

Pd-catalyzed one-pot approach for installation of 9-aminoacridines via Buchwald-Hartwig amination and cycloaromatization

Kovuru Gopalaiah,^{*,a} Renu Choudhary,^a and K. R. S. Sambasiva Rao^b

^a Department of Chemistry, University of Delhi, Delhi 110007, India

^b Department of Biotechnology, Mizoram University (Central University), Aizawl 796009, Mizoram, India

Email: gopal@chemistry.du.ac.in

In Honor of Prof. Sambasivarao Kotha on the occasion of his 65th birthday

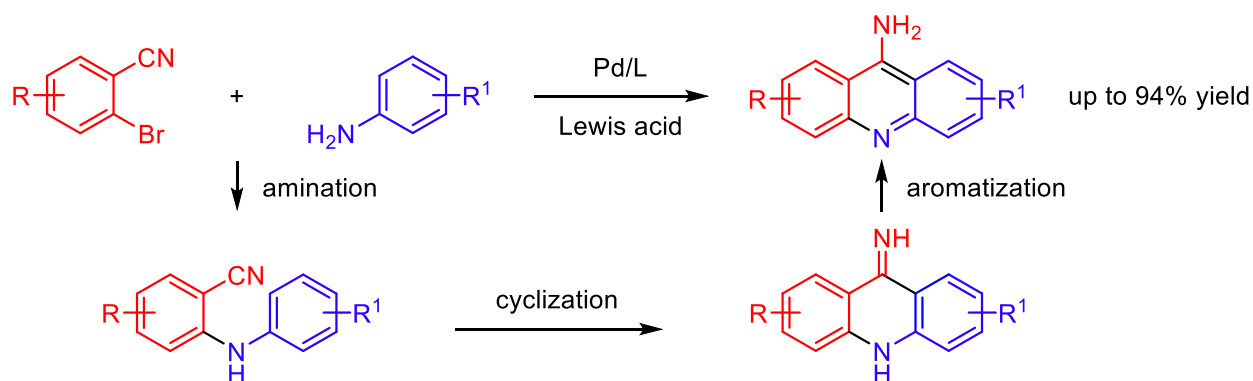
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Abstract

We developed a one-pot, two-stage synthetic route to access 9-aminoacridines involving a Buchwald-Hartwig coupling reaction followed by acid-mediated cycloaromatization. This one-pot reaction affords pharmaceutically valuable 9-aminoacridines from readily available 2-bromobenzonitriles and arylamines. The reaction was easily scaled-up to gram quantities. This methodology was extended to the preparation of various useful 9-aminoacridines, and further exemplified by the synthesis of 9-amino-6-chloro-2-methoxy acridine, an important scaffold of marketed drugs such as mepacrine and quinpramine.



Keywords: 9-Aminoacridine, Buchwald-Hartwig amination, palladium catalyst, cycloaromatization, one-pot synthesis, diphenylamine intermediate

Introduction

Acridines represent an important class of nitrogen-containing heteroaromatic molecules have attracted considerable interest because of their broad range of pharmaceutical properties and industrial applications.¹⁻² Among them, 9-aminoacridine is a featured structural motif in medicinally relevant compounds and synthetic drugs (Figure 1).³⁻⁷ It has been well-known that 9-aminoacridine derivatives possess versatile biological properties such as anti-Alzheimer, antibacterial, anti-BVDV, anticancer, anti-inflammatory, antiproliferative, antimalarial and antituberculous activities,⁸⁻¹⁵ and has also been studied for DNA and RNA intercalating properties.¹⁶⁻¹⁸ 9-Aminoacridine derivatives and related compounds have been used as dyes, pigments, corrosion inhibitors, and electrode materials for rechargeable lithium-ion batteries.¹⁹⁻²³ Additionally, 9-aminoacridine derivatives with extended conjugated systems were reported to exhibit unusual electronic and photophysical properties, i.e., high fluorescence quantum yields, and high molar absorption coefficients.²⁴⁻²⁷

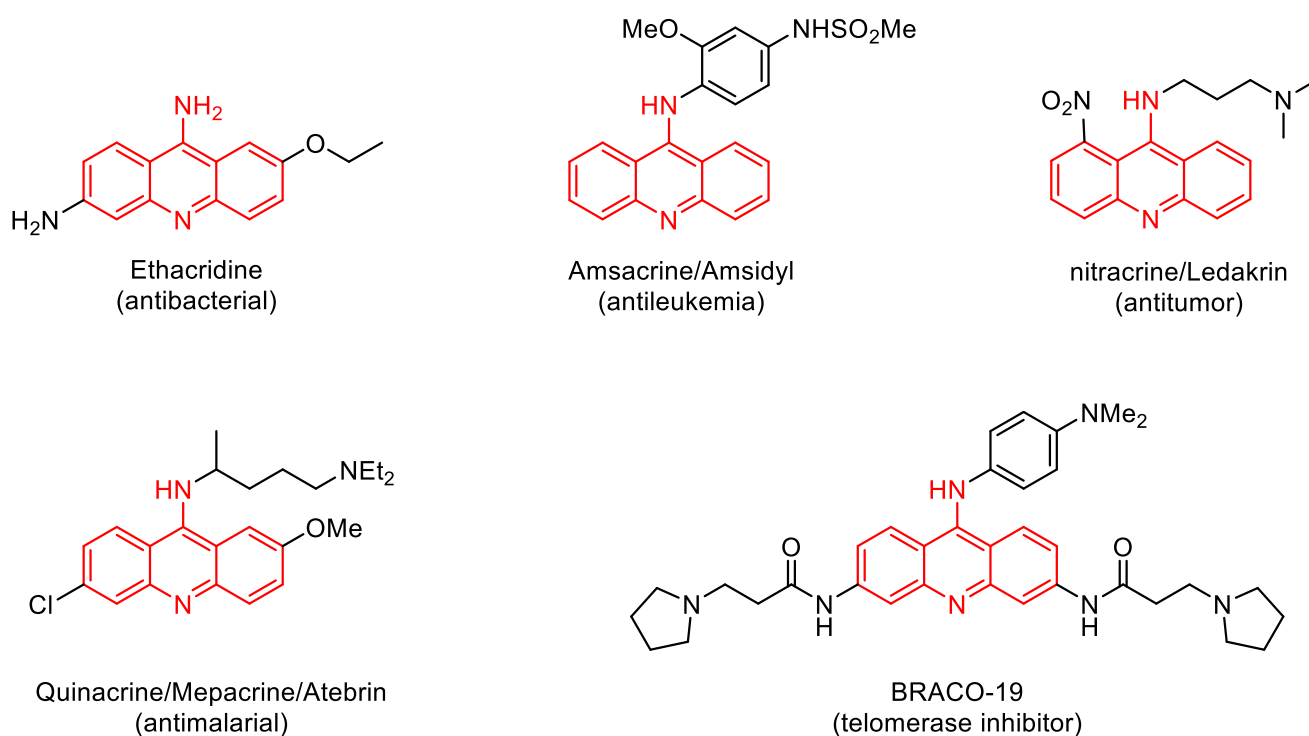


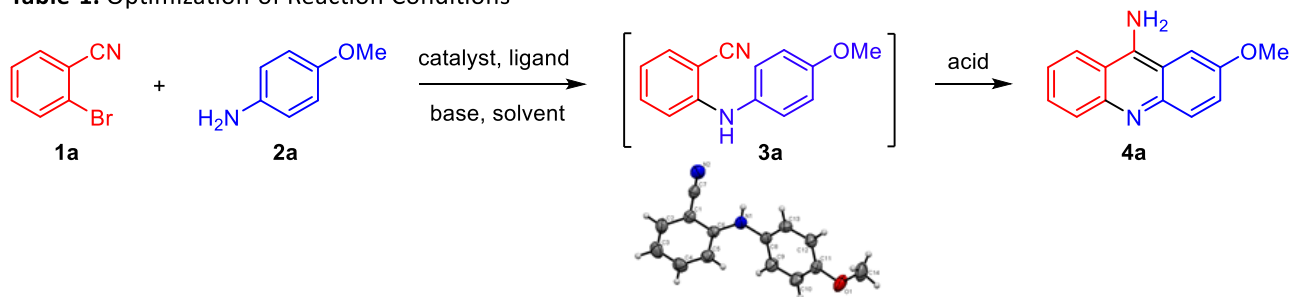
Figure 1. Representative drug molecules containing the 9-aminoacridine moiety.

