Cascade cyclization and photophysical properties of quinoline/ isoquinoline-based heteroacenes

（キノリン/イソキノリン骨格を有する

ヘテロアセンのカスケード環化と光物理的特性）

Amol D. Sonawane

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MATERIAL ENGINEERING DIVISION
GRADUATE SCHOOL OF ENGINEERING
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JAPAN

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February, 2020

Preface

The studies presented in this thesis have been carried out under the guidance of Professor Mamoru Koketsu at Department of Chemistry and Biomolecular Science, Materials Engineering Division, Graduate School of Engineering, Gifu University, Gifu, during 2017-2020.

The studies are concerned with cascade cyclization of alkynes, characterization and photophysical properties of quinoline- and isoquinoline based heteroacenes.

Feb. 2020

Amol D. Sonawane

Abstract

Nitrogen-containing heterocycles are gaining more importance as being the center of activity. Among the *N*-heterocycles, quinoline and isoquinoline subunits are prevalent in natural products and pharmaceutical molecules and are important intermediates for asymmetric synthesis. Further, the synthesis of their fused heterocycles has attracted considerable attention because of their interesting optical properties and biological activities.

This thesis consists of 5 chapters. The first chapter describes synthesis of thieno[2,3-*b*]quinoline and selenopheno[2,3-*b*]quinoline derivatives and their DFT mechanistic study. The second chapter describes synthesis of thieno[2,3-*c*]acridine and furo[2,3-*c*]acridine derivatives, their fluorescence properties and DFT mechanistic study. The third chapter is iron-promoted intramolecular cascade cyclization for the synthesis of selenophene-fused, quinoline-based heteroacenes. Chapter four involves the synthesis of isoquinoline-fused benzquinazolinone through Ag (I)-catalyst. Finally, the fifth chapter describes the *in-situ* air oxidation and photophysical studies of isoquinoline-based *N*-heteroacenes.

In chapter 1, the regioselective iodocyclization reaction of 3-alkynyl-2-(methylthio)quinolines and 3-alkynyl-2-(methylseleno)quinolines were carried out for the synthesis of thieno[2,3-*b*]quinoline and selenopheno[2,3-*b*]quinoline derivatives. Further, DFT calculations for synthesized sulfur and selenium compounds were carried out to study the effect of iodinating reagent and substituents on the reactivity of the iodocyclization. DFT results clearly explain the effect of substituents on alkyl group affects the ΔG^a value and determine the reactivity of molecules, and are consistent with experimental results. The presence of iodine on the thieno[2,3-*b*]quinoline product is an interesting feature of the iodocyclization which allowed us further structural elaboration, including Suzuki coupling, Sonogashira coupling, Heck reaction, dehydroiodination and alkyne annulation reaction to afford the corresponding diversified quinoline moieties.

In chapter 2, the novel synthesis of thieno[2,3-*c*]acridine and furo[2,3-*c*]acridine derivatives were carried out *via* intramolecular iodocyclization reaction. The thieno[2,3-*c*] acridine derivatives showed blue fluorescence (*F*max: 415-430 nm, *Φ*f: 0.04-0.09) in hexane. DFT and time-dependent (TD) DFT studies were carried out. DFT study resulted that these reactions have

only one transition state (TS) in ring closure process and the elimination of HI proceeds without energy barrier. The presence of iodine on the 5-iodothieno[2,3-*c*]acridine product allowed further structural elaboration, most notable by Suzuki coupling, the palladium catalysed triethylammonium formate reduction of the iodide, Heck reaction, and alkyne annulation reaction to afford the corresponding diversified acridine based *N*-heterocycles.

In chapter 3, the synthesis of linear 1,3-diyne and 1,3,5-triyne was successfully achieved. Further the cascade cyclization of linear 1,3-diyne and 1,3,5-triyne were carried out by using different internal nucleophiles including thiophene, furan, sulphur and selenium. The 1,3-diyne cascade cyclization were successfully achieved under Fe(III) (2.5 equiv.) and dibutyl diselenide (2.0 equiv.) conditions and the 1,3,5-triyne cascade cyclization were successfully achieved under Fe(III) (3.0 equiv.) and dibutyl diselenide (2.5 equiv.) conditions; the two core system formed acridine and quinoline. Herein, the diorganyl diselenide acts as dual role, one is cyclizing agent and secondly insertion of one and / or two selenium atom and one R′-Se group in the final product. Finally, the synthesized selenophene-fused derivatives showed λ_{max}, F_{max} and Φ_f values in the range from 370-411 nm, 427-472 nm and 0.003-0.059, respectively in DCM.

In chapter 4, we have developed a new route for the expedient synthesis of specific regioisomer of isoquinoline-fused quinazolinone heterocycles through silver (I)-catalyzed cascade cyclization of 2-amino benzamides and 2-alkynyl benzaldehydes which underwent *in-situ* oxidation has been developed.

In chapter 5, we have discussed an efficient, metal free and environment friendly synthesis of isoquinoline-fused benzimidazole *via in-situ* air oxidation. Also, syntheses of isoquinoline-fused quinazolinone heteroacenes were successfully achieved. The synthesized isoquinoline-fused benzimidazole and isoquinoline-fused quinazolinone derivatives showed λ_{max}, F_{max} and Φ_f values in the range from 356-394 nm, 403-444 nm and 0.063-0.471, respectively in chloroform solvent.

Table of Contents

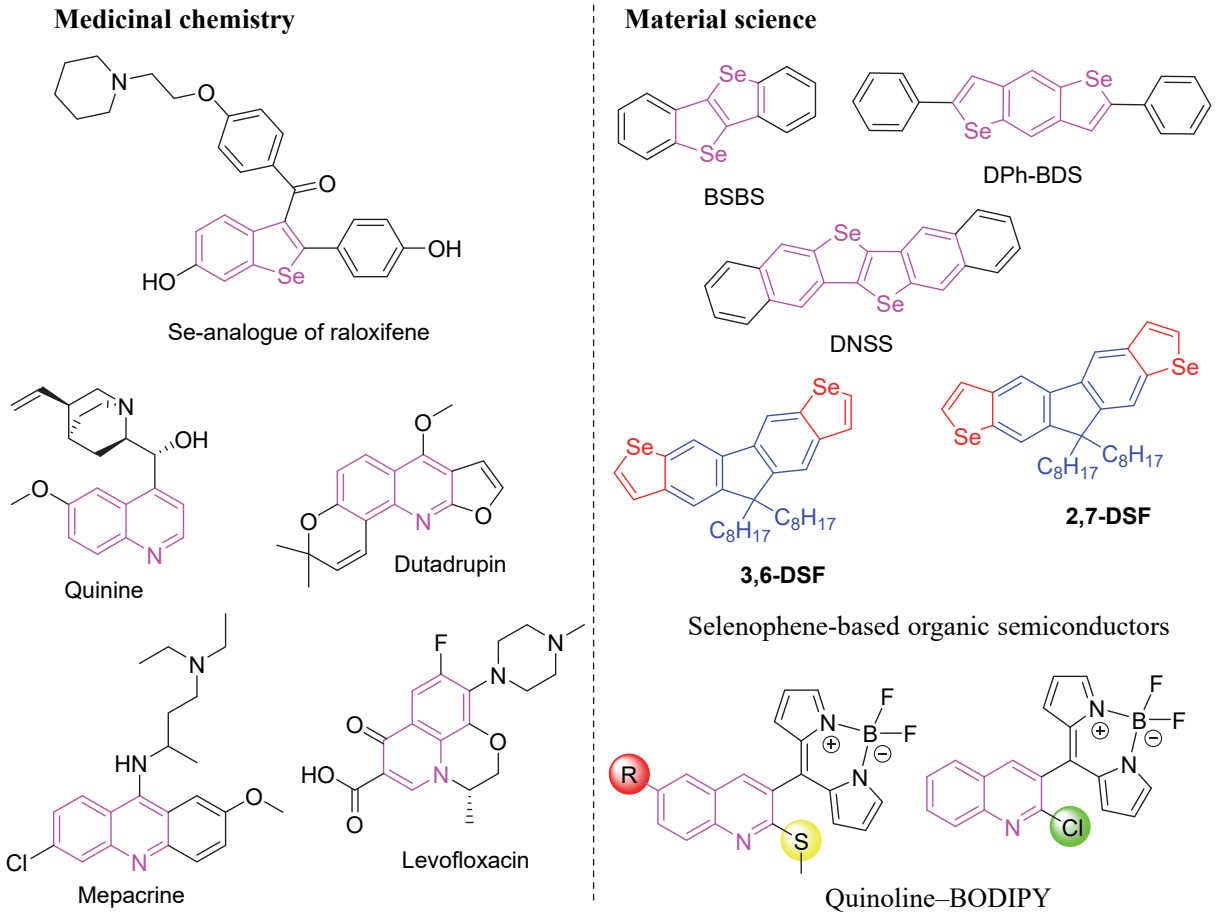
Abbreviations

Ac_2O	Acetic anhydride
AcOH	Acetic acid
aq.	Aqueous
CH_3CN	Acetonitrile
Ar	Aryl
br.	Broad
Bu	Butyl
COSY	Correlation spectroscopy
δ	Chemical shift (ppm)
$CHCl_3$	Chloroform
Δ	Heating
d	Doublet
DBU	1, 8-Diazabicyclo-1,4-benzoquinone
CH_2Cl_2	Dichloromethane
DIEA	Diisopropylethylamine
DEPT	Distortionless enhancement by polarization transfer
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
equiv.	Equivalent
Et	Ethyl
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOH	Ethanol
EtOAc	Ethyl acetate
h	Hour(s)
n-Hex	Normal hexane
HMBC	Heteronuclear multiple bond connectivity
HMQC	Heteronuclear multiple quantum coherence
HRMS	High resolution mass spectrometry

Hz	Hertz
J	Coupling constant (Hz)
IR	Infrared spectroscopy
m	Multiple
M	Molar
Me	Methyl
MeO	Methoxy
MeOH	Methanol
min	Minute(s)
mmol	Milli mol
MS	Mass spectrometry
m/z	Mass/charge
NMR	Nuclear magnetic resonance
NOESY	Nuclear overhauser enhancement spectroscopy
$Pd(PPh_3)_2Cl_2$	Bis(triphenylphosphine)palladium(II) dichloride
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
Ph	Phenyl
PPh_3	Triphenylphosphine
q	Quartet
r.t.	Room temperature
Na_2SO_4	Sodium sulfate
$NaHCO_3$	Sodium hydrogen carbonate
SiO_2	Silica gel
TEA	Triethylamine
THF	Tetrahydrofuran
TLC	Thin layer chromatography

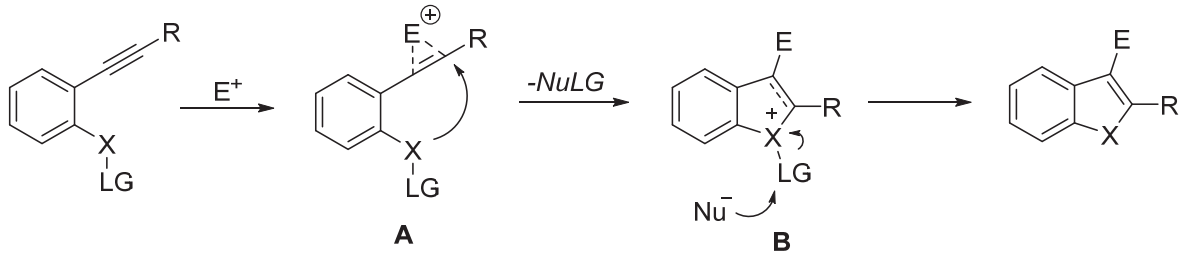
General Introduction

It is well known that the heterocyclic compounds play an important role in developing a new class of structural entities for pharmaceutical applications. Among heterocycles, the six- and five-membered *O*- and *N*-heterocycles are probably one of the most common structural motifs spread across natural products, from simple glucose to structurally complex metabolites present in the structure of several biologically interesting compounds. Among the *N*-heterocycles quinoline/isoquinoline and its derivatives are pharmacologically important because of their wide spectrum of biological activities [1]. It is observed that the quinoline ring substituted at all positions with different substituents has produced effective anti-TB and anticancer activities [2]. Recently, quinoline derivatives have attracted an enormous attention from chemists as well as biologists as it is an important key building component for many naturally occurring bioactive compounds; especially quinoline alkaloids which are found in many different plants including Rutaceae, Fumariaceae, Berberidaceae and Papavaraceae [3]. The quinoline derivatives belong to a significant class of bioactive molecules in the field of drugs and pharmaceuticals. They display significant activity against numerous viruses and bacteria including antimalarial [4], antibiotic [5], anticancer [6], anti-inflammatory, antihypertensive properties [7]. Quinoline nucleus occurs in several natural products (cinchona alkaloids). Some of the quinoline derivatives such as dutadrupine, mepacrine and levofloxacin are in clinical use. Apart from the biological studies; compounds containing the selenophene nucleus are also used as applications in the preparation of physical materials that show potentially useful optical and fluorescent properties. The interesting biological and optical properties of quinoline and selenophene-heterocycles encouraged synthetic chemists to develop novel synthetic strategies to access structurally different motifs **Fig. 1** [8].



In the point of biological studies, it is important to use the organoselenium compounds containing quinoline heterocycles, which exhibit different pharmacological properties, such as antioxidant action [9]. The study of a quinoline derivative containing selenium could be an alternative to search for new compounds with antioxidant properties for the treatment of diseases related to oxidative stress.

Electrophilic cyclizations which is defined as those processes that involve addition of the electrophilic source to C(sp) or C(sp^2) bonds of alkenes or alkynes and other carbon-carbon multiple bonds. The typical courses of this cyclization reaction involves (i) coordination of the electrophilic source to unsaturated carbon-carbon bond to generate intermediate **A**, which activates the carbon-carbon bond toward nucleophilic attack; (ii) nucleophilic anti attack of the heteroatom on the activated intermediate to produce the salt **B**; and (iii) facile removal of the group bonded to heteroatom, *via* SN^2 displacement by the Nu- present in the reaction mixture, generates the heterocycle product (Scheme 1) [10].



Scheme 1. Electrophilic cyclization

The metal-catalyzed activation of alkynes [11] has been an effective strategy for various bond forming and bond breaking processes. One of the aspects of this chemistry is annulation reactions *via* the intramolecular attack of appropriate nucleophiles onto alkynes [12]. With the turn of century, scope and utility of these reactions have seen further exploration with the introduction of dual electrophilic site skeletons using metal catalysis (Figure 1). These reactions are initiated *via* nucleometalation of alkynes and quenched by 1,2-addition to carbon-heteroatom multiple bonds for the synthesis of various carbocycles and heterocycles. In these intramolecular reactions, the nucleophiles first attack at the metal-activated carbon-carbon triple bond followed by the addition to carbon-heteroatom multiple bonds to form various cyclized products (Figure 1, *path a*) [13]. In this type of annulation, the course of reaction follows as same trend where alkynes acting as the primary electrophile and other electrophile set as the secondary electrophile partner. However, an alternate path includes the carbon-carbon triple bonds of ortho functionalized acetylenic aldehydes/nitriles can be activated by transition metals which undergo facile intramolecular attack by the first electrophilic partner (i.e. aldehyde oxygen or nitrile nitrogen) triggered by a nucleophile (oxygen, nitrogen, sulphur etc) (Figure 1, *path b*) [14].

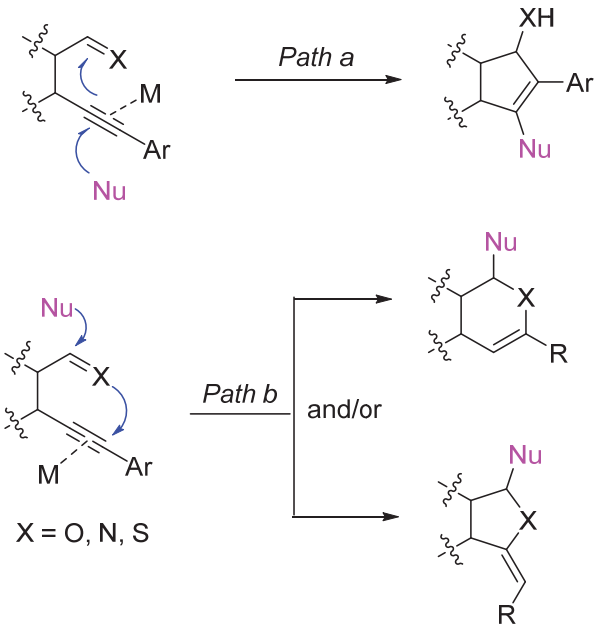


Figure 1. Modes of annulations of ortho-functionalized alkynes

Among a variety of synthetic methodologies, transition-metal-catalyzed cyclization reactions of simple acyclic precursors are one of the most attractive ways to directly construct complex heterocycles under mild conditions. The synthesis of quinoline fused seven- eight and nine-membered heterocycles are more rarely found in nature and hardly isolated by synthetic approaches, hence synthesis of such heterocycles are also gaining more importance [15].

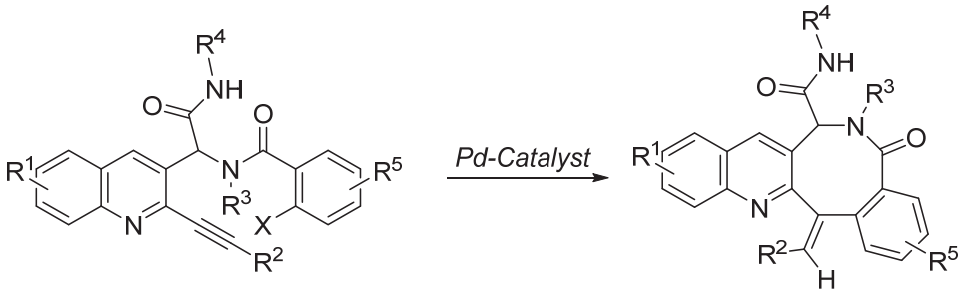


Figure 2. Azocinoquinoline scaffolds

In this thesis, we have carried out synthesis of quinoline fused five-, and six-membered heterocycles. The cyclization was carried out *via* various internal nucleophiles including amine, selenium, sulfur, 3-thiphene, and 3-furan. The substituted alkynes were activated by $AgNO_3$, Iodine and Fe (III) catalysts. The outline of research is shown in Fig. 3.

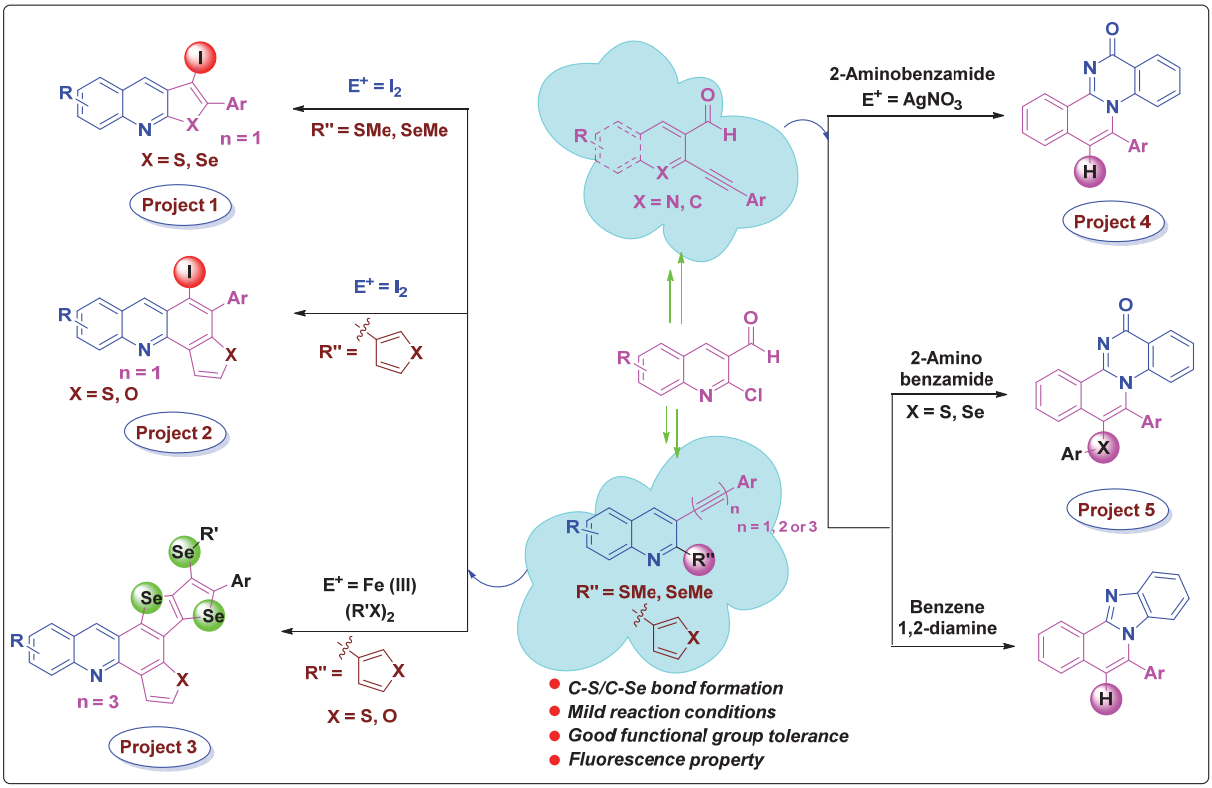


Fig. 3. Outline of research

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Chapter 1

Synthesis of thieno[2,3-*b*]quinoline and selenopheno[2,3-*b*]quinoline derivatives *via* iodocyclization reaction and DFT mechanistic study

1.1 Introduction

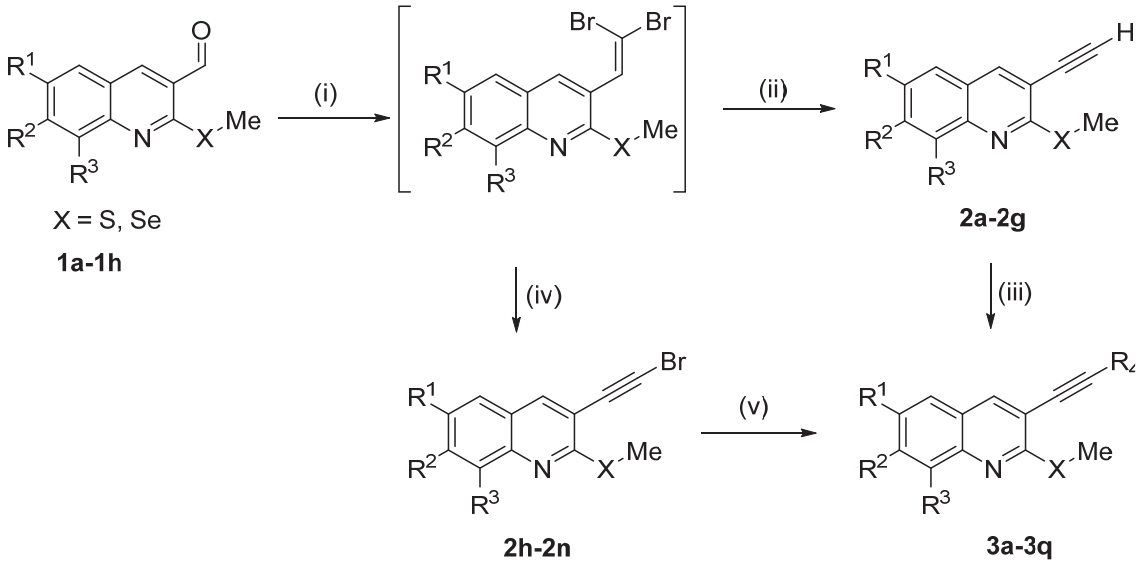
Nitrogen-containing heterocycles are gaining more importance as being the centre of activity [1]. Among the *N*–heterocycles, quinoline subunits are prevalent in natural products [2] and pharmaceutical molecules [3] and are important intermediates for asymmetric synthesis [4]. Further, the synthesis of quinoline fused heterocycles has attracted considerable attention because of their interesting properties and biological activities [5]. In this regard, little is known about annulated furoquinoline and thienoquinoline heterocycles with different features and applications in the literature [6]. The iodocyclization of acetylenic substrates bearing a suitably placed nucleophilic group has become a powerful synthetic tool for the synthesis of structurally diverse heterocycles [7]. In our continuing efforts toward the synthesis of heterocycles, we used this iodocyclization methodology for the synthesis of 4-alkyl-2-imino-1,3-oxaselenolanes [8], 3-aryl-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazoles or 2-aryl-5*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazines [9] and for the construction of bicyclic β-lactams starting from allyl–thioureas [10], alkyne–thioureas [11], alkyne–selenoureas [12] and allene–thioureas [13]. These results prompted us to investigate the applicability of iodocyclization reaction for the synthesis of thieno[2,3–*b*]quinoline and selenopheno[2,3–*b*]quinoline heterocycles. Moreover, the quinoline fused S/Se-heterocycles synthesized *via* electrophilic iodocyclization will be useful for the development of polycyclic aromatic hydrocarbons/acenes [14]. Herein, we describe for the first time, the synthesis of thieno[2,3–*b*]quinoline and selenopheno[2,3–*b*]quinoline derivatives *via* iodine-mediated electrophilic cyclization of 3-alkynyl-2-(methylthio)quinolines and 3-alkynyl-2-(methylseleno)quinolines respectively and their density functional theory (DFT) mechanistic study.

1.2 Results and discussion

Our investigations in this direction were began with 2-(methylthio)- and 2-(methylseleno)-quinoline-3-carbaldehydes **1a-1h** which were readily prepared from corresponding 2-

chloroquinoline-3-carbaldehydes using a literature procedure [15]. In recent years, the preparation of alkynes from carbonyl compounds *via* a one-carbon homologation by Corey-Fuchs reaction [16] has become a very useful pathway for the synthesis of acetylenes [17]. The quinoline-3-carbaldehydes **1a-1h** were converted to the corresponding dibromo olefin which on treatment with *n*-butyl lithium readily yielded the terminal alkynes **2a-2g** in good yields (Table 1, entries 1-7). However, the dibromo intermediate on treatment with DBU in DMSO at room temperature via dehydrohalogenation afforded the bromoalkyne compounds **2h–2n** in 75-86% yields (Table 1, entries 8-13). Next, under Sonogashira coupling conditions, the terminal alkynes **2a–2g** were alkylated to with aryl halides to give substituted alkynes **3a–3j** in good yields (Table 1, entries 14-23). Further, to study the effect of substitution at the alkyne part, the bromoalkyne derivatives **2h–2n** were converted to the corresponding dialkynes **3k–3q** under Sonogashira coupling reaction conditions (Table 1, entries 24-30) [18].

Table 1. Synthesis of 3-alkynyl-2-(methylthio/Seleno)quinolines



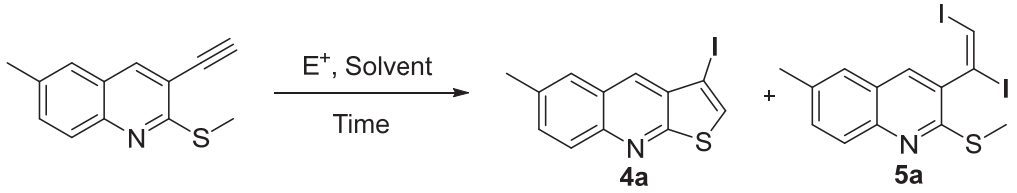
Entry	X	R^1	R^2	R^3	R^4	2 or 3 yield (%)[a, b]
1	S	$-CH_3$	-H	-H	-H	**2a** (67%)
2	S	-H	$-CH_3$	-H	-H	**2b** (69%)
3	S	-H	-H	$-CH_3$	-H	**2c** (72%)
4	S	-H	-H	-H	-H	**2d** (75%)
5	Se	$-CH_3$	-H	-H	-H	**2e** (65%)
6	Se	-H	$-CH_3$	-H	-H	**2f** (66%)

7	Se	-H	-H	-H	-H	**2g** (71%)
8	S	$-CH_3$	-H	-H	-Br	**2h** (77%)
9	S	-H	$-CH_3$	-H	-Br	**2i** (86%)
10	S	-H	-H	-H	-Br	**2j** (84%)
11	Se	$-CH_3$	-H	-H	-Br	**2k** (81%)
12	Se	-H	$-CH_3$	-H	-Br	**2l** (77%)
13	Se	-H	-H	$-CH_3$	-Br	**2m** (71%)
14	Se	-H	-H	-H	-Br	**2n** (75%)
15	S	$-CH_3$	-H	-H	$-C_6H_5$	**3a** (76%)
16	S	-H	$-CH_3$	-H	$-C_6H_5$	**3b** (79%)
17	S	-H	-H	-H	$-C_6H_5$	**3c** (87%)
18	S	$-CH_3$	-H	-H	$-m-CH_3C_6H_4$	**3d** (80%)
19	S	-H	$-CH_3$	-H	$-m-CH_3C_6H_4$	**3e** (75%)
20	S	-H	-H	-H	$-m-CH_3C_6H_4$	**3f** (72%)
21	S	$-CH_3$	-H	-H	$-p-CH_3OC_6H_4$	**3g** (70%)
22	Se	$-CH_3$	-H	-H	$-C_6H_5$	**3h** (70%)
23	Se	-H	$-CH_3$	-H	$-C_6H_5$	**3i** (72%)
24	Se	-H	-H	-H	$-C_6H_5$	**3j** (67%)
25	S	$-CH_3$	-H	-H	$-CCC_6H_5$	**3k** (65%)
26	S	-H	$-CH_3$	-H	$-CCC_6H_5$	**3l** (71%)
27	S	-H	-H	-H	$-CCC_6H_5$	**3m** (67%)
28	Se	$-CH_3$	-H	-H	$-CCC_6H_5$	**3n** (70%)
29	Se	-H	$-CH_3$	-H	$-CCC_6H_5$	**3o** (73%)
30	Se	-H	-H	$-CH_3$	$-CCC_6H_5$	**3p** (76%)
31	Se	-H	-H	-H	$-CCC_6H_5$	**3q** (70%)

[a]Reaction conditions: (i) CBr_4, PPh_3, DCM, 0°C, 1 h (ii) n-BuLi, -78°C, Et_2O, 1 h (iii) aryl iodide, $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, THF, rt, 12 h; or Phenylboronic acid, 2M Na_2CO_3, $Pd(PPh_3)_2Cl_2$, DME, 90°C (iv) DBU, DMSO, 1 h (v) Phenyl acetylene, CuI, $Pd(PPh_3)_2Cl_2$, NEt_3, PPh_3, 70°C, 5 h. [b]Isolated yields.

We first examined the iodocyclization reaction of unsubstituted alkyne **2a** with 2 equiv of iodine in DCM at room temperature. The reaction resulted in the formation of thieno[2,3-*b*]quinoline derivative **4a** in 25% yield along with the diiodo compound **5a** in 23% yield. Further, the use of K_2CO_3 as a base with 2 equiv of iodine in the iodocyclization reaction provided the desired thieno[2,3-*b*]quinoline **4a** in 32% yield along with traces of diiodo compound **5a**. To improve the yield of cyclization product, different reaction conditions were screened (Table 2). Best result was obtained, when the iodocyclization reaction was carried out using 2 equiv. of NIS in CH_2Cl_2 at room temperature to afford desired thieno[2,3-*b*]quinoline **4a** in 69% yield with traces of diiodo compound **5a** (Table 2, Entry 3). Under optimal conditions, the iodocyclization reaction of other unsubstituted alkyne **2b-2d** and bromoalkyne **2h-2j** was carried out and the corresponding thieno[2,3-*b*]quinoline derivatives **4b-4g** were obtained in good yields (entries 2-7).

