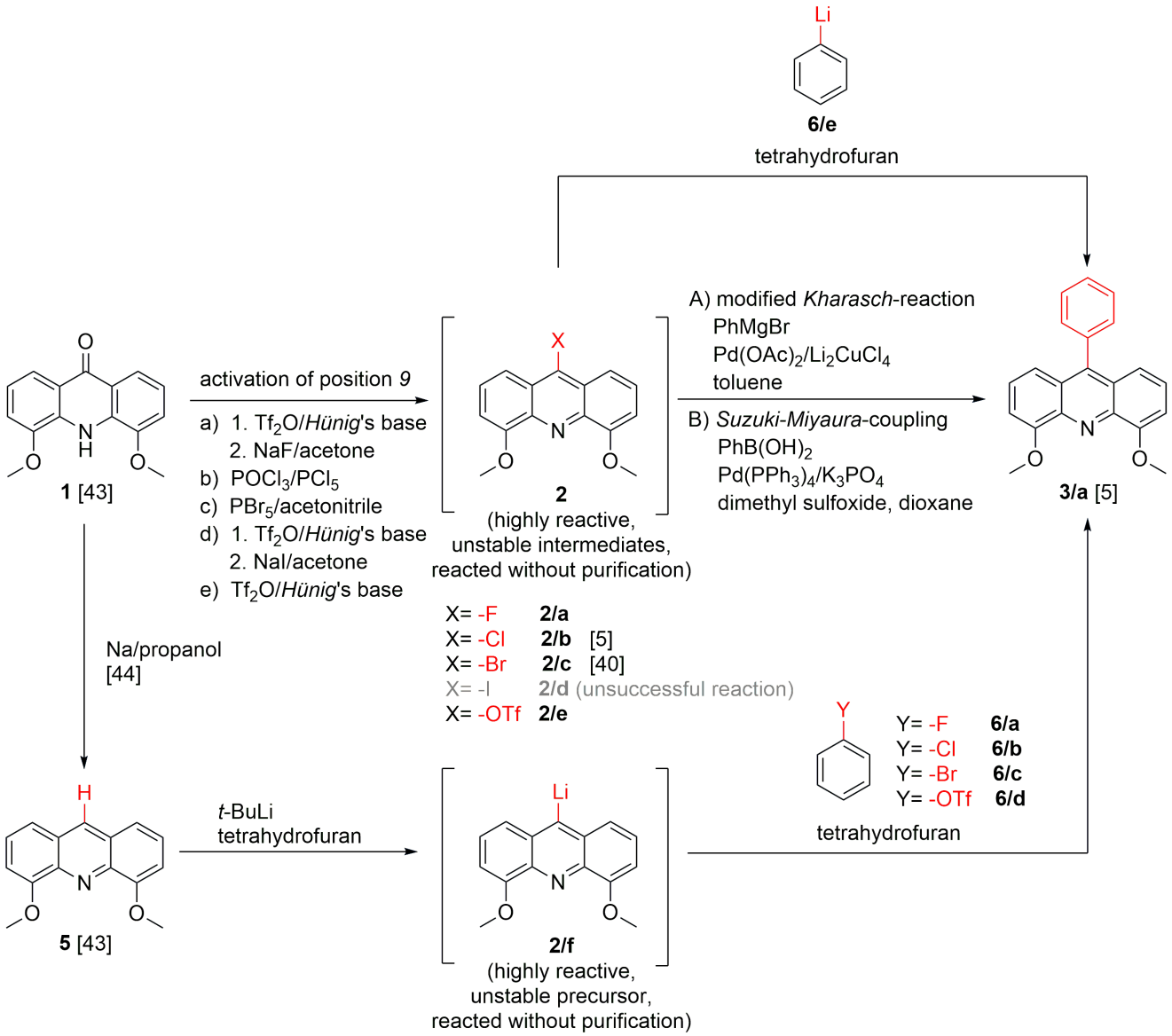
2.2 Model reactions starting from the 9-position-activated 4,5-dimethoxyacridine building blocks

The synthesis of two 9-haloacridine analogues (**2/a**,**2/d**) (missing from the series of the recently reported ones (**2/b**,**2/c**) [5, 40]) as well as that of the 9-triflate (**2/e**) and 9-Li-organic derivative (**2/f**) were attempted to extend the synthetic possibilities for the proposed building blocks. Then these highly reactive, unstable 9-activated 4,5-dimethoxyacridines (**2/a**-**2/e** except **2/d**) were converted without purification using the previously optimized modified Kharasch- and Suzuki-Miyaura-couplings or Li-organic reactions resulting in the same, stable 9-phenylacridine (**3/a**) as a model compound (Scheme 2) [5, 40, 43, 44].

The new 9-fluoro- (**2/a**) and 9-triflate (**2/e**) derivatives were synthesized based on analogies of the corresponding unsubstituted acridines [45], while the 9-chloro- (**2/b**) and 9-bromoacridine (**2/c**) were prepared according to the reported methods [5, 40].