9-Aminoacridines have been constructed using multi-step reactions, the final stage of the synthesis being nucleophilic substitution of chlorine or another nucleofuge in position 9 of the acridine molecule (S_NAr reaction).²⁸⁻³⁰ Bauer synthesized the 9-aminoacridine through Chichibabin reaction of acridine with sodium amide in dimethylaniline at 150 °C.³¹ However, in an attempt to reproduce this experiment, the authors³² obtained a different result which led the isolation of three compounds – the starting material acridine (14%), 9-aminoacridine (31%), and 9,9'-diacridanyl. Pang and co-workers reported efficient tandem reaction to construct *N*-aryl acridines with easily accessible *o*-cyanoanilines and diaryliodonium salts.³³ Chen et al. demonstrated the synthesis of oxadisilole-fused 9-aminoacridines via nucleophilic addition and 1,5-hydrogen shift reaction of arynes with 2-aminobenzonitriles.³⁴ Recently, Garcia and co-workers reported the synthesis of 5,12-diazapentacenes through coupling of 4-substituted aniline derivatives with 2,5-dibromoterephthalonitrile.³⁵

Despite these impressive advances, finding practical and straightforward synthetic methods to reproduce the 9-aminoacridine basic core molecules would be highly desirable. Encouraged by the numerous bioactivities of 9-aminoacridines and in continuation of our ongoing research on the synthesis of *N*-heterocycles,³⁶⁻⁴² we report an efficient method for the synthesis of 9-aminoacridines from the readily available 2-bromobenzonitriles and arylamines via Buchwald-Hartwig coupling reaction followed by acid-mediated cycloaromatization in one-pot process. This reaction provides convenient access to various substituted 9-aminoacridines in good to excellent yields with a high tolerance to many functional groups.

Results and Discussion

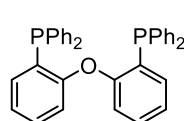
Our initial efforts were focused on the optimization of reaction conditions by taking 2-bromobenzonitrile (**1a**) and *p*-anisidine (**2a**) as model substrates. Delightfully, the intermediate 2-(4-methoxyanilino)benzonitrile (**3a**) was obtained in 38% yield using 10 mol % Pd(OAc)₂, 20 mol % DPEPhos, 2 equiv Cs₂CO₃ at 100 °C in toluene for 15 h under nitrogen atmosphere (Table 1, entry 1). Compound **3a** was crystallized in ethyl acetate/hexane solution and performed the single crystal X-ray analysis to confirm the structure of 2-(4-methoxyanilino)benzonitrile. To further improve the yield of **3a**, various reaction parameters such as ligands, palladium salts, bases, solvents, and temperature were evaluated systematically. The results of these studies are summarized in Table 1. A range of ligands such as XantPhos, Dppf, DavePhos, RuPhos, and rac-BINAP were first screened (Table 1, entries 2-6), and rac-BINAP showed the highest efficiency (Table 1, entry 6). Then, several palladium salts were evaluated (Table 1, entries 7-11), and the results indicated that the use of Pd(OAc)₂ as a catalyst provided the optimum yield. This transformation was also performed with various other bases (Table 1, entries 12-15), and cesium carbonate proved to be the most effective (compare entries 6 and 12-15). Among the several solvents we screened, toluene and xylene were the most compatible, affording **3a** in the highest yield of 92% (Table 1, entries 16-19). The yield of **3a** was decreased to 69% when the temperature was 80 °C (Table 1, entry 20). No significant enhancement of yield was observed by elevating the reaction temperature to 120 °C (Table 1, entry 21). The Pd/L loading for this transformation was also investigated. The yield remains the same when Pd and ligand loading was 5 mol % and 10 mol %, respectively (Table 1, entry 22). However, a further decrease of catalyst loading resulted in low yield of **3a** (Table 1, entry 23). Besides, testing the pre-catalyst BrettPhos Pd G1, methyl *t*-butyl ether adduct in the presence of cesium carbonate in *t*-butanol, furnished the Buchwald-Hartwig coupling product **3a** in 86% yield (Table 1, entry 24). Subsequently, we screened various acids for the cycloaromatization to obtain the 9-aminoacridine **4a**. The reaction proceeded well with boron trifluoride etherate (Table 1, entry 25), and the use of trifluoroacetic acid, trifluoromethanesulfonic acid, polyphosphoric acid (PPA), and titanium tetrachloride led to lower yields (Table 1, entries 26-29). We concluded that the best reaction conditions are Pd(OAc)₂ (5 mol %), rac-BINAP (10 mol %), Cs₂CO₃ (2 equiv), BF₃·OEt₂ (3 equiv) in toluene at 100 °C for 24 h, allowing the above one-pot reaction to occur smoothly providing the 9-aminoacridine **4a** in 89 % isolated yield (Table 1, entry 25).

Table 1. Optimization of Reaction Conditions^a

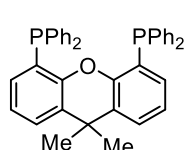
| entry | Pd catalyst | ligand | base | solvent | Brønsted/ Lewis acid | temp (°C) | yield ^b (%) | |
|-----------------|--|--------|---------------------------------|--------------------|-----------------------------------|--------------|------------------------|----|
| | | | | | | | 3a | 4a |
| 1 | Pd(OAc) ₂ | L1 | Cs ₂ CO ₃ | toluene | -- | 100 | 38 | nd |
| 2 | Pd(OAc) ₂ | L2 | Cs ₂ CO ₃ | toluene | -- | 100 | 76 | nd |
| 3 | Pd(OAc) ₂ | L3 | Cs ₂ CO ₃ | toluene | -- | 100 | 59 | nd |
| 4 | Pd(OAc) ₂ | L4 | Cs ₂ CO ₃ | toluene | -- | 100 | 30 | nd |
| 5 | Pd(OAc) ₂ | L5 | Cs ₂ CO ₃ | toluene | -- | 100 | 44 | nd |
| 6 | Pd(OAc) ₂ | L6 | Cs ₂ CO ₃ | toluene | -- | 100 | 92 | nd |
| 7 | Pd ₂ (dba) ₃ | L6 | Cs ₂ CO ₃ | toluene | -- | 100 | 75 | nd |
| 8 | Pd(acac) ₂ | L6 | Cs ₂ CO ₃ | toluene | -- | 100 | trace | nd |
| 9 | PdCl ₂ | L6 | Cs ₂ CO ₃ | toluene | -- | 100 | 58 | nd |
| 10 | PdCl ₂ (PPh ₃) ₂ | L6 | Cs ₂ CO ₃ | toluene | -- | 100 | 40 | nd |
| 11 | Pd(TFA) ₂ | L6 | Cs ₂ CO ₃ | toluene | -- | 100 | 84 | nd |
| 12 | Pd(OAc) ₂ | L6 | NaOEt | toluene | -- | 100 | 65 | nd |
| 13 | Pd(OAc) ₂ | L6 | <i>t</i> -BuOK | toluene | -- | 100 | 81 | nd |
| 14 | Pd(OAc) ₂ | L6 | K ₃ PO ₄ | toluene | -- | 100 | 46 | nd |
| 15 | Pd(OAc) ₂ | L6 | K ₂ CO ₃ | toluene | -- | 100 | 73 | nd |
| 16 | Pd(OAc) ₂ | L6 | Cs ₂ CO ₃ | xylene | -- | 100 | 92 | nd |
| 17 | Pd(OAc) ₂ | L6 | Cs ₂ CO ₃ | 1,4-dioxane | -- | 100 | 67 | nd |
| 18 | Pd(OAc) ₂ | L6 | Cs ₂ CO ₃ | <i>t</i> -BuOH | -- | 100 | 74 | nd |
| 19 | Pd(OAc) ₂ | L6 | Cs ₂ CO ₃ | CH ₃ CN | -- | 100 | 70 | nd |
| 20 | Pd(OAc) ₂ | L6 | Cs ₂ CO ₃ | toluene | -- | 80 | 69 | nd |
| 21 | Pd(OAc) ₂ | L6 | Cs ₂ CO ₃ | toluene | -- | 120 | 93 | nd |
| 22 ^c | Pd(OAc) ₂ | L6 | Cs ₂ CO ₃ | toluene | -- | 100 | 92 | nd |
| 23 ^d | Pd(OAc) ₂ | L6 | Cs ₂ CO ₃ | toluene | -- | 100 | 61 | nd |
| 24 ^e | -- | -- | Cs ₂ CO ₃ | <i>t</i> -BuOH | -- | 80 | 86 | nd |
| 25 ^f | Pd(OAc) ₂ | L6 | Cs ₂ CO ₃ | toluene | BF ₃ ·OEt ₂ | 100 | -- | 89 |
| 26 ^f | Pd(OAc) ₂ | L6 | Cs ₂ CO ₃ | toluene | CF ₃ CO ₂ H | 100 | -- | 68 |
| 27 ^f | Pd(OAc) ₂ | L6 | Cs ₂ CO ₃ | toluene | CF ₃ SO ₃ H | 100 | -- | 71 |
| 28 ^f | Pd(OAc) ₂ | L6 | Cs ₂ CO ₃ | toluene | PPA | 100 | -- | 39 |
| 29 ^f | Pd(OAc) ₂ | L6 | Cs ₂ CO ₃ | toluene | TiCl ₄ | 100 | -- | 64 |

^aReaction conditions: **1a** (1.0 mmol), **2a** (1.1 mmol), Pd catalyst (10 mol %), ligand (20 mol %), base (2 equiv), solvent (1 mL), 100 °C, 15 h, N₂. ^bIsolated yield, nd = not detected. ^cPd(OAc)₂ (5 mol %), L6 (10 mol %). ^dPd(OAc)₂ (2 mol %), L6 (4 mol %).