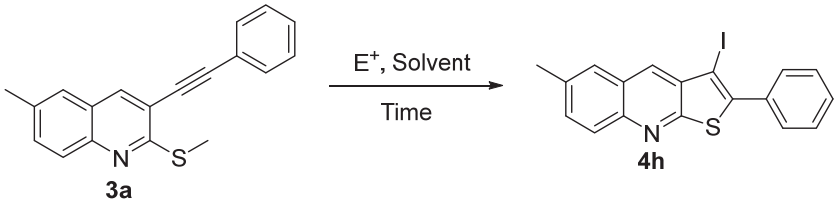
Table 2. Standardization table for synthesis of 3-iodo-6-methylthieno[2,3-*b*]quinoline



Sr. No.	Solvent	E^+ (2 eq.)	Base	Time	Temp.	Yield (%)	
						4a	5a
1	DCM	I_2	-	6	rt	25	23
2	DCM	I_2	K_2CO_3	6	rt	32	traces
3	DCM	NIS	-	6	rt	69	traces
4	Toluene	NIS		6	90	54	-
5	ACN	NIS	-	12	90	56	-
6	DCM	ICl	-	6	12	-	21
7	Toluene	NIS	K_2CO_3	6	90	39	-

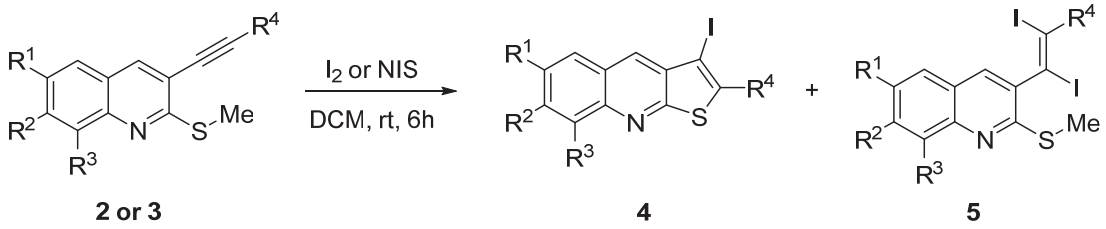
The iodocyclization reaction of substituted alkyne **3a** under similar reaction conditions afforded desire product **4h** in 83% yield (Table 3, Entry 4). However, when the iodocyclization reaction of **3a** was carried out using 2 equiv. of iodine in CH_2Cl_2 at room temperature, the thieno[2,3-*b*]quinoline **4h** was obtained in 90% yield (Table 3, entry 3). To further expand the application scope of this reaction, the iodocyclization reaction of other substituted alkynes **3b-3g** and **3k-3m** was carried out using 2 equiv. of iodine in CH_2Cl_2 at room temperature and the corresponding thieno[2,3-*b*]quinoline derivatives **4i-4q** were obtained in good to excellent yields (Table 4, entries 9-17). The structure of thieno[2,3-*b*]quinoline derivatives **4** was confirmed by the studies of IR, ^{1}H-NMR, ^{13}C-NMR, and HRMS spectral analysis. Finally, the molecular structure of the representative thieno[2,3-*b*]quinoline compound **4a** was confirmed by the X-ray crystallography [19].

Table 3. Standardization table for 3-iodo-6-methyl-2-phenylthieno[2,3-*b*]quinoline



Sr. No.	Solvent	E^+	Time	4h Yield (%)
1	DCM	I_2 (1 eq.)	12	79
2	DCM	I_2 (1.5 eq.)	8	87
3	DCM	I_2 (2 eq.)	6	90
4	DCM	NIS (2 eq.)	6	83
5	THF	I_2 (2 eq.)	14	61
6	$CHCl_3$	I_2 (2 eq.)	8	79
7	DMSO	I_2 (2 eq.)	6	58
8	MeOH	I_2 (2 eq.)	12	72
9	ACN	I_2 (2 eq.)	8	76
10	Toluene	I_2 (2 eq.)	12	79

Table 4. Synthesis of thieno[2,3-*b*]quinoline derivatives

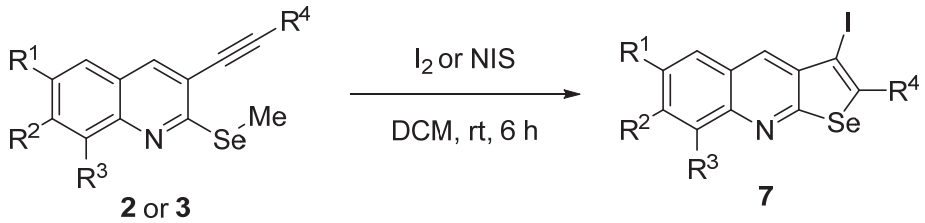


Entry	R^1	R^2	R^3	R^4	4 yield (%)[b]	ΔG^{ad}
1	$-CH_3$	-H	-H	-H	**4a** (69%)[c]	21.2
2	-H	$-CH_3$	-H	-H	**4b** (70%)[c]	21.5
3	-H	-H	$-CH_3$	-H	**4c** (72%)[c]	21.4
4	-H	-H	-H	-H	**4d** (61%)[c]	21.5
5	$-CH_3$	-H	-H	-Br	**4e** (81%)[c]	17.7
6	-H	$-CH_3$	-H	-Br	**4f** (85%)[c]	17.9
7	-H	-H	-H	-Br	**4g** (84%)[c]	18.0

8	-CH_3	-H	-H	-C_6H_5	**4h** (90%)	7.7
9	-H	-CH_3	-H	-C_6H_5	**4i** (79%)	7.7
10	-H	-H	-H	-C_6H_5	**4j** (86%)	8.8
11	-CH_3	-H	-H	-*m*-$CH_3C_6H_4$	**4k** (83%)	5.9
12	-H	-CH_3	-H	-*m*-$CH_3C_6H_4$	**4l** (80%)	6.9
13	-H	-H	-H	-*m*-$CH_3C_6H_4$	**4m** (86%)	7.2
14	-CH_3	-H	-H	-*p*-$CH_3OC_6H_4$	**4n** (77%)	5.0
15	-CH_3	-H	-H	-CCC_6H_5	**4o** (81%)	9.5
16	-H	-CH_3	-H	-CCC_6H_5	**4p** (84%)	9.0
17	-H	-H	-H	-CCC_6H_5	**4q** (91%)	9.5

[a]All iodocyclization reactions were conducted at room temperature with 2.0 equiv of I_2 in CH_2Cl_2 unless and otherwise stated. [b]Isolated yields. [c]Reaction was carried out using 2 equiv of NIS in CH_2Cl_2 at room temperature. [d]Calculated by M06-2X/6-311+G**+Midi!//M06-2X/6-31G*+Midi! method. Thermal correction was calculated at T = 298 K and solvent effect (CH_2Cl_2) was taken into account by SCRF-PCM method.

Table 5. Synthesis of selenopheno[2,3-*b*]quinoline derivatives

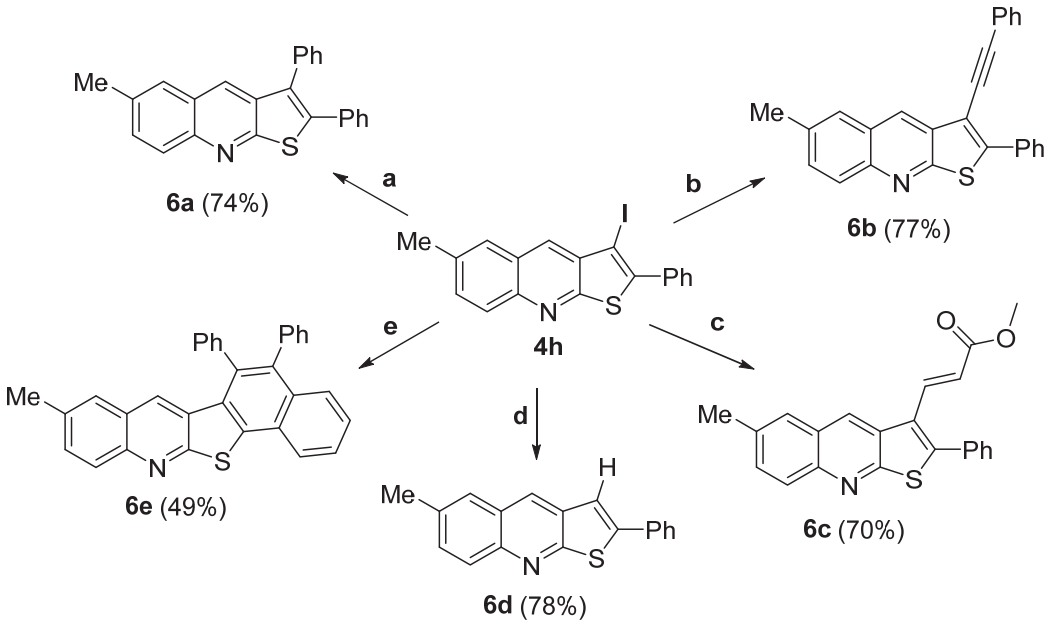


Entry	R^1	R^2	R^3	R^4	7 yield (%)[b]	ΔG^{ad}
1	-CH_3	-H	-H	-H	**7a** (64%)[c]	20.0
2	-H	-CH_3	-H	-H	**7b** (54%)[c]	20.1
3	-H	-H	-H	-H	**7c** (60%)[c]	20.1
4	-CH_3	-H	-H	-Br	**7d** (75%)[c]	16.5
5	-H	-CH_3	-H	-Br	**7e** (61%)[c]	16.6
6	-H	-H	-H	-Br	**7f** (71%)[c]	17.0
7	-CH_3	-H	-H	-C_6H_5	**7g** (79%)	4.5
8	-H	-CH_3	-H	-C_6H_5	**7h** (86%)	4.2
9	-H	-H	-H	-C_6H_5	**7i** (85%)	4.7
10	-CH_3	-H	-H	-CCC_6H_5	**7j** (79%)	8.5
11	-H	-CH_3	-H	-CCC_6H_5	**7k** (80%)	8.2
12	-H	-H	-CH_3	-CCC_6H_5	**7l** (87%)	8.4
13	-H	-H	-H	-CCC_6H_5	**7m** (85%)	8.4

[a]All iodocyclization reactions were conducted at room temperature with 2.0 equiv of I_2 in CH_2Cl_2 unless and otherwise stated. [b]Isolated yields. [c]Reaction was carried out using 2 equiv of NIS in CH_2Cl_2 at room

temperature. [d]Calculated by M06-2X/6-311+G**+Midi!//M06-2X/6-31G*+Midi! method. Thermal correction was calculated at T = 298 K and solvent effect (CH_2Cl_2) was taken into account by SCRF-PCM method.

1.2.1 Scheme 1 Functionalization of the 3-iodo-6-methyl-2-phenylthieno[2,3-*b*]quinoline



Reaction conditions: (a) Phenylboronic acid, $Pd(OAc)_2$, Cs_2CO_3, DMF, 110°C. (b) Phenyl acetylene, $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, THF, room temperature. (c) Methyl acrylate, PPh_3, $Pd(OAc)_2$, K_2CO_3 DMF, 110°C. (d) $Pd(PPh_3)_2Cl_2$, NEt_3, HCOOH, DMF, 60°C. (e) Diphenylacetylene, $Pd(OAc)_2$, NaOAc, LiCl, DMF, 100°C.

1.3 DFT Study

To investigate the reaction mechanism of iodocyclization of **2** or **3**, we performed DFT calculations. The relative Gibbs free energy profiles and the stationary point structures of the reactions leading to **4a-4d** (R^4 = -H) are presented in Figure 1, and those for the other reactions are in Figures S2–S6 in Supporting Information. All reactions proceed by a stepwise mechanism and have two transition states (TSs) corresponding to iodine addition (TS1) and elimination of CH_3I or *N*-methylsuccinimide (TS2). The rate-determining step is iodine addition process (TS1) in all reactions, since the relative Gibbs free energy of TS1 is always higher than that of TS2. We can see that energy profiles for reactions **2a-2d** are similar to each other. For instance, relative energies of TS1 in reactions **2a-2d** are 21.2, 21.5, 21.4, and 21.5 kcal/mol, respectively. The shapes of the potential energy profiles of iodocyclization reactions depend only on R^4 on alkynyl

group, and are hardly affected by R^1-R^3 groups on quinoline ring system. Figure 2 shows the optimized TS structures with the characteristic interatomic distances (C···I, I···N, and C···S distances in TS1, and S···C and C···N ones in TS2) in reactions **2a-2d**. Clearly, R^1-R^3 groups on quinoline ring hardly affect the TS structures, as well as the potential energy profiles.

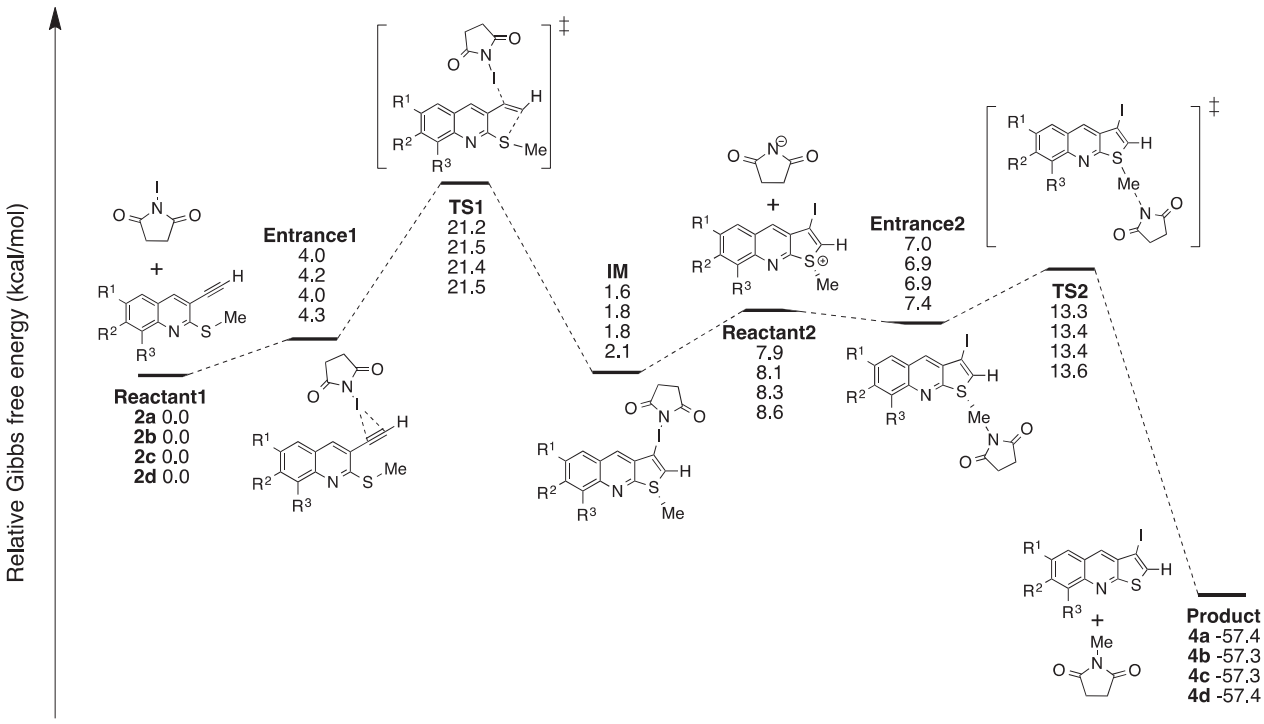


Figure 1. Relative Gibbs free energy profiles at T = 298K of the reactions leading to **4a-4d** obtained by M06-2X/6-311+G**+Midi!//M06-2X/6-31G*+Midi! calculations. Solvent effect (solvent = CH_2Cl_2) was taken into account by SCRF-PCM method.

Next, to explain the reactivity of **2** or **3** for iodocyclization, we focus on the charge of the carbon atom in alkynyl group, which forms a new C–S bond in the reaction. Figure 3 shows the relationship between natural charge of the carbon atom and the activation Gibbs free energy (ΔG^a), which correspond to the highest relative Gibbs free energy in each reaction. Since the relative Gibbs free energy of TS1 (iodine addition process) is always higher than that of TS2, as stated above, ΔG^a values correspond to the relative Gibbs free energies of TS1. A clear linear relationship (Coefficient of determination = 0.935) between these values can be found. Iodocyclization reaction proceeds more easily with the less electron-rich carbon atom. In addition, the charge of the carbon atom in

alkynyl group clearly depends on R^4 group. Therefore, our DFT results indicated that R^4 group was important to determine the reactivity for iodocyclization, which fact was consistent with experimental results.

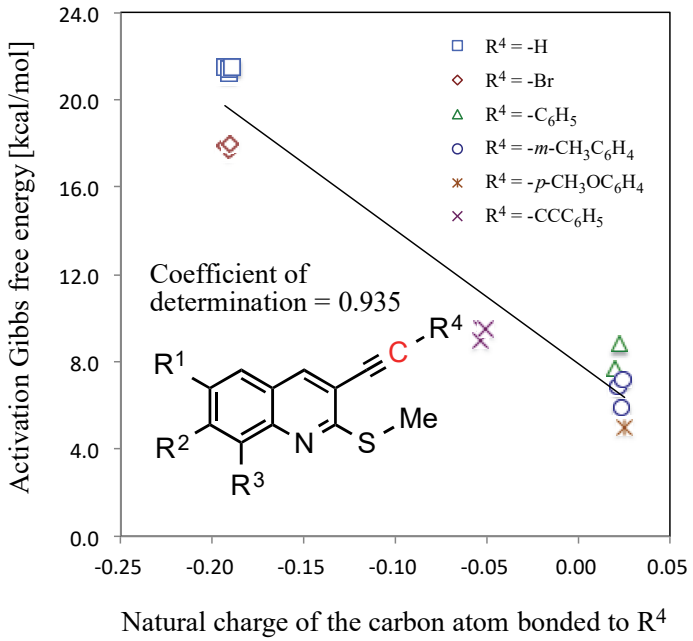


Figure 2. Relationship between natural charge of the carbon atom bonded to R^4 group (red-marked) and ΔG^a values of sulfur-containing systems.

Further, the presence of iodine on the thieno[2,3-*b*]quinoline product **4h** is an interesting feature of the iodocyclization which allowed us further structural elaboration, most notable by Suzuki coupling [20], Sonogashira coupling [21], Heck reaction [22], dehydroiodination [23] and alkyne annulation reaction [24] to afford the corresponding diversified quinoline moieties **6a–6e** (Scheme 1).

1.4 Summary and conclusions

In summary, we have developed a new, simple and general synthetic route for the construction of thieno[2,3–*b*]quinoline and selenopheno[2,3-*b*]quinoline derivatives *via* iodocyclization reaction. The structures of the products were confirmed by IR, NMR and HRMS, as well as X-ray diffraction experiments. DFT calculations were also carried out to study the effect of iodinating reagent and substituents on the reactivity of the iodocyclization. Finally, the structural elaboration was done by Suzuki coupling, Sonogashira coupling, Heck reaction,

dehydroiodination and alkyne annulation reaction. Further expansion of current strategies and evaluation of biological activity is in progress.

1.5 Experimental section

1.5.1 General Methods: All solvents and reagents were purchased from the suppliers and used without further purification. IR spectra were recorded on a JASCO FT/IR-460 Plus spectrophotometer. Reactions were monitored by TLC on silica plates using UV-light or Iodine chamber for visualization. Evaporation and condensation were carried out in vacuo. NMR spectra were recorded with JEOL JNM-ECS 400 spectrometers with tetramethylsilane as an internal standard. Chemical shifts δ and coupling constants *J* are given in ppm (parts per million) and Hz (hertz) respectively. The following abbreviations were used as follows: s: singlet, d: doublet, t: triplet, m: multiplet. All known compounds data are in consistent with the given literature reports. Scale up reactions also performed as per the given general procedure without any deviation. Melting points were measured by a Yanaco micromelting point apparatus.

1.5.2 General procedure and spectral data

General procedure for synthesis of compounds 4a-4g, 5a, 5b, 5d and 7a-7f:

To a stirred solution of 3-ethynyl-6-methyl-2-(methylthio)quinoline **2a** (30 mg, 0.140 mmol, 1 equiv.), NIS (63 mg, 0.281 mmol, 2 equiv.) in dry DCM (5 mL) was stirred for 6 h, After completion of reaction (monitored by TLC), reaction mixture was quenched by saturated sodium thiosulfate and extracted with DCM (15 mL). Solvent was evaporated under reduced pressure to afford a crude residue. The crude was purified by silica gel chromatography using hexane/ethyl acetate (98:2) as eluent to afford **4a** 32 mg as white solid, Yield: 69%; Melting point: 176-178°C; IR (neat): 3086, 1595, 1548, 1488, 1330, 1136, 1055, 912, 790, 773, 699, 628, 562, 504 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.06 (d, *J* = 9.0 Hz, 1H), 7.78 (s, 1H), 7.75 (s, 1H), 7.62 (d, *J* = 9.0 Hz, 1H), 2.58 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.59, 146.03, 135.95, 132.74, 131.77, 131.16, 127.84, 127.07, 126.08, 75.15, 21.76; HRMS (ESI): m/z = 325.9500 calcd. For $C_{12}H_9NSI$, found 325.9511 $[M+H]^+$.

(*E*)-3-(1,2-diiodovinyl)-6-methyl-2-(methylthio)quinoline (5a)

Yield: 23%; Sticky; IR (KBr): 2923, 2367, 2341, 1554, 1490, 1334, 1155, 1052, 824 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 9.4 Hz, 1H), 7.69 (s, 1H), 7.52 (d, *J* = 6.7 Hz, 2H), 7.49 (s, 1H), 2.70 (s, 3H), 2.51 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.29, 146.40, 136.07,

135.60, 134.13, 132.71, 127.75, 126.95, 125.32, 91.41, 87.37, 21.54, 13.40; HRMS (ESI): m/z = 467.8780 calcd. For $C_{13}H_{12}NSI_2$, found 467.8780 $[M+H]^+$.

3-Iodo-7-methylthieno[2,3-*b*]quinoline (4b)

Yield: 70%; Melting point: 130-133°C; IR (neat): 2931, 1931, 1732, 1619, 1604, 1573, 1385, 1360, 1259, 1091, 1049, 1040, 809, 797, 779, 766, 697, 574 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.92 (d, *J* = 8.5 Hz, 2H), 7.73 (s, 1H), 7.43 (d, *J* = 9.9 Hz, 1H), 2.62 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.52, 147.56, 140.74, 132.23, 132.12, 130.63, 128.62, 128.15, 127.00, 124.19, 75.14, 22.24; HRMS (ESI): m/z = 325.9500 calcd. For $C_{12}H_9NSI$, found 325.9496 $[M+H]^+$.

(*E*)-3-(1,2-diiodovinyl)-7-methyl-2-(methylthio)quinoline (5b)

Yield: 21%; Melting point: 99-102°C; IR (neat): 3076, 2915, 1904, 1730, 1693, 1605, 1625, 1395, 1327, 1311, 1258, 1088, 1057, 1010, 816, 795, 780, 688 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.72 (s, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.49 (s, 1H), 7.30 (s, 1H), 2.70 (s, 3H), 2.54 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.31, 147.97, 141.10, 135.31, 134.40, 127.94, 127.67, 127.28, 123.30, 91.51, 87.41, 22.05, 13.40; HRMS (ESI): m/z = 467.8780 calcd. For $C_{13}H_{12}NSI_2$, found 467.8759 $[M+H]^+$.

3-Iodo-8-methylthieno[2,3-*b*]quinoline (4c)

Yield: 72%; Melting point: 179-182°C; IR (neat): 2917, 2551, 1971, 1944, 1684, 1614, 1592, 1562, 1544, 1330, 1165, 1093, 889, 762, 558, 488 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.77 (s, 1H), 7.63 (d, *J* = 6.7 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 2.88 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.56, 146.60, 136.25, 132.64, 132.36, 131.31, 130.00, 126.53, 125.97, 125.83, 74.96, 18.53; HRMS (ESI): m/z = 325.9500 calcd. For $C_{12}H_9INS$, found 325.9529 $[M+H]^+$.

3-Iodothieno[2,3-*b*]quinoline (4d)

Yield: 61%; Melting point: 152-154°C; IR (neat): 3084, 1798, 1586, 1542, 1388, 1325, 1051, 948, 901, 769, 742, 701, 594, 503 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 8.04 (d, *J* = 7.6 Hz, 1H), 7.79 (m, 2H), 7.61 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.52, 147.23, 132.74, 132.55, 131.41, 130.18, 128.57, 128.25, 126.09, 125.99, 75.10; HRMS (ESI): m/z = 311.9344 calcd. For $C_{11}H_7NSI$, found 311.9362 $[M+H]^+$.

(*E*)-3-(1,2-diiodovinyl)-2-(methylthio)quinoline (5d)

Yield: 20%; Melting point: 135-138°C; IR (neat): 2922, 1732, 1603, 1549, 1309, 1380, 1139, 1043, 952, 963, 813, 778, 747, 596, 477 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.1 Hz, 1H), 7.74-7.77 (m, 2H), 7.69 (m, 1H), 7.51 (s, 1H), 7.46 (t, *J* = 6.7 Hz, 1H), 2.71 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.50, 147.77, 136.16, 134.62, 130.53, 128.06, 128.02, 125.76, 125.34, 91.12, 87.51, 13.43; HRMS (ESI): m/z = 453.8624 calcd. For $C_{12}H_{10}NSI_2$, found 453.8594 $[M+H]^+$.

2-Bromo-3-iodo-6-methylthieno[2,3-*b*]quinoline (4e)

Yield: 81%; Melting point: 134-136°C; IR (neat): 2920, 1584, 1551, 1389, 1323, 1136, 1066, 951, 905, 813, 565, 519, 749 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.76 (s, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 2.58 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.00, 146.01, 136.38, 133.89, 132.85, 131.97, 127.84, 127.04, 126.62, 122.04, 83.97, 21.76; HRMS (ESI): m/z = 403.8606 calcd. For $C_{12}H_8NSBrI$, found 403.8595 $[M+H]^+$.

2-Bromo-3-iodo-7-methylthieno[2,3-*b*]quinoline (4f)

Yield: 85%; Melting point: 201-203°C; IR (neat): 1996, 2011, 1705, 1627, 1588, 1549, 1478, 1331, 1308, 1145, 1082, 895, 870, 797, 614, 586, 537, 466 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 1H), 2.60 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.91, 147.53, 140.96, 133.28, 132.40, 128.94, 128.08, 127.03, 124.69, 121.43, 83.94, 22.26; HRMS (ESI): m/z = 403.8606 calcd. For $C_{12}H_8NSBrI$, found 403.8590 $[M+H]^+$.

2-Bromo-3-iodothieno[2,3-*b*]quinoline (4g)

Yield: 84%; Melting point: 178-180°C; IR (neat): 2357, 1919, 1801, 1614, 1587, 1547, 1479, 1391, 1321, 1228, 1133, 945, 927, 900, 834, 779, 742, 719, 546, 510 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.07 (dd, *J* = 44.2, 7.9 Hz, 2H), 7.79 (s, 1H), 7.59 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.94, 147.22, 133.91, 132.68, 130.32, 128.49, 128.24, 126.51, 126.45, 122.36, 83.93; HRMS (ESI): m/z = 389.8449 calcd. For $C_{11}H_6NSBrI$, found 389.8420 $[M+H]^+$.

3-Iodo-6-methylselenopheno[2,3-*b*]quinoline (7a)

Yield: 64%; Melting point: 181-183°C; IR (neat): 3083, 2162, 1778, 1731, 1586, 1527, 1549, 1329, 1263, 1035, 911, 815, 766, 757, 716, 621, 517, 479 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.28 (s, 1H), 8.03 (d, *J* = 9.0 Hz, 1H), 7.77 (s, 1H), 7.62 (d, *J* = 9.0 Hz, 1H), 2.58 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.42, 145.71, 136.09, 135.05, 133.87, 132.78, 132.32, 127.66, 127.21, 126.12, 76.79, 21.76; ^{77}Se-NMR (400 MHz, $CDCl_3$) δ 582.01; HRMS (ESI): m/z = 373.8945 calcd. For $C_{12}H_9NSeI$, found 373.8925 $[M+H]^+$.

3-Iodo-7-methylselenopheno[2,3-*b*]quinoline (7b)

Yield: 54%; Sticky; IR (KBr): 2362, 2347, 1616, 1585, 1555, 1486, 1317, 1132, 753, 669 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.27 (s, 1H), 7.92-7.94 (m, 2H), 7.45 (d, *J* = 8.5 Hz, 1H), 2.62 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 141.04, 134.54, 134.39, 131.86, 128.75, 128.24, 127.23, 126.73, 126.70, 124.22, 77.65, 22.24; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 631.83; HRMS (ESI): m/z = 373.8945 calcd. For $C_{12}H_9NSeI$, found 373.8959 $[M+H]^+$.

3-Iodoselenopheno[2,3-*b*]quinoline (7c)

Yield: 60%; Sticky; IR (KBr): 2927, 2854, 2378, 2158, 1676, 1616, 1486, 1137, 1048, 956, 914, 860, 752, 668, 583 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.32 (s, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.79-7.83 (m, 1H), 7.61 (t, *J* = 7.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.49, 146.92, 135.13, 134.57, 132.58, 130.29, 128.65, 128.05, 126.23, 126.06, 76.77; ^{77}Se-NMR (400 MHz, $CDCl_3$) δ 584.41; HRMS (ESI): m/z = 359.8788 calcd. For $C_{11}H_7NSeI$, found 359.8797 $[M+H]^+$.

2-Bromo-3-iodo-6-methylselenopheno[2,3-*b*]quinoline (7d)

Yield: 75%; Melting point: 187-188°C; IR (neat): 2917, 1682, 1584, 1567, 1548, 1488, 1392, 1329, 1259, 1099, 1061, 1028, 909, 813, 782, 763, 631, 480 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.69 (s, 1H), 7.55 (d, *J* = 9.0 Hz, 1H), 2.51 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.58, 146.02, 136.50, 136.30, 134.38, 132.89, 127.64, 127.20, 126.78, 120.54, 87.58, 21.75; ^{77}Se-NMR (400 MHz, $CDCl_3$) δ 661.99; HRMS (ESI): m/z = 451.8050 calcd. For $C_{12}H_8NSeBrI$, found 451.8061 $[M+H]^+$.

2-Bromo-3-iodo-7-methylselenopheno[2,3-*b*]quinoline (7e)

Yield: 61%; Melting point: 203-206°C; IR (neat): 1800, 1614, 1587, 1547, 1322, 1134, 945, 900, 774, 741, 597, 546, 473 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$ and Acetone-d_6) δ 8.27 (d, *J* = 4.6 Hz, 1H), 7.78-7.85 (m, 2H), 7.38 (d, *J* = 8.2 Hz, 1H), 2.53 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$ and Acetone-d_6) δ 147.19, 141.34, 135.80, 135.02, 129.07, 128.16, 128.12, 126.33, 124.82, 119.90, 87.43, 22.07; ^{77}Se-NMR (400 MHz, $CDCl_3$ and Acetone-d_6) δ 664.55; HRMS (ESI): m/z = 451.8050 calcd. For $C_{12}H_8NSeBrI$, found 451.8031 $[M+H]^+$.

2-Bromo-3-iodoselenopheno[2,3-*b*]quinoline (7f)

Yield: 71%; Melting point: 178-182°C; IR (neat): 2923, 2028, 1733, 1613, 1581, 1551, 1326, 1316, 1140, 1129, 1070, 900, 892, 823, 752, 742, 496, 474 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.81 (t, *J* = 7.0 Hz, 1H), 7.61 (t,

J = 8.1 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.66, 147.25, 136.39, 135.04, 130.43, 128.59, 128.04, 126.72, 126.58, 120.89, 87.48; ^{77}Se-NMR (400 MHz, $CDCl_3$) δ 664.24; HRMS (ESI): m/z = 437.7894 calcd. For $C_{11}H_6NSeBrI$, found 437.7906 $[M+H]^+$.

General procedure for the synthesis of 4h-4q and 7g-7m:

To a stirred solution of 6-methyl-2-(methylthio)-3-(phenylethynyl)quinoline **3a** (10 mg, 0.034 mmol, 1 equiv.) and iodine (18 mg, 0.069 mmol, 2 equiv.) in dry DCM (5 mL) was stirred for 6 h, After completion of reaction (monitored by TLC), reaction mixture was quenched by saturated sodium thiosulfate and extracted with DCM (15 mL). Solvent was evaporated under reduced pressure to afford a crude residue. The crude was purified by silica gel chromatography using hexane/ethyl acetate (97:3) as eluent to afford **4h** as white crystal, Yield: 90%; Melting point: 183-186°C; IR (neat): 2916, 1674, 1629, 1588, 1575, 1550, 1488, 1440, 1181, 1093, 1074, 902, 839, 814, 754, 693, 569, 558 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.07 (d, *J* = 9.0 Hz, 1H), 7.81 (s, 1H), 7.76 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.62 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.48-7.54 (m, 3H), 2.59 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.44, 146.29, 143.53, 135.83, 135.23, 134.41, 133.18, 132.55, 132.48, 130.41, 130.00, 129.52, 128.75, 127.81, 127.09, 126.67, 75.93, 21.76; HRMS (ESI): m/z = 401.9813 calcd. For $C_{18}H_{13}NSI$, found 401.9842 $[M+H]^+$.