Scheme 1 Transformation of 4,5-dimethoxyacridone (**1**) *via* highly reactive 9-activated acridino-precursors (**2**) to get trifunctionalizable scaffolds (**4**)



Scheme 2 Procedures for preparation of 4,5,9-trifunctionalized acridino-precursors

For the preparation of triflate **2/e**, using Hünig's base proved to be essential as only a partial conversion could be achieved in its absence. Warming and contact with protic media or air should be avoided during the whole work-up. Extraction with aqueous solutions is also not applicable (investigated by pouring the reaction mixture into a large excess of vigorously stirred 40 w/w% aqueous trimethylammonium hydroxide solution at 0 °C and extracting with dichloromethane) as a significant decomposition was observed. In the case of 9-fluoroacridine **2/a** to the contrary, extraction with aqueous solutions is allowed as decomposition did not take place. The synthesis of the 9-iodo-analogue **2/d** was also attempted *via* triflate **2/e**, but the desired product could not be isolated. Probably it is due to the extreme degradability of 9-iodoacridine **2/d**. Although a total conversion of 9-position-activated intermediates (**2/a**-**2/e** except **2/d**) could be reached in all cases, the reconversion to acridone could not be totally avoided even in optimized conditions. No other by-products could be isolated besides parent acridone **1**.

The strong electropositivity at position 9 of the acridine moiety resulted in a quite acidic *9*-H, which is also supported by the observed chemical shift of its singlet peak in the ^{1}H-NMR spectrum of compound **5** (δ = 8.75 ppm in $CDCl_3$ [43]). It allows the regioselective lithiation of acridine **5** at position 9. According to the experiences, the application of *t*-BuLi instead of n-BuLi resulted in a higher conversion to **3/a** in the Li-organic pathways.

The hydroxyl groups at positions 4 and 5 of acridines can also be functionalized easily and effectively [5, 43]. Among many possibilities, the formation of dimesylate **8** is demonstrated in Scheme 3, which can act as an active substrate in nucleophilic substitutions.

It is suggested to modify positions 4 and 5 after stabilizing the acridines by introducing a 9-substituent according to the possibilities shown in Scheme 2.

2.3 Comparison of reactivity and stability

Although all of the studied intermediates can be considered unstable, they showed quite different stabilities. The tendencies of the reported 9-activated intermediates to degradation during the work-up, purification or storage were compared in Table 1.

Naturally, the 9-Li precursor (**2/f**) is only stable under inert atmosphere dissolved in an ethereal solution cooled to −78 °C. It can be seen that the stability of the halogen derivatives (**2/a-c**) changes depending on the "goodness" of the leaving groups at position 9. From the aspect of this tendency and also considering the pK_a values of the conjugate acids of the corresponding leaving groups at position 9, triflate **2/e** showed an unexpectedly high stability compared to bromine **2/c** (Table 1). Overall, because of the relatively low stabilities, all of the studied intermediates are suggested to be reacted without any purification using only the optimized procedure for working up as reported in Sections 4.2.1 and 4.2.2.

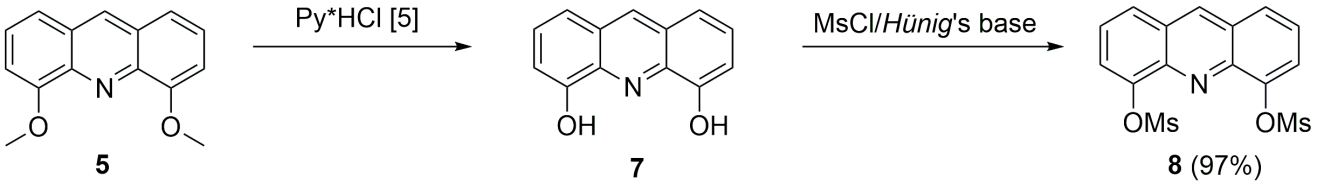
The applied three types of model reactions (modified Kharasch, Suzuki-Miyaura and Li-organic) required different times to complete, thus also became suitable for comparing the reactivity of the reported 9-activated intermediates. The Kharasch-analogue reaction was worked up after 20 h of stirring, while the Suzuki-coupling and the Li-organic reactions needed 5 h and 1 h to complete in optimized conditions, respectively. The applicability of the intermediates was compared by the yields for the preparation of 4,5-dimethoxy-9-phenylacridine (**3/a**) as the same product of the corresponding model reactions. Initially, the results of the modified Kharasch-coupling were summarized in Table 2.

It can be seen that the yields did not exactly follow the order of the pK_a values of the conjugate acids of the leaving groups. On the other hand, the reactivity strongly depends on agthe electrophilic character of the precursors. The lower yield using bromide **2/c** in this reaction is probably due to its lowest stability among the studied intermediates, which can strongly influence the outcome of the C-C-coupling.

The reactivities were similarly studied in *Suzuki-Miyaura*-coupling as shown in Table 3.

Fluoride **2/a** and chloride **2/b** did not work for this reaction. Bromide **2/c** was more effective as the required reaction time was much shorter than in the case of the *Kharasch*-analogue reaction. Although a large amount of the precursor was reconverted to the parent acridone **1**, the relatively favorable stability and high reactivity of triflate **2/e** were reflected from the result.

Finally, in contrast to the previous cases, acridino-intermediate **5** was tested as a nucleophilic agent after its lithiation, while the electrophiles contained series of leaving groups. The reverse case was also studied in Li-organic reactions. Results are summarized in Table 4.



5 **7** **8** (97%)

Scheme 3 Suggested procedure for modifying positions 4 and 5 of the acridine scaffold

Table 1 Comparison of the stabilities of the studied 9-activated acridino-intermediates

Intermediate	Extraction with aqueous solution	Acidic conditions (10% HCl aqueous solution)	Liquid chromatographic purification	Storage at r.t. in the air[1]	Storage at −30 °C under inert atmosphere[1]
2/a	A	N	A	15 h	3 days
2/b	A	N	N	6 h	2 days
2/c	N	N	N	order of minutes	order of minutes
2/e	N	N	N	1 h	20 h

'A' means applicable.
'N' means not applicable.
[1] The reported periods of time indicate the maximum shelf life under the corresponding conditions, while no significant decomposition, - i.e., absence of additional visible dots on TLC plates - was observed based on TLC-analysis.