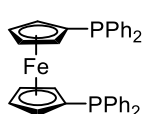
^eemployed pre-catalyst BrettPhos Pd G1, methyl *t*-butyl ether adduct (2 mol %), ^fAcid (3 equiv), reaction time was 24 h.



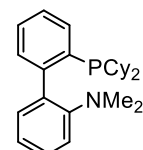
L1: DPEPhos



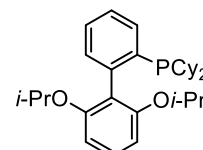
L2: XantPhos



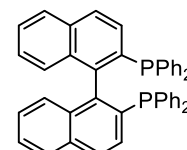
L3: Dppf



L4: DavePhos



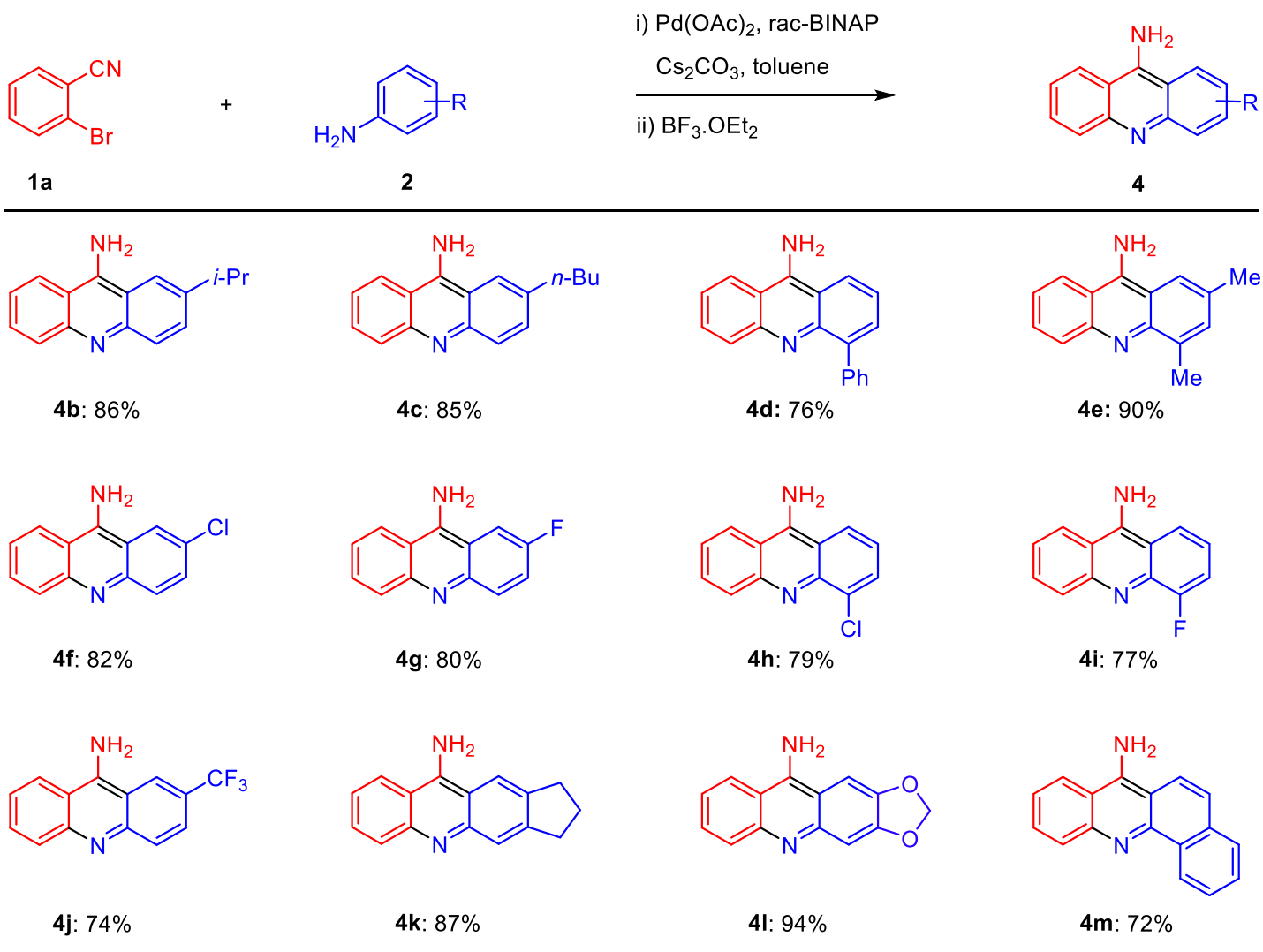
L5: RuPhos



L6: rac-BINAP

With this established reaction conditions in hand, we investigated the substrate scope with respect to arylamines (Table 2). As shown, the arylamines containing electron-donating substituents such as isopropyl, *n*-butyl, or phenyl at the para or ortho positions of the aryl ring were efficiently coupled with 2-bromobenzonitrile, producing the desired products with good yields (**4b-d**). Electron-rich disubstituted arylamine also furnished high yield of the product (**4e**). Arylamines bearing electron-withdrawing substituents such as chloro, fluoro groups at the para or ortho positions smoothly underwent the reaction to furnish the corresponding products in good yields (**4f-i**). The arylamine containing trifluoromethyl group also gave the acridine product **4j** in 74 % yield, but nitro substrate namely 4-nitroaniline failed to afford the desired product. The ring-fused arylamines viz., 5-indanamine, 1,3-benzodioxol-5-amine also served as suitable coupling partners to offer good to high yields, as exemplified by **4k** and **4l**. The naphthyl-substituted amine was tolerated in this one-pot transformation, producing benzo[*c*]acridin-7-amine (**4m**) in 72 % yield.

