Chapter 4

Silver-Catalyzed Synthesis of Acridines, Quinolines and Naphthalenes
4.1 INTRODUCTION

The biochemical properties and therapeutic applications of polycyclic compounds largely depend on substituents in the basic structure. Acridines, quinolines and naphthalenes have demonstrated significant biological activity against cancer, viruses, bacteria, parasites, fungus, Alzheimer’s disease and HIV/AIDS. Substrates with diketoacid (DKAs) functionality have been disclosed as promising HIV-1 integrase (IN) inhibitor.

From beginning of the last century, acridine based heterocycles have been recognized as drug and were used for therapeutic purposes. Some of them with various functional group are summarized in Table 1.

**Table 1. Clinically used Acridines**

<table>
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<tr>
<th>Substrate</th>
<th>R^2</th>
<th>R^3</th>
<th>R^4</th>
<th>R^5</th>
<th>R^6</th>
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<td>CH_3O</td>
<td>H</td>
<td>CH_3</td>
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<tr>
<td>Flavicid</td>
<td>CH_3</td>
<td>NH_2</td>
<td>H</td>
<td>(CH_3)_2N</td>
<td>H</td>
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<td>CH_3CH_2O</td>
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<td>H</td>
<td>NH_2</td>
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</tr>
<tr>
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<td>H</td>
<td>H</td>
<td>H</td>
<td>NH_2</td>
<td>H</td>
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<tr>
<td>Salacrin</td>
<td>H</td>
<td>H</td>
<td>CH_3</td>
<td>H</td>
<td>NH_2</td>
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</tbody>
</table>

Acridone alkaloids were also known as potential antitumor agents since acronycine (Figure 1, A) was found to have potent antitumor activity in the middle of the 1960s. A series of anti-proliferative activity of a series of acridone alkaloids (Glyfoline) (Figure 1, B) was found to be the most cytotoxic against human leukemia HL-60 cell growth in vitro. The alkaloid was first isolated from Glyfoline citrifolia (Willd.) Lindl. (Rutaceae), an indigenous plant from Taiwan. Glyfoline was about 10-fold more potent than acronycine and exhibited moderate in vivo antitumor activity in mice bearing murine and human tumors xenograft.
Figure 1. Selected Biologically Active Acridines

Quinoline based compound A (Figure 2) with analogous DKAs functionality found to be selective inhibitors of the strand transfer reaction. Because these compounds effectively prevent viral DNA integration and inhibit HIV-1 replication in cell culture, so, the presence of the biologically labile 1,3-diketoacid moiety in the molecules is a concern for development of these compounds as chemotherapeutic agents. It has also been found that 1,3-diketoacid functionality is essential for the enzyme inhibitory activity of these inhibitors. Thus, the development of novel and efficient routes for rapid access to such functionalized heterocycles under mild conditions are of high demand.

Figure 2. Anti-HIV Active Compounds with DKAs Functionality

4.2 REVIEW OF LITERATURE

4.2.1 Synthetic Methods for Acridines and Quinolines

Keeping in view the importance of these heterocyclic compounds, synthesis of these moieties with different substituents is an area of research for organic and medicinal chemists from more than a century. Friedländer prepared quinolines 3 in 1882 by the condensation of o-amino-benzaldehyde 1 with acetaldehyde in the presence of sodium hydroxide. This type of reaction has since been extensively explored and, in its most general form, can be defined as an acid- or base-catalyzed condensation followed by a cyclodehydration between an o-amino-substituted aromatic aldehydes, ketone or derivatives 1 thereof with an appropriately substituted aldehyde, ketone or other carbonyl compounds containing a reactive α-methylene group 2 (Scheme 1).
Scheme 1. Friedländer Quinolines Synthesis (Friedländer approach)

Since then several modified reports are available for the construction of these heterocycles, the efficient and general routes for the synthesis of such compounds with requisite functionality under mild reaction condition has to be explored. The most common approaches for the synthesis of acridines proceed via corresponding acridones, aminobenzannulation and by [4+2] annulations of benzynes. Most of the methods for synthesis of acridines require rather harsh conditions. Stacy and Lisk have shown the synthesis of ethyl 7-chloro-4-hydroxy-8-methylquinoline-2-carboxylate (7). When ethyl β-carbethoxy-β-(m-chloroanilino)-acrylate (4) was subjected to thermal cyclization in limited amounts of diluent, virtually all 3-carbethoxy-5-chloro-4-hydroxyquinoline (6) was formed. On the other hand, when larger amounts of diluent were employed, as much as sixty per cent of the corresponding 7-isomer was obtained (Scheme 2).

Scheme 2. Synthesis of 7-Chloro-4-hydroxyquinoline Derivatives Employing Oxalacetic Ester (Stacy approach)

Coming to the synthesis of acridines with alcoholic or ester substituent in past decade, Barnett and co-workers has described the synthesis of 9-chloro-4-ethoxyacridine 11 starting with 2-chlorobenzoic acid 8 and 2-ethoxyaniline 9. They have further utilized the 9-chloro-4-ethoxyacridine for the synthesis of 4-acridinol-1-sulphonic acid (Scheme 3).

Scheme 3. Synthesis of 9-Chloro-4-ethoxyacridine (Barnett approach)
Belmont and Tahar have developed aminobenzannulation methodology, and applied successfully to the synthesis of 1-amino-acridines 15. The methodology developed by them is efficient and easy to perform since only powdered 4 Å molecular sieves were required for the enamine synthesis step. Also, pyrrolidine 14 has proven to be the best trigger for the aminobenzannulation reaction and without any additional catalyst (Scheme 4).\textsuperscript{22}

**Scheme 4.** Synthesis of 1-Amino-acridines using Pyrrolidine as a Trigger for the Reaction (Belmont approach)

Further, Belmont and co-workers have reported the synthesis of 17 using catalytic amounts of gold and/or silver salts. The reaction of silyl enol ethers with alkynes 16 occurred under mild conditions to produce the corresponding polycyclic aromatic systems 17 (acridine, quinoline or naphthalene cores) in good to high yields (Scheme 5).\textsuperscript{23}

**Scheme 5.** Silver(I) Catalysis in Benzannulation Reaction for Synthesis of Acridines (Belmont approach)

Larock and Rogness have synthesized substituted acridines 20 by the reaction of reaction of 2-aminoaryl ketones 18 and arynes generated by the treatment of various o-(trimethylsilyl)aryl triflates 19 with CsF resulting in [4 + 2] annulations (Scheme 6).\textsuperscript{24}

**Scheme 6.** Synthesis of Acridines by the [4 + 2] Annulation of Arynes and 2-Aminoaryl Ketones (Larock approach)
Cikotiene and co-workers have developed an efficient, and powerful methyl mercaptoacetate 22 triggered benzannulation reaction, which involved various heterocyclic, aromatic or acyclic compounds bearing a carbonyl group at ortho position to an internal/terminal alkyne 21. The methodology did not require transition metal catalysts and moreover, it was general for the preparation of wide range of benzoannelated heterocycles 23 (Scheme 7).

**Scheme 7. Rapid Access to Benzo-Annelated Heterocycles from ortho-Alkynyl Aldehydes (Cikotiene approach)**

![Scheme 7](image)

Recently, Singh and co-workers have achieved the synthesis of acridine-9-carboxylic acid 25 and its subsequent esterification was carried out to obtain desired bromo-alkyl esters 26 and bis-alkyl esters 27 in good yield by microwave irradiation using PTC (Scheme 8).

**Scheme 8. Microwave Assisted Synthesis of Bromo-alkyl esters of Acridine-9-carboxilic acid (Singh approach)**

![Scheme 8](image)

On the other hand, Liu and co-workers have achieved persubstituted phenols/anilines with up to six different functional groups on the benzene ring along with a series of acridine derivatives 31, 32 from persubstituted phenols/anilines 30. They utilized benzannulation strategy that proceeds via a regiospecific [4 + 2] cycloaddition of readily available cyclobutenones 28 and active methylene ketones 29 (Scheme 9).
Scheme 9. Synthesis of Acridines and Persubstituted Phenols from Cyclobutenones and Active Methylene Ketones (Liu approach)

Sakai and co-workers shown copper-catalyzed [5 + 1] annulation of 2-ethynylanilines 33 with an N,O-acetal 34 which functioned as a C1 part, leading to the preparation of quinoline derivatives 35 with an ester substituent on the 2-position. They have also reported that a combination of CuBr$_2$ and trifluoroacetic acid (TFA) promoting [5 + 1] annulation of the 2-ethynylaniline with ethyl glyoxylate (Scheme 10).