Table 2 Comparison of reactivities of 9-activated 4,5-dimethoxyacridines in a Kharasch-type model reaction giving **3/a** as a product after 20 h of reaction time

Starting material	Reagent	Yield (%)[1]
2/a	PhMgBr	10
2/b	PhMgBr	58 [38]
2/c	PhMgBr	39
2/e	PhMgBr	75

[1] Reaction, work-up and purification were carried out according to a previously optimized [40] synthetic procedure reported in Section 4.2.5.

Table 3 Comparison of reactivities of 9-activated 4,5-dimethoxyacridines in a Suzuki-Miyaura-type model reaction giving **3/a** as a product after 5 h of reaction time

Starting material	Reagent	Yield (%)[1]
2/a	$PhB(OH)_2$	0
2/b	$PhB(OH)_2$	0
2/c	$PhB(OH)_2$	26 [38]
2/e	$PhB(OH)_2$	31

[1] Reaction, work-up and purification were carried out according to a previously optimized [40] synthetic procedure reported in Section 4.2.6.

Table 4 Comparison of reactivities of 9-activated 4,5-dimethoxyacridines in Li-organic model reactions giving **3/a** as a product after 1 h of reaction time

Starting material	Reagent	Yield (%)[1]
2/f	PhF (**6/a**)	0
2/f	PhCl (**6/b**)	0
2/f	PhBr (**6/c**)	35
2/f	PhOTf (**6/d**)	22
2/a	PhLi (**6/e**)	0
2/b	PhLi (**6/e**)	39
2/c	PhLi (**6/e**)	57
2/e	PhLi (**6/e**)	45

[1] Reaction, work-up and purification were carried out as reported in Sections 4.2.3 and 4.2.4.

The fluorides (**2/a**,**6/a**) did not work in both cases and the chlorides (**2/b**,**6/b**) showed low reactivity. The exceptionally high reactivity of bromide **2/c** could manifest in these fast reactions. The rate of decomposition of compound **2/c** did not exceed the conversion rate as much as in the other studied cases. (It also supports the assumption regarding the reduced yield in Kharasch-reaction when starting from bromide **2/c**.) Thus, using bromide **2/c** resulted in the highest yield. Parent acridone **1** could only be isolated as a by-product from the reaction mixtures of the studied other two cross-couplings. However, in the cases of the Li-organic reactions, the formation of biphenyls also took place, especially when acridines were the nucleophiles. It indicates, that the metal-halogen exchange is in a competition with the orbital-controlled C-C-coupling.

3 Conclusion

The earlier synthesized 9-chloro- (**2/b**) and 9-bromo (**2/c**) -4,5-dimethoxyacridine were supplemented with their new 9-fluoro- (**2/a**), triflate- (**2/e**) and lithiated (**2/f**) analogues to get a series of 4,5,9-trisubstituted multifunctionalizable fluorescent building blocks. Studies on these precursors establish a new synthetic chemical platform with replacing conventional procedures, which produce the multifunctional acridines by ring closure reactions using intermediates obtained from multistep pathways. The post-modifications of the acridine moieties were carried out regioselectively at position 9 starting from the activated precursors (2) in Kharasch-analogue, Suzuki-Miyaura- and Li-organic C-C-couplings. Moreover, the stabilities of the reported precursors (**2**) were also studied, which increased in the following order: 9-Br<9-OTf<9-Cl<9-F. There was a reverse correlation between the determined orders of stability and reactivity based on the comparison of yields for 4,5-dimethoxy-9-phenylacridine (**3/a**) as a model compound. For high-rate reactions, which require at least one hour to be completed bromide **2/c** is suggested. In the cases of slower conversions, reaction times between 2 and 24 h, triflate **2/e** is the most favorable one, while fluoride **2/a** can be advantageous for very slow reactions with a time requirement of several days. For C-C-couplings at position *9*, the acridino-precursors are preferred to be the electrophiles. The reconversion to the more stable acridone form can also be avoided by substitutions at position *9* unless the substituent contains an *a*-H. After the substitution at position *9* of the acridine moiety, the resulting intermediates can be further modified at positions *4* and *5* by the almost quantitative cleavage of the methyl groups. The present work opens new ways for post-synthetic modifications of the acridine backbone to gain 4,5,9-trisubstituted acridino-intermediates as common building blocks of drugs, chemosensors and fluorescent dyes.

4 Experimental

4.1 General

Starting materials and reagents were purchased from Sigma-Aldrich Corporation (USA, owned by Merck, Germany) and used without further purification unless otherwise noted. Solvents were dried and purified according to well established methods [46]. Silica Gel 60 F254 (Merck, Germany) plates were used for thin-layer chromatography (TLC). All reactions were monitored by TLC and visualized by UV-lamp. Purifications were carried out by preparative thin-layer chromatography (PTLC) using Silica gel 60

F254 (Merck, Germany) plates. Ratios of solvents for the eluents are given in volumes (mL/mL). Evaporations were carried out under reduced pressure unless otherwise stated.

The new compounds were characterized by their physical constants such as melting point, thin-layer chromatography retention factor (R_f), infrared, ^{1}H-NMR and ^{13}C-NMR spectroscopies and MS spectrometry. Elemental analyses and HRMS measurements could not be performed due to the instability of the new compounds. Melting points were taken on a Boetius micro-melting point apparatus and are uncorrected. Infrared spectra were recorded on a Bruker Alpha-T FT-IR spectrometer (Bruker Corporation, USA) using KBr pastilles. NMR spectra were recorded on a Bruker 300 Avance spectrometer (Bruker Corporation, USA; at 300 MHz for ^{1}H and at 75.5 MHz for ^{13}C spectra).