3-Iodo-7-methyl-2-phenylthieno[2,3-*b*]quinoline (4i)

Yield: 79%; Melting point: 143-146°C; IR (neat): 2914, 2373, 1631, 1530, 1474, 1440, 1304, 1144, 1073, 897, 868, 795, 758, 737, 691, 616, 598, 465 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.93-7.95 (m, 2H), 7.76 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.48-7.54 (m, 3H), 7.43 (d, *J* = 9.9 Hz, 1H), 2.63 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.35, 147.82, 142.93, 140.58, 134.63, 134.42, 132.92, 130.00, 129.48, 128.74, 128.50, 128.13, 127.00, 124.76, 75.91, 22.24; HRMS (ESI): m/z = 401.9813 calcd. For $C_{18}H_{13}NSI$, found 401.9835 $[M+H]^+$.

3-Iodo-2-phenylthieno[2,3-*b*]quinoline (4j)

Yield: 86%; Melting point: 163-166°C; IR (neat): 2922, 1613, 1583, 1548, 1476, 1327, 1143, 1075, 891, 853, 836, 762, 748, 738, 694, 599, 470 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.76-7.81 (m, 3H), 7.59 (t, *J* = 7.0 Hz, 1H), 7.49-7.55 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.36, 147.49, 143.69, 135.25, 134.33, 133.21, 130.01, 129.59, 128.77, 128.54, 128.19, 126.56, 125.99, 75.86; HRMS (ESI): m/z = 387.9657 calcd. For $C_{17}H_{11}NSI$, found 387.9656 $[M+H]^+$.

3-Iodo-6-methyl-2-(m-tolyl)thieno[2,3-*b*]quinoline (4k)

Yield: 83%; Melting point: 156-160°C; IR (neat): 2913, 1809, 1771, 1582, 1548, 1487, 1335, 1138, 1083, 1075, 904, 815, 793, 728, 698, 565, 478 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.06 (d, *J* = 9.0 Hz, 1H), 7.80 (s, 1H), 7.59 (q, *J* = 9.0 Hz, 3H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 2.59 (s, 3H), 2.47 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.45, 146.25, 143.67, 138.55, 135.78, 135.24, 134.30, 132.49, 132.39, 130.56, 130.30, 128.62, 127.80, 127.10, 126.66, 75.75, 21.76, 21.54; HRMS (ESI): m/z = 415.9970 calcd. For $C_{19}H_{15}NSI$, found 415.9976 $[M+H]^+$.

3-Iodo-7-methyl-2-(m-tolyl)thieno[2,3-*b*]quinoline (4l)

Yield: 80%; Melting point: 104-107°C; IR (neat): 2918, 1732, 1624, 1451, 1478, 1333, 1144, 1085, 893, 885, 873, 790, 779, 768, 621, 468 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.87 (t, *J* = 4.0 Hz, 2H), 7.50 (d, *J* = 9.0 Hz, 2H), 7.34 (q, *J* = 7.5 Hz, 2H), 7.22 (d, *J* = 7.6 Hz, 1H), 2.55 (s, 3H), 2.40 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.37, 147.78, 143.15, 140.52, 138.55, 134.64, 134.30, 132.84, 130.57, 130.26, 128.61, 128.47, 128.12, 127.10, 126.99, 124.75, 75.72, 22.24, 21.54; HRMS (ESI): m/z = 415.9970 calcd. For $C_{19}H_{15}INS$, found 415.9969 $[M+H]^+$.

3-Iodo-2-(m-tolyl)thieno[2,3-*b*]quinoline (4m)

Yield: 86%; Melting point: 131-134°C; IR (neat): 3052, 1806, 1615, 1600, 1548, 1329, 1128, 1084, 899, 851, 805, 771, 746, 694, 736, 599, 475 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 8.04 (d, *J* = 9.0 Hz, 1H), 7.75-7.79 (m, 1H), 7.56-7.60 (m, 3H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 2.47 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.37, 147.45, 143.91, 138.59, 135.26, 134.21, 133.11, 130.56, 130.38, 129.96, 128.65, 128.52, 128.18, 127.11, 126.56, 125.95, 75.67, 21.55; HRMS (ESI): m/z = 401.9813 calcd. For $C_{18}H_{13}NSI$, found 401.9803 $[M+H]^+$.

3-Iodo-2-(4-methoxyphenyl)-6-methylthieno[2,3-*b*]quinoline (4n)

Yield: 77%; Melting point: 178-180°C; IR (neat): 2988, 1775, 1731, 1605, 1490, 1459, 1435, 1295, 1252, 1178, 1112, 1087, 1027, 825, 813, 792, 764, 559, 525 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.06 (d, *J* = 9.0 Hz, 1H), 7.80 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 9.0 Hz, 1H), 7.04 (d, *J* = 8.5 Hz, 2H), 3.90 (s, 3H), 2.59 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.60, 146.12, 143.40, 135.77, 135.41, 132.40, 132.13, 131.36, 127.75, 127.06, 126.69, 126.64, 114.17, 75.09, 55.52, 21.76; HRMS (ESI): m/z = 431.9919 calcd. For $C_{19}H_{15}NOS$, found 431.9924 $[M+H]^+$.

3-Iodo-6-methyl-2-(phenylethynyl)thieno[2,3-*b*]quinoline (4o)

Yield: 81%; Melting point: 208-211°C; IR (neat): 2206, 1728, 1678, 1588, 1548, 1488, 1440, 1331, 1135, 1070, 907, 864, 816, 792, 757, 690, 560, 554 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.77 (s, 1H), 7.64-7.67 (m, 2H), 7.61 (d, *J* = 9.0 Hz, 1H), 7.40-7.42 (m, 3H), 2.58 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.94, 146.81, 136.13, 133.59, 132.92, 132.23, 131.95, 129.59, 128.64, 127.83, 127.17, 126.54, 126.20, 122.05, 101.17, 84.71, 84.36, 21.75; HRMS (ESI): m/z = 425.9813 calcd. For $C_{20}H_{13}NSI$, found 425.9788 $[M+H]^+$.

3-Iodo-7-methyl-2-(phenylethynyl)thieno[2,3-*b*]quinoline (4p)

Yield: 84%; Melting point: 212-215°C; IR (neat): 2920, 2163, 1911, 1688, 1625, 1590, 1545, 1439, 1331, 1148, 1071, 895, 888, 878, 787, 760, 693, 593, 545 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.90 (t, *J* = 4.0 Hz, 2H), 7.64-7.66 (m, 2H), 7.40-7.42 (m, 4H), 2.61 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.86, 148.30, 141.05, 132.96, 132.67, 131.93, 129.56, 128.74, 128.63, 128.22, 127.01, 125.66, 124.63, 122.08, 101.01, 84.75, 84.36, 22.29; HRMS (ESI): m/z = 425.9813 calcd. For $C_{20}H_{13}NSI$, found 425.9827 $[M+H]^+$.

3-Iodo-2-(phenylethynyl)thieno[2,3-*b*]quinoline (4q)

Yield: 91%; Melting point: 222-224°C; IR (neat): 2964, 2201, 1813, 1614, 1586, 1546, 1329, 1146, 1128, 1070, 900, 778, 753, 723, 687, 540, 472 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.78 (t, *J* = 7.2 Hz, 1H), 7.64-7.67 (m, 2H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.40-7.43 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.88, 147.99, 133.62, 132.97, 131.97, 130.37, 129.65, 128.65, 128.22, 126.45, 126.24, 121.99, 101.41, 84.63, 84.29, 76.78; HRMS (ESI): m/z = 411.9657 calcd. For $C_{19}H_{11}NSI$, found 411.9632 $[M+H]^+$

3-Iodo-6-methyl-2-phenylselenopheno[2,3-*b*]quinoline (7g)

Yield: 79%; Melting point: 179-182°C; IR (neat): 2920, 2345, 1805, 1718,1674, 1571, 1549, 1488, 1438, 1333, 1301, 902, 814, 767, 704, 745, 692,556, 513 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.80 (s, 1H), 7.68 (dd, *J* = 8.1, 1.3 Hz, 2H), 7.62 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.46-7.52 (m, 3H), 2.59 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.82, 146.16, 145.59, 137.86, 136.81, 136.04, 134.74, 132.69, 130.07, 129.36, 128.76, 127.68, 127.32, 126.86, 76.85, 21.84; ^{77}Se-NMR (400 MHz, $CDCl_3$) δ 628.19; HRMS (ESI): m/z = 449.9258 calcd. For $C_{18}H_{13}NSeI$, found 449.9253 $[M+H]^+$.

3-Iodo-7-methyl-2-phenylselenopheno[2,3-*b*]quinoline (7h)

Yield: 86%; Melting point: 129-132°C; IR (neat): 2915, 1748, 1622, 1575, 1474, 1440, 1331, 1223, 1057, 898, 798, 761, 692, 593, 468 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.91 (d, *J* = 7.6 Hz, 2H), 7.66-7.68 (m, 2H), 7.45-7.51 (m, 3H), 7.42 (d, *J* = 8.5 Hz, 1H), 2.62 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.79, 147.58, 144.96, 140.72, 137.18, 136.72, 135.03, 130.00, 129.25, 128.69, 128.56, 128.21, 126.85, 124.84, 79.03, 22.26; ^{77}Se-NMR (400 MHz, $CDCl_3$) δ 629.89; HRMS (ESI): m/z = 449.9258 calcd. For $C_{18}H_{13}NSeI$, found 449.9255 $[M+H]^+$.

3-Iodo-2-phenylselenopheno[2,3-*b*]quinoline (7i)

Yield: 85%; Melting point: 139-142°C; IR (neat): 2922, 1847, 1819, 1731, 1614, 1577, 1551, 1479, 1441, 1328, 1261, 1133, 1076, 1056, 1027, 760, 742, 690, 606, 465 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.77-7.81 (m, 1H), 7.68 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.60 (t, *J* = 7.0 Hz, 1H), 7.47-7.52 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.81, 147.28, 145.76, 137.85, 136.64, 135.32, 130.14, 130.00, 129.35, 128.72, 128.62, 127.98, 126.70, 126.11, 78.96; ^{77}Se-NMR (400 MHz, $CDCl_3$) δ 630.59; HRMS (ESI): m/z = 435.9101 calcd. For $C_{17}H_{11}NSeI$, found 435.9128 $[M+H]^+$.

3-Iodo-6-methyl-2-(phenylethynyl)selenopheno[2,3-*b*]quinoline (7j)

Yield: 79%; Melting point: 200-203°C; IR (neat): 2920, 1913, 1722, 1579, 1549, 1479, 1439, 1331, 1136, 902, 856, 814, 753, 697,686, 517, 479 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.75 (s, 1H), 7.59-7.64 (m, 3H), 7.41 (t, *J* = 2.7 Hz, 3H), 2.57 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.17, 146.57, 136.24, 136.17, 134.43, 132.93, 131.85, 129.53, 128.64, 127.62, 127.32, 126.64, 125.74, 122.28, 102.77, 87.42, 86.55, 21.75; ^{77}Se-NMR (400 MHz, $CDCl_3$) δ 648.77; HRMS (ESI): m/z = 473.9258 calcd. For $C_{20}H_{13}NSeI$, found 473.9250 $[M+H]^+$.

3-Iodo-7-methyl-2-(phenylethynyl)selenopheno[2,3-*b*]quinoline (7k)

Yield: 80%; Melting point: 183-186°C; IR (neat): 3006, 2364, 2348, 2341, 1714, 1427, 1364, 1223, 1093, 895, 798, 687, 529 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.88 (d, *J* = 8.2 Hz, 2H), 7.62-7.65 (m, 2H), 7.41 (q, *J* = 2.9 Hz, 4H), 2.60 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.22, 148.05, 141.17, 135.56, 134.82, 131.84, 129.49, 128.79, 128.63, 128.32, 126.88, 125.25, 124.72, 122.32, 102.60, 87.40, 86.56, 22.28; ^{77}Se-NMR (400 MHz, $CDCl_3$) δ 650.19; HRMS (ESI): m/z = 473.9258 calcd. For $C_{20}H_{13}NSeI$, found 473.9262 $[M+H]^+$.

3-Iodo-8-methyl-2-(phenylethynyl)selenopheno[2,3-*b*]quinoline (7l)

Yield: 87%; Melting point: 231-234°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.61-7.66 (m, 3H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.41 (t, *J* = 2.7 Hz, 3H), 2.86 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.13, 147.12, 136.15, 135.89, 135.27, 131.85, 130.37, 129.50, 128.63, 126.68, 126.58, 126.08, 122.34, 102.68, 87.31, 86.65, 18.43; ^{77}Se-NMR (400 MHz, $CDCl_3$) δ 651.94.

3-Iodo-2-(phenylethynyl)selenopheno[2,3-*b*]quinoline (7m)

Yield: 85%; Melting point: 194-197°C; IR (neat): 2961, 2191, 1729, 1546, 1478, 1439, 1332, 1258, 1069, 1013, 852, 792, 773, 748, 694, 685, 589 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 6.7 Hz, 1H), 7.63-7.66 (m, 2H), 7.60 (s, 1H), 7.42 (q, *J* = 2.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.79, 136.27, 135.12, 131.86, 130.45, 129.59, 128.75, 128.66, 128.65, 128.03, 126.59, 126.37, 126.04, 122.22, 103.02, 87.24, 86.48; ^{77}Se-NMR (400 MHz, $CDCl_3$) δ 651.01; HRMS (ESI): m/z = 459.9101 calcd. For $C_{19}H_{11}NSeI$, found 459.9104 $[M+H]^+$.

General procedure for the synthesis of 6-methyl-2,3-diphenylthieno[2,3-*b*]quinoline (6a)

To a solution of 3-iodo-6-methyl-2-phenylthieno[2,3-*b*]quinoline **4h** (20 mg, 0.050 mmol) the phenyl boronic acid (9.1 mg, 0.075 mmol) in 4 ml DMF, Pd $(OAc)_2$ (1.1 mg, 1 mol %), Cs_2CO_3 (48.7 mg, 0.150 mmol) were added. The resulting mixture was then heated at 60°C for 12 h. The solvent was removed under reduced pressure, the residue was extracted with ethyl acetate: brine; The crude was purified by silica gel chromatography using hexane/ethyl acetate (95:5) as eluents to afford **6a** 13 mg, Yield: 74%; Melting point: 186-188°C; IR (neat): 2917, 1978, 1626, 1599, 1584, 1556, 1491, 1442, 1298, 1357, 1090, 908, 820, 755, 698, 559, 478 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.05 (d, *J* = 9.0 Hz, 1H), 7.62 (s, 1H), 7.56-7.58 (m, 1H), 7.42-7.48 (m, 3H), 7.39 (td, *J* = 3.9, 1.9 Hz, 4H), 7.28 (t, *J* = 3.1 Hz, 3H), 2.53 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.42, 145.65, 140.23, 135.23, 134.84, 134.10, 133.84, 131.98, 130.38, 130.25, 129.85, 129.13, 129.05, 128.57, 128.43, 127.94, 127.92, 127.08, 126.09, 21.71; HRMS (ESI): m/z = 352.1160 calcd. For $C_{24}H_{18}NS$, found 352.1159 $[M+H]^+$.

General procedure for synthesis of 6-methyl-2-phenyl-3-(phenylethynyl)thieno[2,3-*b*] quinoline (6b)

To a solution of the corresponding 3-iodo-6-methyl-2-phenylthieno[2,3-b]quinoline **4h** (0.062 mmol) and the phenyl acetylene (0.080 mmol, 1.3 equiv) in 5ml THF; Et_3N (1 mL), $PdCl_2(PPh_3)_2$ (4.4 mg, 1 mol %) and copper(I) iodide (1.19 mg, 1 mol %) were added. The

resulting mixture was then stirred under nitrogen atmosphere for 14 h. The solvent was removed under reduced pressure, the residue was extracted with ethyl acetate and purified by silica gel column chromatography using hexane: ethyl acetate (97:3) as eluent to afford **6b** 18 mg, Yield: 77%; Melting point: 129-132°C; IR (neat): 2919, 1791, 1732, 1624, 1587, 1478, 1451, 1333, 1261, 1445, 897, 790, 778, 768, 694, 621, 468 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.14 (d, *J* = 7.2 Hz, 2H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.78 (s, 1H), 7.62-7.64 (m, 2H), 7.59 (d, *J* = 9.0 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 2H), 7.41-7.47 (m, 4H), 2.58 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.82, 147.11, 146.11, 135.69, 133.71, 133.66, 132.25, 131.75, 129.59, 129.18, 128.88, 128.76, 128.64, 128.04, 127.11, 126.78, 126.24, 123.10, 110.78, 95.36, 83.41, 21.75; HRMS (ESI): m/z = 376.1160 calcd. For $C_{26}H_{18}NS$, found 376.1154 $[M+H]^+$.

General procedure for the synthesis of methyl (*E*)-3-(6-methyl-2-phenylthieno[2,3-*b*]quinolin-3-yl)acrylate (6c)

To a solution of the corresponding 3-iodo-6-methyl-2-phenylthieno[2,3-b]quinoline **4h** (20 mg, 0.037 mmol) and the methyl acrylate (6.5 mg, 0.074 mmol) in 4 ml DMF; Pd $(OAc)_2$ (0.4 mg, 0.5 mol %), PPh_3 (9.8 mg, 0.037 mmol) and K_2CO_3 (10.3 mg, 0.074 mmol) were added. The resulting mixture was then heated under nitrogen atmosphere for 12 h. The solvent was removed under reduced pressure, the residue was extracted with ethyl acetate and purified by silica gel column chromatography using hexane: ethyl acetate (97:3) as eluent to afford **6c** 12 mg, along with 23% **6d**; Yield: 70%; Melting point: 186-190°C; IR (neat): 2917, 1716, 1627, 1587, 1491, 1443, 1423, 1305, 1283, 1222, 1174, 1158, 1080, 1095, 1013, 898, 817, 691, 563 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 16.2 Hz, 1H), 7.78 (s, 1H), 7.58-7.63 (m, 3H), 7.51 (t, *J* = 7.4 Hz, 3H), 6.66 (d, *J* = 16.6 Hz, 1H), 3.85 (s, 3H), 2.60 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.65, 161.09, 148.79, 145.54, 137.42, 135.89, 133.14, 132.52, 130.87, 130.28, 129.73, 129.33, 129.07, 127.94, 127.22, 126.06, 124.18, 119.96, 51.95, 21.76; HRMS (ESI): m/z = 360.1058 calcd. For $C_{22}H_{18}NO_2S$, found 360.1057 $[M+H]^+$.

General procedure for the synthesis of 6-methyl-2-phenylthieno[2,3-*b*]quinoline (6d)

To a solution of the corresponding 3-iodo-6-methyl-2-phenylthieno[2,3-b]quinoline **4h** (30 mg, 0.074 mmol) the formic acid (6.9 mg, 0.149 mmol) in 5 ml DMF, Pd $(PPh_3)_2Cl_2$ (2.6 mg, 0.5 mol %), NEt_3 (22.7 mg, 0.224 mmol) were added. The resulting mixture was then heated at 60°C for 12 h. The solvent was removed under reduced pressure, the residue was extracted with ethyl acetate: brine and purified by silica gel column chromatography using hexane: ethyl acetate

(98:2) as eluent to afford **6d** 16 mg, Yield: 78%; Melting point: 239-243°C; IR (neat): 1738, 1646, 1625, 1587, 1552, 1533, 1489, 1444, 1341, 1217, 1068, 913, 903, 817, 750, 680, 700, 691, 560, 473 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.02 (d, *J* = 9.0 Hz, 1H), 7.76-7.78 (m, 2H), 7.68 (s, 1H), 7.54-7.57 (m, 2H), 7.47 (dd, *J* = 8.1, 6.7 Hz, 2H), 7.41 (d, *J* = 7.2 Hz, 1H), 2.56 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.35, 145.45, 145.24, 135.35, 133.95, 133.45, 131.79, 129.15, 128.86, 128.05, 126.88, 126.79, 126.21, 116.24, 21.72; HRMS (ESI): m/z = 275.0769 calcd. For $C_{18}H_{13}NS$, found 275.0746 $[M+H]^+$.

General procedure for the synthesis of 9-methyl-1,2-diphenylbenzo[4,5]thieno[2,3-*b*]quinoline (6e)

To a solution of 3-iodo-6-methyl-2-phenylthieno[2,3-*b*]quinoline 4h (20 mg, 0.049 mmol), Pd $(OAc)_2$ (0.6 mg, 5 mol %), NaOAc (8 mg, 0.099 mmol), LiCl (6 mg, 0.149 mmol), in 4 mL DMF; Diphenylacetylene (9 mg, 0.049 mmol) were added. The resulting mixture was heated at 100°C for 4 days. The mixture was allowed to cool to room temperature, diluted with diethyl ether (15 mL); dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography using hexane: ethyl acetate (98:2) as eluent to afford 6e 11 mg (49%) as a yellow solid; Melting point: >300°C; IR (neat): 1961, 1801, 1601, 1585, 1548, 1493, 1439, 1327, 1256, 1103, 1070, 1030, 911, 823, 813, 755, 726, 698, 564 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.1 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 5.8 Hz, 3H), 7.26-7.29 (m, 5H), 7.20-7.24 (m, 2H), 7.16 (s, 1H), 6.99 (s, 1H), 2.47 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.09, 145.48, 139.61, 138.41, 137.11, 136.88, 135.89, 135.10, 132.22, 132.16, 131.35, 131.31, 130.37, 130.24, 128.66, 128.26, 128.15, 128.07, 127.72, 127.63, 127.50, 127.48, 127.32, 126.82, 126.81, 125.23, 125.20, 21.54; HRMS (ESI): m/z = 452.1496 calcd. For $C_{32}H_{22}NS$, found 452.1473 $[M+H]^+$.

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Chapter 2

Synthesis of thieno[2,3-*c*]acridine and furo[2,3-*c*]acridine derivatives *via* iodocyclization reaction, fluorescence properties and DFT mechanistic study

2.1 Introduction

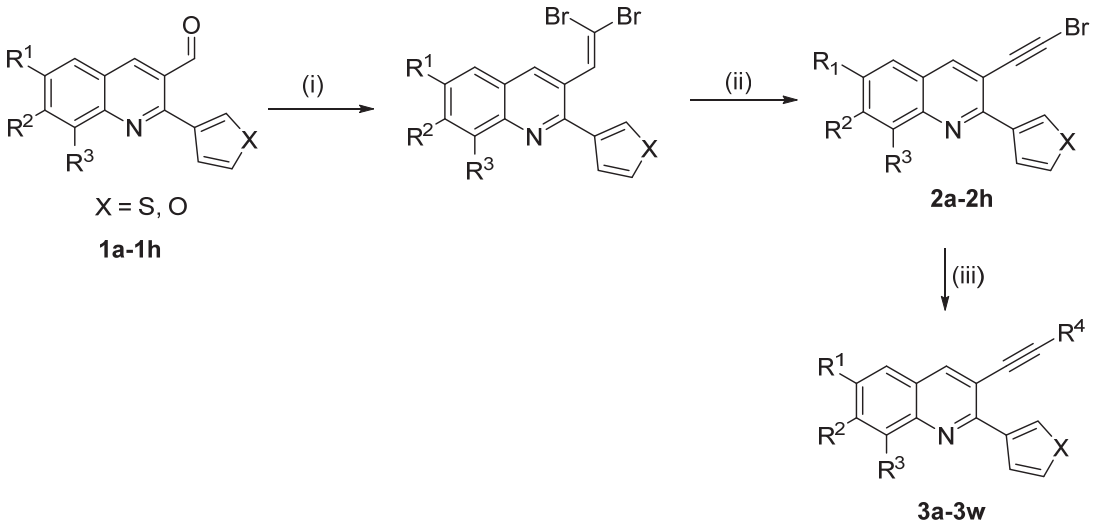
Acridines [1], a nitrogen-containing heteroaromatic molecules, are one of the privileged scaffolds possess wide range of biological activities such as antimicrobial agents [2], antibacterial [3], antimalarial [4], anti-leishmanial and antitrypanosomal [5], antiviral [6], antiprion [7], anticancer agents [8], anti-AD [9], anti-inflammatory [10], and analgesic activities [11]. In addition, acridine derivatives have been applied for acute lymphoblastic leukemia [12], and as a fluorescent indicator for cell lysosomal dye [13]. The interesting biological activities and chemical properties of acridines encouraged synthetic chemists to develop novel synthetic strategies to access structurally different acridines [14]. However, to the best of our knowledge, little is known in the literature about furo[2,3-*c*]acridines and thieno[2,3-*c*]acridines [15]. In recent years, molecular iodine mediated iodocyclization reactions has emerged as an efficient tool to activate a triple bond for nucleophilic attack [16-47]. Our group has shown the efficacy of iodocyclization reaction to access nitrogen- [18], oxygen- [19], sulphur- [20], and selenium-containing [21] heterocyclic compounds. Within an on-going project aimed at the development of novel approaches to access structurally diverse heterocycles, we disclose here an efficient method for the synthesis of furo[2,3-*c*]acridine and thieno[2,3-*c*]acridine derivatives *via* iodocyclization reaction of 3-alkynyl-2-(furan-3-yl)quinolines and 3-ethynyl-2-(thiophen-3-yl)quinolines, respectively. Further, we report their density functional theory (DFT) mechanistic study and fluorescence properties.

2.2 Results and discussion

The starting materials 2-(thiophen-3-yl)-3-carbaldehydes **1a-1d** and 2-(furan-3-yl)quinoline-3-carbaldehydes **1e-1h** required for our approach were readily prepared from corresponding 2-chloroquinoline-3-carbaldehydes with a known literature procedure [22]. Further, the (2-(thiophen-3-yl))-3-carbaldehydes **1a-1d** and 2-(furan-3-yl)quinoline-3-carbaldehydes **1e-1h** were converted to dibromo olefins by Corey–Fuchs reaction [23]. Next, the dibromo olefins *in situ* were converted to corresponding alkynes **2a-2h** in 75-

87% yields (Table 1, entries 1-8) *via* dehydrohalogenation reaction using DBU in DMSO at room temperature. Furthermore, to study the effect of substitution at the alkyne part, the synthesized bromoalkyne derivatives **2a-2h** were alkylated by boronic acid coupling reactions with Pd(II)-catalyst and 2M Na_2CO_3 in DME to obtain corresponding various substituted alkynes **3a-3w** in 70-90% yields (Table 1, entries 9-31). The synthesized compounds **1a-1h, 2a-2h** and **3a-3w** were characterized by IR, HRMS, ^{1}H-NMR and ^{13}C-NMR spectral analysis.

Table 1. Synthesis of 3-(alkynyl)-2-(thiophene/furan-3-yl)quinolines



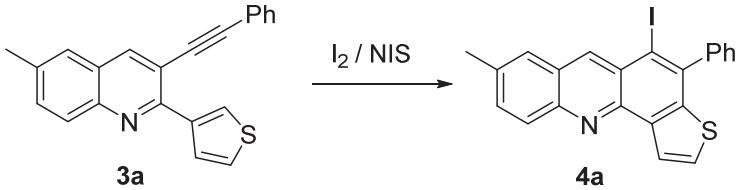
Entry	X	R^1	R^2	R^3	R^4	2 or 3 yield (%)[b]
1	S	CH_3-	H-	H-	Br-	**2a** (87%)
2	S	H-	CH_3-	H-	Br-	**2b** (79%)
3	S	H-	H-	CH_3-	Br-	**2c** (75%)
4	S	H-	H-	H-	Br-	**2d** (77%)
5	O	CH_3-	H-	H-	Br-	**2e** (75%)
6	O	H-	CH_3-	H-	Br-	**2f** (85%)
7	O	H-	H-	CH_3-	Br-	**2g** (83%)
8	O	H-	H-	H-	Br-	**2h** (78%)
9	S	CH_3-	H-	H-	Ph-	**3a** (81%)
10	S	H-	CH_3-	H-	Ph-	**3b** (73%)
11	S	H-	H-	CH_3-	Ph-	**3c** (75%)
12	S	H-	H-	H-	Ph-	**3d** (77%)
13	O	CH_3-	H-	H-	Ph-	**3e** (74%)
14	O	H-	CH_3-	H-	Ph-	**3f** (78%)

15	O	H-	H-	CH_3-	Ph-	**3g** (77%)
16	O	H-	H-	H-	Ph-	**3h** (81%)
17	S	CH_3-	H-	H-	*p*-$CH_3OC_6H_4$-	**3i** (72%)
18	S	H-	CH_3-	H-	*p*-$CH_3OC_6H_4$-	**3j** (77%)
19	S	H-	H-	CH_3-	*p*-$CH_3OC_6H_4$-	**3k** (74%)
20	S	H-	H-	H-	*p*-$CH_3OC_6H_4$-	**3l** (70%)
21	O	CH_3-	H-	H-	*p*-$CH_3OC_6H_4$-	**3m** (74%)
22	O	H-	CH_3-	H-	*p*-$CH_3OC_6H_4$-	**3n** (76%)
23	O	H-	H-	CH_3-	*p*-$CH_3OC_6H_4$-	**3o** (70%)
24	O	H-	H-	H-	*p*-$CH_3OC_6H_4$-	**3p** (77%)
25	S	CH_3-	H-	H-	*p*-$PhCH_2OC_6H_4$-	**3q** (74%)
26	S	H-	H-	CH_3-	*p*-$PhCH_2OC_6H_4$-	**3r** (72%)
27	S	H-	H-	H-	*p*-$PhCH_2OC_6H_4$-	**3s** (78%)
28	O	CH_3-	H-	H-	*p*-$PhCH_2OC_6H_4$-	**3t** (90%)
29	O	H-	CH_3-	H-	*p*-$PhCH_2OC_6H_4$-	**3u** (83%)
30	O	H-	H-	CH_3-	*p*-$PhCH_2OC_6H_4$-	**3v** (77%)
31	O	H-	H-	H-	*p*-$PhCH_2OC_6H_4$-	**3w** (74%)

[a]Reaction conditions: (i) CBr_4, PPh_3, DCM, 0°C, 1 h (ii) DBU, DMSO, rt, 1 h (iii) Phenylboronic acid, 2M Na_2CO_3, $Pd(PPh_3)_2Cl_2$, DME, 90°C; [b]Isolated yields.

Our study began by examining the iodocyclization reaction of alkyne **3a** which was used as a model compound with 2.0 equiv of iodine in dichloromethane at room temperature (Table 2, entry 1). To our surprise, the reaction resulted in the formation of desired 5-iodo-8-methyl-4-phenylthieno[2,3-*c*]acridine **4a** in 87% yield along with the unreacted starting material as an inseparable mixture (Table 2, entry 1). To improve the yield of iodocyclization reaction, different reaction conditions were then screened (Table 2, entries 2-16). As shown in Table 2, CH_3CN was found to be a suitable solvent for the iodocyclization and the best result was obtained when 6 equiv of iodine and 6 equiv of $NaHCO_3$ were used in the reaction (91% yield, entry 7).