Scheme 10. Synthesis of Quinoline Derivatives via Copper-Catalyzed [5 + 1] Annulation (Sakai approach)

4.2.2 Silver-Catalyzed Synthesis of Heterocycles

Transition metal-catalyzed electrophilic cyclization of alkynes and carbon-carbon bond formation using enolates have made a large contribution in organic chemistry for the synthesis of a variety of natural products, heterocycles and carbocycles. Because of their d$^{10}$ electronic configuration, coinage metals are at the borderline between main group elements and transition metals. Transition metals usually exhibit Lewis acid character, more or less pronounced depending on their position in the Mendeleev Periodic Table. In the coinage metal series, silver and gold nevertheless exhibit special properties due to the availability of the f orbitals and relativistic contraction of their electron cloud.
Thus, the applications of silver salts in organic synthesis are indeed mostly driven by its Lewis acidity. However, in several applications, it seems that it is much more the (in)solubility properties of silver salts which actually are driving reactions. The d$^{10}$ electronic configuration favored interactions of Ag salt with unsaturated systems having low-lying empty orbitals, especially alkynes, and to a lesser extent allenes and alkenes. This alkynophilicity is probably reinforced by f orbitals and relativistic effects. 29

Nevertheless, silver salts are able to act either or both as $\sigma$-Lewis acid or $\pi$-Lewis acid. From an organic point of view, this alkynophilicity and $\pi$-coordination in general, have dramatic consequences on the behavior of alkynes and any $\pi$-system. Upon coordination, the $\pi$-system becomes prone to nucleophilic addition, and if a (hetero)nucleophile is included within the same molecule, the formation of (hetero)cycles 38, 39 is expected (Scheme 11). 30

**Scheme 11. Silver-Catalyzed Synthesis of Cyclic Compounds**

Earlier investigations revealed that silver has been used as catalyst from past century, one of earliest use of silver catalyst was reported by Dahlen and Hunter in 1932. 31 The silver salt of the new phenol was decomposed in benzene suspension by the action of ethyl iodide, iodine and heat, respectively. In each case, an amorphous oxide was obtained corresponding the empirical formula (C$_{12}$H$_{4}$O$_{2}$Cl$_{2}$)$_{x}$ 43 (Scheme 12).

**Scheme 12. Silver Salt Phenol Decomposition (Dahlen approach)**
Among the earliest silver-catalyzed synthesis of heterocycles, synthesis of 3-Substituted $\Delta^1$-Corbapenems was shown by Liebeskind and Prasad in 1988. Starting with 4-Alkynyl-and-4-(2-Propynyl)azetidinones 44a, b they used Ag(I) as catalyst to obtain $\Delta^1$-Corbapenems and $\Delta^2$-Corbapenems respectively 46a, b (Scheme 13).32

**Scheme 13.** Silver- Catalyzed Synthesis of 3-Substituted $\Delta^1$-Corbapenems and $\Delta^2$-Corbapenems

(Liebeskind approach)

Coming to the recent reported silver-catalyzed synthesis, Wang and co-workers have successfully developed a general strategy for the construction of structurally diverse bridged oxa-/aza-[n.3.1] and oxa-/aza-[n.2.1] skeletons 48 by a novel [4+2] and [3+2] intramolecular cross-cycloaddition reaction of alkynylcyclopropane ketones 47 with carbonyl compounds and imines (Scheme 14).33

**Scheme 14.** Lewis Acid-Catalyzed Intramolecular [4+2] and [3+2] Cross-Cycloaddition of Alkynylcyclopropane Ketones (Wang approach)

Liu and co-workers demonstrated silver-catalyzed intramolecular oxidative aminofluorination of allenes 49 in which NFSI functioned as the fluorinating reagent. The methodology provided an efficient route to synthesize 4-fluoro-2,5-dihydropyrrole 51 compounds (Scheme 15).34

**Scheme 15.** Silver-Catalyzed Intramolecular Aminofluorination of Activated Allenes (Liu approach)
Fan and Ye have developed an efficient method to prepare 4-indole benzofurans 54 from 4-alkyl-2-ynylphenols 52 and indoles 53 via a hypervalent iodine-induced oxidative de-aromatization, a silver-catalyzed cascade Michael addition cyclization, and an aromatization (Scheme 16). 35

**Scheme 16.** Silver-Catalyzed Synthesis of 4-Substituted Benzofurans via a Cascade Oxidative Coupling-Annulation (**Fan approach**)

![Scheme 16 Image]

Wu and co-workers have developed an efficient approach to functionalized 1-aminoisoquinolines 57 via silver triflate-catalyzed reaction of 2-alkynylbenzaldoxime 55 with amine 56. They have shown that presence of PyBroP was essential for the successful transformation. The good functional groups tolerance at different positions of the substrates was achieved by them (Scheme 17). 36

**Scheme 17.** Synthesis of 1-Aminoisoquinolines via AgOTf-Catalyzed Reaction (**Wu approach**)

![Scheme 17 Image]

Further in another report, Wu and co-workers have shown a three-component reaction of 2-alkynylbenzaldehyde 58, sulfonohydrazide 59, and nitrile 60 catalyzed by silver triflate under mild conditions which generated pyrazolo[5,1-α]isoquinolin-2-amines 61 in good to excellent yields (Scheme 18). 37

**Scheme 18.** Synthesis of Pyrazolo[5,1-α]isoquinolin-2-amines via a Silver(I)-Catalyzed Three-Component Reaction (**Wu approach**)

![Scheme 18 Image]
Chan and co-workers have demonstrated an efficient silver(I) catalyzed synthetic route to (Z)-2-methylene-1-sulfonylindolin-3-ols 63 via intramolecular hydroamination of 1-(2-(sulfonylamino)phenyl)prop-2-yn-1-ols 62. They achieved the products under mild conditions at room temperature without the need to exclude air or moisture (Scheme 19).\(^{38}\)

**Scheme 19. Ag(I)-Catalyzed Synthesis of (Z)-2-Methylene-1-sulfonylindolin-3-ols (Chan approach)**

Moses and co-workers have developed a silver-mediated one-step synthesis of di- and trisubstituted oxazoles 66 from primary amides 64 and activated β-bromo-R-ketones 65. The method was simple, performed under mild conditions. They have shown that silver salt (AgBr) can be readily recovered at the end of the reaction by simple filtration (Scheme 20).\(^{39}\)

**Scheme 20. Silver-Mediated One-Step Synthesis of Oxazoles (Moses approach)**

Wu and co-workers have depicted reaction of 2-alkynylbenzaldoxime 67 with aryne 68 in the presence of silver-triflate (10 mol %) under mild conditions leading to 2-oxa-6-azabicyclo[3.2.2]nona-6,8-diene 69. This reaction proceeded through 6-endo-cyclization, [3+2] cycloaddition, and rearrangement leading to desired product in moderate to good yields (Scheme 21).\(^{40}\)
4.3 PREVIOUS APPROACHES OF OTHER LABORATORIES

Previously, Ciufolini and Weiss have reported electrophilic cyclization on the parent benzaldehyde moiety using camphor sulphonic acid (CSA) in CHCl₃ under reflux condition for 8–12 h (Scheme 22, A). However, the methodology failed on quinolinecarbaldehyde moiety when Belmont and co-workers used same reaction condition and ended up only with the 15% yield of the desired product {Scheme 22, B(i)}. This forced them to design a new strategy for the synthesis of acridinol derivatives {Scheme 22, B(ii)}.