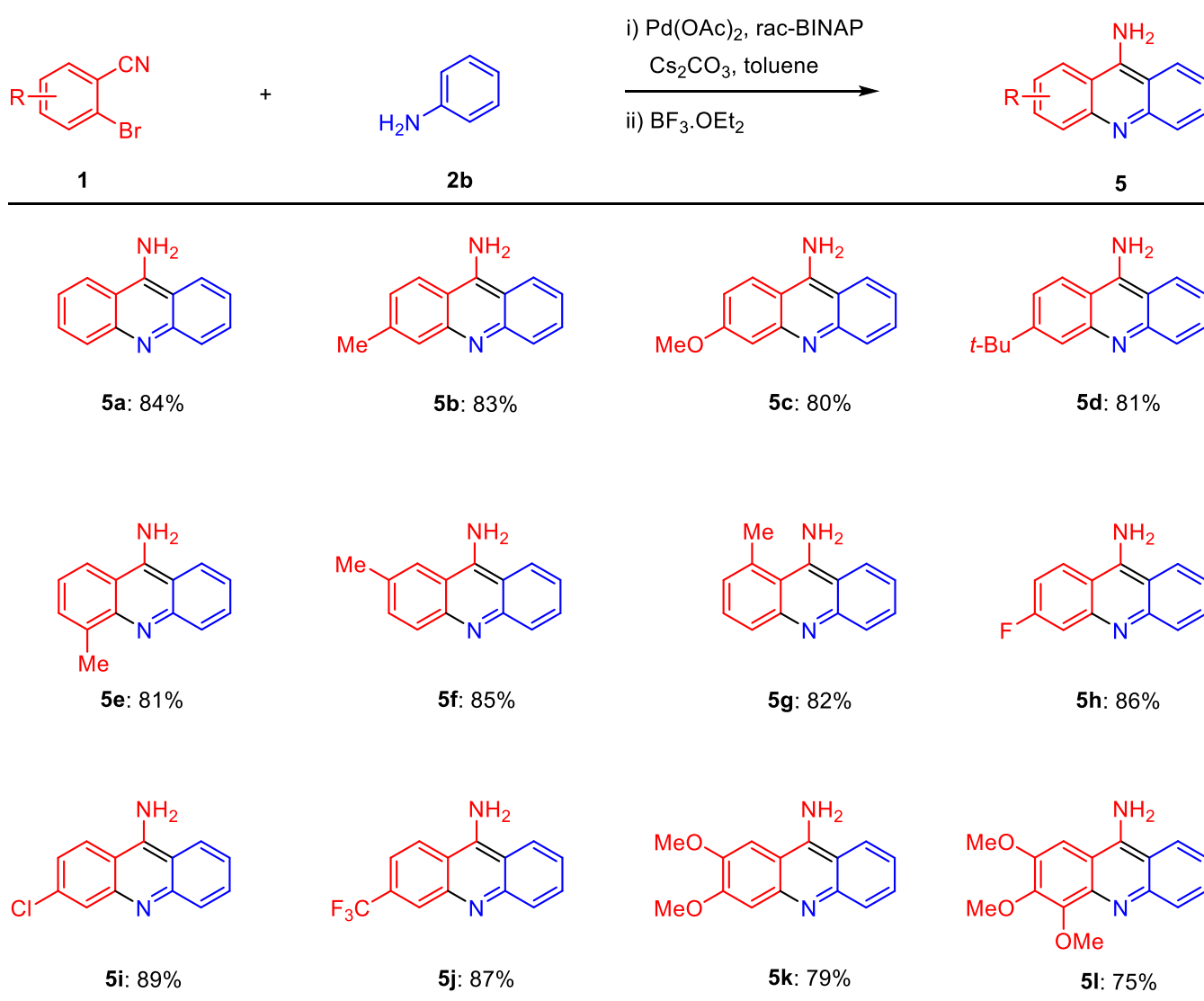
Table 2. Substrate Scope of Arylamines^{a,b}



^aReaction conditions: **1a** (1.0 mmol), **2** (1.1 mmol), Pd(OAc)₂ (5 mol %), rac-BINAP (10 mol %), Cs₂CO₃ (2 equiv), toluene (1 mL), BF₃·OEt₂ (3 equiv), 100 °C, 24 h, N₂. ^bIsolated yields.

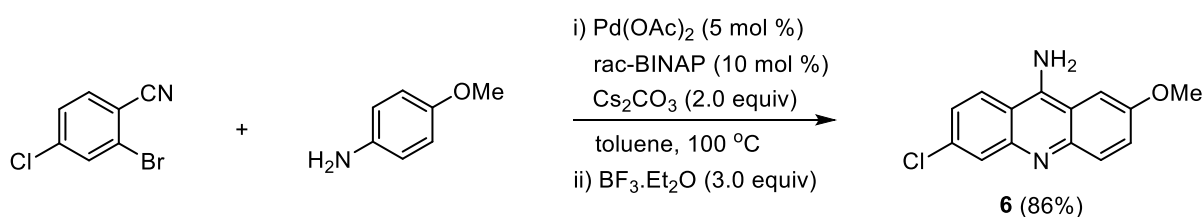
Subsequently, we evaluated the substrate scope of this one-pot reaction with regard to the 2-bromobenzonitriles (Table 3). Gratifyingly, both electron-neutral (4-H) and electron-donating (4-Me, 4-OMe, 4-*t*Bu) groups on the phenyl rings of 2-bromobenzonitriles were compatible and provided the corresponding products in 80-84% yields (**5a-d**). Presence of methyl group at 3, 5 and 6 positions of phenyl ring of 2-bromobenzonitrile also worked well (**5e**, **5f** and **5g**). Halogen-substituted 2-bromobenzonitriles (4-F, 4-Cl) afforded the desired products in good yields (**5h** and **5i**), therefore providing the possibility for further derivatization. Besides, the method was equally effective for strong electron-withdrawing trifluoromethyl group containing substrate, namely, 2-bromo-4-(trifluoromethyl)benzonitrile to give the corresponding product **5j** in 87% yield under the standard reaction conditions. Furthermore, the electron-rich disubstituted and trisubstituted 2-bromobenzonitriles also smoothly underwent the reaction to provide the desired products in good yields (**5k** and **5l**).

Table 3. Substrate Scope of 2-Bromobenzonitriles^{a,b}

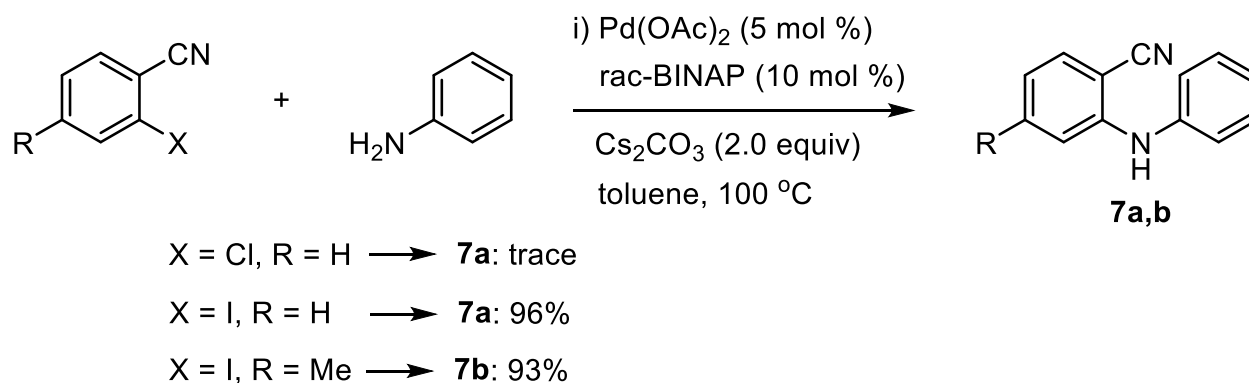


^aReaction conditions: **1** (1.0 mmol), **2b** (1.1 mmol), Pd(OAc)₂ (5 mol %), *rac*-BINAP (10 mol %), Cs₂CO₃ (2 equiv), toluene (1 mL), BF₃·OEt₂ (3 equiv), 100 °C, 24 h, N₂. ^bIsolated yields.

The efficiency of this reaction protocol was further demonstrated by conducting the transformation on a laboratory preparative scale. For example, the one-pot reaction of 2-bromobenzonitrile with *p*-anisidine was performed on a gram scale (5 mmol), and **4a** was obtained in 82% isolated yield. Furthermore, the utility of this methodology was applied to the synthesis of 9-amino-6-chloro-2-methoxy acridine (ACMA, Scheme 1), which is an important scaffold in drug compounds such as mepacrine (antimalarial) and quinpramine (antiprion).⁴³⁻⁴⁴ Besides, many of the synthesized 9-aminoacridine compounds, viz., 2-methoxy-9-acridinamine (**4a**), 3-methyl-9-acridinamine (**5b**) and 4-methyl-9-acridinamine (**5e**) are used as precursors for the synthesis of bioactive molecules.⁴⁵⁻⁴⁷ To test the feasibility of the Buchwald-Hartwig amination for different halogen partners, we performed the reactions with 2-chlorobenzonitrile, 2-iodobenzonitrile, and 2-iodo-4-methylbenzonitrile under the optimized catalytic conditions (Scheme 2). Iodo-substituted benzonitriles underwent the coupling reactions smoothly with aniline to give the corresponding products in 93-96 % yields, whereas the chloro compound produced only trace amount of product.