Table 2. Optimization conditions for 5-iodo-8-methyl-4-phenylthieno[2,3-*c*]acridine



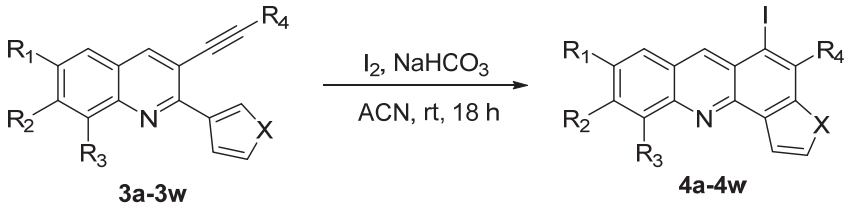
Entry	Solvent	E^+	Base	Time	Temp.	(4a)[a]

		(equiv.)	(equiv.)	(h)	(°C)	% yield
1	CH_2Cl_2	I_2 (2)	-	8	rt	87[b]
2	CH_2Cl_2	NIS (2)	-	18	rt	58[b]
3	CH_2Cl_2	I_2 (2)	$NaHCO_3$ (2)	12	rt	75[b]
4	CH_3CN	I_2 (3)	CS_2CO_3 (6)	48	rt	46
5	$C_2H_4Cl_2$	NIS (2)	-	48	60	70[b]
6	CH_3CN	I_2 (6)	$NaHCO_3$ (6)	12	rt	89
7	CH_3CN	I_2 (6)	$NaHCO_3$ (6)	18	rt	91
8	CH_2Cl_2	I_2 (4)	-	12	rt	66[b]
9	CH_3CN	I_2 (4)	-	12	rt	87[b]
10	CH_3CN	I_2 (6)	$NaHCO_3$ (3)	18	rt	87
11	CH_2Cl_2	I_2 (6)	$NaHCO_3$ (3)	18	rt	78[b]
12	CH_3CN	NIS (6)	$NaHCO_3$ (6)	18	rt	n.r.
13	CH_3Ph	I_2 (6)	$NaHCO_3$ (6)	18	rt	n.r.
14	DMSO	I_2 (6)	$NaHCO_3$ (6)	18	rt	Traces
15	DMSO	NIS (6)	$NaHCO_3$ (6)	18	rt	n.r.
16	THF	I_2 (6)	$NaHCO_3$ (6)	18	rt	n.r.

[a]Isolated Yields; [b]Inseparable mixture of starting and product; n.r.: No reaction.

With the optimized conditions in hand, the scope and generality of the iodocyclization reaction were further extended with other substrates (Table 3). The alkyl substitution at the quinoline part and aryl substitution at the alkynyl part were well tolerated under the present reaction conditions and the corresponding 5-iodofuro[2,3-*c*]acridine and 5-iodothieno[2,3-*c*]acridine derivatives **4a-4w** were obtained in good yield (Table 3, entries 1-23). The 5-iodothieno[2,3-*c*]acridine derivatives were obtained slightly in higher yield compared to 5-iodofuro[2,3-*c*]acridine derivatives. In contrast, the iodocyclization reaction of bromoalkynes **2e-2h** under the optimized reaction conditions resulted in the formation of diiodo compounds **5a-5d** instead of cyclized 5-iodothieno[2,3-*c*]acridine derivatives **4**. All the synthesized compounds **4a-4w** was well characterized by IR, HRMS, ^{1}H and ^{13}C-NMR spectral analysis. **4a** was confirmed by the X-ray crystallography [24].

Table 3. Synthesis of 5-iodofuro[2,3-*c*]acridine and 5-iodothieno[2,3-*c*]acridine derivatives

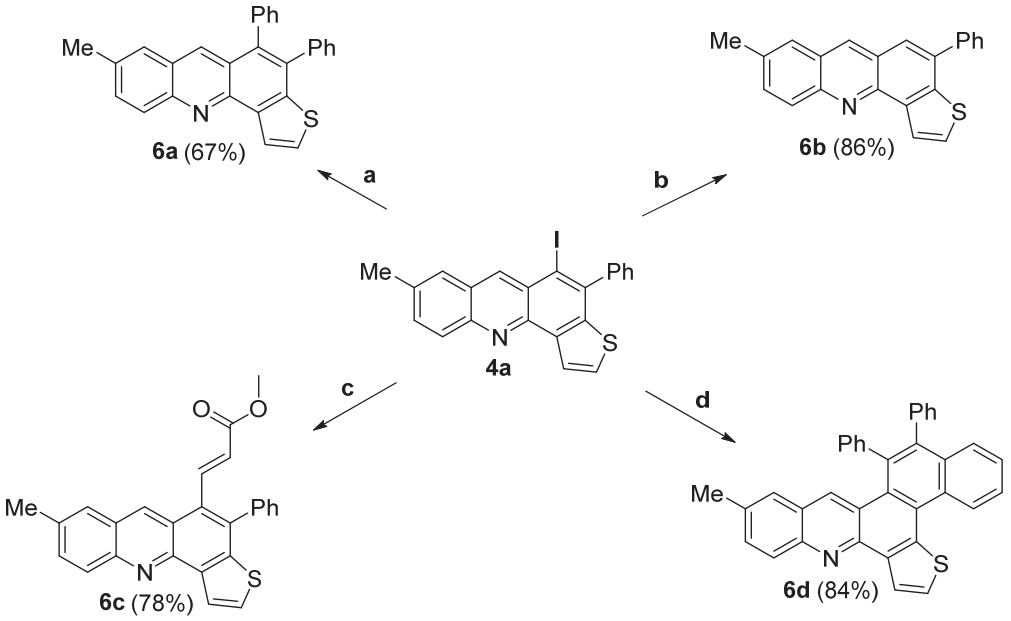


Entry	X	R_1	R_2	R_3	R_4	4 (% yield)[b]	ΔG[a] (kcal/mol)
1	S	CH_3-	H-	H-	Ph-	**4a** (91%)	18.4
2	S	H-	CH_3-	H-	Ph-	**4b** (89%)	18.4
3	S	H-	H-	CH_3-	Ph-	**4c** (84%)	18.2
4	S	H-	H-	H-	Ph-	**4d** (86%)	18.5
5	O	CH_3-	H-	H-	Ph-	**4e** (87%)	17.4
6	O	H-	CH_3-	H-	Ph-	**4f** (80%)	17.8
7	O	H-	H-	CH_3-	Ph-	**4g** (85%)	17.6
8	O	H-	H-	H-	Ph-	**4h** (81%)	17.8
9	S	CH_3-	H-	H-	*p*-$CH_3OC_6H_4$-	**4i** (89%)	16.6
10	S	H-	CH_3-	H-	*p*-$CH_3OC_6H_4$-	**4j** (86%)	16.3
11	S	H-	H-	CH_3-	*p*-$CH_3OC_6H_4$-	**4k** (78%)	16.2
12	S	H-	H-	H-	*p*-$CH_3OC_6H_4$-	**4l** (88%)	16.9
13	O	CH_3-	H-	H-	*p*-$CH_3OC_6H_4$-	**4m** (81%)	15.7
14	O	H-	CH_3-	H-	*p*-$CH_3OC_6H_4$-	**4n** (77%)	15.5
15	O	H-	H-	CH_3-	*p*-$CH_3OC_6H_4$-	**4o** (73%)	14.8
16	O	H-	H-	H-	*p*-$CH_3OC_6H_4$-	**4p** (68%)	15.6
17	S	CH_3-	H-	H-	*p*-$PhCH_2OC_6H_4$-	**4q** (77%)	16.3
18	S	H-	H-	CH_3-	*p*-$PhCH_2OC_6H_4$-	**4r** (75%)	16.8
19	S	H-	H-	H-	*p*-$PhCH_2OC_6H_4$-	**4s** (81%)	17.4
20	O	CH_3-	H-	H-	*p*-$PhCH_2OC_6H_4$-	**4t** (71%)	15.4
21	O	H-	CH_3-	H-	*p*-$PhCH_2OC_6H_4$-	**4u** (70%)	15.2
22	O	H-	H-	CH_3-	*p*-$PhCH_2OC_6H_4$-	**4v** (73%)	15.1
23	O	H-	H-	H-	*p*-$PhCH_2OC_6H_4$-	**4w** (69%)	15.7

[a]All iodocyclization reactions were conducted at room temperature with 6.0 equiv of I_2, 6.0 equiv. of $NaHCO_3$ in ACN unless and otherwise stated. [b]Isolated yields.

Next, to demonstrate the synthetic potential of the iodocyclization reaction, the presence of iodine on the 5-iodothieno[2,3-*c*]acridine product 4a allowed us further structural elaboration, most notable by Suzuki coupling [25], the palladium catalysed triethylammonium formate reduction of the iodide [26], Heck reaction [27], and alkyne annulation reaction [28] to afford the corresponding diversified quinoline moieties **6a**-**6d** (Scheme 1) in good to excellent yields.

2.2.1 Scheme 1 Functionalization of the 3-iodo-6-methyl-2-phenylthieno[2,3-*b*]quinoline



Reaction conditions: (a) Phenylboronic acid, $Pd(OAc)_2$, Cs_2CO_3, DMF, 110°C. (b) $Pd(PPh_3)_2Cl_2$, NEt_3, HCOOH, DMF, 60°C. (c) Methyl acrylate, PPh_3, $Pd(OAc)_2$, K_2CO_3, DMF, 110°C. (d) Diphenylacetylene, $Pd(OAc)_2$, NaOAc, LiCl, DMF, 100°C.

2.3 DFT Study and fluorescence properties

To study the reaction mechanism of iodocyclization of 3 in detail, we carried out DFT calculations. The calculated relative Gibbs free energy profile and stationary point structures of the reactions leading to 4a-4d (X = S and R^4 = Ph) are shown in Figure 2, and those of other reactions are shown in Figures S1 and S3-S6 in the ESI. These reactions have only one transition state (TS) in ring closure process, and the elimination of HI proceeds without energy barrier. The reaction energy profiles of reactions leading to **4a-4d** are similar to each other. We can deduce that the reactivity of the compound depends on the only R^4 group on the alkynyl group. Indeed, the ΔG^a values of TS shown in Table 3 are clearly different between the reactions, which have different R^4 groups.

Table 4. Photophysical properties

Compound[a]	λ_{max} (ε) / nm	F_{max} / nm	ϕ_f[c, d]
4a	250 (44,800), 277 (65,000), 361 (11,800), 377 (11,300), 391 (7,400)	—[b]	—[b]
4e	266 (38,900), 348 (4,900), 362 (6,700), 379 (5,000), 399 (4,200)	—[b]	—[b]
6a	250 (38,500), 277 (68,000), 362 (9,100), 377 (11,200)	415, 434	0.09
6b	247 (41,100), 278 (72,300), 365 (14,100), 381 (15,500)	404, 424	0.07
6c	239 (29,500), 277 (48,800), 366 (9,300), 381 (12,400), 399 (6,500)	420, 443	0.04
6d	297 (52,700), 353 (9,400), 377 (9,100), 387 (8,700), 411 (5,900)	430, 451	0.09

[a] Measured at a concentration of 1.0 x 10^{-5} M in hexane.
[b] Nonfluorescence.
[c] The excitation wavelengths (λ_{ex}) was 380 nm
[d] Measured using a Quantaurus-QY.

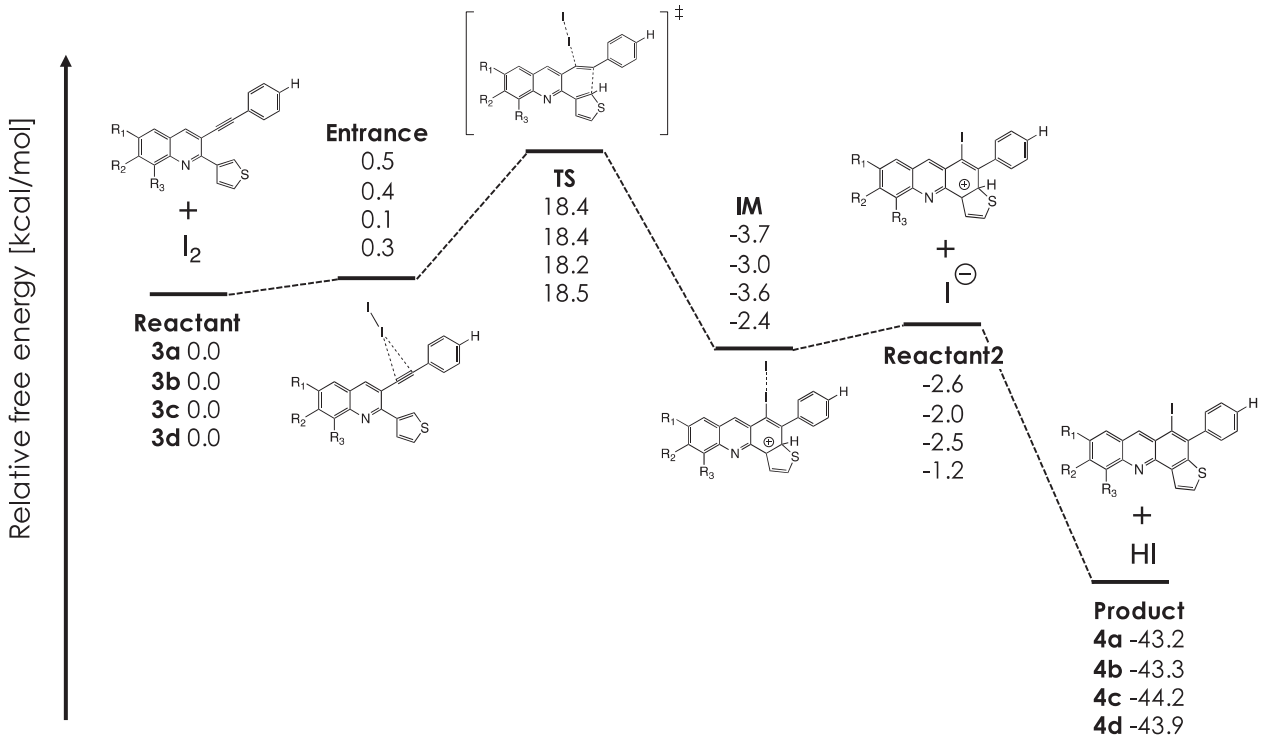


Figure 2. Relative Gibbs free energy profiles at T = 298 K of the reactions leading to 4a-4d obtained by B3LYP/6-311+G**+Midi!//B3LYP/6-31G*+Midi! calculations. Solvent effect (Acetonitrile) was taken into account by the SCRF-PCM method.

In recent years, anthracene derivatives emerged as one of the important blue-light emitting fluorescent dyes and have widespread applications such as fluorescence sensors [29] and organic light-emitting diodes [30]. On the other hand, although 2-azaanthracene derivatives have been reported to show interesting fluorescent properties [31], little has been reported on the fluorescence properties of azaanthracene derivatives. Thus, the absorption and fluorescence properties of the synthesized thieno[2,3-*c*]acridine and furo[2,3-*c*]acridine derivatives were studied. The UV-vis absorption spectra of **4a**, **4e**, and **6a**-**6d** in hexane are shown in Figure 3. The absorption maximum (λ_{max}) and molar extinction coefficient (ε) values are listed in Table 4. All the synthesized compounds showed weak and intense absorption bands at around 380 nm (λ_{max}: 348–411 nm, ε: 4,200–15,500) and 280 nm (λ_{max}: 266–297 nm, ε: 38,900–72,300), respectively. The λ_{max} value of furan-fused derivative **4e** (399 nm) was slightly red-shifted compared to that of thiophene-fused derivative **4a** (391 nm). The annulation of the naphthalene ring to the thieno[2,3-*c*]acridine moiety led to a red shift in the λ_{max} value (**6d**: 411 nm) due to the extension of the π-conjugation.

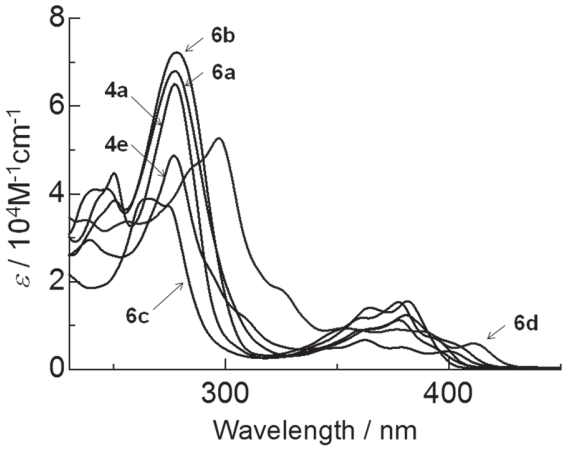


Figure 3. UV-Vis absorption spectra in n-hexane.

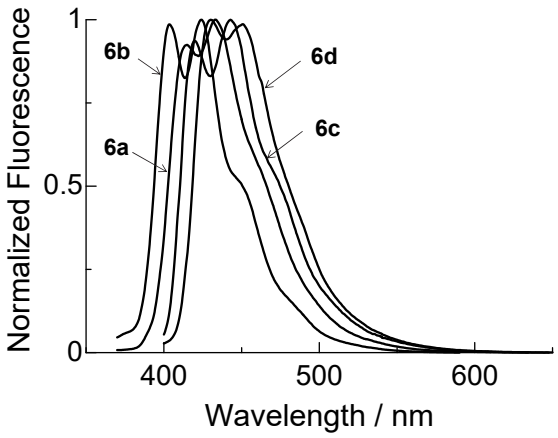


Figure 4. Normalized fluorescence spectra in *n*-hexane.

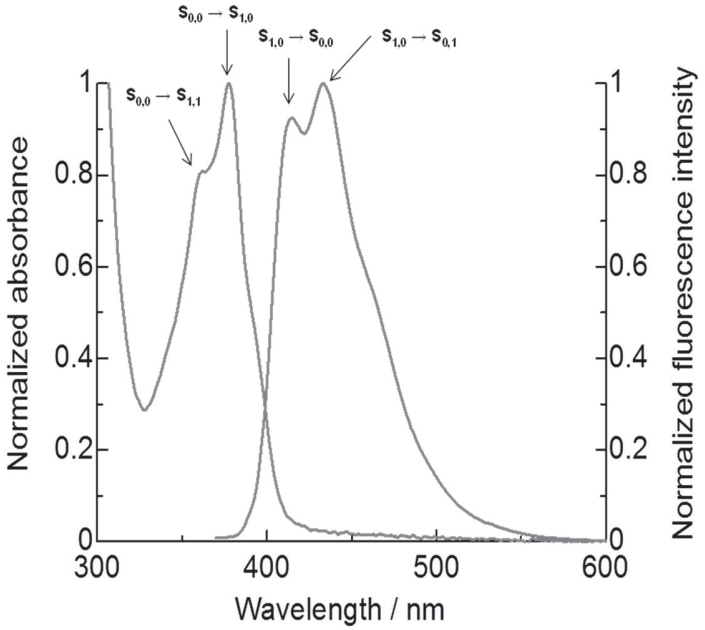


Figure 5. Normalized absorption and fluorescence spectra of **6a** in hexane.

The fluorescence spectra of compounds **6a-6d** in hexane are shown in Figure 4. Although thieno[2,3-*c*]acridine derivatives **6a-6d** exhibited fluorescence, iodine derivatives **4a** and **4e** did not show fluorescence probably due to the heavy atom effect [32]. As observed with the absorption spectra, the fluorescence spectra of **6a-6d** were structured. Compound **6a** exhibited a mirror image between the absorption and fluorescence spectra in hexane (Figure 5). Therefore, the observed two fluorescence peaks of **6a** at 415 and 434 nm are probably assigned to the $S_{1,0} \rightarrow S_{0,0}$ and $S_{1,0} \rightarrow S_{0,1}$ transitions, respectively. In accordance with the absorption spectra, naphthalene-fused derivative **6d** showed the most red-shifted maximum fluorescence wavelength (F_{max}) value (Table 4). The fluorescence quantum yield (ϕ_f) values of **6a-6d** are in the range of 0.04 to 0.09. The relatively lower ϕ_f value of **6c** may be due to the contribution of the carbonyl group which easily promotes the intersystem crossing [33].

2.4 Summary and conclusions

In summary, we have developed a synthetic route for the construction of thieno[2,3-*c*]acridine and furo[2,3-*c*]acridine derivatives *via* iodocyclization reaction. The structures of the products were confirmed by IR, NMR, and HRMS, as well as X-ray diffraction experiments. Thieno[2,3-*c*] acridine derivatives showed blue fluorescence in hexane (F_{max}: 415-430 nm, ϕ_f: 0.04-0.09). DFT calculations were also carried out to study the

effect of iodinating reagent and substituents on the reactivity of the iodocyclization. Finally, the structural elaboration was done by Suzuki coupling, Heck reaction, dehydroiodination and alkyne annulation reaction.

2.5 Experimental section

2.5.1 General methods: All solvents and reagents were purchased from the suppliers and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica plates using UV-light or Iodine chamber for visualization. Column chromatography was performed on silica gel (60-120 mesh) using n-hexane and ethyl acetate as eluents. IR spectra were recorded on a JASCO FT/IR-460 Plus spectrophotometer. Evaporation and condensation was carried out in vacuo. NMR spectra were recorded with JEOL JNM-ECS 400 spectrometer with tetramethylsilane as an internal standard. Chemical shifts δ and coupling constants *J* are given in ppm (parts per million) and Hz (hertz), respectively. The following abbreviations were used as follows: s: singlet, d: doublet, t: triplet and m: multiplet. Additionally unknown compounds are characterized by HRMS analysis. All known compounds data are inconsistent with the given literature reports. Scale up reactions also performed as per the given general procedure without any deviation. Melting points were measured by a Yanaco micro melting point apparatus. UV-vis spectra were taken on a Hitachi U4100 spectrophotometer. Fluorescence spectra were measured on a FP-8600 spectrofluorometer. Fluorescence quantum yields were recorded on a Quantaurus-QY.

2.5.2 General procedure and spectral data

General procedure for the synthesis of 5-iodo-8-methyl-4-phenylthieno[2,3-*c*]acridine 4a-4w:

To a stirred solution of 6-methyl-3-(phenylethynyl)-2-(thiophen-3-yl)quinoline **3a** (27 mg, 0.083 mmol, 1 equiv.); iodine (126 mg, 0.498 mmol, 6 equiv.) and $NaHCO_3$ (41.82 mg, 0.497 mmol, 6 equiv.) in dry ACN (5 mL) was stirred for 18 h, After completion of reaction (monitored by TLC), reaction mixture was quenched by saturated sodium thiosulfate and extracted with ethyl acetate (15 mL). The solvent was evaporated under reduced pressure to afford a crude residue. The crude was purified by silica gel chromatography using n-hexane/ethyl acetate (97:3) as eluent to afford **4a** (34 mg). Yield: 91%; Melting point: 228-230°C; IR (neat): 3052, 2915, 2182, 1585, 1551, 1491, 1353, 1314, 1139, 1029, 968, 913, 888, 815, 710, 694, 632, 532, 467 cm-1; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.43 (d, *J* = 5.4 Hz, 1H), 8.16 (d, *J* = 9.0 Hz, 1H),

7.78 (s, 1H), 7.60 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.46-7.50 (m, 4H), 7.39 (dd, *J* = 7.4, 2.0 Hz, 2H), 2.53 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.43, 144.02, 143.93, 142.36, 141.45, 141.20, 137.37, 135.97, 133.60, 129.40, 128.83, 128.76 (2C), 128.56, 127.53, 127.36, 126.91, 126.79, 124.54, 99.21, 21.94; HRMS (ESI): *m/z* = 451.9970 calcd. For $C_{22}H_{15}NSI$, found 451.9980 $[M+H]^+$.

5-Iodo-9-methyl-4-phenylthieno[2,3-*c*]acridine (4b)

Yield: 89%; Melting point: 145-147°C; IR (neat): 3111, 3048, 2936, 1626, 1601, 1587, 1550, 1489, 1443, 1363, 1143, 1033, 907, 871, 748, 714, 702, 659, 632, 577 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.51 (d, *J* = 5.4 Hz, 1H), 8.11 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.54-7.58 (m, 4H), 7.43-7.48 (m, 3H), 2.65 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.87, 144.62, 143.92, 142.65, 142.07, 141.41, 140.87, 137.29, 129.43, 128.86, 128.83, 128.77, 128.14, 127.43, 127.28, 126.38, 125.76, 124.59, 99.30, 22.42; HRMS (ESI): *m/z* = 451.9970 calcd. For $C_{22}H_{15}NSI$, found 451.9950 $[M+H]^+$.

5-Iodo-10-methyl-4-phenylthieno[2,3-*c*]acridine (4c)

Yield: 84%; Melting point: 118-119°C; IR (neat): 3023, 2962, 2911, 2027, 1617, 1588, 1560, 1495, 1439, 1361, 1142, 1076, 1069, 892, 884, 810, 753, 712, 692, 637, 629, 528 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.49 (d, *J* = 5.4 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.51-7.62 (m, 5H), 7.41-7.46 (m, 3H), 2.97 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.69, 143.91, 143.41, 142.21, 141.06, 137.84, 136.88, 130.14, 129.45, 128.83, 128.76, 127.34, 127.22, 126.52, 126.40, 125.90, 124.68, 99.07, 18.35; HRMS (ESI): *m/z* = 451.9970 calcd. For $C_{22}H_{15}NSI$, found 451.9949 $[M+H]^+$.

5-Iodo-4-phenylthieno[2,3-*c*]acridine (4d)

Yield: 86%; Melting point: 131-133°C; IR (neat): 3101, 3055, 2924, 1791, 1732, 1618, 1587, 1548, 1491, 1439, 1360, 1323, 1138, 1128, 1031, 897, 884, 776, 766, 755, 721, 628, 530, 469 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.53 (d, *J* = 5.4 Hz, 1H), 8.35 (d, *J* = 8.5 Hz, 1H), 8.11 (d, *J* = 7.6 Hz, 1H), 7.85 (t, *J* = 7.0 Hz, 1H), 7.56-7.63 (m, 5H), 7.47 (dd, *J* = 7.4, 2.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.56, 144.59, 143.84, 142.77, 142.45, 141.37, 137.33, 130.79, 129.38, 128.94, 128.89, 128.79, 128.55, 127.47, 127.42, 126.85, 126.11, 124.65, 99.14; HRMS (ESI): *m/z* = 451.9813 calcd. For $C_{21}H_{13}NSI$, found 437.9796 $[M+H]^+$.

5-Iodo-8-methyl-4-phenylfuro[2,3-*c*]acridine (4e)

Yield: 87%; Melting point: 248-250°C; IR (neat): 3126, 3057, 1607, 1574, 1551, 1524, 1441, 1356, 1333, 1211, 1053, 905, 880, 812, 716, 701, 533 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.25 (d, *J* = 9.0 Hz, 1H), 7.88 (s, 1H), 7.68-7.73 (m, 3H), 7.55-7.60 (m, 3H), 7.49-7.51 (m, 2H), 2.61 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 152.99, 147.66, 144.88, 143.11, 142.22, 139.64, 135.75, 135.07, 133.87, 130.15, 128.78, 128.48, 128.23, 127.17, 126.98, 126.37, 123.99, 107.34, 99.53, 21.90; HRMS (ESI): *m/z* = 436.0198 calcd. For $C_{22}H_{15}NOI$, found 436.0186 $[M+H]^+$.

5-Iodo-9-methyl-4-phenylfuro[2,3-*c*]acridine (4f)

Yield: 80%; Melting point: 219-220°C; IR (neat): 3059, 3017, 1609, 1576, 1560, 1467, 1442, 1418, 1398, 1157, 1002, 890, 759, 719, 701, 643, 480 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.10 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.71 (dd, *J* = 6.3, 1.8 Hz, 2H), 7.54-7.60 (m, 3H), 7.49-7.51 (m, 2H), 7.43 (d, *J* = 6.7 Hz, 1H), 2.65 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.16, 149.08, 144.83, 143.74, 142.79, 141.67, 139.64, 134.72, 130.18, 128.77, 128.66, 128.47, 128.37, 127.09, 125.84, 125.41, 123.92, 107.35, 99.67, 22.44; HRMS (ESI): *m/z* = 436.0198 calcd. For $C_{22}H_{15}NOI$, found 436.0190 $[M+H]^+$.

5-Iodo-10-methyl-4-phenylfuro[2,3-*c*]acridine (4g)

Yield: 85%; Melting point: 148-149°C; IR (neat) 3146, 2866, 1602, 1575, 1518, 1502, 1452, 1243, 1178, 1013, 999, 835, 821, 753, 740, 694, 619 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.67-7.73 (m, 3H), 7.57 (dd, *J* = 9.0, 6.7 Hz, 3H), 7.47-7.52 (m, 3H), 3.01 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 152.97, 148.09, 144.78, 142.94, 142.68, 139.65, 136.73, 134.95, 130.31, 130.20, 128.76, 128.46, 127.06, 126.67, 126.08, 125.72, 124.50, 107.43, 99.32, 18.30; HRMS (ESI): *m/z* = 436.0198 calcd. For $C_{22}H_{15}NOI$, found 436.0178 $[M+H]^+$.

5-Iodo-4-phenylfuro[2,3-*c*]acridine (4h)

Yield: 81%; Melting point: 168-170°C; IR (neat): 3057, 3026, 1607, 1524, 1441, 1356, 1333, 1212, 1175, 1053, 905, 880, 812, 716, 701, 562 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.34 (d, *J* = 8.5 Hz, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.83-7.87 (m, 1H), 7.73 (q, *J* = 2.2 Hz, 2H), 7.49-7.62 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.19, 148.79, 144.93, 143.73, 143.19, 139.56, 135.27, 130.99, 130.15, 128.83, 128.77, 128.63, 128.49, 127.05, 126.30, 125.88, 124.01, 107.43, 99.53; HRMS (ESI): *m/z* = 422.0042 calcd. For $C_{21}H_{13}NOI$, found 422.0034 $[M+H]^+$.

5-Iodo-4-(4-methoxyphenyl)-8-methylthieno[2,3-*c*]acridine (4i)

Yield: 89%; Melting point: 198-200°C; IR (neat): 3103, 2959, 2926, 1792, 1604, 1587, 1574, 1509, 1489, 1439, 1353, 1245, 1172, 1134, 1025, 894, 835, 821, 813, 720, 689, 470 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.51 (d, *J* = 5.4 Hz, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 7.87 (s, 1H), 7.69 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.57 (d, *J* = 5.4 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H), 3.93 (s, 3H), 2.61 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.85, 147.37, 144.03, 142.83, 141.47, 140.95, 137.23, 136.45, 135.95, 133.56, 130.71, 128.56, 127.53, 127.33, 127.03, 126.80, 124.58, 114.04, 99.88, 55.42, 21.94; HRMS (ESI): *m/z* = 482.0076 calcd. For $C_{23}H_{17}NOSI$, found 482.0064 $[M+H]^+$.

5-Iodo-4-(4-methoxyphenyl)-9-methylthieno[2,3-*c*]acridine (4j)

Yield: 86%; Melting point: 218-220°C; IR (neat): 3104, 3084, 2954, 1629, 1608, 1585, 1513, 1361, 1289, 1248, 1170, 1141, 1030, 903, 886, 831, 796, 725, 717, 578, 525 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.50 (d, *J* = 5.4 Hz, 1H), 8.11 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.56 (d, *J* = 5.4 Hz, 1H), 7.42 (dd, *J* = 13.9, 8.5 Hz, 3H), 7.09 (d, *J* = 8.5 Hz, 2H), 3.93 (s, 3H), 2.65 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.84, 148.79, 144.61, 143.13, 142.08, 141.35, 140.62, 137.15, 136.43, 130.73, 128.83, 128.14, 127.40, 127.24, 126.50, 125.75, 124.63, 114.04, 99.96, 55.42, 22.40; HRMS (ESI): *m/z* = 482.0076 calcd. For $C_{23}H_{17}NOSI$, found 482.0053 $[M+H]^+$.

5-Iodo-4-(4-methoxyphenyl)-10-methylthieno[2,3-*c*]acridine (4k)

Yield: 78%; Melting point: 222-224°C; IR (neat): 3098, 3084, 2929, 1607, 1587, 1572, 1511, 1460, 1275, 1244, 1173, 1026, 1013, 892, 831, 721, 544, 506 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.50 (d, *J* = 5.4 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 6.7 Hz, 1H), 7.53 (d, *J* = 4.9 Hz, 1H), 7.38-7.47 (m, 3H), 7.08 (d, *J* = 8.5 Hz, 2H), 3.92 (s, 3H), 2.99 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.84, 147.65, 143.45, 142.73, 142.24, 140.83, 137.72, 136.89, 136.43, 130.75, 130.10, 127.81, 127.36, 127.19, 126.42, 125.88, 124.72, 114.03, 99.70, 55.42, 18.33; HRMS (ESI): *m/z* = 482.0076 calcd. For $C_{23}H_{17}NOSI$, found 482.0057 $[M+H]^+$.