Scheme 22. Previous Approaches of Other Laboratories

A. Synthesis of Naphthalenols by Ciufolini and Wiess

B (i). Attempt to Synthesize Acridinols by Belmont and Co-workers

B (ii). Synthesis of Acridinols Derivative by Belmont and Co-workers
4.4 OBJECTIVE AND STRATEGY OF THE PRESENT WORK

Prompted by importance of these heterocycles and in continuation of our ongoing efforts in the synthesis of heterocycles by the electrophilic cyclization of alkynes, we envisioned a straight forward approach for the synthesis of acridinol, quinolinol, naphthalenol and benzo thiophenol via silver-catalyzed electrophilic cyclization of 3-(2-alkynyl)aryl-β-ketoesters with requisite DKAs functionality in excellent regioselectivity at room temperature. The starting substrate ortho-alkynyl-β-ketoesters 74 required for the reaction may be readily prepared from easily accessible ortho-alkynylaldehydes 72, by reacting it with ethyl 2-diazoacetate 73 using NbCl₅ in CH₂Cl₂ at 25 °C.¹⁸ Alkynes 74 may subjected to electrophilic cyclization using AgOTf as a catalyst in CH₂Cl₂ to afford the desired product 75 (Scheme 23).

Scheme 23. Designed Reaction Pathway

4.5 RESULTS AND DISCUSSION

4.5.1 Preparation of ortho-Alkynylaldehydes

To probe the viability of the envisioned sequential catalytic protocol, we first carried out Sonogashira reaction of ortho-haloaldehydes 70 with terminal alkynes 71 using palladium complex PdCl₂(PPh₃)₂ (5 mol %) in presence of CuI (1 mol %) as co-catalyst and Et₃N (2 equiv) as base in CH₂CN for 1–2 h at 60 °C under inert atmosphere to obtain ortho-alkynyl aldehydes 72 (Scheme 24).

Scheme 24. Synthesis of ortho-Alkynylaldehyde
4.5.2 Preparation of 3-(2-Alkynyl)subst-β-ketoesters

The ortho-alkynylquinoline-carbaldehyde substrate 72 was then treated with ethyl-2-diazoacetate 73 and 10.0 mol% of NbCl₅ in CH₂Cl₂ 25 °C for 16–24 h under inert atmosphere to obtain 3-(2-alkynyl)subst-β-ketoesters (Table 2).

**Table 2. Synthesis of 3-(2-Alkynyl)subst-β-ketoesters**

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<tr>
<th>entry</th>
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<th>yields (%)</th>
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<td><img src="73.png" alt="Image" /></td>
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</tr>
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<td><img src="73.png" alt="Image" /></td>
<td><img src="74d.png" alt="Image" /></td>
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<td>5</td>
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<td>73</td>
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*All reactions were performed with 0.5 mmol of the alkynes 72a-k, 1.2 equiv of 73 and NbCl₅ (10 mol %) was added in CH₂Cl₂ (2.0 mL) at 25 °C for 16–24 h under inert condition. *Isolated yields

### 4.5.3 Establishment of the Optimized Reaction Condition

In order to find the optimal reaction condition, we first analyzed various factors affecting reaction using ethyl 3-oxo-3-(2-phenylethynyl)quinolin-3-yl)propanoate 74a (0.5 mmol) as a starting substrate. First of all, the reaction was performed with 5.0 mol % AgNO₃ in 2.0 mL of CHCl₃ at 25 °C, after 3h the cyclized product 75a was obtained in only 22% yield (Table 3, entry 1). However, when the reaction was further allowed to stir for 5 h, product 75a was obtained in 30% yield (entry 2). Increasing the amount of AgNO₃ from 5 mol % to 10 mol %, led to the formation of 75a in 44% yield (entry 3). The results were encouraging as the electrophilic cyclization was working at low catalyst amount and temperature. Further efforts were made to come up with better conditions which could afford the product in good yield. Among the various factors, we first varied silver salt. On trying AgOTf instead of AgNO₃, led to the formation of
desired product 75a in 58% yield (entry 4). After having found AgOTf little better over AgNO₃, different solvents like CH₃CN, CH₂Cl₂, H₂O, DMSO, DMF and methanol were screened at low and elevated temperatures to find out an appropriate system for the proposed cyclization reaction. It is clear from table 2, that CH₂Cl₂ at ambient temperature was more suitable solvent for electrophilic cyclization (entries 5–10). The use of AgOAc afforded the desired product 75a only in 45% yield; whereas, other triflates like CuOTf and HOTf were found to be ineffective (entries 11–13). The combination of AgOTf (10.0 mol %) in CH₂Cl₂ (2.0 mL) at 25 °C was found to be the standard condition electrophilic cyclization.

Table 3. Optimization of Reaction Condition

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<td>13</td>
<td>CH₂Cl₂</td>
<td>HOTf (10)</td>
<td>25</td>
<td>5 h</td>
<td>trace</td>
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</tbody>
</table>

*All reactions were performed using 0.5 mmol of the alkyne 74a, in 2.0 mL of solvent. Isolated yields.*
4.5.4 Synthesis of 3-Aryl/alkylacridinol-2-carboxylates

Employing the optimized protocol, scope and limitations of electrophilic cyclization was then examined to alkynes bearing different substituents *i.e.* ethyl 3-oxo-3-(2-(arylethynyl)quinolin-3-yl)propanoate 74a–k afforded the desired ethyl 1-hydroxy-3-arylacridine-2-carboxylate 75a–k in 64–83% yields (Table 4, entries 1–11). The alkyne 74a bearing phenyl substituent at triple bond resulted the desired cyclized product 75a in 75% yield (Table 4, entry 1). Substrates 74b–d bearing methyl, ethyl and methoxy group *para* to the triple bond resulted 6-endo-dig cyclized product 75b–d in 78–83% yields (entries 2–4). Alkyne bearing biphenyl substituent 74e afforded the cyclized product 75e in 76% yield (entry 5). On the other hand, when electron-withdrawing substituent CF$_3$ group was present at the *para* position to triple-bond, resulted the product 75f in 64% yield (entry 6). Having studied the effect of phenyl ring, we further employed the protocol for alkyne bearing an electron-rich heterocycle, *i.e.* thiophene, afforded the desired product 75g in 82% yield (entry 7). Different alkyl substituents at alkynes 74h–j were also evaluated and the desired cyclized products 75h–j were obtained in 70–72% yields (entries 8–10). The propargylphenoxy substituted alkyne 74k was also subjected to this cyclization and we were pleased to obtain cyclized product 75k in 69% yield (entry 11). It is evident from Table 4, that presence of electron-donating group *para* to the triple bond has favored 6-endo-dig cyclization.

**Table 4.** Synthesis of 3-Aryl/alkylacridinol-2-carboxylates

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield(^a) (%)</th>
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<sup>a</sup>All reactions were performed with 0.5 mmol of the alkynes 74a–k, AgOTf (10 mol %) in CH$_2$Cl$_2$ (2.0 mL) at 25 °C for 3–5 h under inert condition. <sup>Isolated yields</sup>
4.5.5 Charge Density Calculations

It is evident from Table 4 that substituents attached to the triple bond impart a major impact on the success of the regioselective cyclization as shown in figure 3, structure A. The presence of electron-donating group para to the triple bond increases the electron density on the distal end of the triple bond (C_β), which subsequently makes C_α more electrophilic in comparison to C_β, thereby favors 6-endo-dig cyclization. The observation was further supported by theoretical calculation using HyperChem software. The charge density was calculated by performing a single point calculation using semi-empirical method. It is evident from the calculation as shown in figure 3 that in structures B and C if methoxy group is present para to triple bond, it increases charge density difference between C_α and C_β, due to which C_α becomes more electrophilic than C_β, which in turn makes the cyclization more feasible and leads to regioselective 6-endo-dig cyclization rather than 5-exo-dig cyclization.