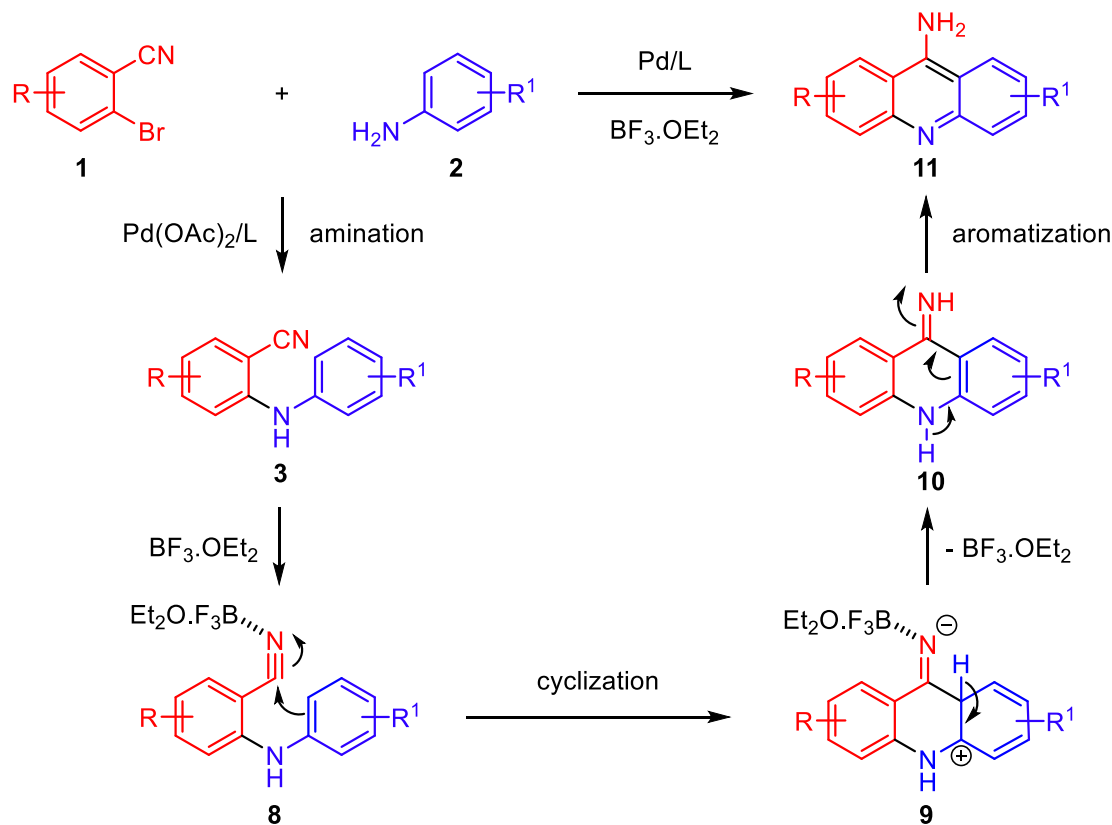


Scheme 1. Synthesis of 9-Amino-6-chloro-2-methoxy acridine (ACMA).



Scheme 2. Buchwald-Hartwig coupling for chloro- or iodo-substituted benzonitriles.

On the basis of our results and previous studies,³⁴ a preliminary mechanism of this one-pot reaction was proposed as shown in Scheme 3. The first step was the Pd-catalyzed Buchwald-Hartwig amination reaction to form the diphenylamine intermediate **3**, which was isolated for the reaction of 2-bromobenzonitrile and *p*-anisidine. Subsequently, the cyano group of intermediate **3** was activated by the boron trifluoride etherate. Then, the cyclization occurred for the formation of intermediate **9** through intramolecular nucleophilic attack from intermediate **8**. After releasing the boron trifluoride etherate, the aromatization reaction occurred to generate the final product 9-aminoacridine.



Scheme 3. Proposed Mechanism for the One-Pot Buchwald-Hartwig Amination/Cycloaromatization Reaction.

Conclusions

In summary, we have developed a novel and practical approach for the synthesis of 9-aminoacridine moiety through Pd-catalyzed Buchwald-Hartwig amination followed by acid-mediated cycloaromatization in one-pot process. A library of functionalized novel 9-aminoacridine molecules were synthesized from 2-bromobenzonitriles and arylamines in good to excellent yields under relatively mild conditions. This one-pot transformation proceeds with C-N bond formation via Pd-catalyzed Buchwald-Hartwig coupling, followed by intramolecular cyclization and aromatization, delivering the 9-aminoacridine compounds. The developed reaction protocol has been found to be applicable for the construction of important building blocks for drug molecules and pharmaceutically active compounds. Further efforts to extend this reaction protocol to the preparation of other biologically important heterocycles are currently underway in our laboratories.

Experimental Section

General. All reagents and starting materials were purchased from commercial sources and used without further purification unless mentioned specifically. The palladium catalyst was purchased from Sigma-Aldrich. Toluene was dried with sodium metal using benzophenone as an indicator. Melting points of dried samples were recorded on a Büchi melting point apparatus and were uncorrected. ¹H and ¹³C NMR spectra were recorded on 400 MHz and 100 MHz spectrometers, respectively. Chemical shifts (in ppm) were recorded with respect to

tetramethylsilane (TMS, $\delta=0$ ppm) internal reference standard. Proton coupling patterns were labeled as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), multiplet (m), septet (sept). Mass of the samples were recorded with high-resolution mass spectra (HRMS) equipped with ESI source and a TOF detector. The X-ray data for compound **3a** was collected at 298 K with an Oxford XCalibur CCD diffractometer equipped with graphite monochromatic Mo-K α radiation ($\lambda = 0.71073$ Å). Column chromatography was performed on silica gel (100–200 mesh) using CHCl₃/CH₃OH as eluents.

General procedure for the synthesis of 9-aminoacridines. To a flame dried Schlenk tube equipped with nitrogen balloon, 2-bromobenzonitrile **1** (1.0 mmol), arylamine **2** (1.1 mmol), palladium(II) acetate (5 mol %), rac-BINAP (10 mol %), cesium carbonate (2.0 equiv) and toluene (1 mL) were added. The Schlenk tube was immersed in silicon oil bath placed over magnetic stirrer and heated at 100 °C with constant stirring for 15h. Then the reaction mixture was cooled to 0 °C, BF₃.OEt₂ (3.0 equiv) added dropwise under N₂ atmosphere. After the addition is over, the reaction mixture was stirred at 100 °C until the complete consumption of intermediate observed on TLC. The solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography using chloroform and methanol (95 : 5) as eluents to afford the titled compounds **4**, **5** and **6**. Compounds **4b-f**, **4h-m**, **5b-d**, **5g-h**, **5j-l** and **7a-b** are new and all these characterized by spectroscopic data. Compounds **4a**, **4g**, **5a**, **5e-f**, **5i** and **6** are already known and their spectroscopic data match well with literature (see Supplementary Material).

2-(Propan-2-yl)-9-acridinamine (4b). Yield: 86%, dark green semi-solid; ¹H NMR (400 MHz, DMSO-d₆) δ 9.86 (brs, 2H), 8.60 (d, *J* 8.4 Hz, 1H), 8.45 (s, 1H), 8.01-7.95 (m, 2H), 7.84-7.79 (m, 2H), 7.58 (t, *J* 8.0 Hz, 1H), 3.09 (sept, *J* 6.8 Hz, 1H), 1.32 (d, *J* 6.8 Hz, 6H); ¹³C NMR (100 MHz, DMSO-d₆) δ 157.6, 146.5, 144.7, 139.3, 138.2, 135.6, 126.7, 124.7, 124.0, 120.8, 119.1, 119.0, 114.1, 33.8, 23.9; HRMS (ESI, *m/z*): calcd for C₁₆H₁₆N₂ [M + H]⁺ 237.1386, found 237.1397.

2-*n*-Butyl-9-acridinamine (4c). Yield: 85%, yellow brown solid, mp 252-254 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 9.94 (brs, 2H), 8.68 (d, *J* 8.4 Hz, 1H), 8.51 (s, 1H), 7.99-7.87 (m, 4H), 7.55 (t, *J* 7.2 Hz, 1H), 2.77 (t, *J* 7.6 Hz, 2H), 1.71-1.64 (m, 2H), 1.39-1.29 (m, 2H), 0.93 (t, *J* 7.2 Hz, 3H); ¹³C NMR (100 MHz, DMSO-d₆) δ 171.7, 157.3, 139.3, 138.4, 138.0, 136.9, 135.3, 124.8, 123.8, 122.9, 118.9, 111.6, 111.5, 34.7, 32.8, 22.6, 21.8, 13.9; HRMS (ESI, *m/z*): calcd for C₁₇H₁₈N₂ [M + H]⁺ 251.1543, found 251.1535.

4-Phenyl-9-acridinamine (4d). Yield: 76%, yellow solid, mp 236-239 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 10.1 (brs, 2H), 8.67-8.63 (m, 2H), 8.14 (d, *J* 8.8 Hz, 1H), 7.98-7.94 (m, 1H), 7.87 (dd, *J* 7.2, 0.8 Hz, 1H), 7.70-7.66 (m, 1H), 7.63-7.58 (m, 5H), 7.45-7.38 (m, 1H); ¹³C NMR (100 MHz, DMSO-d₆) δ 158.5, 139.8, 137.1, 136.3, 135.6, 132.1, 129.9, 129.5, 124.4, 124.3, 124.2, 123.9, 120.1, 116.9, 115.4, 112.5, 111.7; HRMS (ESI, *m/z*): calcd for C₁₉H₁₄N₂ [M + H]⁺ 271.1229, found 271.1242.