4.2 Synthesis

4.2.1 The synthesis of 9-fluoro-4,5-dimethoxyacridine (2/a, Scheme 2)

Triflate **2/e** (see Section 4.2.2) (150 mg, 0.39 mmol), sodium fluoride (82 mg, 1.95 mmol) and Hünig's base (68 µL, 50 mg, 0.39 mmol) were stirred in dry acetonitrile under an Ar atmosphere at room temperature. The reaction mixture was stirred for 5 min. The temperature was raised and the reaction mixture was refluxed for 2 h, when TLC analysis indicated the total conversion of the starting material (**2/e**). The mixture was evaporated and the residue was taken up in dichloromethane (50 mL) and water (100 mL). The phases were shaken well and separated. The aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic phase was dried over magnesium sulphate, filtered and the solvent was removed. The crude product was purified by PTLC using silica gel adsorbent with dichloromethane as an eluent to give fluoride **2/a** (95 mg, 95%) as an orange solid.

M.p. = 190–198 °C (decomposition). R_f = 0.39 (silica gel TLC, dichloromethane). ^{1}H-NMR ($CDCl_3$): δ [ppm]: 4.11 (s, 6H); 7.09 (d, J = 7.6 Hz, 2H); 7.61 (t, J = 8.2 Hz, 2H); 7.76 (d, J = 8.7 Hz, 2H). ^{13}C-NMR ($CDCl_3$): δ [ppm]: 56.31; 107.23; 112.35; 119.98; 120.80; 128.85; 141.48; 155.15. IR: ν_{max} [cm^{-1}]: 3416, 3338, 3091, 3025, 2948, 2850, 1732, 1626, 1594, 1533, 1489, 1457, 1413, 1356, 1323, 1272, 1225, 1161, 1081, 1032, 971, 926, 801, 751, 639. LC-MS: m/z = [MH$^+$]: 258.08, (Calcd. for $C_{15}H_{12}FNO_2$, 257.09).

4.2.2 The synthesis of 4,5-dimethoxyacridin-9-yl trifluoromethanesulfonate (2/e, Scheme 2)

4,5-Dimethoxyacridone (**1**, 300 mg, 1.18 mmol) was dissolved in dry and pure dichloromethane (10 mL) in a flame-dried flask equipped with a septum and an Ar inlet. The solution was cooled to 0 °C by using an external ice-bath. Then, triflic anhydride (595 µL, 999 mg, 3.54 mmol) was added to the stirred solution by a syringe. Hünig's base (1233 µL, 915 mg, 7.08 mmol) was also added using a syringe and the reaction mixture was stirred for 30 min. The volatile components were removed at 20 °C. (If the reaction mixture was poured onto a large excess of 40 w/w% aqueous tetramethylammonium hydroxide at 0 °C and was extracted with dichloromethane, the majority of the product was hydrolyzed.) Based on TLC analysis, a quantitative conversion was achieved and the crude product as a dark red solid was further reacted without purification.

M.p. = 176–180 °C (decomposition). R_f = 0.26 (silica gel TLC, dichloromethane). ^{1}H-NMR ($CDCl_3$): δ [ppm]: 4.22 (s, 6H); 7.46 (d, J = 7.7 Hz, 2H); 7.64 (t, J = 8.3 Hz, 2H); 8.18 (d, J = 8.7 Hz, 2H). ^{13}C-NMR ($CDCl_3$): δ [ppm]: 56.99; 114.12; 115.60; 116.03; 126.73; 131.38; 131.64; 147.65; 169.51. IR: ν_{max} [cm^{-1}]: 3101, 3042, 2947, 2844, 1636, 1625, 1559, 1503, 1459, 1442, 1408, 1362, 1306, 1282, 1182, 1085, 1070, 1018, 965, 925, 819, 790, 753, 688, 633, 614. LC-MS: m/z [MH$^+$]: 388.05, (Calcd. for $C_{16}H_{12}F_3NO_5S$, 387.04).

4.2.3 General procedure for C-C couplings using 9-lithio-4,5-dimethoxyacridine (2/f) and different phenyl electrophiles (6/a-6/d) (Scheme 2)

4,5-Dimethoxyacridine (**5**, 100 mg, 0.42 mmol) was dissolved in dry THF (3 mL) under Ar atmosphere. The reaction vessel was cooled to −78 °C. Tert-butyllithium (1.7 M in pentane, 370 µL, 0.63 mmol) was added to the solution through a septum using a syringe and a needle. The reaction mixture was stirred at −78 °C for 1 h. Then, the corresponding electrophile (1.50 molar equivalent related to **5**) in THF (3 mL) was slowly added to the reaction mixture. After 1 h of stirring, the reaction mixture was quenched by adding an aqueous solution of HCl (5 w/w%, 20 mL) and it was allowed to warm up to room temperature. The mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic phase was dried over magnesium sulphate, filtered and the solvent was removed. The crude product was purified by PTLC using silica gel adsorbent and ethyl acetate as an eluent to give 4,5-dimethoxy-9-phenylacridine (**3/a**). All of the physical data and spectroscopic properties of **3/a** concurred with those reported in the literature [5].

4.2.4 General procedure for C-C couplings using 9-position-activated 4,5-dimethoxyacridines (2/a–2/e except 2/d) and phenyllithium (6/e) (Scheme 2)

The 9-position-activated 4,5-dimethoxyacridines (**2/a**–**2/e** except **2/d**) were synthesized as reported ([5, 40], Sections 4.2.1 and 4.2.2 in the present work).