![Figure 3. Charge Density Calculations](image-url)

**Figure 3.** Charge Density Calculations
**Figure 4.** Structure showing charge density of 74a (Semi-empirical calculation)

**Figure 5.** Structure showing charge density of 74d (Semi-empirical calculation)
4.5.6 Characterization of a Representative Compound ethyl 1-hydroxy-3-(4-methoxyphenyl)acridine-2-carboxylate (75d)

Figure 6. $^1$H NMR of compound 75d (400MHz, CDCl$_3$)
Figure 7. $^{13}$C NMR of compound 75d (100MHz, CDCl$_3$)
The regioselective formation of 6-endo-dig cyclized product was fully characterized by $^1$H, $^{13}$C NMR and Mass spectroscopic data. In $^1$H NMR spectrum in CDCl$_3$ at 400 MHz (Figure 6), the appearance of a singlet peak at 3.80 with the integral value of three confirmed the presence of ‘-OCH$_3$’ group respectively. Further, a quartet at 4.02 ppm and a triplet at 0.81 ppm showed the presence of a ‘-OCH$_2$CH$_3$’ group. Additionally, a singlet at 9.28 ppm showed the presence of H$_9$ proton. Presence of a broad singlet at 12.6 ppm depicted the presence of OH group. Rest all observed peaks were lying in aromatic region along with matched proton count signified the formation of fully aromatized compound 75d. In $^{13}$C NMR spectrum in CDCl$_3$ at 100 MHz (Figure 7), presence of peaks at 61.3 and 55.4 ppm confirmed the presence of ‘-OCH$_2$’ and ‘-OCH$_3$’ groups respectively. Methyl group’s presence was justified by its presence at 13.2 ppm. Peak at 171.6 ppm showed the presence of carbon of COOEt group. Presence of two double intensity peaks of that of tertiary carbon clearly depicted the presence of two pairs of symmetrical carbons i.e. 2’,6’ and 3’, 5’. Finally, its high resolution mass spectrum showed ([M+H]$^+$) peak at m/z 338.1546 firmly stated the formation of 75d.

4.5.7 Preparation of 3-(2-Alkynyl)subst-β-ketoesters

Given the success of electrophilic reaction ortho-alkynylquinoline-carbaldehyde, we wished to extend this methodology to include other aldehydes. The reaction well accommodated the moieties such as benzaldehyde, nicotinaldehyde and benzothiophenecarbaldehyde (Table 5).

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Table 5. Synthesis of 3-(2-alkynyl)subst-β-ketoesters$^a$
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<sup>a</sup>All reactions were performed with 0.5 mmol of the alkynes 72f-t, 1.2 equiv of 73 and NbCl<sub>5</sub> (10 mol %) was added in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) at 25 °C for 16–24 h under inert condition. <sup>b</sup>Isolated yields
4.5.8 Synthesis of 2-Carboxylates Derivatives of Naphthalenols, Quinolinols and Dibenzo thiophenol

Further, scope and generality of electrophilic reaction were to extend nicotinaldehyde, benzaldehyde and benzo thiophenecarbaldehyde moieties. In substrate, ethyl 3-oxo-3-(2-(arylethynyl)pyridin-3-yl)propanoate where alkynes bearing *p*-tolyl and 1,3-dimethoxybenzyl substituent 74l–m afforded the desired cyclized product 75l–m in 77 and 73 % yield respectively (Table 6, entries 1–2). Furthermore, ethyl 3-oxo-3-(3-(p-tolylethynyl)pyridin-4-yl)propanoate 74n afforded the cyclized product 75n in 72 % yield (entry 3).

Further exploring the developed protocol to ethyl 3-oxo-3-(2-(arylethynyl)phenyl)propanoate 74o–s, the desired products 75o–s were obtained in moderate to good yields (Table 6, entries 4–8). The methyl and methoxy group present at *para* of alkynes 74p–q, triple bond, resulted the cyclized product in 74% and 78% yields respectively (entries 5–6). The electron-rich thiophene substituted alkyne 74r, proved to be favorable for the reaction and afforded desired product 75r in 79% yield (entry 7). The substitution at *meta* position accomplished the cyclized product 75s in comparatively lower i.e. 68% yield (entry 8). Also, the ethyl 3-(3-((4-methoxyphenyl)ethynyl)benzo-[*b*]thiophen-2-yl)-3-oxopropanoate 74t afforded the desired cyclized product 75t in 72% yield (entry 9).

**Table 6.** Synthesis of Naphthalenes, Quinolines and Dibenzo thiophenenes with DKA’s Functionality

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\(^a\)All reactions were performed with 0.5 mmol of the alkynes 74l-t, AgOTf (10 mol %) in CH\(_2\)Cl\(_2\) (2.0 mL) at 25 °C for 3–5 h under inert condition. \(^b\)Isolated yields
4.5.9 Characterization of a Representative Compound ethyl 5-hydroxy-7-(p-tolyl)quinoline-6-carboxylate (75l)

![Chemical Structure](image)

Ethyl 5-hydroxy-7-(p-tolyl)quinoline-6-carboxylate

The regioselective formation of 6-endo-dig cyclized product was fully characterized by $^1$H, $^{13}$C NMR and Mass spectroscopic data. In $^1$H NMR spectrum in CDCl$_3$ at 400 MHz (Figure 8) the appearance of a quartet at 4.05 ppm and a triplet at 0.82 ppm showed the presence of a ‘-OCH$_2$CH$_3$’ group. Moreover, peak at 2.42 ppm showed presence of ‘-CH$_3$’ group. Presence of a singlet at 12.2 ppm depicted the presence of OH group. Rest all observed peaks were lying in aromatic region signifying the formation of fully aromatized compound 75l. In $^{13}$C NMR spectrum in CDCl$_3$ at 100 MHz (Figure 9), presence of peaks at 61.3 and 12.9 confirmed the presence of ‘-OCH$_2$’ and ‘-CH$_3$’ in a OEt group. On the other hand, peak at 21.1 ppm showed presence of ‘-CH$_3$’ group. Presence of two peaks with double intensity to that of a tertiary carbon at 128.3 and 128.2 ppm clearly showed the presence of two pairs of symmetrical carbons i.e. 2’,6’ and 3’, 5’. Finally, Its high resolution mass spectrum showed ([M+H]$^+$) peak at $m/z$ 338.1546 firmly stated the formation of 75l.
Figure 8. $^1$H NMR of compound 75l (400MHz, CDCl$_3$)
Figure 9. $^{13}$C NMR of compound 75I (100MHz, CDCl$_3$)
The regioselective 6-endo-dig cyclization was unambiguously confirmed by X-ray crystal structure analysis of compound 75f and 75p (Figure 10). Atomic coordinates, bond lengths, bond angles, and thermal parameters for compound 75f and 75p has been deposited at the Cambridge Crystallographic Data Centre. CCDC number for 75f and 75p are 864805 and 847471 respectively.

**Figure 10A.** Crystal Structure of 75f (ORTEP drawing)

**Figure 10B.** Crystal Structure of 75p (ORTEP drawing)
4.6 EXPERIMENTS TO ASERTAIN REACTION MECHANISM

To ascertain the mechanism, reaction of 74d was performed in CHCl₃ and quenched with D₂O, product 76 was observed (Scheme 25). Similar result was obtained, when we performed the reaction in CDCl₃ and quenched it with D₂O/CD₃OD. The product 75d was obtained when the same reaction was carried out in CDCl₃ and quenched with H₂O. However, when the reaction was carried out in CDCl₃ with 10.0 equiv of CD₃OD, both the compounds 76 and 77 were obtained in 2:3 ratios. Whereas, the formation of compound 77 occurred because of the presence of D⁺ ion in the reaction medium, sourced by CD₃OD. These experiments indicated that H⁺ ion which replaced Ag⁺ ion, was being accomplished before workup. The observation was supported by ¹H NMR of, disappearance of peak of 12–13 ppm region in figure 11 indicated that OH has been replaced by OD resulting in the deuterium labeled compound 76. On the other hand, the peak of 7.60 ppm which has integral value of 0.4 (Figure 12) in comparison with ¹H NMR spectra of compound 75d (Figure 6), indicated that the mixture of compound 76 and 77 has the ratio of 2:3.