2,4-Dimethyl-9-acridinamine (4e). Yield: 90%, yellow green solid, mp 340-342 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 9.92 (brs, 2H), 8.65 (d, *J* 8.8 Hz, 1H), 8.34-8.29 (m, 2H), 8.01-7.97 (m, 1H), 7.73 (s, 1H), 7.59-7.56 (m, 1H), 2.69 (s, 3H), 2.47 (s, 3H); ¹³C NMR (100 MHz, DMSO-d₆) δ 157.7, 139.5, 138.2, 136.8, 135.2, 133.3, 127.3, 124.5, 124.1, 121.3, 119.7, 111.8, 111.6, 20.9, 18.2; HRMS (ESI, *m/z*): calcd for C₁₅H₁₄N₂ [M + H]⁺ 223.1230, found 223.1234.

2-Chloro-9-acridinamine (4f). Yield: 82%, yellow brown semi-solid; ¹H NMR (400 MHz, DMSO-d₆) δ 9.98 (brs, 2H), 8.78 (s, 1H), 8.61 (d, *J* 8.4 Hz, 1H), 8.05-8.02 (m, 2H), 7.86 (t, *J* 9.2 Hz, 2H), 7.62 (t, *J* 7.6 Hz, 1H); ¹³C NMR (100 MHz, DMSO-d₆) δ 157.3, 139.5, 138.2, 136.1, 135.9, 128.3, 124.7, 124.5, 123.8, 121.4, 119.2, 112.6, 111.8; HRMS (ESI, *m/z*): calcd for C₁₃H₉ClN₂ [M + H]⁺ 229.0527, found 229.0520.

4-Chloro-9-acridinamine (4h). Yield: 79%, fluorescent green solid, mp 304-306 °C; ¹H NMR (400 MHz, CD₃OD) δ 8.48 (t, *J* 8.0 Hz, 2H), 8.19 (d, *J* 8.4 Hz, 1H), 8.14-8.12 (m, 1H), 8.06-8.02 (m, 1H), 7.66-7.62 (m, 1H), 7.58-7.54

(m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 160.4, 141.1, 137.7, 137.4, 136.9, 126.4, 125.3, 125.2, 124.6, 124.0, 120.4, 114.3, 113.2; HRMS (ESI, m/z): calcd for $\text{C}_{13}\text{H}_9\text{ClN}_2$ $[\text{M} + \text{H}]^+$ 229.0527, found 229.0535.

4-Fluoro-9-acridinamine (4i). Yield: 77%, light green solid, mp 232-234 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 10.1 (brs, 2H), 8.61 (s, 1H) 8.44 (s, 1H), 8.11-7.95 (m, 3H), 7.64-7.56 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.0, 151.3 (d, $^1J_{\text{CF}} = 250.1$ Hz), 139.4, 136.1, 129.6 (d, $^2J_{\text{CF}} = 16.3$ Hz), 124.7, 124.5, 123.3, 123.2, 120.6, 119.4, 113.5, 111.9; HRMS (ESI, m/z): calcd for $\text{C}_{13}\text{H}_9\text{FN}_2$ $[\text{M} + \text{H}]^+$ 213.0822, found 213.0821.

2-(Trifluoromethyl)-9-acridinamine (4j). Yield: 74%, fluorescent green solid, mp 238-240 °C; ^1H NMR (400 MHz, CD_3OD) δ 8.48 (d, J 8.8 Hz, 1H), 8.38 (d, J 8.4 Hz, 1H), 8.01-7.96 (m, 1H), 7.84-7.77 (m, 1H), 7.66-7.56 (m, 2H), 7.45-7.37 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.6, 149.3, 141.1 (d, $^2J_{\text{CF}} = 40.5$ Hz), 138.9, 136.8, 136.7, 136.3, 128.6, 127.7, 119.7, 118.7, 118.6 (d, $^1J_{\text{CF}} = 137.2$ Hz), 117.9, 113.1, 111.2; HRMS (ESI, m/z): calcd for $\text{C}_{14}\text{H}_9\text{F}_3\text{N}_2$ $[\text{M} + \text{H}]^+$ 263.0790, found 263.0780.

2,3-Dihydro-1H-cyclopenta[b]acridin-10-amine (4k). Yield: 87%, yellow brown solid, mp 270-272 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 9.66 (brs, 2H), 8.63-8.58 (m, 1H), 8.37 (s, 1H), 7.96-7.92 (m, 1H), 7.85-7.83 (m, 1H), 7.61 (s, 1H), 7.51 (t, J 7.6 Hz, 1H), 3.05-2.96 (m, 4H), 2.13-2.05 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.8, 154.3, 141.3, 138.8, 138.7, 135.0, 132.3, 124.6, 123.6, 118.4, 113.0, 111.2, 110.4, 32.8, 31.7, 25.3; HRMS (ESI, m/z): calcd for $\text{C}_{16}\text{H}_{14}\text{N}_2$ $[\text{M} + \text{H}]^+$ 235.1229, found 235.1222.

[1,3]Dioxolo[4,5-b]acridin-10-amine (4l). Yield: 94%, yellow brown semi-solid; ^1H NMR (400 MHz, DMSO-d_6) δ 9.36 (brs, 2H), 8.52 (d, J 8.4 Hz, 1H), 7.96-7.92 (m, 2H), 7.79 (s, 1H), 7.56 (t, J 7.6 Hz, 1H), 7.20 (s, 1H), 6.32 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.5, 155.1, 146.5, 138.7, 138.2, 134.6, 124.1, 118.6, 115.1, 111.5, 106.9, 103.6, 99.6, 95.9; HRMS (ESI, m/z): calcd for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$ 239.0815, found 239.0812.

Benzo[c]acridin-7-amine (4m). Yield: 72%, yellow solid, mp 296-298 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 9.68 (brs, 2H), 9.18 (d, J 6.8 Hz, 1H), 8.66 (d, J 8.4 Hz, 1H), 8.42 (d, J 8.4 Hz, 1H), 8.33 (d, J 8.0 Hz, 1H), 8.16 (d, J 6.8 Hz, 1H), 8.08-8.04 (m, 1H), 7.98-7.93 (m, 3H), 7.68 (t, J 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.6, 138.9, 138.7, 135.1, 134.8, 131.0, 128.9, 127.8, 125.0, 124.9, 124.1, 123.9, 122.7, 120.1, 119.8, 113.1, 108.5; HRMS (ESI, m/z): calcd for $\text{C}_{17}\text{H}_{12}\text{N}_2$ $[\text{M} + \text{H}]^+$ 245.1073, found 245.1072.

3-Methyl-9-acridinamine (5b). Yield: 83%, yellow-green solid, mp 254-256 °C; ^1H NMR (400 MHz, CD_3OD) δ 8.47 (d, J 8.0 Hz, 1H), 8.38 (d, J 8.8 Hz, 1H), 8.01-7.97 (m, 1H), 7.80 (d, J 8.4 Hz, 1H), 7.60-7.56 (m, 2H), 7.44 (dd, J 8.8, 1.2 Hz, 1H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 158.9, 149.1, 140.8, 140.4, 136.7, 127.6, 125.3, 124.9, 124.8, 119.5, 118.4, 112.6, 110.7, 22.2; HRMS (ESI, m/z): calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2$ $[\text{M} + \text{H}]^+$ 209.1073, found 209.1072.

3-Methoxy-9-acridinamine (5c). Yield: 80%, brown solid, mp 204-206 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 9.69 (brs, 2H), 8.59-8.52 (m, 2H), 7.97 (t, J 7.6 Hz, 1H), 7.79 (d, J 8.8 Hz, 1H), 7.56 (t, J 7.6 Hz, 1H), 7.22 (dd, J 9.2, 2.4 Hz, 1H), 7.12 (d, J 2.4 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 167.1, 158.5, 143.5, 140.6, 137.8, 136.5, 127.0, 125.2, 125.0, 119.4, 117.9, 107.3, 98.4, 56.7; HRMS (ESI, m/z): calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 225.1022, found 225.1016.

3-tert-Butyl-9-acridinamine (5d). Yield: 81%, pale yellow solid, mp 276-279 °C; ^1H NMR (400 MHz, CD_3OD) δ 8.49 (d, J 8.8 Hz, 1H), 8.44 (d, J 9.2 Hz, 1H), 8.02-7.98 (m, 1H), 7.82-7.78 (m, 2H), 7.73 (dd, J 8.8, 2.0 Hz, 1H), 7.59 (t, J 8.0 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD) δ 161.7, 159.4, 141.4, 141.0, 136.8, 125.4, 125.2, 125.1, 124.5, 119.8, 115.2, 113.2, 111.1, 36.7, 30.9; HRMS (ESI, m/z): calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2$ $[\text{M} + \text{H}]^+$ 251.1543, found 251.1536.