5-Iodo-4-(4-methoxyphenyl)thieno[2,3-*c*]acridine (4l)

Yield: 88%; Melting point: 212-214°C; IR (neat): 3086, 2926, 2851, 1605, 1586, 1573, 1510, 1492, 1452, 1362, 1288, 1247, 1172, 1030, 835, 748, 717, 698, 619, 469 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.52 (d, *J* = 5.4 Hz, 1H), 8.34 (d, *J* = 8.5 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.85 (t, *J* = 7.2 Hz, 1H), 7.57-7.63 (m, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H), 3.93 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.89, 148.50, 144.59, 143.24, 142.45,

141.13, 137.20, 136.36, 130.70, 128.92, 128.54, 127.42, 126.95, 126.08, 124.68, 114.06, 99.80, 55.43; HRMS (ESI): *m/z* = 467.9919 calcd. For $C_{22}H_{15}NOSI$, found 467.9909 $[M+H]^+$.

5-Iodo-4-(4-methoxyphenyl)-8-methylfuro[2,3-*c*]acridine (4m)

Yield: 81%; Melting point: 218-219°C; IR (neat): 3048, 2970, 1633, 1578, 1472, 1395, 1363, 1219, 1084, 1010, 971, 923, 822, 772, 756, 561 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 7.88 (s, 1H), 7.68-7.74 (m, 3H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 3.93 (s, 3H), 2.61 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.87, 153.18, 147.61, 144.81, 143.13, 142.16, 135.69, 134.77, 133.77, 131.87, 131.48, 128.24, 127.16, 126.97, 126.48, 123.92, 113.85, 107.34, 100.02, 55.41, 21.90; HRMS (ESI): *m/z* = 466.0304 calcd. For $C_{23}H_{17}NO_2I$, found 466.0294 $[M+H]^+$.

5-Iodo-4-(4-methoxyphenyl)-9-methylfuro[2,3-*c*]acridine (4n)

Yield: 77%; Melting point: 188-190°C; IR (neat): 3020, 2963, 1025, 1604, 1476, 1459, 1441, 1242, 1215, 1176, 1140, 958, 903, 756, 668 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.11 (s, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.72 (dd, *J* = 9.6, 2.0 Hz, 2H), 7.44-7.46 (m, 3H), 7.11 (d, *J* = 9.0 Hz, 2H), 3.93 (s, 3H), 2.66 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.86, 153.38, 149.01, 144.77, 143.75, 142.79, 141.60, 134.45, 131.86, 131.50, 128.64, 128.37, 127.08, 125.96, 125.42, 123.83, 113.86, 107.38, 100.17, 55.41, 22.44; HRMS (ESI): *m/z* = 466.0304 calcd. For $C_{23}H_{17}NO_2I$, found 466.0300 $[M+H]^+$.

5-Iodo-4-(4-methoxyphenyl)-10-methylfuro[2,3-*c*]acridine (4o)

Yield: 73%; Melting point: 205-206°C; IR (neat): 3019, 2839, 1718, 1606, 1454, 1441, 1419, 1397, 1355, 1248, 1215, 1157, 1133, 1034, 913, 893, 833, 756, 651 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.66-7.73 (m, 3H), 7.47 (t, *J* = 9.2 Hz, 3H), 7.10 (d, *J* = 9.0 Hz, 2H), 3.92 (s, 3H), 3.00 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.86, 153.17, 147.99, 144.69, 142.89, 142.66, 136.69, 134.64, 131.87, 131.53, 130.24, 127.03, 126.66, 126.16, 125.67, 124.41, 114.20, 113.84, 107.44, 99.81, 55.42, 18.30; HRMS (ESI): *m/z* = 466.0304 calcd. For $C_{23}H_{17}NO_2I$, found 466.0304 $[M+H]^+$.

5-Iodo-4-(4-methoxyphenyl)furo[2,3-*c*]acridine (4p)

Yield: 68%; Melting point: 234-235°C; IR (neat): 2923, 2836, 1719, 1575, 1544, 1516, 1504, 1438, 1285, 1244, 1025, 881, 830, 792, 761, 748, 603 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.34 (d, *J* = 9.0 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.86 (t, *J* = 7.2 Hz, 1H), 7.74 (dd, *J* = 9.0, 1.8 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 9.0 Hz, 2H), 3.93

(s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.91, 153.42, 148.73, 144.87, 143.76, 143.19, 134.99, 131.79, 131.48, 130.93, 128.77, 128.61, 127.06, 126.44, 125.87, 123.91, 113.88, 107.43, 100.01, 55.42; HRMS (ESI): *m/z* = 452.0148 calcd. For $C_{22}H_{15}NO_2I$, found 452.0175 $[M+H]^+$.

4-(4-(Benzyloxy)phenyl)-5-iodo-8-methylthieno[2,3-*c*]acridine (4q)

Yield: 77%; Melting point: 220-221°C; IR (neat): 3116, 2896, 2922, 1733, 1605, 1582, 1550, 1509, 1453, 1376, 1244, 1172, 1022, 819, 795, 731, 696, 634, 492 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.52 (d, *J* = 5.4 Hz, 1H), 8.25 (d, *J* = 9.0 Hz, 1H), 7.89 (s, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.58 (d, *J* = 5.4 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.39-7.46 (m, 5H), 7.17 (d, *J* = 8.5 Hz, 2H), 5.18 (s, 2H), 2.62 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.17, 147.38, 144.04, 142.81, 141.50, 140.93, 137.25, 136.86, 136.70, 135.97, 133.58, 130.76, 128.76, 128.56, 128.24, 127.81, 127.54, 127.35, 127.04, 126.81, 124.59, 114.88, 99.85, 70.23, 21.94; HRMS (ESI): *m/z* = 558.0389 calcd. For $C_{29}H_{21}NOSI$, found 558.0405 $[M+H]^+$.

4-(4-(Benzyloxy)phenyl)-5-iodo-10-methylthieno[2,3-*c*]acridine (4r)

Yield: 75%; Melting point: 175-176°C; IR (neat): 3034, 2892, 2955, 1724, 1604, 1588, 1494, 1449, 1361, 1246, 1171, 1107, 1035, 1025, 760, 734, 716, 693, 621, 531, 499 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.53 (d, *J* = 5.4 Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.66 (d, *J* = 6.7 Hz, 1H), 7.37-7.56 (m, 9H), 7.16 (d, *J* = 8.5 Hz, 2H), 5.16 (s, 2H), 3.00 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.15, 147.70, 143.49, 142.72, 142.29, 140.81, 137.75, 136.91, 136.86, 136.67, 130.80, 130.14, 128.77, 128.25, 127.83, 127.40, 127.23, 126.70, 126.44, 125.92, 124.72, 114.86, 99.69, 70.22, 18.34; HRMS (ESI): *m/z* = 558.0389 calcd. For $C_{29}H_{21}NOSI$, found 558.0402 $[M+H]^+$.

4-(4-(Benzyloxy)phenyl)-5-iodothieno[2,3-*c*]acridine (4s)

Yield: 81%; Melting point: 169-171°C; IR (neat): 3034, 2920, 2214, 1620, 1603, 1583, 1549, 1508, 1453, 1360, 1240, 1175, 1009, 1001, 919, 910, 832, 734, 725, 715, 698, 632, 509 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.53 (d, *J* = 5.4 Hz, 1H), 8.35 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.1 Hz, 1H), 7.86 (t, *J* = 7.2 Hz, 1H), 7.58-7.64 (m, 2H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.37-7.46 (m, 5H), 7.18 (d, *J* = 8.5 Hz, 2H), 5.17 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.20, 148.52, 144.62, 143.21, 142.49, 141.10, 137.22, 136.84, 136.61, 130.76, 128.93, 128.77, 128.56, 128.25, 127.82, 127.45, 126.97, 126.09, 124.69, 114.89, 99.78, 70.23; HRMS (ESI): *m/z* = 544.0232 calcd. For $C_{28}H_{19}NOSI$, found 544.0223 $[M+H]^+$.

4-(4-(Benzyloxy)phenyl)-5-iodo-8-methylfuro[2,3-*c*]acridine (4t)

Yield: 71%; Melting point: 195-196°C; IR (neat): 3031, 3009, 2914, 2174, 1722, 1602, 1578, 1547, 1517, 1292, 1219, 1173, 1052, 1021, 912, 836, 819, 760, 747, 732, 694, 535 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 7.87 (s, 1H), 7.67-7.73 (m, 3H), 7.35-7.51 (m, 7H), 7.18 (d, *J* = 8.5 Hz, 2H), 5.16 (s, 2H), 2.60 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.18, 153.16, 147.60, 144.82, 143.13, 142.18, 136.89, 135.70, 134.73, 133.80, 132.12, 131.55, 128.77, 128.23, 127.78, 127.16, 126.98, 126.48, 123.92, 114.66, 107.35, 100.02, 70.20, 21.91; HRMS (ESI): *m/z* = 542.0617 calcd. For $C_{29}H_{21}NO_2I$, found 542.0626 $[M+H]^+$.

4-(4-(Benzyloxy)phenyl)-5-iodo-9-methylfuro[2,3-*c*]acridine (4u)

Yield: 70%; Melting point: 190-192°C; IR (neat): 3031, 2920, 2851, 1738, 1598, 1515, 1500, 1352, 1231, 1207, 997, 904, 830, 741, 689, 646, 587, 511, 473, 464 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.11 (s, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.73 (dd, *J* = 9.9, 2.2 Hz, 2H), 7.37-7.52 (m, 8H), 7.19 (d, *J* = 9.0 Hz, 2H), 5.17 (s, 2H), 2.66 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.17, 153.37, 149.05, 144.78, 143.78, 142.80, 141.62, 136.90, 134.41, 132.12, 131.55, 128.76, 128.65, 128.38, 128.21, 127.77, 127.09, 125.97, 125.43, 123.86, 114.66, 107.37, 100.13, 70.20, 22.43; HRMS (ESI): *m/z* = 542.0617 calcd. For $C_{29}H_{21}NO_2I$, found 542.0620 $[M+H]^+$.

4-(4-(Benzyloxy)phenyl)-5-iodo-10-methylfuro[2,3-*c*]acridine (4v)

Yield: 73%; Melting point: 165-167°C; IR (neat): 3146, 2911, 2866, 1717, 1602, 1575, 1518, 1502, 1352, 1243, 1178, 1013, 999, 835, 821, 753, 740, 694, 619, 588 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.69-7.75 (m, 3H), 7.47 (td, *J* = 16.5, 7.8 Hz, 8H), 7.19 (d, *J* = 9.0 Hz, 2H), 5.18 (s, 2H), 3.01 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.17, 153.18, 148.05, 144.72, 142.95, 142.71, 136.91, 136.72, 134.64, 132.13, 131.57, 130.27, 128.76, 128.21, 127.76, 126.68, 126.21, 125.70, 124.43, 115.18, 114.66, 107.45, 99.77, 70.21, 18.28; HRMS (ESI): *m/z* = 542.0617 calcd. For $C_{29}H_{21}NO_2I$, found 542.0613 $[M+H]^+$.

4-(4-(Benzyloxy)phenyl)-5-iodofuro[2,3-*c*]acridine (4w)

Yield: 69%; Melting point: 177-178°C; IR (neat): 3142, 2969, 1663, 1603, 1574, 1519, 1503, 1355, 1219, 1175, 1048, 1025, 1002, 831, 773, 739, 697, 591 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.33 (d, *J* = 9.0 Hz, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.82-7.86 (m, 1H), 7.72 (dd, *J* = 8.1, 1.8 Hz, 2H), 7.57-7.61 (m, 1H), 7.34-7.51 (m, 7H), 7.17-7.20 (m, 2H), 5.16 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.23, 153.38, 148.73, 144.87, 143.75, 143.17, 136.90, 134.94, 132.05, 131.56, 130.93, 128.77, 128.62, 128.23, 127.77, 127.05, 126.42, 125.87, 123.94, 114.70,

107.45, 100.01, 70.22; HRMS (ESI): *m/z* = 528.0461 calcd. For $C_{28}H_{19}NO_2I$, found 528.0455 $[M+H]^+$.

General procedure and spectral data for the synthesis of (*E*)-3-(2-bromo-1,2-diiodovinyl)-2-(furan-3-yl)-6-methylquinoline 5a-5d:

To a stirred solution of (*E*)-3-(2-bromo-1,2-diiodovinyl)-2-(furan-3-yl)-6-methylquinoline **2a** (20 mg, 0.064 mmol, 1 equiv.) and iodine (97.6 mg, 0.384 mmol, 6 equiv.); $NaHCO_3$ (32.3 mg, 0.384 mmol, 6 equiv.) in dry ACN (5 mL) was stirred for 18 h, After completion of reaction (monitored by TLC), reaction mixture was quenched by saturated sodium thiosulfate and extracted with ethyl acetate (20 mL). Solvent was evaporated under reduced pressure to afford a crude residue. The crude was purified by silica gel chromatography using n-hexane/ethyl acetate (97:3) as eluent to afford **5a** (21 mg). Yield: 58%; Melting point: 103-105°C; IR (neat): 3020, 2977, 1593, 1556, 1514, 1487, 1215, 1166, 1159, 1087, 931, 874, 826, 669, 622, 594 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.93-8.00 (m, 3H), 7.54-7.60 (m, 3H), 7.13 (d, *J* = 1.8 Hz, 1H), 2.55 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 146.99, 146.37, 143.41, 143.17, 138.85, 137.08, 135.78, 133.19, 129.12, 126.54, 126.34, 110.90, 110.77, 103.81, 61.30, 21.72; HRMS (ESI): *m/z* = 565.8114 calcd. For $C_{16}H_{11}NOBrI_2$, found 565.8138 $[M+H]^+$.

(*E*)-3-(2-Bromo-1,2-diiodovinyl)-2-(furan-3-yl)-7-methylquinoline (5b)

Yield: 43%; Sticky; IR (KBr): 2970, 2922, 1709, 1625, 1573, 1550, 1514, 1452, 1215, 1159, 1054, 1007, 874, 806, 756, 706, 667, 594 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.96-7.99 (m, 2H), 7.88 (s, 1H), 7.68-7.71 (m, 1H), 7.54 (d, *J* = 1.8 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.12 (d, *J* = 9.0 Hz, 1H), 2.56 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.95, 143.57, 143.18, 141.43, 138.10, 136.19, 135.49, 129.38, 128.43, 127.39, 125.70, 124.38, 110.94, 103.89, 61.42, 22.15; HRMS (ESI): *m/z* = 565.8114 calcd. For $C_{16}H_{11}NOBrI_2$, found 565.8123 $[M+H]^+$.

(*E*)-3-(2-Bromo-1,2-diiodovinyl)-2-(furan-3-yl)-8-methylquinoline (5c)

Yield: 59%; Melting point: 82-84°C; IR (neat): 2954, 2920, 1614, 1592, 1572, 1513, 1573, 1410, 1377, 1215, 1066, 1040, 1004, 932, 923, 874, 792, 710, 667, 593 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.97-8.01 (m, 2H), 7.54-7.65 (m, 3H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.21-7.25 (m, 1H), 2.84 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 146.63, 146.15, 143.62, 143.11, 138.44, 137.47, 136.62, 135.93, 130.83, 126.85, 126.20, 125.68, 111.05, 103.92, 61.34, 17.85; HRMS (ESI): *m/z* = 565.8114 calcd. For $C_{16}H_{11}NOBrI_2$, found 565.8133 $[M+H]^+$.

(*E*)-3-(2-Bromo-1,2-diiodovinyl)-2-(furan-3-yl)quinoline (5d)

Yield: 51%; Sticky; IR (KBr): 2963, 2928, 1726, 1618, , 1591, 1545, 1513, 1484, 1418, 1215, 1158, 1053, 1005, 936, 873, 783, 667, 593 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.01-8.11 (m, 3H), 7.73-7.82 (m, 2H), 7.52-7.56 (m, 2H), 7.14 (d, *J* = 9.4 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.90, 143.67, 143.24, 138.88, 136.48, 135.77, 130.83, 129.46, 127.76, 127.06, 126.32, 125.63, 110.81, 103.58, 61.53; HRMS (ESI): *m/z* = 551.7982 calcd. For $C_{15}H_9NOBrI_2$, found 551.7957 $[M+H]^+$.

General procedure for the synthesis of 8-Methyl-4,5-diphenylthieno[2,3-*c*]acridine (6a)

To a solution of 5-iodo-8-methyl-4-phenylthieno[2,3-*c*]acridine **4a** (30 mg, 0.075 mmol, 1 equiv.) the phenyl boronic acid (11.9 mg, 0.097 mmol, 1.3 equiv.) in 5 ml DMF, $Pd(OAc)_2$ (1.7 mg, 1 mol %), Cs_2CO_3 (73.08 mg, 0.224 mmol, 3 equiv.) were added. The resulting mixture was then heated at 110^0C for 12 h. The solvent was removed under reduced pressure, the residue was extracted with ethyl acetate: brine; the crude was purified by silica gel chromatography using n-hexane/ethyl acetate (95:5) as eluents to afford **6a** (18 mg). Yield: 67%; Melting point: 257-259°C; IR (neat): 3054, 3022, 2979, 1738, 1601, 1586, 1574, 1550, 1439, 1373, 1310, 1123, 1027, 911, 894, 820, 808, 744, 696, 633, 536, 469 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 5.4 Hz, 1H), 8.41 (s, 1H), 8.24 (d, J = 8.5 Hz, 1H), 7.61-7.65 (m, 3H), 7.25-7.32 (m, 10H), 2.53 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 146.74, 144.88, 143.28, 139.37, 138.04, 136.71, 135.20, 134.93, 134.18, 133.64, 133.02, 131.68, 130.08, 128.88, 128.15, 128.01, 127.56, 127.17, 126.90, 126.47, 126.35, 125.75, 124.80, 21.79; HRMS (ESI): *m/z* = 402.1316 calcd. For $C_{28}H_{20}NS$, found 402.1344 $[M+H]^+$.

General procedure for the synthesis of 8-Methyl-4-phenylthieno[2,3-*c*]acridine (6b)

To a solution of the corresponding 5-iodo-8-methyl-4-phenylthieno[2,3-*c*]acridine **4a** (34 mg, 0.075 mmol, 1 equiv.) the formic acid (5.68 mml, 0.150 mmol, 2 equiv.) in 5 ml DMF, Pd $(PPh_3)_2Cl_2$ (2.64 mg, 0.5 mol %), NEt_3 (31.54 mml, 0.226 mmol, 3 equiv.) were added. The resulting mixture was then heated at 60ºC for 12 h. The solvent was removed under reduced pressure, the residue was extracted with ethyl acetate: brine and purified by silica gel column chromatography using n-hexane: ethyl acetate (95:5) as eluent to afford **6b** (21 mg). Yield: 86%; Melting point: 146-148°C; IR (neat): 3098, 3048, 2970, 1633, 1600, 1578, 1547, 1472, 1395, 1363, 1219, 1084, 1010, 971, 957, 923, 822, 772, 756, 715, 694, 561 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.59-8.65 (m, 2H), 8.23 (d, *J* = 9.0 Hz, 1H), 7.83 (d, *J* = 7.2 Hz, 2H), 7.75 (d, *J* = 4.9 Hz, 2H), 7.64 (t, *J* = 4.9 Hz, 2H), 7.52 (dt, *J* = 26.0, 7.3 Hz, 3H), 2.58 (s, 3H); ^{13}C-NMR (100

MHz, $CDCl_3$) δ 147.19, 144.94, 140.93, 140.06, 137.89, 135.47, 135.42, 134.99, 132.88, 129.23, 128.97, 128.51, 126.80, 126.42, 126.14, 125.48, 124.78, 123.5, 21.90; HRMS (ESI): *m/z* = 326.1003 calcd. For $C_{22}H_{16}NS$, found 326.0984 $[M+H]^+$.

General procedure for the synthesis of Methyl (*E*)-3-(8-methyl-4-phenylthieno[2,3-*c*]acridin-5-yl)acrylate (6c)

To a solution of the corresponding 5-iodo-8-methyl-4-phenylthieno[2,3-*c*]acridine **4a** (30 mg, 0.066 mmol, 1 equiv.) and the methyl acrylate (11.4 mg, 0.133 mmol, 2 equiv.) in 4 ml DMF; Pd $(OAc)_2$ (0.7 mg, 0.5 mol %), PPh_3 (17.4 mg, 0.066 mmol, 1 equiv.) and K_2CO_3 (18.4 mg, 0.133 mmol, 2 equiv.) were added. The resulting mixture was then heated under nitrogen atmosphere for 12 h. The solvent was removed under reduced pressure, the residue was extracted with ethyl acetate and purified by silica gel column chromatography using hexane: ethyl acetate (97:3) as eluent to afford **6c** (21 mg). Yield: 78%; Melting point: 170-172°C; IR (neat): 2948, 2916, 1712, 1702, 1633, 1587, 1503, 1428, 1375, 1315, 1288, 1258, 1170, 1160, 988, 898, 819, 738, 718, 703, 640, 467 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.55 (d, *J* = 5.4 Hz, 1H), 8.22 (d, *J* = 9.0 Hz, 1H), 8.05 (d, *J* = 16.6 Hz, 1H), 7.79 (s, 1H), 7.63-7.69 (m, 2H), 7.48-7.53 (m, 5H), 6.13 (d, *J* = 16.2 Hz, 1H), 3.79 (s, 3H), 2.60 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.97, 146.81, 144.78, 143.00, 141.87, 138.52, 137.70, 135.78, 135.21, 133.36, 133.20, 129.84, 128.88, 128.73, 128.04, 126.87, 126.48, 125.59, 124.98, 123.67, 51.89, 21.91; HRMS (ESI): *m/z* = 410.1215 calcd. For $C_{26}H_{20}NO_2S$, found 410.1245 $[M+H]^+$.

General procedure for the synthesis of 11-Methyl-14,15-diphenylnaphtho[2,1-*a*]thieno[2,3-*c*]acridine (6d)

To a solution of 5-iodo-8-methyl-4-phenylthieno[2,3-*c*]acridine 4a (30 mg, 0.067 mmol, 1 equiv.), Pd $(OAc)_2$ (0.3 mg, 5 mol %), NaOAc (11 mg, 0.133 mmol, 2 equiv.), LiCl (8.45 mg, 0.199 mmol, 3 equiv.), in 4 mL DMF; Diphenylacetylene (17 mg, 0.099 mmol, 1.5 equiv.) were added. The resulting mixture was heated at 100°C for 2 days. The mixture was allowed to cool to room temperature, diluted with ethyl acetate (15 mL); dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography using n-hexane: ethyl acetate (95:5) as eluent to afford 6d (28 mg). Yield: 84%; Melting point: 274-276°C; IR (neat): 3052, 2917, 2850, 1582, 1548, 1515, 1473, 1388, 1293, 1081, 1071, 924, 821, 807, 752, 727, 716, 698, 656, 639, 551 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.40 (d, *J* = 8.5 Hz, 1H), 8.67 (d, *J* = 5.4 Hz, 1H), 8.23 (s, 1H), 8.09 (d, *J* = 9.0 Hz, 1H), 7.71-

7.81 (m, 3H), 7.52-7.58 (m, 2H), 7.26 (d, *J* = 8.5 Hz, 3H), 7.13-7.19 (m, 5H), 7.07 (d, *J* = 6.3 Hz, 2H), 6.95 (s, 1H), 2.44 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 145.85, 145.79, 143.07, 139.59, 138.71, 138.28, 137.63, 137.57, 137.50, 134.98, 132.95, 132.42, 131.67, 131.40, 129.10, 128.40, 128.13, 127.95, 127.67, 127.16, 127.08, 126.90, 126.59, 126.35, 126.02, 125.03, 123.58, 21.76; HRMS (ESI): *m/z* = 502.1629 calcd. For $C_{36}H_{24}NS$, found 502.1611 $[M+H]^+$.

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Chapter 3

Iron-promoted intramolecular cascade cyclization for the synthesis of selenophene-fused, quinoline-based heteroacenes

3.1 Introduction

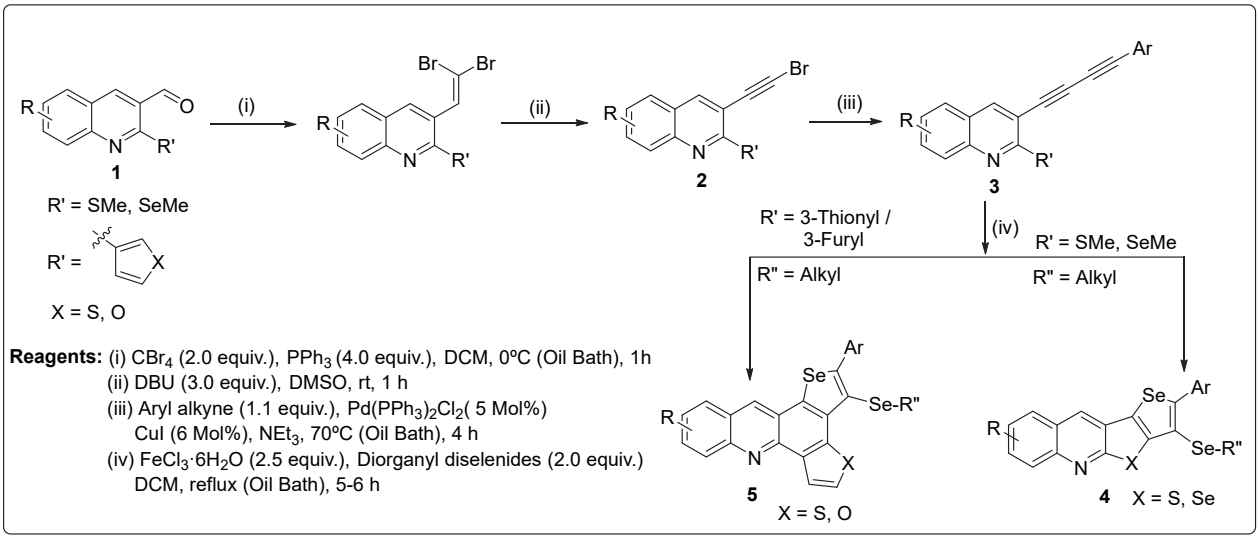
Compounds containing C-Se bonds have a pivotal position in medicinal chemistry because of their broad range of biological and pharmacological activities [1]. A number of selenophene and quinoline derivatives are known to display a wide range of biological activities, such as antibacterial [2], antioxidant [3], antimicrobial [4], antidepressant [5], and antitumoral activities [6]. Apart from the biological studies, compounds containing the selenophene nucleus are also used as applications in the preparation of physical materials that show potentially useful optical and fluorescent properties [7-12]. The interesting biological and optical properties of quinoline and selenophene-heterocycles encouraged synthetic chemists to develop novel synthetic strategies to access structurally different motifs [13]. Also, the synthesis of linear alkynes has much attention due to versatile applications in the material chemistry [14]. In recent literature survey, few reports are available for the synthesis of alkynes and their cyclization *via* diorganyl diselenides with versatile internal nucleophiles to afford the biologically important heterocycles [15]. In our continuing efforts toward the preparation of seleno-heterocycles, we have successfully achieved synthesis of 2′-alkylselenouridine [16], 2-amino-4*H*-5,6-dihydro-1,3-selenazin-4-ones, 2-selenoxoperhydro-1,3-selenazin-4-ones, 2-selenoxo-1,3-selenazolidin-4-ones[17], 1,3-selenazole-5-carboxylic acids [18], 2-imino-1,3-selenazolidin-4-one [19]. Recently Zeni and coworkers reported the cascade cyclization of 1,3-diynyl chalcogen derivatives to afford selenophene-fused benzo[*b*]furans and chalcogenisochromene-fused chalcogenophene [20]. To the best of our knowledge, there are no reports for 1,3-diyne and 1,3,5-triyne cascade cyclization on quinoline moiety which resulted in the formation of two core systems quinoline and acridine. Within our ongoing project, we have successfully developed synthetic pathway for two and three linear alkynes and their novel cascade cyclization for the construction of selenophene-fused thieno[2,3-*b*]quinolines, selenopheno[2,3-*b*]quinolines, thieno[2,3-*c*] acridine and furo[2,3-*c*] acridine derivatives. Herein, quinoline and acridine-based thiophene and selenophene may become a new class of heteroacenes and the targeted compounds will be achieved by novel alkyne intramolecular cascade cyclization by Fe(III) using diorganyl

diselenides as cyclizing agents. The key step for synthesis of these novel heterocycles involved 1,3-diyne and 1,3,5-triyne cascade cyclization by using diselenides having various internal nucleophiles. The diorganyl diselenide plays dual role, first as cyclizing agent and secondly insertion of two and three selenium atoms in the final product, hence it is highly important in terms of atom economy.

3.2 Result and Discussion

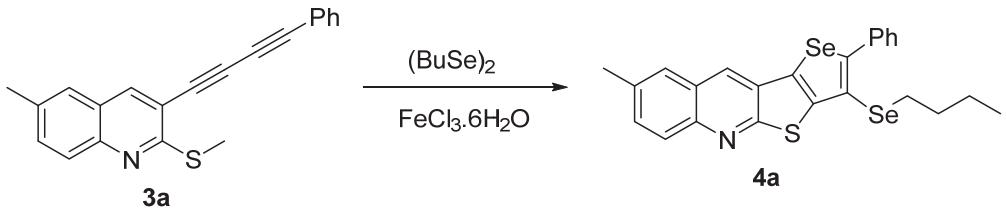
Our investigations in this direction were begun with 2-(methylthio)- and 2-(methylseleno)-quinoline-3-carbaldehydes as well as 2-(3-thienyl)- and 2-(3-furyl)-quinoline-3-carbaldehydes (1) which were readily prepared from corresponding 2-chloroquinoline-3-carbaldehydes [17]. Further, the preparation of alkynes from carbonyl compounds was successfully obtained by Corey–Fuchs reaction [21]. The quinoline-3-carboxyaldehydes (1) were converted to dibromo intermediate by treatment with CBr_4 and PPh_3. Further, the dibromo intermediate allow to stir with 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) in DMSO at room temperature *via* dehydrohalogenation afforded the corresponding bromoalkyne compounds (2) in good yields. Next, under Sonogashira coupling conditions, the compounds (2) were alkylated with various aromatic alkynes to afford the corresponding di-substituted alkynes (3) in 56-73% yields. Finally, the cascade cyclization was achieved by Fe(III) by using diorganyl diselenides to afford the products (4) and (5), respectively (3.2.1). The structures of (2) [17-18], and (3) were confirmed by the IR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectral analysis.

3.2.1 General scheme: synthesis of 1,3-diyne



Further, towards the cascade pathway, we initiated with the dialkynes (**3**), and examined various optimization conditions (Table 1, Entries 1-18). First, the reaction was carried out in presence of 1 equiv. of $FeCl_3 \cdot 6H_2O$. Interestingly we obtained 47% cyclized compound **4a** (Table 1, Entry 1). Later, we analysed the reaction with increased equiv. of various catalysts and observed the smooth progression under $FeCl_3 \cdot 6H_2O$ (2.5 equiv.) and dibutyl diselenide $(BuSe)_2$ (2.0 equiv.) conditions (Table 1, Entry 10). The use of 1 equiv. of $(BuSe)_2$ gives **4a** in 42% yield (Table 1, Entry 19). As we increased the $(BuSe)_2$ the yield of product increased. The use of $FeCl_3.6H_2O$ (2.0) gives **4a** in 85% yield (Table 1, Entry 3) while the $FeCl_3$ gives 4a in 67% yield (Table 1, Entry 6), this indicates that reaction is favorable for $FeCl_3.6H_2O$ it might be due to solubility and different reactivity. The reaction was found not to proceed at high temperature with polar solvents (Table 1, Entries 12-16). With standard conditions in hand (Table 1, Entry 10) we have successfully synthesized various substrates for selenophene-fused thieno [2,3-*b*]quinolines and selenopheno [2,3-*b*]quinolines (**4**) (Chart 1) and selenophene-fused thieno[2,3-*c*] acridine and furo [2,3-*c*] acridine (**5**) (Chart 2) to consolidate this methodology.