Scheme 25. Deuterium-Labeling Experiments

\[ 74d \] (a) \[ \rightarrow \] \[ 76 \]
\[ 74d \] (b) \[ \rightarrow \] \[ 75d \]
\[ 74d \] (c) \[ \rightarrow \] \[ 76; P = H; 77; P = D (2:3 ratio) \]
\[ 74d \] (d) \[ \rightarrow \] \[ 76; P = H; 77; P = D (2:3 ratio) \]
Figure 11. $^1$H NMR Spectra of Compound 76 (400 MHz, CDCl$_3$). Disappearance of peak of 12–13 ppm region indicates that OH has been replaced by OD resulting in the deuterium labeled compound 76.
**Figure 12.** $^1$H NMR Spectra of Compound 76 + 77 (400 MHz, CDCl$_3$). The peak of 7.60 ppm which has integral value of 0.4, indicated that in the mixture of compound 76 and 77 has the ratio of 2:3.
4.7 PLAUSIBLE REACTION MECHANISM

On the basis of above observations, along with deuterium labeling experiments, an assumed pathway for the formation of cyclized product 75 is illustrated in Scheme 26. Firstly, the AgOTf coordinates to the triple bond of 74 to form a π-complex T, which undergoes intramolecular nucleophilic attack by the C2 position of β-keto ester onto alkynyl carbon to form the species U. The silver ion gets replaced by H⁺ ion to obtain the species V, and keto-enol tautomerization of V led to desired cyclized product 75.

Scheme 26. Probable mechanism

4.8 CONCLUSIONS

In summary, a milder and efficient approach for the direct synthesis of medicinally important acridinols, naphthlenols, quinolinols and benzothiophenol bearing 2-carboxylate group have been demonstrated. This milder and feasible silver-catalyzed electrophilic cyclization has been advantageously employed to tolerate high functional group variation thereby achieving diversity and regioselectivity in good yields which made it ideal for the generation of libraries of functionally-substituted scaffolds. The regioselective 6-endo-dig formation was supported by charge density calculation and was further confirmed by X-ray crystallographic studies. The deuterium level experiment proved to be an additional support for proposed mechanism.
4.9 EXPERIMENTAL SECTION

4.9.1 General Method

$^1$H NMR (300 MHz or 400 MHz) and $^{13}$C NMR (75 MHz or 100 MHz) spectra were recorded in CDCl$_3$ or in DMSO as specified and were obtained using Jeol JNM ECX400P (400 MHz) spectrometer and Bruker AV300(300 MHz) spectrometer. Chemical shifts for protons are reported in ppm from tetramethylsilane with the residual CHCl$_3$ resonance as internal reference. Chemical shifts for carbons are reported in ppm from tetramethylsilane and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd = doublet of doublet), coupling constants in Hertz, and integration. High-resolution mass spectra were recorded on Applied Biosystems QSTAR® Elite Hybrid (QqTOF). Crystal structure analysis was accomplished on Oxford diffraction (Xcaliber S) single crystal X-ray diffractometer. TLC analysis was performed on commercially prepared 60 F$_{254}$ silica gel plates and visualized by either UV irradiation or by staining with I$_2$. Anhydrous forms of all reagents such as diethyl ether, hexanes, ethyl acetate, CH$_2$Cl$_2$, 2-chloroquinoline-3-carbaldehyde, 2-bromonicotinaldehyde, 3-bromoisonicotinaldehyde, 2-bromobenzaldehyde, 3-bromobenzothiophene-2-carbaldehyde, ethyl diazoacetate, terminal alkynes, Et$_3$N and the silver salts were used directly as obtained commercially unless otherwise noted.

4.9.2 General procedure for the silver-catalyzed formation of the 2-carboxylate-acridinols, quinolinols, naphthalenols and benzothiophenol (75a–t)

To a solution of CH$_2$Cl$_2$ (2 mL), and AgOTf (10 mol %), ortho-alkynyl-β-keto esters (74a–t) (0.5 mmol) were added and the reaction mixture was allowed to stir at 25 °C for 3–5 h. The completion of reaction was monitored by TLC. The reaction mixture was filtered and diluted with ethyl acetate and washed with brine solution. The combined organic fractions were dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum to yield the crude product. The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane as the eluent.
4.9.3 Analytical Data of Acridinols, Quinolinols, Naphthalenols and Benzothiophenol

**Ethyl 1-hydroxy-3-phenylacridine-2-carboxylate**

The product was obtained as brown crystals in hexane/CH$_2$Cl$_2$ (128.7 mg, 75%); mp 140–144 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ: 12.67 (s, 1H), 9.30 (s, 1H), 8.12 (d, $J$ = 8.8 Hz, 1H), 8.02 (d, $J$ = 8.8 Hz, 1H), 7.77 (t, $J$ = 7.3 Hz, 1H), 7.52–7.48 (m, 2H), 7.33–7.28 (m, 5H), 3.99 (q, $J$ = 6.6 Hz, 2H), 0.73 (t, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 171.5, 162.6, 150.9, 149.6, 143.4, 142.9, 134.2, 131.9, 127.6, 127.6, 126.8, 126.0, 125.9, 122.4, 118.7, 104.5, 61.2, 12.9; HRMS calcd for C$_{22}$H$_{18}$NO$_3$ ([M+H]$^+$) 344.1287; found 344.1285.

**Ethyl 1-hydroxy-3-p-tolylacridine-2-carboxylate**

The product was obtained as light yellow crystalline solid from hexane/CH$_2$Cl$_2$ (141.2 mg, 79%); mp 155–157 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ: 12.19 (s, 1H), 9.32 (s, 1H), 8.20 (d, $J$ = 6.88 Hz, 1H), 8.00 (d, $J$ = 8.2 Hz, 1H), 7.81–7.77 (m, 1H), 7.56 (m, 1H), 7.53–7.49 (m, 1H), 7.19 (d, $J$ = 8.7 Hz, 2H), 7.13 (d, $J$ = 6.9 Hz, 2H), 4.02 (q, $J$ = 6.4 Hz, 2H), 2.35 (s, 3H), 0.75 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 171.5, 162.4, 149.8, 148.4, 144.5, 139.6, 136.7, 135.2, 132.5, 129.2, 128.3, 128.1, 126.1, 125.9, 121.2, 118.6, 104.9, 61.4, 21.2, 13.0; HRMS calcd C$_{23}$H$_{20}$NO$_3$ (M$^+$) 357.1365; found 357.1366.
Ethyl 3-(4-ethylphenyl)-1-hydroxyacridine-2-carboxylate

The product was obtained as brown crystals in hexane/CH₂Cl₂ (144.7 mg, 78%); mp 138–141 °C; ¹H NMR (400 MHz, CDCl₃) δ: 12.60 (s, 1H), 9.29 (s, 1H), 8.12 (d, J = 8.8 Hz, 1H), 8.00 (d, J = 8.1 Hz, 1H), 7.78–7.74 (m, 1H), 7.52–7.49 (m, 2H), 7.22 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 7.09 (q, J = 7.3 Hz, 2H), 2.64 (q, J = 7.0 Hz, 2H), 1.22 (t, J = 7.3 Hz, 3H), 0.73 (t, J = 7.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 171.6, 162.5, 150.9, 149.7, 143.5, 143.0, 140.0, 134.2, 131.8, 129.2, 128.2, 127.1, 126.0, 125.8, 122.3, 118.7, 104.7, 61.2, 28.6, 15.9, 12.9; HRMS calcd for C₂₃H₂₂NO₃ ([M+H]^⁺) 372.1600; found 372.1589.