1-Methyl-9-acridinamine (5g). Yield: 82%, dark green semi-solid; ^1H NMR (400 MHz, DMSO-d_6) δ 10.02 (s, 1H), 8.74 (s, 1H), 8.60 (d, J 8.8 Hz, 1H), 7.99 (t, J 8.0 Hz, 1H), 7.86-7.84 (m, 1H), 7.82-7.78 (m, 1H), 7.66 (d, J 8.8 Hz, 1H), 7.57 (t, J 8.0 Hz, 1H), 7.35 (d, J 7.2 Hz, 1H), 3.00 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.6, 141.2, 138.6, 137.7, 135.5, 135.0, 127.0, 124.7, 123.9, 118.2, 116.7, 112.9, 111.6, 23.3; HRMS (ESI, m/z): calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2$ $[\text{M} + \text{H}]^+$ 209.1073, found 209.1085.

3-Fluoro-9-acridinamine (5h). Yield: 86%, dark green semi-solid; ^1H NMR (400 MHz, DMSO- d_6) δ 10.0 (brs, 2H), 8.73-8.69 (m, 1H), 8.59 (d, J 8.8 Hz, 1H), 8.01 (t, J 7.2 Hz, 1H), 7.80 (d, J 7.6 Hz, 1H), 7.61-7.47 (m, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 165.9 (d, $^1J_{\text{CF}} = 253.9$ Hz), 157.7, 141.2 (d, $^3J_{\text{CF}} = 12.5$ Hz), 139.6, 136.0, 129.7, 124.8, 124.3, 118.7, 113.9 (d, $^2J_{\text{CF}} = 24.9$ Hz), 111.7, 108.9, 103.3 (d, $^2J_{\text{CF}} = 24.9$ Hz); HRMS (ESI, m/z): calcd for $\text{C}_{13}\text{H}_9\text{FN}_2$ [$\text{M} + \text{H}$] $^+$ 213.0822, found 213.0818.

3-(Trifluoromethyl)-9-acridinamine (5j). Yield: 87%, yellow semi-solid; ^1H NMR (400 MHz, DMSO- d_6) δ 10.2 (brs, 2H), 8.85 (d, J 9.2 Hz, 1H), 8.65 (d, J 8.4 Hz, 1H), 8.16 (s, 1H), 8.07 (t, J 8.0 Hz, 1H), 7.89 (t, J 8.8 Hz, 2H), 7.66 (t, J 7.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 153.3, 150.5, 148.5, 133.1 (d, $^2J_{\text{CF}} = 31.6$ Hz), 132.6, 128.5, 126.9, 124.3, 124.2, 123.9, 117.7, 115.1 (d, $^1J_{\text{CF}} = 48.9$ Hz); HRMS (ESI, m/z): calcd for $\text{C}_{14}\text{H}_9\text{F}_3\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 263.0790, found 263.0786.

2,3-Dimethoxy-9-acridinamine (5k). Yield: 79%, grey solid, mp 299-301 $^\circ\text{C}$; ^1H NMR (400 MHz, DMSO- d_6) δ 9.39 (brs, 2H), 7.95-7.91 (m, 1H), 7.84 (s, 1H), 7.76 (d, J 8.8 Hz, 1H), 7.56 (t, J 8.0 Hz, 1H), 7.33 (t, J 7.6 Hz, 1H), 7.12-7.06 (m, 2H), 3.99 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 156.8, 155.0, 147.7, 138.1, 137.0, 134.3, 129.5, 123.7, 118.5, 111.3, 105.7, 102.8, 98.2, 56.4, 56.3; HRMS (ESI, m/z): calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_2$ [$\text{M} + \text{H}$] $^+$ 255.1128, found 255.1121.

2,3,4-Trimethoxy-9-acridinamine (5l). Yield: 75%, yellow solid, mp 242-245 $^\circ\text{C}$; ^1H NMR (400 MHz, CD_3OD) δ 8.34 (d, J 8.4 Hz, 1H), 8.01 (d, J 8.4 Hz, 1H), 7.89 (t, J 8.0 Hz, 1H), 7.54-7.50 (m, 2H), 4.14 (s, 3H) 4.09 (s, 3H), 4.02 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 157.6, 153.0, 149.1, 141.9, 139.9, 135.8, 132.5, 125.4, 124.6, 120.1, 112.8, 108.9, 98.7, 62.4, 62.0, 57.0; HRMS (ESI, m/z): calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3$ [$\text{M} + \text{H}$] $^+$ 285.1233, found 285.1225.

2-(phenylamino)benzotrile (7a). Yield: 96%, Colorless semi-solid; ^1H NMR (400 MHz, CDCl_3) δ 7.50 (dd, J 8.0, 1.2 Hz, 1H), 7.39-7.35 (m, 3H), 7.22-7.19 (m, 3H), 7.16-7.12 (m, 1H), 6.86-6.82 (m, 1H), 6.44 (brs, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.2, 139.8, 133.7, 132.9, 129.5, 124.0, 121.5, 119.1, 117.5, 114.0, 98.3; HRMS (ESI, m/z): calcd for $\text{C}_{13}\text{H}_{10}\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 195.0916, found 195.0917.

4-Methyl-2-(phenylamino)benzotrile (7b). Yield: 93%, Yellow semi-solid; ^1H NMR (400 MHz, CDCl_3) δ 7.48 (dd, J 8.0, 1.2 Hz, 1H), 7.38-7.33 (m, 1H), 7.26-7.24 (m, 1H), 7.19 (d, J 8.4 Hz, 1H), 7.00-6.99 (m, 2H), 6.94 (d, J 8.0 Hz, 1H), 6.84-6.79 (m, 1H), 6.30 (brs, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.4, 139.7, 139.6, 133.8, 132.9, 129.3, 125.0, 122.4, 119.0, 118.7, 117.6, 114.1, 98.2, 21.4; HRMS (ESI, m/z): calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 209.1073, found 209.1069.

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Supplementary Material

Characterization of known compounds, copies of ^1H and ^{13}C NMR spectra of compounds **4a-m**, **5a-l**, **3a**, **6**, **7a-b**, and basic crystallographic data of **3a** are given in the supplementary material file associated with this manuscript.