Table 1. Optimization for the synthesis of 3-(butylselanyl)-8-methyl-2-phenylselenopheno [2',3':4,5]thieno[2,3-*b*]quinoline (**4a**)



3a **4a**

Entry No.	Solvent	E^+ (Eq.)	$(BuSe)_2$ (Eq.)	Time (h)	Temp. (ºC)	4a Yield[a] (%)
1	DCM	$FeCl_3.6H_2O$ (1.0)	1.75	4	45	47
2	DCM	$FeCl_3.6H_2O$ (1.5)	2.0	4	45	61
3	DCM	$FeCl_3.6H_2O$ (2.0)	2.0	4	45	85
4	DCM	CuI/I_2 (2.0)	2.0	12	45	NR
5	DCM	CuI/NIS(2.0)	2.0	12	45	NR
6	DCM	$FeCl_3$ (2.0)	2.0	12	45	67

7	DCM	$CuCl_2.2H_2O$(2.5)	2.0	8	45	79
8	DCM	$CeCl_3.7H_2O$(2.5)	2.0	6	45	n.r.
9	DCM	$BiCl_3$ (2.5)	2.0	8	45	n.r.
10	DCM	$FeCl_3.6H_2O$ (2.5)	2.0	4	45	88
11	ACN	$FeCl_3.6H_2O$ (2.5)	2.0	8	80	83
12	THF	$FeCl_3.6H_2O$ (2.5)	2.0	12	70	n.r.
13	THF	$FeCl_3.6H_2O$ (2.5)	2.0	12	reflux	n.r.
14	DMSO	$FeCl_3.6H_2O$ (2.5)	2.0	6	100	n.r.
15	DCM	---	2.0	6	45	n.r.
16	Dioxane	$FeCl_3.6H_2O$ (2.5)	2.0	6	100	n.r.
17	$CHCl_3$	$FeCl_3.6H_2O$ (2.5)	2.0	6	65	70
18	DCM	$I_2/FeCl_3.6H_2O$ (2.5)	2.0	6	45	50
19	DCM	$FeCl_3.6H_2O$ (2.0)	1.0	6	45	42

[a]Isolated yields; n.r.: No reaction

Chart 1. Substrate scopes of selenophene-fused thieno [2,3-*b*]quinolines and selenopheno [2,3-*b*]quinolines (**4**)

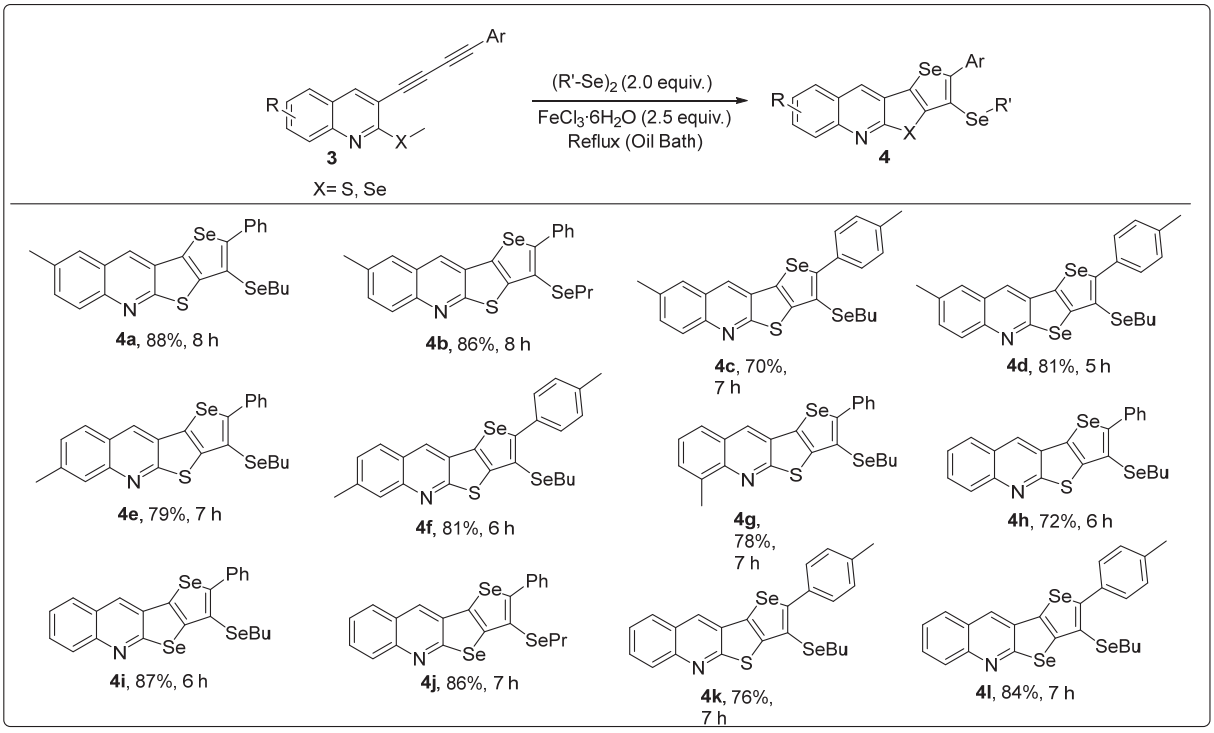
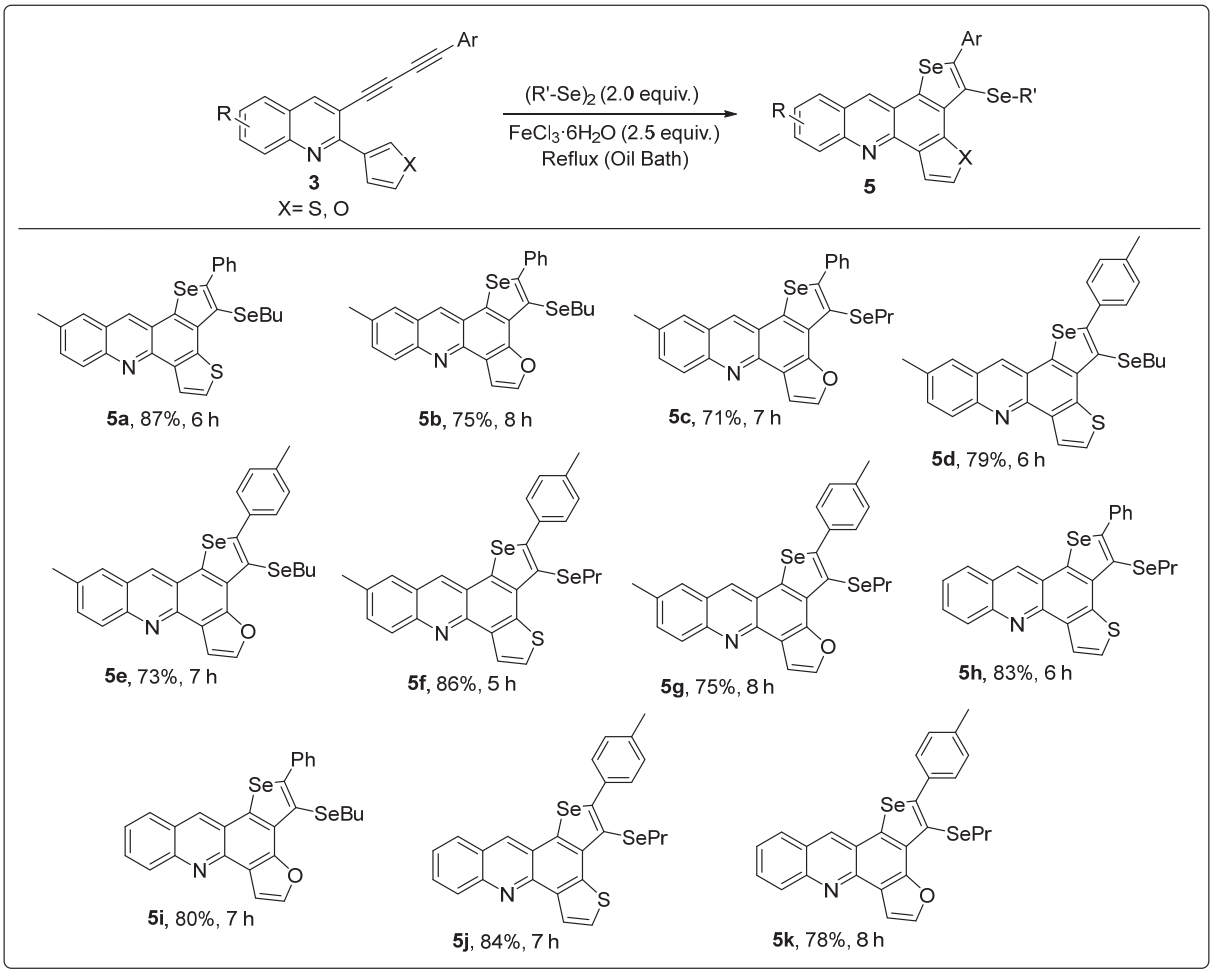
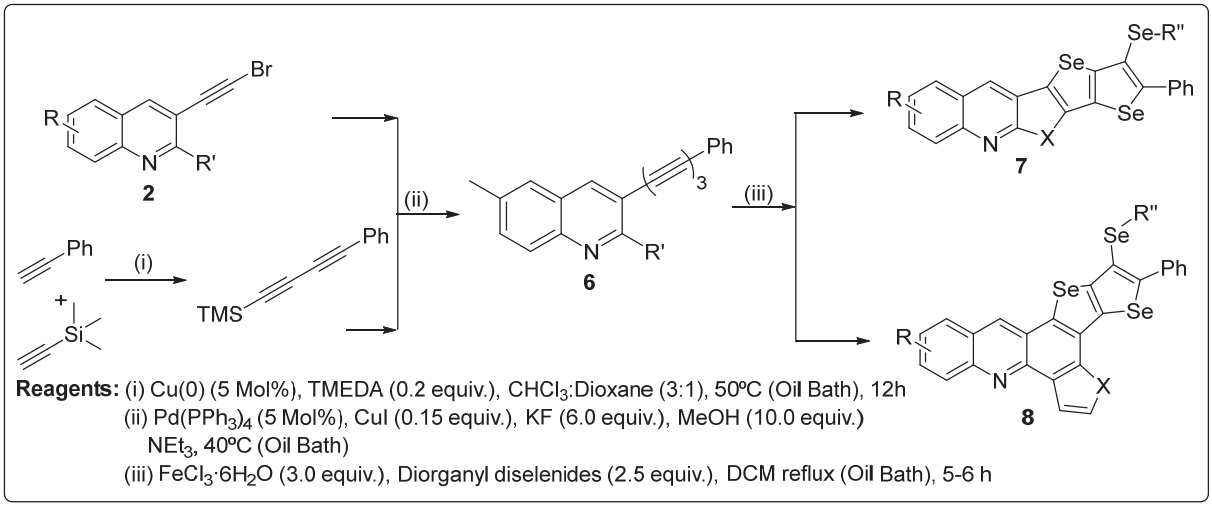


Chart 2. Substrate scopes of selenophene-fused thieno [2,3-*c*] acridine and furo [2,3-*c*] acridine (**5**)



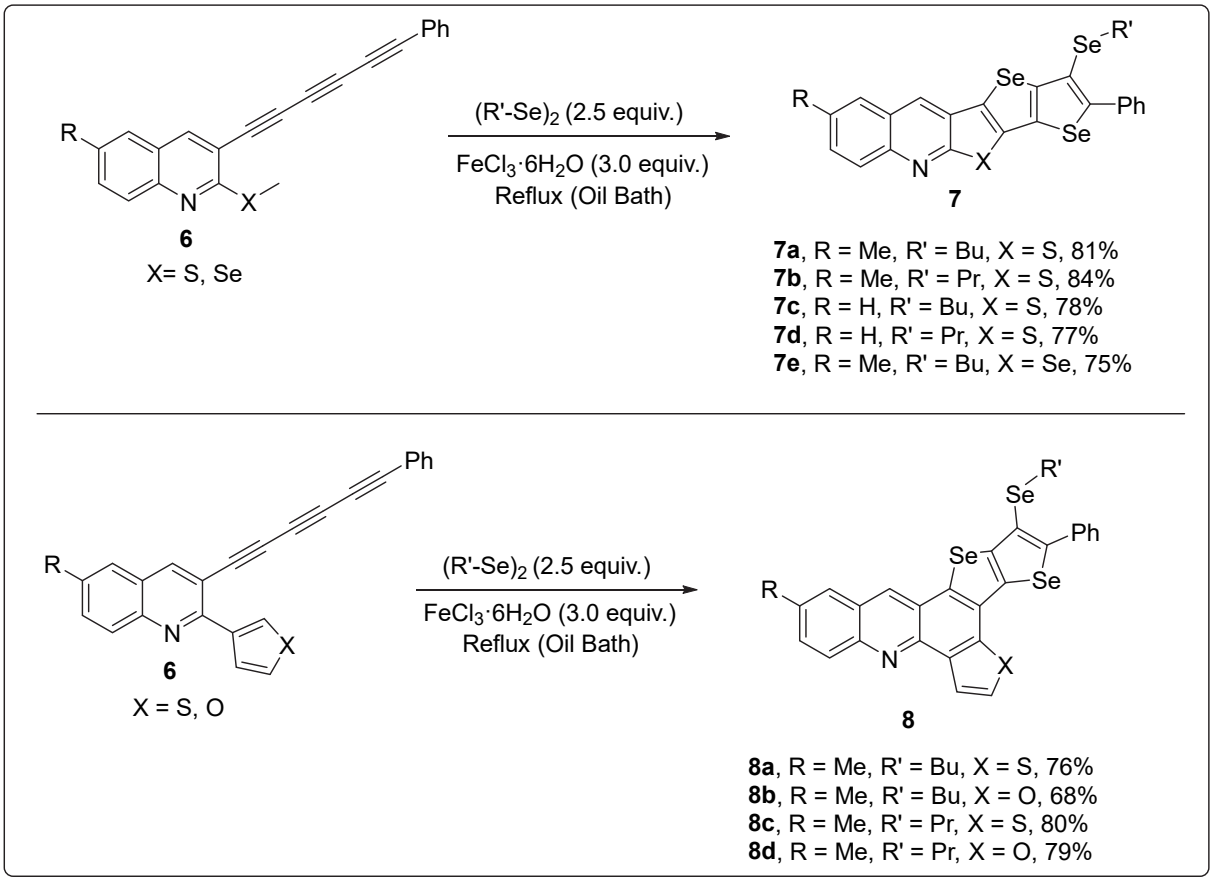
Further, we were interested towards the synthesis of linear trialkynes (**3.2.2**). The phenyl acetylene and trimethylsilyl acetylene were treated with Cu(0) and TMEDA to obtain TMS-dialkyne [22] i.e., trimethyl (phenylbuta-1,3-diyn-1-yl)silane in 43% yield. Next, TMS-dialkyne was treated with (**2**) under given standard conditions to afford the compounds (**6**) in 24-35% yields. The differently substituted compounds (**6**) were confirmed by the IR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectral analysis.

3.2.2 General scheme: synthesis of 1,3,5-triyne



The 1,3,5-triyne cascade cyclization was successfully achieved under Fe(III) (3.0 equiv.) and dibutyl diselenide (2.5 equiv.) conditions to obtain diselenophene-fused thieno [2,3-*b*]quinolines, selenopheno[2,3-*b*]quinolines (7) and diselenophene-fused thieno[2,3-*c*] acridine and furo[2,3-*c*] acridine (8) scaffolds, respectively (Chart 3). Additionally, it was found that the reaction does not proceed when treated with dibutyl selenide $(Bu)_2Se$, $(Ph\text{-}Se)_2$ and dimethyl disulfides $(Me\text{-}S)_2$. Finally, the synthesized compounds (4), (5), (7) and (8) were confirmed by the IR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectral analysis.

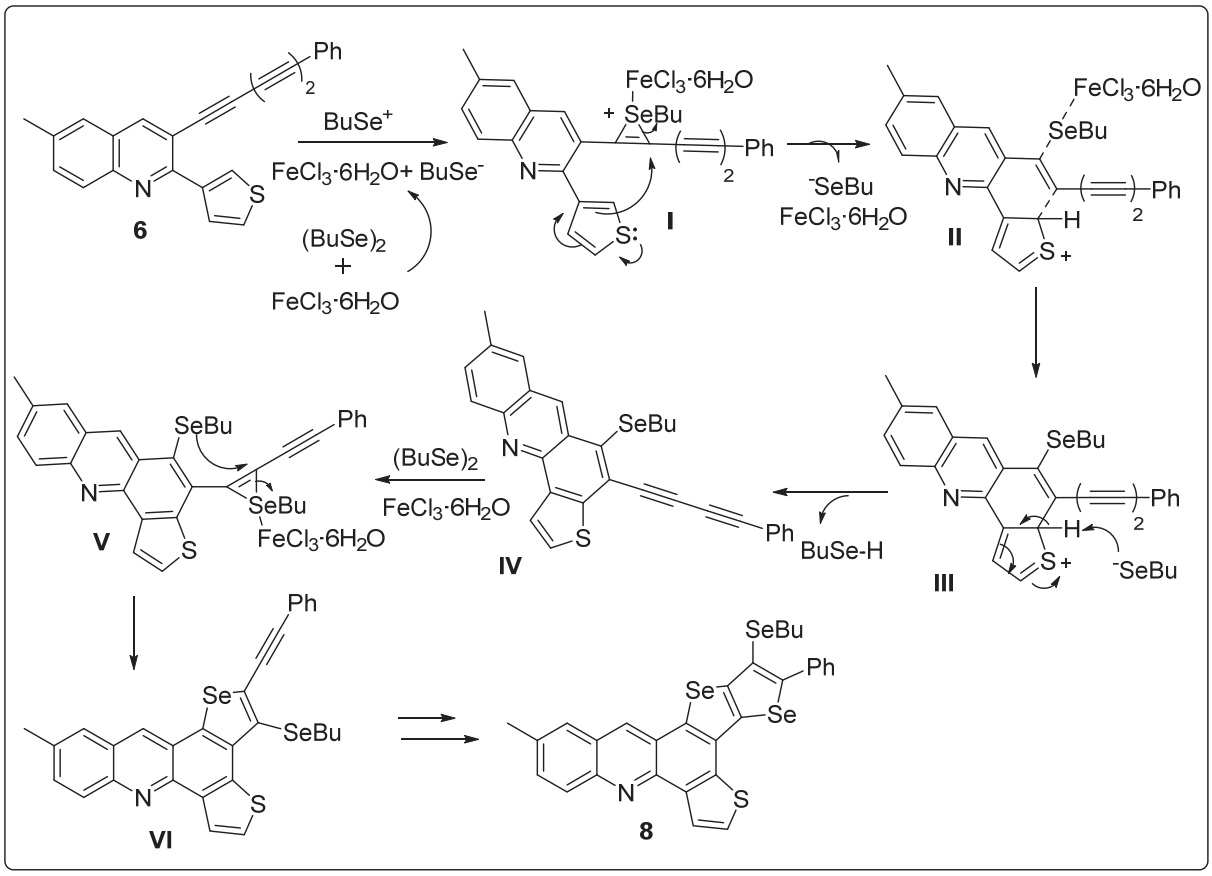
Chart 3. Substrate scope of di-selenophene-fused thieno [2,3-*b*]quinolines, diselenopheno[2,3-*b*]quinolines (**7**) and diselenophene-fused thieno [2,3-*c*] acridine and furo[2,3-*c*] acridine (**8**)



In this study, we have hypothesized the plausible mechanism for the novel cascade cyclization. When the 3-furan and 3-thiophene (R') were used as internal nucleophiles, the nucleophilic attack takes place from 2-position of furan and thiophene which interestingly resulted into the six membered acridine core heterocycles **5** and **8**, at the same time when sulfur and selenium (R') were used as internal nucleophiles which resulted into five membered heterocycles **4** and **7** (Scheme 3). In the first step, iron salt reacts with dibutyl diselenide promoting the cleavage of Se-Se bond to give an organoselenyl cation and an organoselenyl anion [20, 23]. The Fe(III) coordinates with one selenium atom from dibutyl diselenide, which results in the intermediate **I**, further the nucleophilic anti-attack on activated seleniranium ion **I** by thiophene nucleophile results into the intermediate cyclized product **II**. The rearomatization of intermediate **III** is achieved *via* S_N2 displacement by the butyl selenolate anion present in the reaction mixture to afford the thieno[2,3-*c*]acridine **IV**. Second cyclization step proceeds with the Bu-Se nucleophile **V** which resulted into the intermediate selenophene-fused thieno[2,3-*c*]acridine **VI**. On

continuation, the cascade cyclization proceeds for third alkyne **VI** which finally afford the product di-selenophene-fused thieno[2,3-*c*]acridine **8**.

3.3 Scheme 3 Plausible intramolecular cascade cyclization mechanism



3.4 Photophysical study

The UV-vis absorption spectra of **4a**, **4l**, **5a**, **5b**, **7a**, **8a** and **8d** in DCM are shown in Figure 1. In the quinoline derivatives **4a**, **4l** and **7a**, the absorption maximum (λ_{max}) and molar extinction coefficient (ε) values of thiophene-fused (**4a**: λ_{max} = 371 nm, ε = 28,800) and selenophene-fused (**4l**: λ_{max} = 370 nm, ε = 23,900) derivatives were almost same (Figure 1a, Table 2). Annulation of a selenophene ring to **4a** led to the red-shift of λ_{max} and increase of ε values (**7a**: λ_{max} = 401 nm, ε = 40,400) due to the extension of π-conjugation. On the other hand, in the acridine derivatives **5a**, **5b**, **8a** and **8d**, thiophene-fused derivative **5a** (λ_{max} = 402 nm) showed red-shifted λ_{max} value compared to furan-fused derivative **5b** (λ_{max} = 387 nm) (Figure 1b). Similar to the result of

quinoline derivatives, further annulation of a selenophene ring (**8a**: λ_{max} = 411 nm, ε = 23,200, **8b**: λ_{max} = 406 nm, ε = 24,700) resulted in the red-shift of λ_{max} and increase of ε values compared to the corresponding non-fused derivatives (**5a**: ε = 16,600, **5b**: λ_{max} = 406 nm, ε = 15,300).

The fluorescence spectra of **4a**, **4l**, **5a**, **5b**, **7a**, **8a** and **8d** in DCM are shown in Figure 2. The fluorescence maximum (F_{max}) and Stokes shift values were in the range of 433 to 472 nm and 36 to 66 nm, respectively (Table 2). The fluorescence quantum yield (Φ_f) values were relatively low (Φ_f: 0.003–0.059) probably because of heavy atom effect [24]. Interestingly, annulation of a selenophene ring to **4a** (Φ_f = 0.003) led to a slight increase of the Φ_f value (**7a**: Φ_f = 0.009) (Figure 2a, Table 2). According to the Strickler-Berg equation, radiative rate constant (k_f) is proportional to the integral of molar extinction coefficient curve [25]. Thus, the increased Φ_f value of **7a** may be due to the higher ε value (**7a**: ε = 40,400, **4a**: ε = 28,800). Furan-fused selenophenoacridine **5b** (Φ_f = 0.059) showed the highest Φ_f value (Figure 2b, Table 2). Different from the result of **4a**, annulation of a selenophene ring to **5b** caused to a decrease of the Φ_f value (**8d**: Φ_f = 0.003) probably due to the heavy atom effect of the added selenium atom.

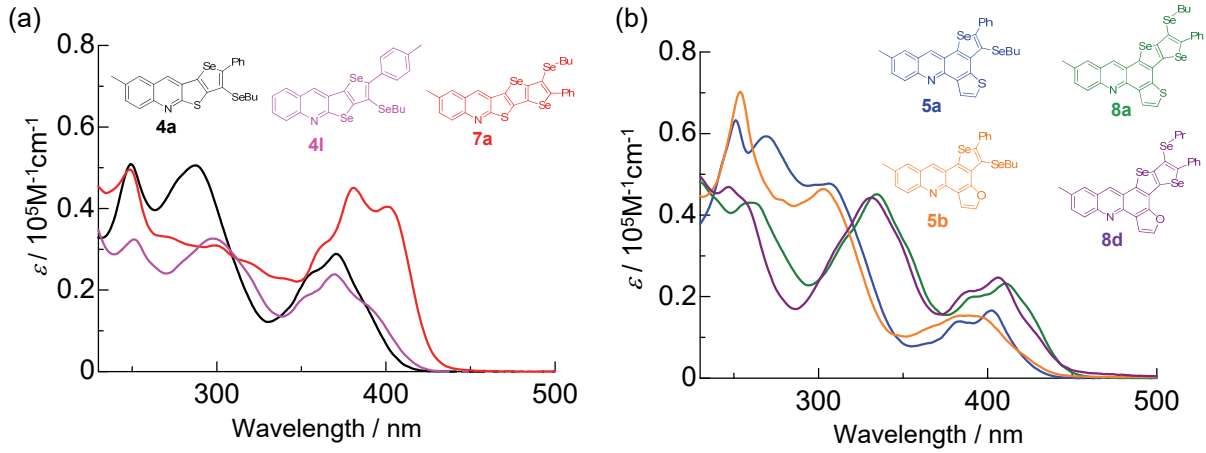


Figure 1. UV-vis absorption spectra of (**a**) quinoline and (**b**) acridine derivatives in DCM.

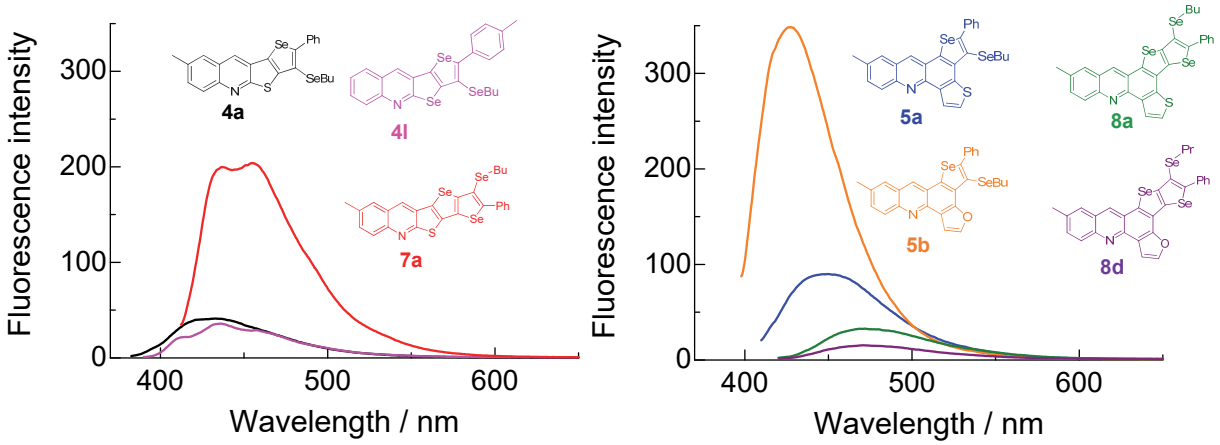


Figure 2. Fluorescence spectra of (a) quinoline and (b) acridine derivatives in DCM.

Table 2. Optical properties in DCM

Compound	λ_{max} (ε) / nm	F_{max} / nm	Stokes shift / nm	$\phi_f{}^b$
4a	249 (50,900), 287 (50,600), 371 (28,800)	433	62	0.003
4l	251 (32,400), 297 (32,600), 370 (23,900)	436	66	0.003
5a	251 (63,300), 269 (59,300), 384 (13,900), 402 (16,600)	450	48	0.007
5b	254 (70,200), 303 (46,400), 387 (15,300)	427	40	0.059
7a	249 (49,600), 381 (45,100), 401 (40,400)	437, 455	36, 54	0.009
8a	260 (43,000), 335 (45,100), 392 (20,000), 411 (23,200)	472	61	0.006
8d	247 (46,900), 331 (44,300), 390 (21,400), 406 (24,700)	471	65	0.003

[a]Measured at a concentration of 1.0 x 10^{-5} mol dm^{-3}. [b]Measured using an integrating sphere method.

3.5 Conclusion

In conclusion, we have successfully developed a methodology for the cascade cyclization of linear 1,3 diyne and 1,3,5 triyne, the use of different internal nucleophiles including thiophene, furan, sulphur and selenium; the two core system formed acridine and quinoline. The diorganyl diselenide acts as dual role, one is cyclizing agent and secondly insertion of one and / or two selenium atom and one R′-Se group in the final product. This is highly important in terms of atom economy. The synthesized selenophene-fused derivatives showed λ_{max}, F_{max} and Φ_f values in the range from 370-411 nm, 427-472 nm and 0.003-0.059, respectively in DCM. We believed

that this methodology provides a novel pathway for the synthesis of linear alkynes as well as quinoline fused two, three and four membered heterocycles. Also, the biological and DFT mechanistic studies for such novel heterocycles are in progress.

3.6 Experimental section

3.6.1 General methods

All solvents and reagents were purchased from the suppliers and used without further purification. IR spectra were recorded on a JASCO FT/IR-460 Plus spectrophotometer. Reactions were monitored by TLC on silica plates using UV-light or Iodine chamber for visualization. Evaporation and condensation were carried out *in vacuo*. NMR spectra were recorded with JEOL JNM-ECS 400 spectrometers with tetramethylsilane as an internal standard. Chemical shifts δ and coupling constants *J* are given in ppm (parts per million) and Hz (hertz) respectively. The following abbreviations were used as follows: s: singlet, d: doublet, t: triplet, m: multiplet. All known compounds data are in consistent with the given literature reports. Scale up reactions also performed as per the given general procedure without any deviation. Melting points were measured by a Yanaco micromelting point apparatus. The HRMS were recorded with the Acquity XEVO QTof MS analyzer. UV-vis spectra were taken on a Hitachi U4100 spectrophotometer. Fluorescence spectra were measured on a FP-8600 spectrofluorometer. Fluorescence quantum yields were recorded on a Quantaurus-QY.

3.6.2 General procedure and spectral data

Preparation of 1,2-Dibutyldiselane:

Selenium (0.200 g, 2.53 mmol) was added to a stirred solution of sodium borohydride (0.191 g, 5.07 mmol) in ethanol (20 mL) at 0°C. Stirring was continued for 30 min; at this temperature an additional Se (0.200 g, 2.53 mmol) was added to reaction mixture and stirred for 30 min at 0°C. Finally the Iodobutane (1.01 mL, 8.87 mmol) was added over a period of 5 min. After stirring for a further hour at room temp., the reaction mixture was extracted with *n*-hexane and washed with water, dried over sodium sulphate and concentrated in vacuo. The crude product was purified over silica gel column chromatography inside the fuming hood (SiO_2: *n*-hexane / toluene = 20/1) to afford the dibutyl diselenide as red coloured liquid[1] having strong smell.

Yield: 89%; yellow coloured liquid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.92 (t, *J* = 7.6 Hz, 4H), 1.68-1.75 (m, 4H), 1.42 (q, *J* = 7.5 Hz, 4H), 0.93 (t, *J* = 7.3 Hz, 6H); ^{13}C{1H}-NMR (100 MHz, $CDCl_3$) δ 33.2, 30.0, 22.7, 13.7; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 307.8.

1,2-Dipropyldiselane

Yield: 90%; Red coloured liquid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.86-2.94 (m, 4H), 1.72-1.81 (m, 4H), 1.00 (t, J = 7.3 Hz, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 32.4, 24.3, 14.2; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 303.4.

General procedure and spectral data for the synthesized compounds 3a-3t.

To a solution of 3-(bromoethynyl)-6-methyl-2-(methylthio)quinoline **2a** (40 mg, 0.136 mmol) dissolved in dry triethylamine (4 ml) was added phenyl acetylene (18.18 mg, 0.177 mmol, 1.3 equiv.), $Pd(PPh_3)_2Cl_2$ (7 mg, 0.6 mmol, 0.6 equiv.), triphenylphosphine (3.59 mg, 0.1 mmol, 0.1 equiv.), and copper(I) iodide (1.30 mg, 0.0068 mmol) at room temperature under nitrogen. The mixture was stirred at 70°C for 8 h. After completion of reaction, the mixture concentrated in vacuo to remove triethylamine. The crude product was dissolved in dichloromethane and extracted with aqueous ammonium chloride solution. The crude product was isolated by evaporating the solvent and purified by column chromatography using *n*-hexane/ethyl acetate (97:3) as eluent to afford **3a** 28 mg as yellow solid.

6-Methyl-2-(methylthio)-3-(phenylbuta-1,3-diyn-1-yl)quinoline (3a)

Yield: 65%; Melting point: 114-116°C; IR (neat): 2918, 2206, 1841, 1678, 1579, 1557, 1488, 1399, 1360, 1309, 1140, 1083, 924, 825, 743, 678, 577, 522 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.55-7.57 (m, 2H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.45 (s, 1H), 7.34-7.40 (m, 3H), 2.70 (s, 3H), 2.50 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.2, 145.8, 139.7, 135.7, 133.0, 132.7, 129.6, 128.6, 127.7, 126.5, 124.8, 121.6, 115.1, 84.1, 81.3, 76.8, 73.7, 21.5, 13.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{16}NS$ 314.1003; Found 314.0978.