Phenyllithium (**6/e**, 1.9 M in dibutyl ether, 1.50 molar equivalent related to electrophiles) was stirred under Ar atmosphere at −78 °C. The corresponding acridines (**2/a**–**2/e** except **2/d**, 100 mg) in THF (5 mL) were added dropwise to the stirred solution of 6/e. The reaction mixture was stirred for 1 h at −78 °C. The reaction mixture was quenched by adding an aqueous solution of HCl (5 w/w%, 20 mL) and it was allowed to warm up to room temperature. The mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic phase was dried over magnesium sulphate, filtered and the solvent was removed. The crude product was purified by PTLC using silica gel adsorbent and ethyl acetate as an eluent to give 4,5-dimethoxy-9-phenylacridine (**3/a**). The product 3/a was identical in every aspect with that reported in the literature [5].

4.2.5 The previously reported optimized general procedure for Kharasch-type cross-coupling [40]

The 9-position-activated 4,5-dimethoxyacridines (**2/a**–**2/e** except **2/d**) were synthesized as reported ([5, 40], Sections 4.2.1 and 4.2.2 in the present work).

A solution of the corresponding crude 9-activated 4,5-dimethoxyacridine (**2/a**–**2/e** except **2/d**, 100 mg) in a mixture of dry and pure toluene (3 mL) and acetonitrile (0.1 mL) was added dropwise to a stirred solution of phenylmagnesium bromide (3 M in THF, 6.00 molar equivalent related to **2**), palladium acetate (0.07 molar equivalent related to **2**), dilithium tetrachlorocuprate (0.1 M in THF, 0.01 molar equivalent related to **2**) under an Ar atmosphere at room temperature. The temperature of the resulting reaction mixture was raised to 60 °C and kept at this temperature for 20 h then cooled down to 20 °C. The solvent was removed and the residue was taken up in ethyl acetate (10 mL) and ice-cold water (10 mL). The pH of the aqueous phase was adjusted to 7 using aqueous hydrochloric acid (5 w/w%). The phases were shaken well and separated. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic phase was dried over magnesium sulphate, filtered and the solvent was removed.

The crude product was purified by PTLC on silica gel using ethyl acetate as an eluent, to give compound **3/a**, which was identical in every aspect with that reported in the literature [5].

4.2.6 The previously reported optimized general procedure for Suzuki-Miyaura-coupling [40]

4,5-Dimethoxyacridines containing an active unit at position 9 (**2/a**–**2/e** except **2/d**) were synthesized as reported ([5, 40], Sections 4.2.1 and 4.2.2 in the present work].

The corresponding crude 9-activated 4,5-dimethoxyacridine (**2/a**–**2/e** except **2/d**, 100 mg) was dissolved in a mixture of dry and pure dimethyl sulfoxide (2 mL) and dioxane (1 mL), and the resulting solution was added dropwise to a stirred suspension of phenylboronic acid (3.00 molar equivalent related to **2**), tetrakis(triphenylphosphine)-palladium(0) (0.02 molar equivalent related to **2**) and potassium phosphate (3.00 molar equivalent related to **2**) in dioxane (3 mL) under Ar at room temperature. The temperature of the resulting mixture was raised to 60 °C and the mixture was kept at this temperature for 5 h then cooled down to 20 °C. Most of the volatile components was removed and the residue was taken up in ethyl acetate (10 mL) and ice-cold water (10 mL). The pH of the aqueous phase was adjusted to 7 using aqueous hydrochloric acid (5 w/w%). The phases were shaken well and separated. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic phase was extracted with water (6 × 10 mL) and then with saturated aqueous sodium chloride solution (2 × 10 mL) to remove the remains of dimethyl sulfoxide. The combined organic phase was dried over magnesium sulphate, filtered then the solvent was removed. The crude product was purified by PTLC on silica gel using ethyl acetate as an eluent, yielding derivative **3/a**. The physical and spectroscopic data of **3/a** concurred with those reported in the literature [5].

4.2.7 The synthesis of 5-(methanesulfonyloxy)acridin-4-yl methanesulfonate (8, Scheme 3)

Acridine-diol **7** (350 mg, 1.65 mmol) was dissolved in DMF (15 mL). Methanesulfonyl chloride (385 µL, 4.97 mmol) and Hünig's base (1.7 mL, 9.94 mmol) were added to this solution at 0 °C under argon atmosphere. The reaction mixture was stirred for 30 min, then the temperature was raised to 80 °C and it was further stirred at this temperature for 8 h. The volatile components were evaporated. The crude product was triturated with dichloromethane (cooled to 0 °C) to get **8** (588 mg, 97%) as an orange solid.

M.p. = 220–221 °C. R_f = 0.95 (SiO_2 TLC, dichloromethane:methanol 10:1), R_f = 0.70 (Al_2O_3 TLC, dichloromethane). ^{1}H-NMR (DMSO-d_6): δ [ppm]: 8.52 (s, ^{1}H), 7.37 (dd, J = 8.4, 1.3 Hz, 2H), 7.07 (dd, J = 7.4, 1.2 Hz, 2H), 6.85 (t, J = 8.5, 7.4 Hz, 2H), 2.79 (s, 6H). ^{13}C-NMR (DMSO-d_6): δ [ppm]: 150.04; 147.08; 143.14; 133.36; 132.98; 131.24; 129.53; 44.25. IR: ν_{max} [cm^{-1}]: 3010, 2958, 2918, 2870, 2853, 1630, 1569, 1541, 1526, 1439, 1430, 1352, 1335, 1220, 1067, 1017, 933, 739, 540. LC-MS: m/z = [MH$^+$]: 368.0, (Calcd. for $C_{15}H_{13}NO_6S_2$, 367.0).