References

1. Denny, W. A. *Curr. Med. Chem.* **2002**, *9*, 1655-65.
<https://doi.org/10.2174/0929867023369277>
2. Collin, G.; Höke, H. Acridine in *Ullmann's Encyclopedia of Industrial Chemistry* 2012, Wiley-VCH, Weinheim.
https://doi.org/10.1002/14356007.a01_147
3. Wang, T.-J.; Chen, W.-W.; Li, Y.; Xu, M.-H. *Org. Biomol. Chem.* **2015**, *13*, 6580-6086.
<https://doi.org/10.1039/C5OB00755K>
4. Cain, B. F.; Seelye, R. N.; Atwell, G. J. *J. Med. Chem.* **1974**, *17*, 922-930.
<https://doi.org/10.1021/jm00255a003>
5. Denny, W. A.; Atwell, G. J.; Roberts, P. B.; Anderson, R. F.; Boyd, M.; Lock, C. J. L.; Wilson, W. R. *J. Med. Chem.* **1992**, *35*, 4832-4841.
<https://doi.org/10.1021/jm00104a008>
6. Ciak, J.; Hahn, F. E. *Science*, **1967**, *156*, 655-656.
<https://www.science.org/doi/abs/10.1126/science.156.3775.655>
7. Harrison, R. J.; Cuesta, J.; Chessari, G.; Read, M. A.; Basra, S. K.; Reszka, A. P.; Morrell, J.; Gowan, S. M.; Incles, C. M.; Tanious, F. A.; Wilson, W. D.; Kelland, L. R.; Neidle, S. *J. Med. Chem.* **2003**, *46*, 4463-4476.
<https://doi.org/10.1021/jm0308693>
8. Munawar, R.; Mushtaq, N.; Arif, S.; Ahmed, A.; Akhtar, S.; Ansari, S.; Meer, S.; Saify, Z. S.; Arif, M. *American Journal of Alzheimer's Disease & Other Dementias*®. **2016**, *31*, 263-269.
<https://doi.org/10.1177/1533317515603115>
9. Benoit, A. R.; Schiaffo, C.; Salomon, C. E.; Goodell, J. R.; Hiasa, H.; Ferguson, D. M. *Bioorg. Med. Chem. Lett.*, **2014**, *24*, 3014-3017.
<http://dx.doi.org/10.1016/j.bmcl.2014.05.037>
10. Loddo, R.; Francesconi, V.; Laurini, E.; Boccardo, S.; Aulic, S.; Fermeglia, M.; Pricl, S.;
<https://doi.org/10.1016/j.bmc.2018.01.001>
11. Goodell, J. R.; Ougolkov, A. V.; Hiasa, H.; Kaur, H.; Rimmel, R.; Billadeau, D. D.; Ferguson, D. M. *J. Med. Chem.* **2008**, *51*, 179-182.
<https://doi.org/10.1021/jm701228e>
12. Chen, Y.-L.; Lu, C.-M.; Chen, I.-L.; Tsao, L.-T.; Wang, J.-P. *J. Med. Chem.* **2002**, *45*, 4689-4694.
<https://doi.org/10.1021/jm020102v>
13. Gellerman, G.; Waintraub, S.; Albeck, A.; Gaisin, V. *Eur. J. Org. Chem.* **2011**, *2011*, 4176-4182
<https://doi.org/10.1002/ejoc.201100133>
14. Pérez, B.; Teixeira, C.; Gomes, A. S.; Albuquerque, I. S.; Gut, J.; Rosenthal, P. J.; Prudêncio, M.; Gomes, P. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 610-613.
<http://dx.doi.org/10.1016/j.bmcl.2012.12.032>
15. Tlegenov, R. T. *Pharm. Chem. J.* **2008**, *42*, 577-578.
<http://doi:10.1007/s11094-009-0185-3>
16. Gasparian, A.V.; Neznanov, N.; Jha, S.; Galkin, O.; Moran, J. J.; Gudkov, A. V.; Gurova, K. V.; Komar, A. A. *J. Virol.* **2010**, *84*, 9390-9397.
<https://doi.org/10.1128/JVI.02569-09>
17. Diederichsen, U. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1743-1746.
[https://doi.org/10.1016/S0960-894X\(97\)00302-8](https://doi.org/10.1016/S0960-894X(97)00302-8)
18. Sundquist, W. I.; Bancroft, D. P.; Lippard, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 1590-1596.

- <https://doi.org/10.1021/ja00160a044>
19. Jesionowski, T.; Przybylska, A.; Kurc, B.; Ciesielczyk, F. *Dyes and Pigments*. **2011**, *88*, 116-124.
<https://doi.org/10.1016/j.dyepig.2010.05.011>
20. Pereira, R. V.; Ferreira, A. N. G.; Gehlen, M. H. *J. Phys. Chem. A*. **2005**, *109*, 5978-5983.
21. <https://doi.org/10.1021/jp044704x>
22. Stroppa, P. H. F.; Glanzmann, N.; Duarte, L. M.; Sato, R. T.; de Oliveira, M. A. L.; da Silva, A. D. *J. Braz. Chem. Soc.* **2017**, *28*, 2334-2340.
<http://dx.doi.org/10.21577/0103-5053.20170084>
23. Zhang, W.; Liu, Y.; Zhang, Y.; Wang, L.-J.; Wu, Y.-C.; Li, H.-J. *New J. Chem.*, **2020**, *44*, 6464-6474.
<http://dx.doi.org/10.1039/D0NJ00440E>
24. Ravikumar, M. M.; Shetty, V. R.; Shivappa, S. G. *Advanced Materials Letters*. **2019**, *10*, 586-594.
<http://doi.org/10.5185/amlett.2019.9909>
25. Szymanska, A.; Wiczak, W.; Lankiewicz, L. *Chem Heterocycl Compd*. **2000**, *36*, 801-808.
<https://doi.org/10.1007/BF02256913>
26. Kubato, Y.; Motoda, Y. *J. Phys. Chem.* **1980**, *84*, 2855-2861.
<https://doi.org/10.1021/j100459a005>
27. Dong, C. Z.; Rocquigny, H. D.; Rémy, E.; Mellac, S.; Fournié-Zaluski, M. C.; Roques, B. P. *J. Pept. Res.* **1997**, *50*, 269-278.
<https://doi.org/10.1111/j.1399-3011.1997.tb01468.x>
28. Mayer, R. T.; Dolence, E. K.; Mayer, G. E.; *Drug. Metab. Dispos.* **2007**, *35*, 103-109.
<https://doi.org/10.1124/dmd.106.011601>
29. Chiron, J.; Galy, J.-P. *Synthesis*, **2004**, *3*, 313-325.
<https://doi.org/10.1055/s-2003-44379>
30. Skonieczny, S. *Heterocycles*, **1980**, *14*, 985-1032.
<https://doi.org/10.3987/R-1980-07-0985>
31. Acheson, R. M. *In Acridines*, 2nd Ed.; John Wiley & Sons: New York, **1973**.
<https://doi/book/10.1002/9780470186596>
32. Bauer, K. *Ber.* **1950**, *83*, 10.
33. Pozharskii, A. F.; Konstantinchenko, A.A. *Chem. Heterocycl. Compd.* **1972**, *8*, 1518-1520.
<https://link.springer.com/article/10.1007/BF00471845>
34. Pang, X.; Chen, C.; Su, X.; Li, M. Wen, L. *Org. Lett.* **2014**, *16*, 6228-6231.
<https://doi.org/10.1021/ol503156g>
35. Chen, X.; Zhang, Y.; Chen, Y.; Zhang, J.; Chen, J.; Li, M.; Cao, W.; Chen, J. *Eur. J. Org. Chem.* **2014**, *2014*, 4170-4178.
<https://doi.org/10.1002/ejoc.201402361>
36. Garcia, R. C.; Pech, M. J.; Sommer, R.; Gorman, C. B. *J. Org. Chem.* **2019**, *84*, 15079-15086.
<https://doi.org/10.1021/acs.joc.9b01628>
37. Gopalaiah, K.; Choudhary, R. *Tetrahedron*, **2021**, *98*, 132429-132435.
<https://doi.org/10.1016/j.tet.2021.132429>
38. Gopalaiah, K.; Rao, D. C.; Mahiya, K.; Tiwari, A. *Asian J. Org. Chem.* **2018**, *7*, 1872-1881.
<https://doi.org/10.1002/ajoc.201800312>
39. Gopalaiah, K.; Saini, A.; Devi, A. *Org. Biomol. Chem.*, **2017**, *15*, 5781-5789.
<https://doi.org/10.1039/C7OB01159H>

40. Gopalaiah, K.; Saini, A.; Chandrudu, S. N.; Rao, D. C.; Yadav, H.; Kumar, B.; *Org. Biomol. Chem.*, **2017**, *15*, 2259-2268.
<https://doi.org/10.1039/C7OB00122C>
41. Gopalaiah, K.; Chandrudu, S. N. *RSC Adv.*, **2015**, *5*, 5015-5023.
<https://doi.org/10.1039/C4RA12490A>
42. Gopalaiah, K.; Tiwari, A. Choudhary, R. Mahiya, K. *ChemistrySelect* **2019**, *4*, 5200-5205.
<https://doi.org/10.1002/slct.201900850>
43. Gopalaiah, K.; Tiwari, A. *Eur. J. Org. Chem.* **2020**, *2020*, 7229–7237.
<https://doi.org/10.1002/ejoc.202001300>
44. Elueze, E. I.; Croft, S. L.; Warhurst, D. C. *J. Antimicrob. Chemother.*, **1996**, *37*, 511-518.
<https://doi.org/10.1093/jac/37.3.511>
45. Thi, H. T. N.; Lee, C.-Y.; Teruya, K.; Ong, W.-Y.; Doh-ura, K.; Go, M.-L. *Bioorg. Med. Chem.*, **2008**, *16*, 6737-6746.
<https://doi:10.1016/j.bmc.2008.05.060>.
46. Arya, S.; Kumar, A.; Kumar, N.; Roy, P.; Sondhi, S. M. *Med. Chem. Res.*, **2015**, *24*, 1942-1951.
<https://doi:10.1007/s00044-014-1268-6>
47. Kumar, N.; Kumar, S.; Abbat, S.; Nikhil, K.; Sondhi, S. M.; Bharatam, P. V.; Roy, P.; Pruthi, V. *Med. Chem. Res.*, **2016**, *25*, 1175-1192.
<https://doi:10.1007/s00044-016-1562-6>
48. Kumar, N.; Geol, N.; Yadav, T. C.; Pruthi, V. *Med. Chem. Res.*, **2017**, *26*, 1822-1834.
<https://doi:10.1007/s00044-017-1893-y>

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