6-Methyl-2-(methylselanyl)-3-(phenylbuta-1,3-diyn-1-yl)quinoline (3b)

Yield: 70%; Melting point: 104-105°C; IR (neat): 2614, 1579, 1531, 1463, 1353, 1065, 915, 823, 755, 688, 541 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.31-7.40 (m, 5H), 2.60 (s, 3H), 2.49 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 157.3, 146.4, 139.1, 136.0, 133.0, 132.7, 129.6, 128.6, 128.0, 126.5, 125.3, 121.6, 117.5, 84.1, 81.0, 76.8, 73.7, 21.6, 6.1; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{16}NSe$ 362.0448; Found 362.0439.

6-Methyl-2-(methylthio)-3-(p-tolylbuta-1,3-diyn-1-yl)quinoline (3c)

Yield: 58%; Sticky; IR (neat): 2918, 1579, 1557, 1439, 1399, 1360, 1309, 1083, 1065, 824, 743, 678, 640, 577, 521 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.80 (d, *J* = 8.7 Hz, 1H),

7.43-7.46 (m, 3H), 7.39 (s, 1H), 7.14 (d, *J* = 7.8 Hz, 2H), 2.68 (s, 3H), 2.47 (s, 3H), 2.36 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.2, 145.8, 140.0, 139.5, 135.7, 133.0, 132.6, 129.4, 127.7, 126.5, 124.8, 118.5, 115.2, 84.5, 81.6, 76.9, 73.3, 21.8, 21.5, 13.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{18}NS$ 328.1160; Found 328.1141.

7-Methyl-2-(methylthio)-3-(phenylbuta-1,3-diyn-1-yl)quinoline (3d)

Yield: 71%; Melting point: 135-136°C; IR (neat): 2923, 1619, 1596, 1579, 1488, 1438, 1397, 1345, 1140, 1079, 899, 875, 683, 648, 579, 524, 465 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.72 (s, 1H), 7.55 (d, *J* = 8.1 Hz, 3H), 7.36 (dd, *J* = 9.2, 7.0 Hz, 3H), 7.26 (d, *J* = 5.4 Hz, 1H), 2.69 (s, 3H), 2.53 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.2, 147.4, 141.6, 140.0, 132.7, 129.5, 128.6, 128.0, 127.3, 127.2, 122.9, 121.7, 114.3, 84.0, 81.2, 76.8, 73.8, 22.1, 13.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{16}NS$ 314.1003; Found 314.0976.

7-Methyl-2-(methylselanyl)-3-(phenylbuta-1,3-diyn-1-yl)quinoline (3e)

Yield: 73%; Melting point: 143-145°C; IR (neat): 2929, 1958, 1870, 1796, 1589, 1586, 1438, 1264, 1141, 1063, 899, 793, 748, 683, 578, 524, 465 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.74 (s, 1H), 7.57 (dt, *J* = 7.9, 2.0 Hz, 3H), 7.37 (dd, *J* = 9.2, 7.0 Hz, 3H), 7.29 (d, *J* = 9.9 Hz, 1H), 2.58-2.60 (m, 3H), 2.54 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 158.5, 147.9, 141.5, 139.4, 132.7, 129.6, 128.6, 128.3, 127.5, 127.3, 123.3, 121.6, 116.6, 84.0, 80.8, 76.8, 73.8, 22.1, 6.1; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{16}NSe$ 362.0448; Found 362.0426.

7-Methyl-2-(methylthio)-3-(p-tolylbuta-1,3-diyn-1-yl)quinoline (3f)

Yield: 60%; Melting point: 114-115°C; IR (neat): 2951, 1579, 1557, 1398, 1360, 1219, 1137, 1083, 924, 824, 743, 678, 577, 521 cm^{-1}; ^{1}H-NMR (400 MHz, $CHCl_3$) δ 8.05 (s, 1H), 7.72 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.24-7.26 (m, 1H), 7.15 (d, *J* = 7.8 Hz, 2H), 2.69 (s, 3H), 2.53 (s, 3H), 2.40-2.36 (3H); ^{13}C-NMR (100 MHz, $CHCl_3$) δ 161.2, 147.3, 141.5, 139.8, 132.6, 129.4, 129.3, 128.0, 127.3, 127.2, 122.9, 118.5, 114.4, 84.4, 81.4, 76.8, 73.2, 22.1, 21.8, 13.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{18}NS$ 328.1160; Found 328.1137.

8-Methyl-2-(methylthio)-3-(phenylbuta-1,3-diyn-1-yl)quinoline (3g)

Yield: 59%; Melting point: 121-123°C; IR (neat): 2923, 1619, 1596, 1579, 1488, 1438, 1397, 1345, 1140, 1079, 899, 875, 683, 648, 579, 524, 465 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.50-7.57 (m, 4H), 7.31-7.38 (m, 4H), 2.73 (s, 3H), 2.70 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.0, 145.9, 140.5, 136.2, 132.7, 131.2, 129.6, 128.6, 125.6, 125.4, 124.6, 121.6,

114.8, 84.1, 81.4, 76.8, 73.8, 17.8, 13.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{16}NS$ 314.1003; Found 314.0982.

8-Methyl-2-(methylselanyl)-3-(phenylbuta-1,3-diyn-1-yl)quinoline (3h)

Yield: 66%; Sticky; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.56-7.58 (m, 2H), 7.53 (s, 1H), 7.34-7.40 (m, 5H), 2.76 (s, 3H), 2.61 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 157.3, 146.4, 140.0, 136.5, 132.7, 131.1, 129.6, 128.6, 128.5, 125.9, 125.5, 125.4, 125.1, 121.6, 117.2, 84.1, 77.7, 17.7, 6.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{16}N^{80}Se$ 362.0448 362.0448; Found 362.0457.

8-Methyl-2-(methylthio)-3-(p-tolylbuta-1,3-diyn-1-yl)quinoline (3i)

Yield: 55%; Melting point: 125-126°C; IR (neat): 3049, 2918, 1579, 1556, 1488, 1398, 1359, 1083, 924, 824, 772, 743, 678, 521 cm^{-1}; ^{1}H-NMR (400 MHz, $CHCl_3$) δ 8.06 (s, 1H), 7.47 (dd, *J* = 20.8, 8.0 Hz, 4H), 7.32 (d, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 2H), 2.72 (s, 3H), 2.69 (s, 3H), 2.36 (s, 3H); ^{13}C-NMR (100 MHz, $CHCl_3$) δ 160.0, 145.8, 140.3, 140.0, 136.2, 132.6, 131.1, 129.4, 125.6, 125.4, 124.7, 118.5, 115.0, 84.5, 81.6, 76.8, 73.5, 21.8, 17.8, 13.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{18}NS$ 328.1160; Found 328.1137.

2-(Methylthio)-3-(phenylbuta-1,3-diyn-1-yl)quinoline (3j)

Yield: 67%; Melting point: 110-112°C; IR (neat): 2922, 1594, 1551, 1580, 1486, 1360, 1351, 1132, 1073, 966, 951, 905, 760, 749, 687, 575, 524, 485 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.63-7.68 (m, 2H), 7.56 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.33-7.44 (m, 4H), 2.71 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.3, 147.2, 140.1, 132.7, 130.9, 129.6, 128.6, 128.1, 127.6, 125.9, 124.8, 121.6, 115.3, 84.2, 81.5, 76.8, 73.7, 13.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{14}NS$ 300.0847; Found 300.0824.

2-(Methylselanyl)-3-(phenylbuta-1,3-diyn-1-yl)quinoline (3k)

Yield: 70%; Melting point: 124-126°C; IR (neat): 2963, 2211, 1725, 1614, 1578, 1552, 1395, 1354, 1261, 1131, 1063, 912, 859, 799, 753, 688, 636, 526 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.65-7.70 (m, 2H), 7.58 (dd, *J* = 8.1, 1.3 Hz, 2H), 7.46 (t, *J* = 7.0 Hz, 1H), 7.35-7.41 (m, 3H), 2.61 (t, *J* = 5.8 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 158.6, 147.7, 139.6, 132.7, 130.8, 129.6, 128.6, 128.2, 127.7, 126.1, 125.3, 121.5, 117.6, 84.2, 81.1, 76.8, 73.7, 6.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{14}NSe$ 348.0291; Found 348.0271.

2-(Methylthio)-3-(p-tolylbuta-1,3-diyn-1-yl)quinoline (3l)

Yield: 61%; Melting point: 79-81°C; IR (neat): 2919, 1611, 1579, 1549, 1390, 1352, 1131, 1075, 1017, 907, 811, 746, 524 cm^{-1}; ^{1}H-NMR (400 MHz, $CHCl_3$) δ 8.12 (s, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.67 (q, *J* = 6.9 Hz, 2H), 7.44 (q, *J* = 7.5 Hz, 3H), 7.16 (d, *J* = 8.2 Hz, 2H), 2.71 (s, 3H), 2.38 (s, 3H); ^{13}C-NMR (100 MHz, $CHCl_3$) δ 161.3, 147.1, 140.1, 140.0, 132.6, 130.8, 129.4, 128.0, 127.5, 125.8, 124.9, 118.4, 115.4, 84.6, 81.7, 76.8, 73.1, 21.8, 13.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{16}NS$ 314.1003; Found 314.0977.

2-(Methylselanyl)-3-(p-tolylbuta-1,3-diyn-1-yl)quinoline (3m)

Yield: 59%; Melting point: 78-79°C; IR (neat): 2927, 1613, 1577, 1548, 1391, 1355, 1131, 1060, 902, 811, 744, 522 cm^{-1}; ^{1}H-NMR (400 MHz, $CHCl_3$) δ 8.06 (s, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.63-7.68 (m, 2H), 7.45 (t, *J* = 8.5 Hz, 3H), 7.15 (d, *J* = 7.8 Hz, 2H), 2.58-2.62 (m, 3H), 2.37 (s, 3H); ^{13}C-NMR (100 MHz, $CHCl_3$) δ 158.7, 147.7, 140.1, 139.5, 132.7, 130.7, 129.4, 128.2, 127.6, 126.1, 125.3, 118.4, 117.7, 84.6, 81.4, 73.1, 21.8, 6.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{16}N^{78}Se$ 360.0448; Found 360.0439.

6-Methyl-3-(phenylbuta-1,3-diyn-1-yl)-2-(thiophen-3-yl)quinoline (3n)

Yield: 56%; Melting point: 105-106°C; IR (neat): 3044, 1574, 1523, 1482, 1438, 1359, 1248, 924, 871, 800, 824, 754, 726, 685, 623, 525 cm^{-1}; ^{1}H-NMR (400 MHz, $CHCl_3$) δ 8.33 (q, *J* = 1.5 Hz, 1H), 8.29 (s, 1H), 7.94-7.97 (m, 2H), 7.50-7.56 (m, 3H), 7.46 (s, 1H), 7.40 (q, *J* = 2.6 Hz, 1H), 7.32-7.37 (m, 3H), 2.49 (s, 3H); ^{13}C-NMR (100 MHz, $CHCl_3$) δ 153.0, 145.8, 142.7, 141.1, 137.1, 133.4, 132.7, 129.6, 129.2, 129.0, 128.6, 127.0, 125.9, 125.2, 121.6, 114.1, 83.5, 80.2, 76.9, 74.0, 21.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{16}NS$ 350.1003; Found 350.0978.

2-(Furan-3-yl)-6-methyl-3-(phenylbuta-1,3-diyn-1-yl)quinoline (3o)

Yield: 58%; Melting point: 122-123°C; IR (neat): 2921, 1583, 1511, 1485, 1361, 1152, 1137, 1053, 929, 826, 805, 738, 598, 589 cm^{-1}; ^{1}H-NMR (400 MHz, $CHCl_3$) δ 8.54 (s, 1H), 8.26 (s, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.50-7.58 (m, 4H), 7.45 (s, 1H), 7.35-7.39 (m, 2H), 7.31-7.32 (m, 2H), 2.49 (s, 3H); ^{13}C-NMR (100 MHz, $CHCl_3$) δ 150.9, 145.8, 143.9, 143.0, 142.3, 137.1, 133.3, 132.7, 129.6, 129.1, 128.6, 126.3, 126.0, 125.7, 121.6, 113.8, 110.8, 83.8, 80.0, 79.7, 73.8, 21.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{16}NO$ 334.1232; Found 334.1202.

6-Methyl-2-(thiophen-3-yl)-3-(p-tolylbuta-1,3-diyn-1-yl)quinoline (3p)

Yield: 60%; Melting point: 164-165°C; IR (neat): 2915, 1600, 1558, 1435, 1263, 1200, 1192, 1162, 920, 825, 815, 800, 773, 724, 636, 527 cm^{-1}; ^{1}H-NMR (400 MHz, $CHCl_3$) δ 8.31-8.34 (m,

2H), 7.96 (t, *J* = 4.3 Hz, 2H), 7.40-7.54 (m, 5H), 7.15 (d, *J* = 8.1 Hz, 2H), 2.51 (s, 3H), 2.37 (s, 3H); ^{13}C-NMR (100 MHz, $CHCl_3$) δ 153.0, 145.7, 142.6, 141.1, 140.0, 137.1, 133.3, 132.6, 129.4, 129.2, 129.0, 127.0, 126.0, 125.9, 125.1, 118.5, 114.2, 83.8, 79.8, 79.5, 73.4, 21.8, 21.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{18}NS$ 364.1160; Found 364.1133.

2-(Furan-3-yl)-6-methyl-3-(p-tolylbuta-1,3-diyn-1-yl)quinoline (3q)

Yield: 66%; Melting point: 129-130°C; IR (neat): 2919, 1582, 1554, 1511, 1484, 1285, 1152, 929, 873, 805, 777, 737, 598, 589, 525 cm^{-1}; ^{1}H-NMR (400 MHz, $CHCl_3$) δ 8.55 (s, 1H), 8.25 (s, 1H), 7.93 (d, *J* = 8.7 Hz, 1H), 7.50-7.53 (m, 2H), 7.46 (d, *J* = 8.2 Hz, 3H), 7.31 (d, *J* = 0.9 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 2H), 2.50 (s, 3H), 2.36 (s, 3H); ^{13}C-NMR (100 MHz, $CHCl_3$) δ 150.9, 145.8, 143.9, 142.9, 142.2, 140.1, 137.0, 133.3, 132.7, 129.4, 129.1, 126.3, 126.0, 125.7, 118.4, 114.0, 110.8, 84.1, 79.9, 79.6, 73.2, 21.8, 21.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{18}NO$ 348.1388; Found 348.1360.

3-(Phenylbuta-1,3-diyn-1-yl)-2-(thiophen-3-yl)quinoline (3r)

Yield: 57%; Melting point: 98-99°C; IR (neat): 2920, 1620, 1574, 1482, 1359, 1337, 1219, 1130, 924, 824, 800, 686, 726, 623 cm^{-1}; ^{1}H-NMR (400 MHz, $CHCl_3$) δ 8.42 (s, 1H), 8.37 (q, *J* = 1.4 Hz, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.99 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.69-7.75 (m, 2H), 7.49-7.57 (m, 3H), 7.42 (q, *J* = 2.7 Hz, 1H), 7.33-7.39 (m, 3H); ^{13}C-NMR (100 MHz, $CHCl_3$) δ 153.8, 147.1, 143.3, 141.0, 132.7, 131.0, 129.6, 129.6, 129.0, 128.6, 127.4, 127.1, 125.9, 125.3, 121.6, 114.2, 83.6, 80.0, 79.5, 74.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{14}NS$ 336.0847; Found 336.0823.

2-(Thiophen-3-yl)-3-(p-tolylbuta-1,3-diyn-1-yl)quinoline (3s)

Yield: 61%; Melting point: 123-125°C; IR (neat): 2918, 1574, 1556, 1480, 1431, 1263, 1180, 920, 853, 800, 813, 778, 748, 724, 694, 527 cm^{-1}; ^{1}H-NMR (400 MHz, $CHCl_3$) δ 8.37-8.41 (m, 2H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.99 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.69-7.74 (m, 2H), 7.41-7.53 (m, 4H), 7.15 (d, *J* = 7.8 Hz, 2H), 2.36 (s, 3H); ^{13}C-NMR (100 MHz, $CHCl_3$) δ 153.8, 147.1, 143.3, 141.0, 140.1, 132.6, 131.0, 129.5, 129.4, 129.0, 127.4, 127.1, 126.0, 125.2, 118.4, 114.4, 84.0, 79.7, 79.6, 77.5, 77.2, 76.8, 73.4, 21.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{16}NS$ 350.1003; Found 350.0987.

2-(Furan-3-yl)-3-(p-tolylbuta-1,3-diyn-1-yl)quinoline (3t)

Yield: 62%; Melting point: 116-118°C; IR (neat): 2917, 1596, 1583, 1509, 1484, 1354, 1154, 1116, 1053, 870, 808, 784, 750, 738, 729, 540, 523 cm^{-1}; ^{1}H-NMR (400 MHz, $CHCl_3$) δ 8.58 (s,

1H), 8.34 (s, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.66-7.70 (m, 2H), 7.54 (s, 1H), 7.46 (dd, *J* = 7.4, 5.7 Hz, 3H), 7.33 (d, *J* = 1.1 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 2.36 (s, 3H); ^{13}C-NMR (100 MHz, $CHCl_3$) δ 151.7, 147.1, 144.1, 143.0, 142.8, 140.2, 132.7, 132.5, 131.0, 129.4, 127.1, 127.0, 126.3, 125.7, 118.4, 114.1, 110.8, 84.3, 80.1, 79.4, 73.2, 21.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{16}NO$ 334.1232; Found 334.1203.

General procedure and spectral data for the synthesized compounds 6a-6f.

To a stirred solution of 3-(bromoethynyl)-6-methyl-2-(methylthio)quinoline **2a** (0.150 g, 1.0 equiv.) in 6 ml NEt_3 were added $Pd(PPh_3)_4$ (0.030 g, 5 mol %), CuI (0.023 g, 15 mol%), and KF (0.275 g, 6.00 equiv.) The reaction vial was flushed with N_2 several times. After that, CuI (0.015 g, 15 mol %) was added, and the reaction vial was sealed and flushed with Ar. TMS-Alkyne (0.132 g, 1.3 equiv.) was added with the syringe. The reaction mixture was stirred at 40°C for the corresponding time (TLC monitoring). After 1 h, the reaction mixture was cooled, poured into a saturated aqueous solution of NH_4Cl, and extracted with ethyl acetate. The combined organic layers were washed with a saturated solution of NH_4Cl solution and two times with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel using *n*-hexane/ethyl acetate (96:4) as the eluent afforded the desired product **6a** 0.045 g.

6-Methyl-2-(methylthio)-3-(phenylhexa-1,3,5-triyn-1-yl)quinoline (6a)

Yield: 26%; Melting point: 124-125°C; IR (neat): 2918, 1578, 1551, 1490, 1402, 1324, 1140, 1110, 1023, 917, 820, 744, 680, 633, 568, 522 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.81 (d, *J* = 8.7 Hz, 1H), 7.54 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.47-7.50 (m, 1H), 7.32-7.42 (m, 4H), 2.68 (s, 3H), 2.48 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.4, 146.0, 140.5, 135.8, 133.3, 133.1, 130.0, 128.6, 127.8, 126.5, 124.7, 121.0, 114.4, 81.8, 80.0, 74.5, 74.2, 69.1, 66.1, 21.5, 13.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{16}NS$ 338.1003; Found 338.0981.

6-Methyl-2-(methylselanyl)-3-(phenylhexa-1,3,5-triyn-1-yl)quinoline (6b)

Yield: 35%; Melting point: 56-57°C; IR (neat): 2922, 2849, 1619, 1580, 1488, 1399, 1347, 1142, 1112, 1079, 874, 794, 751, 685, 619, 581, 525 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 15.5 Hz, 1H), 7.83 (d, *J* = 8.6 Hz, 1H), 7.55 (d, *J* = 6.9 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.33-7.46 (m, 4H), 2.59 (s, 3H), 2.49 (d, *J* = 5.7 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 157.5, 146.5, 140.0, 136.1, 133.3, 133.1, 130.0, 128.6, 128.0, 126.6, 125.2, 120.9, 116.7, 81.4, 80.0, 74.8, 74.4,

69.1, 66.1, 21.6, 6.1; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{16}N^{80}Se$ 386.0448; Found 386.0457.

2-(Methylthio)-3-(phenylhexa-1,3,5-triyn-1-yl)quinoline (6c)

Yield: 24%; Melting point: 70-71°C; IR (neat): 2921, 2175, 1733, 1612, 1579, 1441, 1400, 1357, 1330, 1135, 1107, 1025, 905, 743, 677, 522 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.66 (dd, *J* = 7.8, 6.4 Hz, 2H), 7.54-7.56 (m, 2H), 7.33-7.45 (m, 4H), 2.70 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.5, 147.2, 141.0, 133.1, 131.2, 130.0, 128.6, 128.1, 127.6, 126.0, 124.7, 120.9, 114.5, 82.0, 80.1, 74.4, 74.0, 69.2, 66.1, 13.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{14}NS$ 324.0847; Found 324.0854.

6-Methyl-3-(phenylhexa-1,3,5-triyn-1-yl)-2-(thiophen-3-yl)quinoline (6d)

Yield: 25%; Melting point: 151-152°C; IR (neat): 2852, 1574, 1484, 1439, 1346, 1252, 1219, 1134, 1089, 822, 793, 747, 720, 681, 622, 522 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.26-8.33 (m, 2H), 7.92-7.97 (m, 2H), 7.49-7.56 (m, 4H), 7.32-7.42 (m, 4H), 2.52 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.4, 145.8, 143.4, 140.9, 137.3, 133.7, 133.1, 130.0, 129.2, 128.8, 128.6, 127.0, 126.0, 125.8, 125.3, 120.9, 113.3, 79.8, 79.7, 77.1, 76.8, 74.4, 68.4, 66.3, 21.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{26}H_{16}NS$ 374.1003; Found 374.0980.

3-(Phenylhexa-1,3,5-triyn-1-yl)-2-(thiophen-3-yl)quinoline (6e)

Yield: 28%; Melting point: 146-147°C; IR (neat): 2923, 1742, 1614, 1578, 1482, 1440, 1433, 1185, 1174, 1132, 903, 866, 767, 757, 746, 722, 678, 617, 522cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.30 (q, *J* = 1.5 Hz, 1H), 8.07 (d, *J* = 9.2 Hz, 1H), 7.94 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.70-7.75 (m, 2H), 7.50-7.55 (m, 3H), 7.32-7.43 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 154.1, 147.2, 144.1, 140.8, 133.1, 131.4, 130.0, 129.6, 128.8, 128.7, 127.4, 127.3, 127.2, 125.7, 125.4, 120.7, 113.5, 79.9, 77.5, 77.1, 74.4, 68.6, 66.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{14}NS$ 360.0847; Found 360.0830.

2-(Furan-3-yl)-6-methyl-3-(phenylhexa-1,3,5-triyn-1-yl)quinoline (6f)

Yield: 29%; Melting point: 167-169°C; IR (neat): 2921, 1575, 1558, 1485, 1439, 1346, 1254, 1066, 822, 794, 747, 720, 681, 622, 522 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.30 (s, 1H), 7.94 (d, *J* = 8.7 Hz, 1H), 7.53-7.56 (m, 4H), 7.47 (s, 1H), 7.33-7.41 (m, 3H), 7.25-7.28 (m, 1H), 2.51 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 151.2, 146.0, 143.8, 143.0, 137.1, 133.7, 133.1, 132.7, 130.0, 129.1, 128.7, 126.2, 126.0, 125.6, 120.9, 113.0, 110.7, 80.0, 79.9, 76.8, 74.4,

68.7, 66.1, 21.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{26}H_{16}NO$ 358.1232; Found 358.1225.

General procedure and spectral data for the synthesized compounds 4a-5k.

In a round bottom flask, containing dichloromethane (5 mL) was added into $FeCl_3 \cdot 6H_2O$ (0.108 g, 2.5 equiv.) and dibutyl diselenide (0.087 g, 2.0 equiv.). The resulting solution was stirred at room temperature for 15 min under nitrogen atmosphere. After this time, the appropriate 1,3-diyne **3a** (0.050 g, 1 equiv.) was added and the reaction mixture was stirred under reflux conditions. After completion, the mixture was dissolved in DCM, washed with a saturated solution of NH_4Cl, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography *n*-hexane: ethyl acetate (95:5) to obtained desired product **4a** 0.037 g.

3-(Butylselanyl)-8-methyl-2-phenylselenopheno [2',3':4,5]thieno[2,3-*b*]quinoline (4a)

Yield: 88%; Melting point: 70-72°C; IR (neat): 2922, 1721, 1552, 1459, 1439, 1414, 1342, 1264, 1085, 1071, 899, 813, 761, 698, 637, 554, 479 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.02 (d, *J* = 8.7 Hz, 1H), 7.67 (dd, *J* = 8.2, 1.4 Hz, 3H), 7.55 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.39-7.48 (m, 3H), 2.80 (t, *J* = 7.3 Hz, 2H), 2.55 (s, 3H), 1.46-1.53 (m, 2H), 1.22-1.29 (m, 2H), 0.76 (t, *J* = 7.6 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.7, 153.9, 147.6, 144.9, 136.1, 135.8, 131.7, 129.8, 129.7, 128.8, 128.5, 128.1, 126.8, 126.5, 125.8, 115.3, 32.3, 29.0, 22.6, 21.8, 13.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{22}NS^{78}Se^{82}Se$ 515.9813; Found 515.9787.

8-Methyl-2-phenyl-3-(propylselanyl)selenopheno[2',3':4,5]thieno[2,3-*b*]quinoline (4b)

Yield: 86%; Melting point: 98-99°C; IR (neat): 2927, 1589, 1552, 1488, 1439, 1341, 1225, 1208, 1084, 905, 817, 765, 753, 699, 555, 547 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.02 (d, *J* = 8.7 Hz, 1H), 7.68 (dd, *J* = 8.0, 1.6 Hz, 3H), 7.55 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.41-7.48 (m, 3H), 2.78 (t, *J* = 7.3 Hz, 2H), 2.55 (s, 3H), 1.54 (q, *J* = 7.3 Hz, 2H), 0.83 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.6, 153.9, 147.6, 144.9, 136.1, 135.8, 131.7, 129.9, 129.7, 128.7, 128.54, 128.1, 126.8, 126.5, 125.8, 115.2, 31.4, 23.7, 21.8, 14.2; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 615.01, 199.90; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{20}NS^{78}Se^{82}Se$ 501.9657; Found 501.9637.

3-(Butylselanyl)-8-methyl-2-(p-tolyl)selenopheno[2',3':4,5]thieno[2,3-*b*]quinoline (4c)

Yield: 70%; Melting point: 116-117°C; IR (neat): 2956, 1719, 1621, 1514, 1457, 1311, 1262, 1084, 1035, 1020, 904, 813, 781, 683, 503, 484 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.04 (d, *J* = 8.7 Hz, 1H), 7.70 (s, 1H), 7.56-7.59 (m, 3H), 7.28 (s, 1H), 7.26-7.26 (1H), 2.82 (t, *J*

= 7.3 Hz, 2H), 2.57 (s, 3H), 2.43 (s, 3H), 1.48-1.55 (m, 2H), 1.27 (q, *J* = 7.5 Hz, 2H), 0.77 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.7, 154.2, 147.6, 144.8, 138.9, 135.8, 133.2, 131.7, 129.7, 129.3, 128.2, 128.1, 126.8, 126.5, 125.9, 114.9, 32.3, 29.0, 22.7, 21.8, 21.5, 13.5; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 612.6, 201.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{24}NS^{78}Se^{82}Se$ 529.9970; Found 529.9949.

3-(Butylselanyl)-8-methyl-2-(p-tolyl)selenopheno[2',3':4,5]selenopheno[2,3-*b*]quinoline (4d)

Yield: 81%; Melting point: 119-120°C; IR (neat): 2922, 1721, 1606, 1547, 1515, 1440, 1375, 1347, 1261, 1132, 1064, 904, 815, 807, 776, 623, 491 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.93 (d, *J* = 8.7 Hz, 1H), 7.59 (s, 1H), 7.47-7.53 (m, 3H), 7.18-7.20 (m, 2H), 2.68-2.75 (m, 2H), 2.49 (s, 3H), 2.35 (s, 3H), 1.40-1.47 (m, 2H), 1.19 (td, *J* = 14.8, 7.5 Hz, 2H), 0.69 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.9, 153.7, 147.5, 144.7, 138.8, 135.9, 133.2, 132.8, 131.7, 130.3, 129.6, 129.2, 128.0, 127.4, 126.8, 126.0, 117.5, 32.3, 29.3, 22.7, 21.8, 21.5, 13.5; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 639.3, 521.5, 217.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{24}N^{76}Se^{80}Se^{82}Se$ 575.9433; Found 575.9431.

3-(Butylselanyl)-7-methyl-2-phenylselenopheno[2',3':4,5]thieno[2,3-*b*]quinoline (4e)

Yield: 79%; Melting point: 88-89°C; IR (neat): 2953, 1722, 1622, 1594, 1493, 1376, 1283, 1254, 1143, 1071, 893, 797, 761, 738, 693, 584, 561 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.91 (s, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.68 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.36-7.48 (m, 4H), 2.81 (t, *J* = 7.3 Hz, 2H), 2.59 (s, 3H), 1.47-1.54 (m, 2H), 1.25 (q, *J* = 7.5 Hz, 2H), 0.76 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.6, 153.6, 147.2, 146.4, 139.8, 136.1, 129.9, 129.0, 128.7, 128.6, 128.5, 128.4, 127.8, 127.4, 127.1, 123.9, 115.3, 32.3, 29.0, 22.6, 22.2, 13.5; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 614.2, 202.1; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{22}NS^{78}Se^{80}Se$ 513.9811; Found 513.9789.

3-(Butylselanyl)-7-methyl-2-(p-tolyl)selenopheno[2',3':4,5]thieno[2,3-*b*]quinoline (4f)

Yield: 81%; Melting point: 110-111°C; IR (neat): 2922, 1722, 1621, 1605, 1462, 1435, 1415, 1377, 1282, 1264, 1193, 1144, 1034, 884, 872, 811, 715, 612, 554, 489 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.91 (s, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 10.1 Hz, 1H), 7.26 (d, *J* = 6.9 Hz, 2H), 2.82 (t, *J* = 7.3 Hz, 2H), 2.60 (s, 3H), 2.42 (s, 3H), 1.48-1.55 (m, 2H), 1.27 (q, *J* = 7.5 Hz, 2H), 0.77 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.6, 153.9, 147.2, 146.4, 139.7, 138.8, 133.3, 129.7, 129.3, 129.1, 128.4, 128.3, 127.8, 127.4, 127.0, 123.9, 114.9, 32.3, 29.0, 22.7, 22.2, 21.5, 13.6; ^{77}Se-NMR (75 MHz, $CDCl_3$)

δ 612.1, 201.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{24}NS^{78}Se^{82}Se$ 529.9970; Found 529.9946.

3-(Butylselanyl)-6-methyl-2-phenylselenopheno[2',3':4,5]thieno[2,3-*b*]quinoline (4g)

Yield: 78%; Melting point: 91-92°C; IR (neat): 2952, 2869, 1720, 1611, 1574, 1549, 1458, 1385, 1331, 1258, 1060, 887, 745, 699, 689, 475 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.67 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.55 (d, *J* = 6.9 Hz, 1H), 7.42 (dt, *J* = 16.9, 7.0 Hz, 4H), 2.87 (s, 3H), 2.81 (t, *J* = 7.3 Hz, 2H), 1.46-1.54 (m, 2H), 1.25 (q, *J* = 7.5 Hz, 2H), 0.76 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.6, 153.8, 147.7, 145.4, 136.4, 136.1, 129.9, 129.3, 128.7, 128.5, 127.4, 126.1, 125.7, 115.3, 32.3, 29.0, 22.7, 18.4, 13.6; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{22}NS^{78}Se^{82}Se$ 515.9813; Found 515.9783.