Ethyl 1-hydroxy-3-(4-methoxyphenyl)acridine-2-carboxylate

The product was obtained as brown crystals in hexane/CH₂Cl₂ (154.9 mg, 83%); mp 170–172 °C; ¹H NMR (400 MHz, CDCl₃) δ: 12.61 (s, 1H), 9.28 (s, 1H), 8.11 (d, J = 8.8 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.76 (t, J = 8.1 Hz, 1H) 7.50–7.46 (m, 2H), 7.23 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.02 (q, J = 7.3 Hz, 2H), 3.80 (s, 3H), 0.81 (t, J = 7.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 171.6, 162.5, 158.8, 150.8, 149.6, 143.1, 135.3, 134.2, 131.9, 129.31, 129.13, 129.01, 125.96, 125.81, 122.2, 118.6, 113.0, 104.7, 61.3, 55.3, 13.2; HRMS calcd C₂₅H₂₀NO₄ ([M+H]^⁺) 374.1393; found 374.1395.
Procedure for the silver-catalyzed formation of compound (76 + 77)

To a solution of CDCl$_3$ (2 mL), and AgOTf (10 mol %), ethyl 3-(2-((4-methoxyphenyl)ethynyl)quinolin-3-yl)-3-oxopropionate (74d) (0.5 mmol) was added followed by 10 equiv of CD$_3$OD and reaction mixture was allowed to stir at 25 °C for 5 h and the resulting solution was filtered and washed with D$_2$O and extracted with ethyl acetate (3 X 10 mL). The combined organic fractions was dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum to yield the crude product. The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane as the eluent. The product was obtained as brown crystals in hexane/CH$_2$Cl$_2$; mp 175–176 °C; R$_f$ (10% ethyl acetate/hexane) 0.24; $^1$H NMR (400 MHz, CDCl$_3$) δ: 9.36 (s, 1H), 8.22 (d, $J$ = 8.4 Hz, 1H), 8.05 (d, $J$ = 8.1 Hz, 1H), 7.83 (t, $J$ = 7.3 Hz, 1H), 7.60 (s, 0.4H), 7.55 (t, $J$ = 7.3 Hz, 1H), 7.28 (d, $J$ = 8.0 Hz, 2H), 6.82 (d, $J$ = 8.8 Hz, 2H), 4.08 (q, $J$ = 6.6 Hz, 2H), 3.85 (s, 3H), 0.86 (t, $J$ = 7.3 Hz, 3H)

Ethyl 3-(biphenyl-4-yl)-1-hydroxyacridine-2-carboxylate

The product was obtained as brown crystals in hexane/CH$_2$Cl$_2$ (159.4 mg, 76%); mp 173–175 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ: 12.69 (s, 1H), 9.31 (s, 1H), 8.13 (d, $J$ = 8.8 Hz, 1H), 8.00 (d, $J$ = 8.8 Hz, 1H), 7.79–7.75 (m, 1H), 7.60–7.56 (m, 5H), 7.49 (t, $J$ = 7.3 Hz, 1H), 7.42–7.37 (m, 4H), 7.30 (t, $J$ = 7.3 Hz, 1H), 4.01 (q, $J$ = 7.3 Hz, 2H), 0.74 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 171.5, 162.7, 150.9, 149.6, 143.0, 141.9, 140.8, 139.8, 134.3, 131.9, 129.16, 129.07, 128.8, 128.6, 127.3, 127.0, 126.3, 126.0, 125.9, 122.3, 118.7, 104.5, 61.0, 14.1; HRMS calcd for C$_{28}$H$_{21}$NO$_3$ (M$^+$) 419.1521; found 419.1521.
Ethyl 1-hydroxy-3-(4-(trifluoromethyl) phenyl)acridine-2-carboxylate

The product was obtained as yellow crystals in hexane/CH₂Cl₂ (131.7 mg, 64%); mp 173–175 °C; ¹H NMR (400 MHz, CDCl₃) δ: 12.89 (s, 1H), 9.33 (s, 1H), 8.17 (d, J = 8.8 Hz, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.85–7.81 (m, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.58–7.54 (m, 1H), 7.52 (s, 1H), 7.48 (d, J = 8.0 Hz, 2H), 4.05 (q, J = 7.3 Hz, 2H), 0.77 (t, J = 7.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 171.1, 163.1, 150.9, 149.3, 146.6, 141.7, 134.3, 132.1, 129.13, 129.09, 128.5, 126.2, 126.1, 124.51, 124.47, 124.43, 122.5, 118.8, 103.7, 61.4, 12.8; HRMS calcd for C₂₉H₁₆F₃NO₃ (M⁺) 411.1082; found 411.1082. The structures was solved using SHELXL-97 direct method and refined by the full matrix least-squares technique on F² using the SHELXL-97 program within the WinGX v 1.80.05 software package. All hydrogen atoms were fixed at the calculated positions with isotropic thermal parameters, and all non-hydrogen atoms were refined anisotropically.

Crystal Data for 75f: C₂₉H₁₆F₃NO₃, M = 411.37, Orthorhombic, space group Pbcn, a = 15.4582(13) Å, b = 8.0335(5) Å, c = 31.151(2) Å, α = 90°, β = 90°, γ = 90°, V = 3868.4(5) Å³, Z = 8, T = 296 K, d_calc = 1.413 Mg/m³, R(int.) = 0.0234, R₁ = 0.0982, wR₂ = 0.2531 [I>2σ(I)], R₁ = 0.1124, wR₂ = 0.2638 (all data), GOF = 1.111. Crystallographic data for 75f have been deposited with the Cambridge Crystallographic Data Centre. CCDC 864805, contain all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; Fax: (+44)1223-336-033; or Email : deposit@ccdc.cam.ac.uk.

Ethyl 1-hydroxy-3-(thiophen-3-yl)acridine-2-carboxylate

The product was obtained as brown crystals in hexane/CH₂Cl₂ (143.2 mg, 82%); mp 147–150 °C; ¹H NMR (400 MHz, CDCl₃) δ: 12.69 (s, 1H), 9.28 (s, 1H), 8.11 (d, J =
8.8 Hz, 1H), 7.99 (d, J = 8.1 Hz, 1H), 7.76 (t, J = 7.3 Hz, 1H), 7.56 (s, 1H), 7.49 (t, J = 7.3 Hz, 1H), 7.24–7.21 (m, 2H), 7.02 (d, J = 5.9 Hz, 1H) 4.07 (q, J = 7.3 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 171.5, 162.6, 150.9, 149.6, 142.9, 138.0, 134.2, 131.9, 129.17, 129.12, 128.98, 126.07, 125.96, 124.1, 122.5, 121.5, 118.8, 104.5, 61.4, 13.2; HRMS calcd for C$_{20}$H$_{15}$NO$_3$S (M$^+$) 349.0773; found 349.0779.

![Ethyl 3-cyclohexyl-1-hydroxyacridine-2-carboxylate](image)

The product was obtained as green needle crystals in hexane/CH$_2$Cl$_2$ (122.3 mg, 70%); mp 80–85 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 13.06 (s, 1H), 9.31 (s, 1H), 8.15 (d, J = 8.8 Hz, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.84–7.80 (m, 1H), 7.62 (s, 1H), 7.55–7.51 (m, 1H), 4.53 (q, J = 6.6 Hz, 2H), 3.57–3.49 (m, 1H), 2.50–2.02 (m, 2H), 1.93–1.90 (m, 2H), 1.82–1.79 (m, 1H), 1.56–1.40 (m, 5H), 1.36–1.24 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 172.3, 164.4, 142.4, 139.1, 136.1, 132.8, 130.9, 129.5, 128.8, 128.0, 127.1, 125.5, 118.4, 106.1, 62.0, 48.0, 34.3, 29.7, 25.0, 14.4. HRMS calcd for C$_{22}$H$_{23}$NO$_3$ (M$^+$) 349.1678; found 349.1675.