Supplement

^{1}H-NMR and ^{13}C-NMR spectra of the new compounds can be found in the Supplement.

Acknowledgement

The authors express their thanks to Dániel Ster for his valuable technical assistance during this work. Special thanks to Erzsébet Kiss (NMR-measurements) and to Rita Molnárné Bernáth (IR-measurements) for their excellent work in characterization of the reported unstable compounds.

Author Contributions

Panna Vezse: Investigation, Formal analysis, Visualization, Writing - Original Draft; Ádám Golcs: Conceptualization, Methodology, Investigation, Writing - Original Draft, Project administration; Péter Huszthy: Writing - Review & Editing, Supervision, Funding acquisition, Resources; Tünde Tóth: Writing - Review & Editing, Supervision

Funding

This research was funded by the National Research, Development, and Innovation Office (grant number K128473), supported by the ÚNKP-23-4-II-BME-127 New National Excellence Program of the Ministry for Culture and Innovation from the source of the National Research, Development, and Innovation Fund.

Competing Interests

The authors declare no conflicts of interest. The funding institution had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript and in the decision to publish the results.

References

[1] Korth, C., May, B. C., Cohen, F. E., Prusiner, S. B. "Acridine and phenothiazine derivatives as pharmacotherapeutics for prion disease", Proceedings of the National Academy of Sciences, 98(17), pp. 9836–9841, 2001. https://doi.org/10.1073/pnas.161274798

[2] Fonte, M., Tassi, N., Gomes, P., Teixeira, C. "Acridine-based antimalarials - From the very first synthetic antimalarial to recent developments", Molecules, 263, 600, 2021. https://doi.org/10.3390/molecules26030600

[3] Belmont, P., Dorange, I. "Acridine/acridone: A simple scaffold with a wide range of application in oncology", Expert Opinion on Therapeutic Patents, 18(11), pp. 1211–1224, 2008. https://doi.org/10.1517/13543776.18.11.1211

[4] Shaikh, M., Swamy, Y. M., Pal, H. "Supramolecular host-guest interaction of acridine dye with cyclodextrin macrocycles: Photophysical, pK_a shift and quenching study", Journal of Photochemistry and Photobiology A: Chemistry, 258, pp. 41–50, 2013. https://doi.org/10.1016/j.jphotochem.2013.02.017

[5] Németh, T., Tóth, T., Balogh, G. T., Huszthy, P. "Synthesis and Fluorescence Spectroscopic Studies of Novel 9-phenylacridino-18-crown-6 Ether Type Sensor Molecules", Periodica Polytechnica Chemical Engineering, 61(4), pp. 249–257, 2017. https://doi.org/10.3311/PPch.11277

[6] Vezse, P., Kalóczkai, J. A., Ster, D., Bezúr, L., Golcs, Á., Huszthy, P., Tóth, T. "Dry-column Vacuum Chromatographic Removal of Hg2+ from Wastewater Based on an Acridino-crown Ether-modified Spherical Silica Gel Adsorbent", Periodica Polytechnica Chemical Engineering, 67(2), pp. 205–212, 2023. https://doi.org/10.3311/PPch.21563

[7] Vezse, P., Ster, D., Golcs, Á., Huszthy, P., Tóth, T. "Two Acridone Units in One Crown Ether: Incorporating a Second Acridone", Periodica Polytechnica Chemical Engineering, 67(4), pp. 537–546, 2023. https://doi.org/10.3311/PPch.22768

[8] Schmidt, A., Liu, M. "Recent Advances in the Chemistry of Acridines", Advances in Heterocyclic Chemistry, 115, pp. 287–353, 2015. https://doi.org/10.1016/bs.aihch.2015.04.004

[9] Prager, R. H., Williams, C. M. "Product Class 9: Acridines", In: Science of Synthesis, 15: Category 2, Hetarenes and Related Ring Systems, Thieme, 2005. https://doi.org/10.1055/sos-SD-015-01674

[10] Prager, R. H., Williams, C. M. "Product Class 10: Acridin-9(10H)-ones and Related Systems", In: Science of Synthesis, 15: Category 2, Hetarenes and Related Ring Systems, Thieme, 2005. ISBN 9783131186515 https://doi.org/10.1055/sos-SD-015-01714

[11] Hanger, W. G., Howell, W. C., Johnson, A. W. "87. Actinomycin. Part VI. The structure and synthesis of actinomycinol", Journal of the Chemical Society (Resumed), 1, pp. 496–504, 1958. https://doi.org/10.1039/JR9580000496

[12] Denny, W. A., Atwell, G. J., Baguley, B. C. "Potential antitumor agents. 40. Orally active 4,5-disubstituted derivatives of amsacrine", Journal of Medicinal Chemistry, 27(3), pp. 363–367, 1984. https://doi.org/10.1021/jm00369a021

[13] Rewcastle, G. W., Baguley, B. C., Atwell, G. J., Denny, W. A. "Potential antitumor agents. 52. Carbamate analogs of amsacrine with in vivo activity against multidrug-resistant P388 leukemia", Journal of Medicinal Chemistry, 30(9), pp. 1576–1581, 1987. https://doi.org/10.1021/jm00392a009

[14] Atwell, G. J., Rewcastle, G. W., Baguley, B. C., Denny, W. A. "Potential antitumor agents. 48. 3'-Dimethylamino derivatives of amsacrine: Redox chemistry and in vivo solid tumor activity", Journal of Medicinal Chemistry, 30(4), pp. 652–658, 1987. https://doi.org/10.1021/jm00387a012