![Ethyl 3-cyclopentyl-1-hydroxyacridine-2-carboxylate](image)

The product was obtained as green needle crystals in hexane/CH$_2$Cl$_2$ (120.7 mg, 72%); mp 87–88 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 12.86 (s, 1H), 9.23 (s, 1H), 8.11 (d, J = 8.7 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.74 (t, J = 7.7 Hz, 1H), 7.55 (s, 1H), 7.44 (t, J = 7.3 Hz, 1H), 4.44 (q, J = 7.3 Hz, 2H), 3.46–3.41 (m, 1H), 1.95–1.92 (m, 2H), 1.84–1.81 (m, 2H), 1.73–1.70 (m, 1H), 1.48–1.22 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 172.3, 162.9, 150.1, 147.8, 139.5, 134.3, 131.8, 129.7, 129.2, 128.8, 125.5, 117.3, 105.5, 103.4, 61.2, 43.8, 34.2, 25.0, 13.9; HRMS calcd for C$_{21}$H$_{22}$NO$_3$ ([M+H]$^+$) 336.1600; found 336.1589.
Ethyl 3-butyl-1-hydroxyacridine-2-carboxylate

The product was obtained as greenish yellow needle crystals in hexane/CH₂Cl₂ (113.2 mg, 70%); mp 100–103 °C; ¹H NMR (400 MHz, CDCl₃) δ: 13.33 (s, 1H), 9.31 (s, 1H), 8.16 (d, J = 8.8 Hz, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.84–7.80 (m, 1H), 7.53 (t, J = 7.3 Hz, 1H), 7.49 (s, 1H), 4.52 (q, J = 7.3 Hz, 2H), 3.12 (t, J = 7.3 Hz, 2H), 1.70–1.62 (m, 2H), 1.50–1.41 (m, 5H), 0.96 (t, J = 7.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 172.4, 164.0, 150.8, 150.0, 144.3, 134.4, 131.8, 129.2, 128.9, 125.8, 125.5, 121.1, 118.5, 104.3, 61.9, 37.1, 33.7, 22.8, 14.10, 14.06; HRMS calcd for C₂₀H₁₂NO₃ ([M+H]⁺) 324.1600; found 324.1598.

Ethyl 1-hydroxy-3-(phenoxy methyl)acridine-2-carboxylate

The product was obtained as green semi solid (128.8 mg, 69%); ¹H NMR (400 MHz, CDCl₃) δ: 13.32 (s, 1H), 9.37 (s, 1H), 8.21 (d, J = 8.8 Hz, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.96 (s, 1H), 7.85 (t, J = 7.3 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.33–7.29 (m, 2H), 7.03–6.96 (m, 3H), 5.48 (s, 2H), 4.04 (q, J = 7.3 Hz, 2H), 1.36 (t, J = 7.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 171.8, 169.7, 164.2, 158.7, 143.2, 140.0, 137.8, 135.4, 134.6, 132.2, 129.5, 129.1, 126.1, 120.9, 119.5, 119.0, 114.7, 102.8, 68.2, 61.0, 14.1; HRMS calcd for C₂₃H₁₉NO₄ (M⁺) 373.1314; found 373.1314.

Ethyl 5-hydroxy-7-p-tolylquinoline-6-carboxylate

The product was obtained as brown needle crystals in hexane/CH₂Cl₂ (121.4 mg, 79%); mp 107–110 °C; ¹H NMR (400 MHz, CDCl₃) δ: 12.19 (s, 1H), 8.98 (dd, J = 1.5, 4.4
Hz, 1H), 8.72–8.70 (m, 1H), 7.48 (s, 1H), 7.44–7.40 (m, 1H), 7.23–7.18 (m, 4H), 4.03 (q, \( J = 7.3 \) Hz, 2H), 2.41 (s, 3H), 0.81 (t, \( J = 7.3 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta: 171.4, 160.8, 153.5, 149.9, 143.3, 139.8, 136.5, 132.4, 128.26, 128.16, 122.5, 120.6, 119.2, 106.8, 61.3, 21.2, 13.0; \) HRMS calcd for \( \text{C}_{19}\text{H}_{17}\text{NO}_3 \) (M\(^+\)) 307.1208; found 307.1208.

![Ethyl 7-(3,5-dimethoxyphenyl)-5-hydroxy quinoline-6-carboxylate](image1)

**Ethyl 7-(3,5-dimethoxyphenyl)-5-hydroxy quinoline-6-carboxylate**

The product was obtained as light yellow crystals in hexane/CH\(_2\)Cl\(_2\) (127.2 mg, 72%); mp 260–265 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta: 12.16 \) (s, 1H), 8.92 (dd, \( J = 1.4, 2.2 \) Hz, 1H), 8.65 (dd, \( J = 1.4, 8.8 \) Hz, 1H), 7.44 (s, 1H), 7.39–7.35 (m, 1H), 6.43–6.37 (m, 3H), 4.04 (q, \( J = 7.3 \) Hz, 2H), 3.74 (s, 6H), 1.18 (t, \( J = 7.3 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta: 171.2, 160.8, 160.1, 153.5, 149.8, 144.6, 143.1, 138.5, 132.5, 122.1, 120.8, 119.4, 106.7, 99.2, 61.3, 60.4, 55.4, 14.1; \) HRMS calcd for \( \text{C}_{20}\text{H}_{19}\text{NO}_3 \) (M\(^+\)) 353.1263; found 353.1268.

![Ethyl 5-hydroxy-7-p-tolylisoquinoline-6-carboxylate](image2)

**Ethyl 5-hydroxy-7-p-tolylisoquinoline-6-carboxylate**

The product was obtained as yellow needle crystals in hexane/CH\(_2\)Cl\(_2\) (112.2 mg, 73%); 110–112 mp 0 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta: 12.22 \) (s, 1H), 7.97 (d, \( J = 2.9 \) Hz, 1H), 7.70 (d, \( J = 8.0 \) Hz, 1H), 7.44–7.41 (m, 2H), 7.24–7.18 (m, 4H), 4.06 (q, \( J = 7.3 \) Hz, 2H), 2.42 (s, 3H), 0.81 (t, \( J = 7.3 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta: 171.5, 160.9, 153.7, 149.9, 143.6, 140.1, 136.7, 131.9, 128.2, 128.1, 122.5, 120.6, 119.2, 106.5, 61.7, 20.6, 11.9; \) HRMS calcd \( \text{C}_{19}\text{H}_{17}\text{NO}_3 \) (M\(^+\)) 307.1208; found 307.1205.
Ethyl 1-hydroxy-3-phenyl-2-naphthoate

The product was obtained as light yellow semi solid (102.3 mg, 70%); $^1$H NMR (400 MHz, CDCl$_3$) δ: 12.27 (s, 1H), 8.17 (d, $J = 8.8$ Hz, 1H), 8.00 (d, $J = 8.8$ Hz, 1H), 7.78 (t, $J = 8.0$ Hz, 1H), 7.50 (t, $J = 7.3$ Hz, 1H), 7.36–7.29 (m, 5H), 7.19 (s, 1H), 3.98 (q, $J = 7.3$ Hz, 2H), 0.72 (t, $J = 6.6$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 171.8, 161.1, 140.6, 139.4, 136.1, 135.5, 129.7, 128.3, 128.1, 127.3, 125.6, 123.94, 123.89, 121.2, 106.1, 61.0, 13.0; HRMS calcd C$_{19}$H$_{16}$O$_3$ (M$^+$) 292.1099; found 292.1089.

Ethyl 1-hydroxy-3-$p$-tolyl-2-naphthoate

The product was obtained as white crystals in hexane/CH$_2$Cl$_2$ (113.3 mg, 74%); mp 114–116 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ: 12.21 (s, 1H), 8.41 (d, $J = 7.8$ Hz, 1H), 7.72 (d, $J = 7.2$ Hz, 1H), 7.60–7.58 (m, 1H), 7.54–7.49 (m, 2H), 7.36–7.19 (m, 4H), 4.04 (q, $J = 6.9$ Hz, 2H), 2.41 (s, 3H), 0.79 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 171.8, 161.1, 140.6, 139.4, 136.1, 135.5, 131.8, 129.6, 128.8, 128.1, 127.3, 125.6, 123.9, 121.1, 106.1, 61.0, 21.1, 13.0; HRMS calcd C$_{20}$H$_{18}$O$_3$ (M$^+$) 306.1256; found 306.1251. The compound 75p crystallized in triclinic crystal system with space group P-1. The single-crystal X-ray data were collected using graphite monochromated Mo Kα radiation ($λ = 0.71073$ Å). The structures were solved using SHELXL-97 direct method and refined by the full matrix least-squares technique on $F^2$ using the SHELXL-97 program within the WinGX v 1.80.05 software package. All hydrogen atoms were fixed at the calculated positions with isotropic thermal parameters, and all non-hydrogen atoms were refined anisotropically. Crystal Data for 75p: C$_{20}$H$_{18}$O$_3$, $M =$ 306.34, triclinic, space group P-1, $a = 7.9540(6)$ Å, $b = 9.7670(6)$ Å, $c = 11.8045(8)$ Å, $α = 73.566(6)^°$, $β = 75.711(6)^°$, $γ = 66.438(7)^°$, $V = 796.87(9)$ Å$^3$, $Z = 2$, $T = 296$ K, $d_{calc} = 1.277$ Mg/m$^3$, R(int.) = 0.0204, $R_I = 0.0609$, $wR_2 = 0.1662$ [$I>2σ(I)$], $R_I = 0.0646$.  

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\(wR_2 = 0.1703\) (all data), GOF = 1.215. Crystallographic data for 75p have been deposited with the Cambridge Crystallographic Data Centre. CCDC 847471, contain all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; Fax: (+44)1223-336-033; or Email : deposit@ccdc.cam.ac.uk.

Ethyl 1-hydroxy-3-(4-methoxyphenyl)-2-naphthoate

The product was obtained as white crystals in hexane/CH\(_2\)Cl\(_2\) (127.3 mg, 79%); mp 127–129 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 12.16 (s, 1H), 8.33 (d, \(J = 8.1\) Hz, 1H), 7.64 (d, \(J = 7.8\) Hz, 1H), 7.53 (t, \(J = 6.9\) Hz, 2H), 7.46–7.41 (m, 1H), 7.18–7.14 (m, 2H), 6.84 (d, \(J = 8.4\) Hz, 2H), 3.98 (q, \(J = 7.2\) Hz, 2H), 3.79 (s, 3H), 0.77 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 170.8, 160.2, 157.5, 137.9, 135.1, 134.4, 128.6, 128.4, 126.2, 124.6, 122.8, 120.2, 111.9, 105.1, 60.0, 54.4, 12.2; HRMS calcd C\(_{20}\)H\(_{15}\)O\(_4\) (M\(^+\)) 322.1205; found 322.1205.

Ethyl 1-hydroxy-3-(thiophen-3-yl)-2-naphthoate

The product was obtained as yellow crystals in hexane/CH\(_2\)Cl\(_2\) (119.3 mg, 80%); mp 90–94 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 12.25 (s, 1H), 8.34 (d, \(J = 8.1\) Hz, 1H), 7.64 (d, \(J = 8.1\) Hz, 1H), 7.55–7.51 (m, 1H), 7.46–7.42 (m, 1H), 7.21–7.19 (m, 1H), 7.17 (s, 1H), 7.11–7.09 (m, 1H), 6.96 (d, \(J = 5.9\) Hz, 1H), 4.04 (q, \(J = 7.3\) Hz, 2H), 0.89 (t, \(J = 7.3\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 171.7, 161.3, 143.6, 135.5, 133.9, 129.7, 129.3, 127.2, 125.8, 124.2, 123.93, 123.81, 121.4, 120.9, 106.0, 61.1, 13.1; HRMS calcd C\(_{17}\)H\(_{14}\)O\(_3\)S ([M-H]\(^+\)) 297.0650; found 297.0625.
The product was obtained as white needle crystals in hexane/CH$_2$Cl$_2$ (105.7 mg, 69%); mp 109–111 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 12.24 (s, 1H), 8.42 (d, $J = 8.1$ Hz, 1H), 7.72 (d, $J = 8.1$ Hz, 1H), 7.60 (t, $J = 6.6$ Hz, 1H), 7.51 (t, $J = 7.3$ Hz, 1H), 7.27–7.23 (m, 2H), 7.15–7.09 (m, 3H), 4.03 (q, $J = 7.3$ Hz, 2H), 2.36 (s, 3H), 0.79 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 171.9, 161.2, 143.4, 139.5, 137.0, 135.4, 129.7, 129.2, 127.4, 127.3, 127.1, 125.7, 125.5, 123.9, 121.1, 106.0, 60.9, 21.4, 13.0; HRMS calcd for C$_{20}$H$_{18}$O$_3$ (M$^+$) 306.1256; found 306.1248.

**Ethyl 4-hydroxy-2-(4-methoxyphenyl)dibenzo[b,d]thiophene-3-carboxylate**

The product was obtained as yellow crystals in hexane/CH$_2$Cl$_2$ (141.9 mg, 75%); mp 122–125 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 11.66 (s, 1H), 8.02 (d, $J = 8.0$ Hz, 1H), 7.84 (d, $J = 8.1$ Hz, 1H), 7.48 (s, 1H), 7.44–7.41 (m, 1H), 7.40–7.36 (m, 1H), 7.19–7.16 (m, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 3.99 (q, $J = 7.3$ Hz, 2H), 3.80 (s, 3H), 0.79 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 171.3, 158.7, 157.4, 141.7, 140.9, 139.6, 135.9, 135.2, 129.6, 127.8, 126.2, 124.6, 123.2, 122.6, 115.8, 113.0, 108.7, 61.2, 55.4, 13.2; HRMS calcd C$_{22}$H$_{18}$O$_4$S (M$^+$) 378.0926; found 378.0925.
4.10 REFERENCES


APPENDIX III

(Spectras of Selected Compounds)

Note: All the compounds mentioned here have been published in *Tetrahedron* 2012, 68, 9035. Therefore, only selected spectras have been added in Appendix-III to avoid wastage of paper.
Chapter 4  Silver-Catalyzed Synthesis of Acridines, Quinolines and Naphthalenes

Ethyl 1-hydroxy-3-(p-tolyl)acridine-2-carboxylate (75h)

($^1$H NMR & $^{13}$C NMR)
Chapter 4  Silver-Catalyzed Synthesis of Acridines, Quinolines and Naphthalenes

ethyl 3-((1,1’-biphenyl)-4-yl)-1-hydroxyacridine-2-carboxylate (75e)

(\(^1\)H NMR & \(^{13}\)C NMR)
Chapter 4  Silver-Catalyzed Synthesis of Acridines, Quinolines and Naphthalenes

![Chemical Structure]

ethyl 1-hydroxy-3-(4-(trifluoromethyl)phenyl)acridine-2-carboxylate (75f)

($^1$H NMR & $^{13}$C NMR)
Chapter 4  Silver-Catalyzed Synthesis of Acridines, Quinolines and Naphthalenes

ethyl 1-hydroxy-3-(thiophen-3-yl)acridine-2-carboxylate (75g)

($^1$H NMR & $^{13}$C NMR)
Chapter 4  Silver-Catalyzed Synthesis of Acridines, Quinolines and Naphthalenes

ethyl 3-cyclohexyl-1-hydroxyacridine-2-carboxylate (75h)

(\(^1\)H NMR & \(^{13}\)C NMR)
Chapter 4  Silver-Catalyzed Synthesis of Acridines, Quinolines and Naphthalenes

\[
\text{ethyl 3-butyl-1-hydroxyacridine-2-carboxylate (75j)}
\]

\[
(\text{\textsuperscript{1}H NMR \& \textsuperscript{13}C NMR})
\]
Chapter 4  Silver-Catalyzed Synthesis of Acridines, Quinolines and Naphthalenes

ethyl 1-hydroxy-3-(phenoxyethyl)acridine-2-carboxylate (75k)

(\textsuperscript{1}H NMR & \textsuperscript{13}C NMR)
Chapter 4  Silver-Catalyzed Synthesis of Acridines, Quinolines and Naphthalenes

(\textsuperscript{1}H NMR & \textsuperscript{13}C NMR)

\begin{center}
\includegraphics[width=0.8\textwidth]{image}
\end{center}
Chapter 4  Silver-Catalyzed Synthesis of Acridines, Quinolines and Naphthalenes

\[
\text{ethyl 1-hydroxy-3-(thiophen-3-yl)-2-naphthoate (75r)}
\]

\[(^1\text{H NMR & } ^{13}\text{C NMR})\]
Chapter 4  Silver-Catalyzed Synthesis of Acridines, Quinolines and Naphthalenes

\[ \text{ethyl 1-hydroxy-3-(m-toly)-2-naphthoate (75s)} \]

\[ (^{1}H \text{ NMR} & {^{13}}C \text{ NMR}) \]
Chapter 4  Silver-Catalyzed Synthesis of Acridines, Quinolines and Naphthalenes

(\(^1\)H NMR \& \(^{13}\)C NMR)