[15] Lee, H. H., Wilson, W. R., Ferry, D. M., van Zijl, P., Pullen, S. M., Denny, W. A. "Hypoxia-Selective Antitumor Agents. 13. Effects of Acridine Substitution on the Hypoxia-Selective Cytotoxicity and Metabolic Reduction of the Bis-bioreductive Agent Nitracrine N-Oxide", Journal of Medicinal Chemistry, 39(13), pp. 2508–2517, 1996. https://doi.org/10.1021/jm9600104

[16] Su, T. L., Chen, C. H., Huang, L. F., Chen, C. H., Basu, M. K., Zhang, X. G., Chou, T. C. "Synthesis and Structure-Activity Relationships of Potential Anticancer Agents: Alkylcarbamates of 3-(9-acridinylamino)-5-hydroxymethylaniline", Journal of Medicinal Chemistry, 42(23), pp. 4741–4748, 1999. https://doi.org/10.1021/jm9901226

[17] Bacherikov, V. A., Chang, J. Y., Lin, Y. W., Chen, C. H., Pan, W. Y., Dong, H., Lee, R. Z., Chou, T. C., Su, T. L. "Synthesis and anti-tumor activity of 5-(9-acridinylamino) anisidine derivatives", Bioorganic & Medicinal Chemistry, 13(23), pp. 6513–6520, 2005. https://doi.org/10.1016/j.bmc.2005.07.018

[18] Maurice, H. B., Phillips, R., Karodia, N. "Design, synthesis and biological evaluation of novel acridine-polyamine conjugates against prostate cancer", African Journal of Pharmacy and Pharmacology, 3(12), pp. 602–610, 2009. https://doi.org/10.5897/AJPP.9000095

[19] Belmont, P., Bosson, J., Godet, T., Tiano, M. "Acridine and Acridone Derivatives, Anticancer Properties and Synthetic Methods: Where Are We Now?", Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents), 7(2), pp. 139–169, 2007. https://doi.org/10.2174/187152007780058669

[20] Fujioka, H., Kato, N., Fujita, M., Fujimura, K., Nishiyama, Y. "Activities of new acridone alkaloid derivatives against Plasmodium yoelii in vitro", Arzneimittel-Forschung, 40, pp. 1026–1029, 1990.

[21] Fujihira, E., Otomo, S., Sota, K., Nakazawa, M. "Anti-inflammatory activities of compounds related to anthranilic acid. II. On acridine mono-and dicarboxylic, and oxo-acridan monocarboxylic acid derivatives", Yakugaku Zasshi: Journal of the Pharmaceutical Society of Japan, 91(2), pp. 143–150, 1971. (in Japanese) https://doi.org/10.1248/yakushi1947.91.2_143

[22] Gabriel, I. "'Acridines' as New Horizons in Antifungal Treatment", Molecules, 25(7), 1480, 2020. https://doi.org/10.3390/molecules25071480

[23] Su, T. L., Watanabe, K. A. "Multisubstituted 1-hydroxy-9-acridones with anticancer activity", U.S. Patent and Trademark Office, U.S. Patent No. 5.296.602, 1994.

[24] Winter, R. W., Riscoe, M. K., Hinrichs, D. J. "Xanthone analogs for the treatment of infectious diseases", U.S. Patent and Trademark Office, U.S. Patent No. 5.977.077, 1999.

[25] Chafeev, M., Chakka, N., Cadieux, J. J., Fu, J., Kamboj, R., Kodumuru, V., Langille, J., Liu, S., Sun, J., Sviridov, S., Zhang, Z. "Tricyclic compounds useful in treating iron disorders", U.S. Patent and Trademark Office, U.S. Patent No. 12/044.731, 2009.

[26] Rothberg, J. M., Hinz, W. "Methods and apparatus for detecting molecular interactions using FET arrays", U.S. Patent and Trademark Office, U.S. Patent No. 8.349.167, 2013.

[27] Zhang, B., Li, X., Li, B., Gao, C., Jiang, Y. "Acridine and its derivatives: A patent review (2009–2013)", Expert Opinion on Therapeutic Patents, 24(6), pp. 647–664, 2014. https://doi.org/10.1517/13543776.2014.902052

[28] Chamberlain, B. T., Rice, J. M., Jerningan Iii, F. E., Sherman, W., Kulkarni, M. M., Shechter, S., Allen, B. K., Tan, D., Marino, K. A., Lin, Z. "Oxoacridinyl acetic acid derivatives and methods of use", U.S. Patent and Trademark Office, U.S. Patent No. 10.745.358, 2020.

[29] Omolo, K. O., Bacsa, J., Sadighi, J. P. "Acridine Variations for Coordination Chemistry", Israel Journal of Chemistry, 60(3–4), pp. 433–436, 2020. https://doi.org/10.1002/ijch.202000006

[30] Liu, H., Liu, Z., Li, G., Huang, H., Zhou, C., Wang, Z., Yang, C. "Versatile Direct Cyclization Constructs Spiro-acridan Derivatives for Highly Efficient TADF emitters", Angewandte Chemie, 133(22), pp. 12484–12488, 2021. https://doi.org/10.1002/ange.202103187

[31] Zhang, W., Li, H. J., Wang, M., Wang, L. J., Shang, F., Wu, Y. C. "Halogen-Substituted Acridines as Highly Effective Corrosion Inhibitors for Mild Steel in Acid Medium", The Journal of Physical Chemistry C, 122(44), pp. 25349–25364, 2018. https://doi.org/10.1021/acs.jpcc.8b07015

[32] Rupar, J., Dobričić, V., Grahovac, J., Radulović, S., Skok, Ž., Ilaš, J., Aleksić, M., Brborić, J., Čudina, O. "Synthesis and evaluation of anticancer activity of new 9-acridinyl amino acid derivatives", RSC Medicinal Chemistry, 11(3), pp. 378–386, 2020. https://doi.org/10.1039/C9MD00597H

[33] Madadi Mahani, N. "Studies on the Interaction between Derivatives of 9-acridinyl Amino Acid as Anticancer Drugs and Functionalized Carbon Nanotubes: ONIOM2-PCM Approach", Physical Chemistry Research, 9(1), pp. 99–106, 2021. https://doi.org/10.22036/pcr.2020.244303.1815

[34] Walunj, D., Egarmina, K., Tuchinsky, H., Shpilberg, O., Hershkovitz-Rokah, O., Grynszpan, F., Gellerman, G. "Expedient synthesis and anticancer evaluation of dual-action 9-anilinoacridine methyl triazene chimeras", Chemical Biology & Drug Design, 97(2), pp. 237–252, 2021. https://doi.org/10.1111/cbdd.13776

[35] Tseng, H. J., Lin, M. H., Shiao, Y. J., Yang, Y. C., Chu, … Huang, W. J. "Synthesis and biological evaluation of acridine-based histone deacetylase inhibitors as multitarget agents against Alzheimer's disease", European Journal of Medicinal Chemistry, 192, 112193, 2020. https://doi.org/10.1016/j.ejmech.2020.112193

[36] Bissim, S. M., Kenmogne, S. B., Tcho, A. T., Lateef, M., Ahmed, A., Happi, E. N., Wansi, J. D., Ali, M. S., Waffo, A. F. K. "Bioactive acridone alkaloids and their derivatives from Citrus aurantium (Rutaceae)", Phytochemistry Letters, 29, pp. 148–153, 2019. https://doi.org/10.1016/j.phytol.2018.12.010

[37] Chen, H. Y., Lam, S. H., Yang, M. L., Hung, H. Y., Shieh, P. C., Chen, F. A., Kuo, P. C., Wu, T. S. "Revision of structures of acridone alkaloids from natural sources", Journal of the Chinese Chemical Society, 68(4), pp. 669–677, 2021. https://doi.org/10.1002/jccs.202000345

[38] Nguyen, M. T. T., Dang, P. H., Nguyen, H. X., Le, T. H., Van Do, T. N., Pham, P. V., Nguyen, S. T., Nguyen, N. T. "Paratrimerin I, cytotoxic acridone alkaloid from the roots of Paramignya trimera", Natural Product Research, 35(23), pp. 5042–5047, 2020. https://doi.org/10.1080/14786419.2020.1774760

[39] Mandal, T., Karmakar, S., Kapat, A., Dash, J. "Studies Directed towards the Synthesis of the Acridone Family of Natural Products: Total Synthesis of Acronycines and Atalaphyllidines", ACS Omega, 6(41), pp. 27062–27069, 2021. https://doi.org/10.1021/acsomega.1c03629

[40] Golcs, Á., Ádám, B. Á., Vezse, P., Huszthy, P., Tóth, T. "Synthesis and Spectrophotometric Studies of 9-substituted-4,5-dimethoxyacridine Multifunctionalizable Fluorescent Dyes and their Macrocyclic Derivatives", European Journal of Organic Chemistry, 2021(17), pp. 2485–2497, 2021. https://doi.org/10.1002/ejoc.202100291

[41] Wu, H., Zhang, Z., Ma, N., Liu, Q., Liu, T., Zhang, G. "Synthesis of Acridines from o-Aminoaryl Ketones and Arylboronic Acids by Copper Trifluoroacetate-Mediated Relay Reactions", The Journal of Organic Chemistry, 83(20), pp. 12880–12886, 2018. https://doi.org/10.1021/acs.joc.8b01828

[42] Morioka, R., Hirano, K., Satoh, T., Miura, M. "Unexpected Cyclization of Tritylamines Promoted by Copper Salt through C-H and C-N Bond Cleavages to Produce Acridine Derivatives", Chemistry-A European Journal, 20(40), pp. 12720–12724, 2014. https://doi.org/10.1002/chem.201404656

[43] Huszthy, P., Köntös, Z., Vermes, B., Pintér, Á. "Synthesis of novel fluorescent acridono-and thioacridono-18-crown-6 ligands", Tetrahedron, 57(23), pp. 4967–4975, 2001. https://doi.org/10.1016/S0040-4020(01)00408-2

[44] Kertész, J., Huszthy, P., Kormos, A., Bertha, F., Horváth, V., Horvai, G. "Synthesis of new optically active acridino-18-crown-6 ligands and studies of their potentiometric selectivity toward the enantiomers of protonated 1-phenylethylamine and metal ions", Tetrahedron: Asymmetry, 20, pp. 2795–2801, 2009. https://doi.org/10.1016/j.tetasy.2009.11.011

[45] Singer, B., Maas, G. "Dikationether, 3 [1]. Substitutionen an Bis(acridinium)ethern und 9-Trifloxyacridinium-Salzen mit Halogeniden, Pseudohalogeniden und Schwefel-Nucleophilen", Zeitschrift für Naturforschung B, 39(10), pp. 1399–1408, 1984. (in German) https://doi.org/10.1515/znb-1984-1017

[46] Riddick, J. A., Bunger, W. B., Sakano, T. K. "Organic Solvents: Physical Properties and Methods of Purification", Wiley-Interscience: New York, 1986, pp. 1344–1400. ISBN 0471084670