3-(Butylselanyl)-2-phenylselenopheno[2',3':4,5]thieno[2,3-*b*]quinoline (4h)

Yield: 72%; Melting point: 108-110°C; IR (neat): 2922, 2720, 1514, 1457, 1377, 1341, 1263, 1084, 904, 783, 720, 683, 503, 484 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.68-7.76 (m, 3H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.43-7.49 (m, 3H), 2.81 (t, *J* = 7.3 Hz, 2H), 1.50 (q, *J* = 7.5 Hz, 2H), 1.26 (q, *J* = 7.3 Hz, 2H), 0.77 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.6, 154.1, 147.8, 146.0, 136.0, 129.8, 129.7, 129.2, 128.8, 128.6, 128.5, 128.4, 128.1, 127.1, 125.9, 125.7, 115.3, 32.3, 29.0, 22.6, 13.6; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 615.9, 202.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{20}NS^{78}Se^{82}Se$ 501.9657; Found 501.9633.

3-(Butylselanyl)-2-phenylselenopheno[2',3':4,5]selenopheno[2,3-*b*]quinoline (4i)

Yield: 87%; Melting point: 118-119°C; IR (neat): 2921, 1722, 1612, 1553, 1385, 1340, 1258, 1060, 887, 744, 737, 699, 689, 617, 585, 475 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.72 (q, *J* = 8.2 Hz, 3H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.41-7.48 (m, 3H), 2.78 (t, *J* = 7.3 Hz, 2H), 1.48 (q, *J* = 7.3 Hz, 2H), 1.24 (q, *J* = 7.3 Hz, 2H), 0.75 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.9, 153.6, 147.7, 146.0, 136.0, 132.8, 130.6, 129.7, 129.3, 128.8, 128.6, 128.3, 128.1, 128.1, 126.1, 125.9, 117.9, 32.3, 29.4, 22.6, 13.5; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 642.6, 524.7, 217.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{20}N^{76}Se^{80}Se^{82}Se$ 547.9120; Found 547.9109.

2-Phenyl-3-(propylselanyl)selenopheno[2',3':4,5]selenopheno[2,3-*b*]quinoline (4j)

Yield: 86%; Melting point: 83-84°C; IR (neat): 2959, 1611, 1552, 1458, 1438, 1426, 1336, 1260, 1128, 1058, 884, 759, 743, 701, 686, 616, 478 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H),

8.10 (d, *J* = 8.7 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.68-7.74 (m, 3H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.41-7.47 (m, 3H), 2.74 (t, *J* = 7.3 Hz, 2H), 1.53 (q, *J* = 7.2 Hz, 2H), 0.81 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.9, 153.6, 147.7, 145.9, 136.0, 132.7, 130.6, 129.7, 129.3, 128.7, 128.6, 128.3, 128.1, 128.0, 126.1, 125.9, 117.8, 31.8, 23.7, 14.2; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 642.8, 524.7, 215.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{18}N^{76}Se^{80}Se^{82}Se$ 533.8964; Found 533.8982.

3-(Butylselanyl)-2-(p-tolyl)selenopheno[2',3':4,5]thieno[2,3-*b*]quinoline (4k)

Yield: 76%; Melting point: 129-130°C; IR (neat): 2923, 2869, 1720, 1574, 1548, 1457, 1385, 1258, 1126, 1015, 887, 745, 699, 689, 566, 475 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.15 (d, *J* = 8.2 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.74 (t, *J* = 7.1 Hz, 1H), 7.57 (t, *J* = 8.9 Hz, 3H), 7.28 (s, 1H), 7.26 (d, *J* = 2.3 Hz, 1H), 2.82 (t, *J* = 7.3 Hz, 2H), 2.43 (s, 3H), 1.51 (q, *J* = 7.3 Hz, 2H), 1.27 (q, *J* = 7.5 Hz, 2H), 0.78 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.7, 154.4, 147.8, 146.0, 138.9, 133.2, 129.8, 129.7, 129.3, 129.2, 128.5, 128.1, 127.1, 125.9, 125.8, 114.9, 32.3, 29.0, 22.7, 21.5, 13.5; ^{77}Se-NMR (76 MHz, $CDCl_3$) δ 613.6, 202.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{22}NS^{78}Se^{82}Se$ 515.9813; Found 515.9783.

3-(Butylselanyl)-2-(p-tolyl)selenopheno[2',3':4,5]selenopheno[2,3-*b*]quinoline (4l)

Yield: 84%; Melting point: 132-134°C; IR (neat): 2923, 1724, 1577, 1550, 1458, 1355, 1330, 1284, 1258, 1129, 1059, 889, 810, 745, 690, 609, 526, 473 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 7.3 Hz, 1H), 7.69-7.73 (m, 1H), 7.52-7.59 (m, 3H), 7.25 (t, *J* = 4.1 Hz, 2H), 2.78 (t, *J* = 7.3 Hz, 2H), 2.41 (s, 3H), 1.46-1.54 (m, 2H), 1.25 (q, *J* = 7.3 Hz, 2H), 0.76 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.0, 153.9, 147.7, 145.9, 138.9, 133.2, 132.8, 130.2, 129.6, 129.3, 128.3, 128.1, 128.0, 126.0, 125.9, 117.5, 32.3, 29.4, 22.7, 21.5, 13.5; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 640.5, 524.3, 217.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{22}N^{76}Se^{80}Se^{82}Se$ 561.9277; Found 561.9304.

3-(Butylselanyl)-10-methyl-2-phenylselenopheno[2,3-*a*]thieno[2,3-*c*]acridine (5a)

Yield: 87%; Melting point: 104-105°C; IR (neat): 2957, 1722, 1593, 1490, 1462, 1438, 1367, 1256, 1127, 900, 870, 816, 753, 720, 709, 631, 559 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.54 (t, *J* = 5.0 Hz, 2H), 8.14 (d, *J* = 8.7 Hz, 1H), 7.66 (dd, *J* = 8.0, 1.1 Hz, 3H), 7.55-7.59 (m, 2H), 7.44-7.49 (m, 3H), 2.66 (t, *J* = 7.1 Hz, 2H), 2.55 (s, 3H), 1.40 (q, *J* = 7.5 Hz, 2H), 1.14 (q, *J* = 7.3 Hz, 2H), 0.69 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 152.6, 146.8, 143.7, 138.3, 137.8, 137.6, 137.5, 136.7, 135.8, 132.6, 131.2, 130.6, 129.1, 128.6, 128.3, 126.5, 126.1, 125.7, 124.0,

123.1, 120.4, 31.6, 31.5, 22.7, 21.9, 13.6; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 601.8, 170.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{28}H_{24}NS^{76}Se^{82}Se$ 563.9989; Found 563.9968.

3-(Butylselanyl)-10-methyl-2-phenylfuro[2,3-*c*]selenopheno[2,3-*a*]acridine (5b)

Yield: 75%; Melting point: 120-122°C; IR (neat): 2870, 1716, 1603, 1573, 1463, 1440, 1254, 1184, 1045, 885, 814, 761, 738, 689, 661, 555, 529 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.17 (d, *J* = 8.7 Hz, 1H), 7.87 (d, *J* = 2.3 Hz, 1H), 7.60-7.73 (m, 5H), 7.44-7.50 (m, 3H), 2.81 (t, *J* = 7.3 Hz, 2H), 2.56 (s, 3H), 1.44-1.51 (m, 2H), 1.17-1.25 (m, 2H), 0.73 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 151.8, 151.1, 147.0, 143.1, 142.7, 138.6, 136.5, 135.6, 132.9, 132.0, 131.8, 130.6, 128.8, 128.6, 128.3, 126.3, 126.0, 122.8, 122.7, 117.1, 107.3, 31.9, 29.8, 22.7, 21.8, 13.6; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 607.0, 214.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{28}H_{24}NO^{78}Se^{80}Se$ 548.0196; Found 548.0187.

10-Methyl-2-phenyl-3-(propylselanyl)furo[2,3-*c*]selenopheno[2,3-*a*]acridine (5c)

Yield: 71%; Melting point: 170-172°C; IR (neat): 2924, 1701, 1604, 1575, 1527, 1440, 1363, 1280, 1211, 1045, 899, 815, 729, 704, 697, 555, 529 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.18 (d, *J* = 9.2 Hz, 1H), 7.88 (d, *J* = 2.3 Hz, 1H), 7.73 (t, *J* = 2.7 Hz, 2H), 7.61-7.67 (m, 3H), 7.45-7.50 (m, 3H), 2.79 (t, *J* = 7.1 Hz, 2H), 2.58 (s, 3H), 1.51 (q, *J* = 7.3 Hz, 2H), 0.78 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 151.8, 151.2, 147.0, 143.1, 142.8, 138.6, 136.4, 135.6, 132.9, 132.0, 131.8, 130.6, 128.8, 128.6, 128.3, 126.3, 126.6, 122.8, 122.7, 117.0, 107.3, 32.2, 23.3, 21.7, 14.3; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 607.1, 212.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{27}H_{22}NO^{76}Se^{82}Se$ 534.0061; Found 534.0046.

3-(Butylselanyl)-10-methyl-2-(p-tolyl)selenopheno[2,3-*a*]thieno[2,3-*c*]acridine (5d)

Yield: 79%; Melting point: 124-126°C; IR (neat): 2956, 1732, 1626, 1493, 1475, 1462, 1368, 1412, 1183, 1083, 895, 870, 815, 710, 689, 633, 617, 506 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.55-8.57 (m, 2H), 8.16 (d, *J* = 8.7 Hz, 1H), 7.68 (s, 1H), 7.54-7.60 (m, 4H), 7.28 (d, *J* = 7.8 Hz, 2H), 2.68 (t, *J* = 7.3 Hz, 2H), 2.56 (s, 3H), 2.44 (s, 3H), 1.44 (q, *J* = 7.3 Hz, 2H), 1.17 (q, *J* = 7.5 Hz, 2H), 0.71 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 152.9, 146.8, 143.8, 138.6, 138.3, 137.8, 137.6, 137.4, 135.8, 133.8, 132.6, 131.2, 130.4, 129.2, 129.0, 126.6, 126.1, 125.6, 124.0, 123.2, 120.0, 31.6, 31.5, 22.8, 21.9, 21.5, 13.6; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 599.9, 170.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{26}NS^{76}Se^{82}Se$ 578.0145; Found 578.0157.

3-(Butylselanyl)-10-methyl-2-(p-tolyl)furo[2,3-*c*]selenopheno[2,3-*a*]acridine (5e)

Yield: 73%; Melting point: 158-160°C; IR (neat): 2950, 1629, 1605, 1524, 1464, 1451, 1419, 1360, 1208, 1183, 1040, 900, 818, 809, 795, 750, 743, 659, 559, 509 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.20 (d, *J* = 9.2 Hz, 1H), 7.88 (d, *J* = 1.8 Hz, 1H), 7.73-7.75 (m, 2H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 2.83 (t, *J* = 7.3 Hz, 2H), 2.59 (s, 3H), 2.45 (s, 3H), 1.45-1.53 (m, 2H), 1.22 (q, *J* = 7.5 Hz, 2H), 0.74 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 151.8, 151.4, 147.0, 143.0, 142.7, 138.7, 138.4, 135.6, 133.6, 132.8, 132.1, 131.8, 130.4, 129.0, 128.8, 126.3, 126.0, 122.8, 122.7, 116.7, 107.3, 32.0, 29.8, 22.8, 21.9, 21.5, 13.6; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 605.2, 213.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{26}NO^{76}Se^{82}Se$ 562.0374 362.0448; Found 562.0366.

10-Methyl-3-(propylselanyl)-2-(p-tolyl)selenopheno[2,3-*a*]thieno[2,3-*c*]acridine (5f)

Yield: 86%; Melting point: 152-153°C; IR (neat): 2925, 1026, 1591, 1491, 1441, 1368, 1200, 898, 813, 760, 700, 631, 558 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.55-8.56 (m, 2H), 8.15 (d, *J* = 8.7 Hz, 1H), 7.66 (s, 1H), 7.54-7.59 (m, 4H), 7.28 (d, *J* = 7.8 Hz, 2H), 2.65 (t, *J* = 7.3 Hz, 2H), 2.55 (s, 3H), 2.44 (s, 3H), 1.47 (q, *J* = 7.3 Hz, 2H), 0.75 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 152.9, 146.8, 143.7, 138.6, 138.3, 137.8, 137.6, 137.4, 135.8, 133.8, 132.6, 131.1, 130.5, 129.2, 129.0, 126.6, 126.1, 125.6, 124.0, 123.2, 119.9, 33.8, 23.0, 21.9, 21.5, 14.4; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 600.0, 168.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{28}H_{24}NS^{80}Se_2$ 565.9960; Found 565.9960.

10-Methyl-3-(propylselanyl)-2-(p-tolyl)furo[2,3-*c*]selenopheno[2,3-*a*]acridine (5g)

Yield: 75%; Melting point: 166-167°C; IR (neat): 2953, 1603, 1526, 1463, 1360, 1212, 1184, 885, 814, 761, 753, 738, 689, 555 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.19 (d, *J* = 8.7 Hz, 1H), 7.88 (s, 1H), 7.74 (s, 2H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 2.81 (t, *J* = 7.3 Hz, 2H), 2.58 (s, 3H), 2.45 (s, 3H), 1.53 (q, *J* = 7.3 Hz, 2H), 0.80 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 151.8, 151.5, 147.0, 143.1, 142.7, 138.7, 138.4, 135.6, 133.5, 132.8, 132.1, 131.8, 130.4, 129.0, 128.8, 126.3, 126.1, 122.8, 122.7, 116.7, 107.3, 32.2, 23.3, 21.9, 21.5, 14.4; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 605.2, 211.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{28}H_{24}NO^{76}Se^{82}Se$ 548.0217; Found 548.0204.

2-Phenyl-3-(propylselanyl)selenopheno[2,3-*a*]thieno[2,3-*c*]acridine (5h)

Yield: 83%; Melting point: 130-132°C; IR (neat): 2954, 1699, 1616, 1590, 1494, 1466, 1423, 1372, 1266, 1276, 1075, 887, 848, 763, 747, 719, 689, 712, 637, 468 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.59 (d, *J* = 5.4 Hz, 1H), 8.29 (d, *J* = 8.7 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H),

7.76-7.80 (m, 1H), 7.67 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.58 (d, *J* = 5.5 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.45-7.51 (m, 3H), 2.65 (t, *J* = 7.1 Hz, 2H), 1.42-1.49 (m, 2H), 0.74 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 152.8, 148.0, 144.4, 138.8, 137.8, 137.7, 137.6, 136.6, 132.1, 130.7, 129.9, 129.6, 128.6, 128.3, 127.8, 126.5, 126.0, 125.8, 124.1, 123.1, 120.3, 33.8, 22.9, 14.3; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 602.9, 168.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{26}H_{20}NS^{76}Se^{82}Se$ 535.9676; Found 535.9702.

3-(Butylselanyl)-2-(p-tolyl)furo[2,3-*c*]selenopheno[2,3-*a*]acridine (5i)

Yield: 80%; Brown sticky liquid; IR (neat): 2953, 2870, 1603, 1526, 1463, 1360, 1213, 885, 814, 761, 753, 738, 690, 529 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.30 (d, *J* = 8.7 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 2.3 Hz, 1H), 7.80 (t, *J* = 7.1 Hz, 1H), 7.75 (d, *J* = 1.8 Hz, 1H), 7.55-7.58 (m, 3H), 7.30 (d, *J* = 8.2 Hz, 2H), 2.84 (t, *J* = 7.3 Hz, 2H), 2.45 (s, 3H), 1.48 (q, *J* = 7.5 Hz, 2H), 1.22 (q, *J* = 7.3 Hz, 2H), 0.74 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 152.1, 151.6, 148.2, 143.4, 143.1, 138.7, 138.4, 133.5, 132.7, 132.2, 130.4, 130.1, 129.2, 129.0, 128.0, 126.0, 125.8, 122.8, 122.7, 116.8, 107.3, 32.0, 29.9, 22.8, 21.5, 13.6; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 606.4, 213.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{28}H_{24}NO^{76}Se^{82}Se$ 548.0217; Found 548.0222.

3-(Propylselanyl)-2-(p-tolyl)selenopheno[2,3-a]thieno[2,3-*c*]acridine (5j)

Yield: 84%; Melting point: 153-155°C; IR (neat): 2962, 1618, 1588, 1495, 1470, 1372, 1267, 1204, 1127, 899, 818, 767, 717, 635, 614, 507 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.60 (d, *J* = 5.5 Hz, 1H), 8.30 (d, *J* = 9.2 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.77-7.81 (m, 1H), 7.54-7.60 (m, 4H), 7.29 (d, *J* = 7.8 Hz, 2H), 2.67 (t, *J* = 7.3 Hz, 2H), 2.45 (s, 3H), 1.48 (q, *J* = 7.3 Hz, 2H), 0.76 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.1, 148.0, 144.4, 138.8, 138.7, 137.8, 137.4, 133.7, 132.1, 130.5, 129.8, 129.6, 129.0, 127.8, 126.5, 126.0, 125.7, 124.1, 123.2, 120.0, 33.8, 23.0, 21.5, 14.3; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 601.1, 168.9; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{27}H_{22}NS^{74}Se^{82}Se$ 547.9865; Found 547.9869.

3-(Propylselanyl)-2-(p-tolyl)furo[2,3-*c*]selenopheno[2,3-*a*]acridine (5k)

Yield: 78%; Brown sticky liquid; IR (neat): 2921, 1603, 1526, 1463, 1440, 1360, 1219, 885, 814, 738, 689, 661, 555 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.27 (d, *J* = 8.7 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 2.3 Hz, 1H), 7.78 (t, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 2.3 Hz, 1H), 7.53 (dd, *J* = 11.4, 7.8 Hz, 3H), 7.28 (d, *J* = 8.2 Hz, 2H), 2.80 (t, *J* = 7.3 Hz, 2H), 2.44 (s, 3H), 1.51 (t, *J* = 7.3 Hz, 2H), 0.80 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 152.0,

151.7, 148.2, 143.4, 143.1, 138.7, 138.4, 133.5, 132.7, 132.2, 130.4, 130.0, 129.2, 129.1, 128.0, 125.9, 125.7, 122.8, 122.7, 116.7, 107.3, 32.2, 23.3, 21.5, 14.4; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 606.4, 211.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{27}H_{22}NO^{76}Se^{82}Se$ 534.0061; Found 534.0048.

General procedure and spectral data for the synthesized compounds 7a-8d.

In a round bottom flask, containing dichloromethane (5 mL) was added into $FeCl_3 \cdot 6H_2O$ (0.060 g, 3.0 equiv.) and dibutyl diselenide (0.050 g, 2.5 equiv.). The resulting solution was stirred at room temperature for 15 min under nitrogen atmosphere. After this time, the appropriate 1,3,5-triyne **6a** (0.025 g, 1 equiv.) was added and the reaction mixture was stirred under reflux conditions. After completion, the mixture was dissolved in DCM, washed with a saturated solution of NH_4Cl, dried over Na_2SO_4. The residue was purified by column chromatography *n*-hexane: ethyl acetate (95:5) to obtained desired product **7a** 0.037 g.

3-(butylselanyl)-7-methyl-2-phenylselenopheno[2'',3'':4',5']selenopheno[2',3':4,5]thieno[2,3-*b*]quinoline (7a)

Yield: 81%; Melting point: 153-154°C; IR (neat): 2952, 1721, 1591, 1489, 1460, 1342, 1320, 1257, 1227, 1083, 889, 813, 758, 687, 696, 530 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.65-7.69 (m, 3H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.40-7.46 (m, 3H), 2.77 (t, *J* = 7.4 Hz, 2H), 2.54 (s, 3H), 1.48 (q, *J* = 7.4 Hz, 2H), 1.25 (q, *J* = 7.3 Hz, 2H), 0.76 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.3, 153.0, 152.5, 144.9, 136.1, 135.9, 134.9, 131.7, 130.4, 129.8, 129.7, 129.5, 128.6, 128.6, 128.0, 126.8, 126.1, 126.0, 116.8, 32.4, 29.3, 22.6, 21.8, 13.5 ^{77}Se-NMR (100 MHz, $CDCl_3$) δ 629.3, 538.2, 218.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{26}H_{22}NS^{76}Se^{80}Se^{82}Se$ 617.8997; Found 617.8994.

7-Methyl-2-phenyl-3-(propylselanyl)selenopheno[2'',3'':4',5']selenopheno[2',3':4,5]thieno[2,3-*b*]quinoline (7b)

Yield: 84%; Melting point: 190-192°C; IR (neat): 2862, 1719, 1625, 1591, 1551, 1438, 1322, 1219, 1087, 1027, 900, 815, 698, 623, 529 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.00 (d, *J* = 8.7 Hz, 1H), 7.65-7.70 (m, 3H), 7.53 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.38-7.47 (m, 3H), 2.75 (t, *J* = 7.1 Hz, 2H), 2.55 (s, 3H), 1.53 (q, *J* = 7.2 Hz, 2H), 0.83 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.3, 153.0, 152.5, 144.9, 136.1, 135.9, 134.9, 131.7, 130.4, 129.8, 129.7, 129.5, 128.6, 128.6, 128.0, 126.7, 126.1, 126.0, 116.7, 31.6, 23.8, 21.8, 14.2; ^{77}Se-NMR (75

MHz, $CDCl_3$) δ 629.4, 538.3, 215.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{20}NS^{76}Se^{80}Se^{82}Se$ 603.8841; Found 603.8856.

3-(Butylselanyl)-2-phenylselenopheno[2'',3'':4',5']selenopheno[2',3':4,5]thieno[2,3-*b*]quinoline (7c)

Yield: 78%; Melting point: 182-183°C; IR (neat): 2953, 1615, 1592, 1547, 1463, 1426, 1385, 1320, 1133, 1085, 891, 885, 761, 746, 711, 697, 691, 594, 467 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.11 (d, *J* = 8.7 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.67-7.73 (m, 3H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.40-7.47 (m, 3H), 2.77 (t, *J* = 7.3 Hz, 2H), 1.45-1.52 (m, 2H), 1.25 (q, *J* = 7.3 Hz, 2H), 0.76 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.3, 153.2, 152.7, 146.1, 136.1, 135.0, 130.2, 129.8, 129.7, 129.6, 129.2, 128.7, 128.6, 128.4, 128.1, 126.7, 126.1, 125.9, 116.8, 32.4, 29.3, 22.6, 13.5; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 630.0, 539.3, 218.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{20}NS^{76}Se^{82}Se^{80}Se$ 603.8841; Found 603.8861.

2-Phenyl-3-(propylselanyl)selenopheno[2'',3'':4',5']selenopheno[2',3':4,5]thieno[2,3-*b*]quinoline (7d)

Yield: 77%; Melting point: 196-198°C; IR (neat): 2850, 1723, 1612, 1462, 1428, 1416, 1336, 1187, 1147, 1135, 1103, 809, 791, 766, 754, 697, 493, 469 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$ + 1 drop Trifluro acetic acid) δ 8.96 (s, 1H), 8.28 (d, *J* = 8.7 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 8.01 (t, *J* = 7.3 Hz, 1H), 7.83 (t, *J* = 7.8 Hz, 1H), 7.70 (dd, *J* = 7.2, 2.4 Hz, 2H), 7.46-7.48 (m, 3H), 2.73 (t, *J* = 7.1 Hz, 2H), 1.52 (q, *J* = 7.2 Hz, 2H), 0.83 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$ + 1 drop Trifluro acetic acid) δ 160.6, 160.0, 159.0, 157.3, 155.8, 137.0, 135.3, 134.7, 134.4, 133.8, 132.0, 129.6, 129.4, 129.1, 129.0, 128.8, 128.0, 125.8, 120.3, 116.7, 116.3, 113.5, 32.0, 23.8, 14.1; ^{77}Se-NMR (75 MHz, $CDCl_3$ + 1 drop Trifluro acetic acid) δ 643.3, 557.7, 219.1; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{18}NS^{76}Se^{80}Se^{82}Se$ 589.8684; Found 589.8681.

3-(Butylselanyl)-2-phenylselenopheno[2'',3'':4',5']selenopheno[2',3':4,5]selenopheno[2,3-*b*]quinoline (7e)

Yield: 75%; Melting point: 145-146°C; IR (neat): 2950, 1612, 1592, 1462, 1437, 1384, 1340, 1324, 1194, 1060, 883, 847, 761, 743, 688, 608, 551, 464 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.73 (t, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 6.4 Hz, 2H), 7.57 (t, *J* = 7.1 Hz, 1H), 7.43 (dt, *J* = 18.8, 7.1 Hz, 3H), 2.78 (t, *J* = 7.1 Hz, 2H), 1.46-1.53 (m, 2H), 1.25 (td, *J* = 14.8, 7.2 Hz, 2H), 0.77 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz,

$CDCl_3$) δ 165.8, 152.8, 152.5, 146.1, 136.1, 133.0, 132.7, 132.5, 132.3, 129.7, 129.4, 128.7, 128.6, 128.3, 128.1, 127.7, 126.3, 126.1, 116.8, 32.4, 29.2, 22.6, 13.5; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 632.3, 558.9, 513.5, 222.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{23}NS^{76}Se_4$ 651.9175; Found 651.9117.

1-(Butylselanyl)-10-methyl-2-phenylselenopheno[2',3':4,5]selenopheno[2,3-*a*]thieno[2,3-*c*]acridine (8a)

Yield: 76%; Melting point: 212-213°C; IR (neat): 2849, 1723, 1625, 1591, 1510, 1461, 1366, 1281, 1155, 1135, 890, 817, 802, 755, 714, 700, 688, 634, 545 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.15 (d, J = 8.6 Hz, 1H), 7.75 (d, J = 7.4 Hz, 2H), 7.70 (s, 1H), 7.60 (d, J = 5.2 Hz, 2H), 7.45 (dt, J = 25.6, 7.3 Hz, 3H), 2.81 (t, J = 7.2 Hz, 2H), 2.59 (s, 3H), 1.51 (q, J = 7.4 Hz, 2H), 1.26 (t, J = 7.2 Hz, 2H), 0.77 (t, J = 7.4 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 153.3, 148.8, 146.7, 143.5, 137.4, 136.3, 136.3, 136.0, 133.0, 132.6, 130.9, 130.7, 129.8, 129.2, 128.5, 126.5, 126.1, 125.2, 124.1, 124.0, 116.6, 32.4, 29.3, 22.7, 22.0, 13.6; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 634.7, 529.3, 218.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{30}H_{24}NS^{76}Se^{80}Se^{82}Se$ 667.9154; Found 667.9134.

1-(Butylselanyl)-10-methyl-2-phenylfuro[2,3-*c*]selenopheno[2',3':4,5]selenopheno[2,3-*a*]acridine (8b)

Yield: 68%; Sticky; IR (neat): 2918, 1604, 1524, 1510, 1450, 1360, 1184, 1040, 889, 818, 809, 795, 765, 750, 508 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.17 (d, *J* = 8.7 Hz, 1H), 7.85 (d, *J* = 1.8 Hz, 1H), 7.74-7.76 (m, 3H), 7.71 (d, *J* = 1.8 Hz, 1H), 7.62 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.41-7.49 (m, 3H), 2.82 (t, *J* = 7.3 Hz, 2H), 2.59 (s, 3H), 1.48-1.55 (m, 2H), 1.27 (td, *J* = 14.8, 7.5 Hz, 2H), 0.77 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.6, 150.8, 149.5, 146.8, 145.7, 143.5, 143.0, 136.4, 135.7, 132.8, 131.4, 130.0, 129.8, 128.8, 128.7, 128.5, 126.3, 126.0, 125.5, 123.6, 121.6, 116.2, 107.7, 32.4, 29.2, 22.7, 21.9, 13.6; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 644.2, 530.3, 219.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{30}H_{24}NO^{76}Se^{80}Se^{82}Se$ 651.9382; Found 651.9365.

10-Methyl-2-phenyl-1-(propylselanyl)selenopheno[2',3':4,5]selenopheno[2,3-*a*]thieno[2,3-*c*]acridine (8c)

Yield: 80%; Melting point: 201-203°C; IR (neat): 2923, 1673, 1634, 1407, 1362, 1180, 1126, 1073, 818, 797, 702, 686, 624, 559, 551, 468 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$ + 1 drop Trifluro acetic acid) δ 8.93 (s, 1H), 8.35 (d, *J* = 5.0 Hz, 1H), 8.19 (d, *J* = 8.7 Hz, 1H), 7.80-7.83 (m, 2H),

7.68 (q, *J* = 3.2 Hz, 2H), 7.54 (d, *J* = 5.5 Hz, 1H), 7.48 (t, *J* = 3.2 Hz, 3H), 2.70 (t, *J* = 7.1 Hz, 2H), 2.61 (s, 3H), 1.49 (q, *J* = 7.3 Hz, 2H), 0.82 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$ + 1 drop Trifluro acetic acid) δ 161.0, 160.6, 160.2, 159.8, 156.2, 152.5, 142.8, 140.3, 140.0, 139.2, 136.0, 135.1, 135.1, 134.2, 131.5, 131.0, 129.4, 128.9, 127.5, 127.0, 125.7, 125.4, 123.4, 119.4, 116.6, 115.9, 113.7, 110.8, 32.1, 23.7, 21.7, 14.1; ^{77}Se-NMR (75 MHz, $CDCl_3$ + 1 drop Trifluro acetic acid) δ 642.4, 552.9, 224.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{22}NS^{76}Se^{80}Se^{82}Se$ 653.8997; Found 653.9020.

10-Methyl-2-phenyl-1-(propylselanyl)furo[2,3-*c*]selenopheno[2',3':4,5]selenopheno[2,3-*a*]acridine (8d)

Yield: 79%; Melting point: 194-196°C; IR (neat): 2957, 1626, 1585, 1537, 1477, 1433, 1321, 1217, 1136, 1048, 837, 817, 837, 691, 654, 526 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.15 (d, *J* = 8.7 Hz, 1H), 7.84 (d, *J* = 1.8 Hz, 1H), 7.69-7.75 (m, 4H), 7.60 (dd, *J* = 9.2, 1.8 Hz, 1H), 7.42-7.49 (m, 3H), 2.79 (t, *J* = 7.3 Hz, 2H), 2.58 (s, 3H), 1.56 (q, *J* = 7.3 Hz, 2H), 0.85 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.6, 150.7, 149.5, 146.8, 143.5, 142.8, 137.5, 136.4, 135.7, 132.7, 131.4, 130.0, 129.8, 128.8, 128.5, 128.5, 126.3, 126.0, 125.5, 123.5, 121.6, 116.1, 107.7, 31.5, 23.8, 21.9, 14.3; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 644.3, 530.7, 216.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{22}NO^{76}Se^{80}Se^{82}Se$ 637.9226; Found 637.9199.

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Chapter 4

Synthesis of isoquinoline-fused benzquinazolinone through Ag (I)-catalysed cascade annulation of 2-amino-benzamides and 2-alkynylbenzaldehydes

4.1 Introduction

Transition metal-catalyzed C-H bond functionalizations for C-C bond formation have proved to be the powerful method for constructing of complex chemical compounds [1] in an atom- and step-economic manner [2]. These transformations are widely used in the area of synthesis of both natural products and therapeutic agents. Among the transition-metal-catalyzed organic transformations, Ag-catalyzed C-H/C-C bond functionalization is one of the frontier areas in organic chemistry [3]. Compared with other transition metals such as gold or platinum, Ag(I) salts represent an inexpensive alternative for the electrophilic activation of alkynes under mild conditions [4]. The development of Ag(I)-catalyzed new systems for the C-H/C-C functionalization represents a central challenge to construct various types of fused *N*-heterocycles. Nitrogen-containing heterocycles are important molecular motifs in natural products, materials and bioactive molecules [5]. Quinazolinone derivatives represent a class of the privileged *N*-heterocyclic motifs present in a broad range of alkaloid natural products [6]. Furthermore, they also show a wide range of biological activities [7-8]. Much effort has focused on synthetic methods for ring fused quinazolinone derivatives [9]. In particular, synthetic strategies for ring fused quinazolinones, as the core structural skeletons in a variety of natural products and pharmaceutical molecules, have been intensely explored in recent years. However, isoquinolines are ubiquitous structural motif present in a numerous biologically active natural products and pharmaceutically important compounds [10]. Molecular skeleton which integrates isoquinoline as well as quinazolinone moieties might possess properties of both and enhance the activity [11].

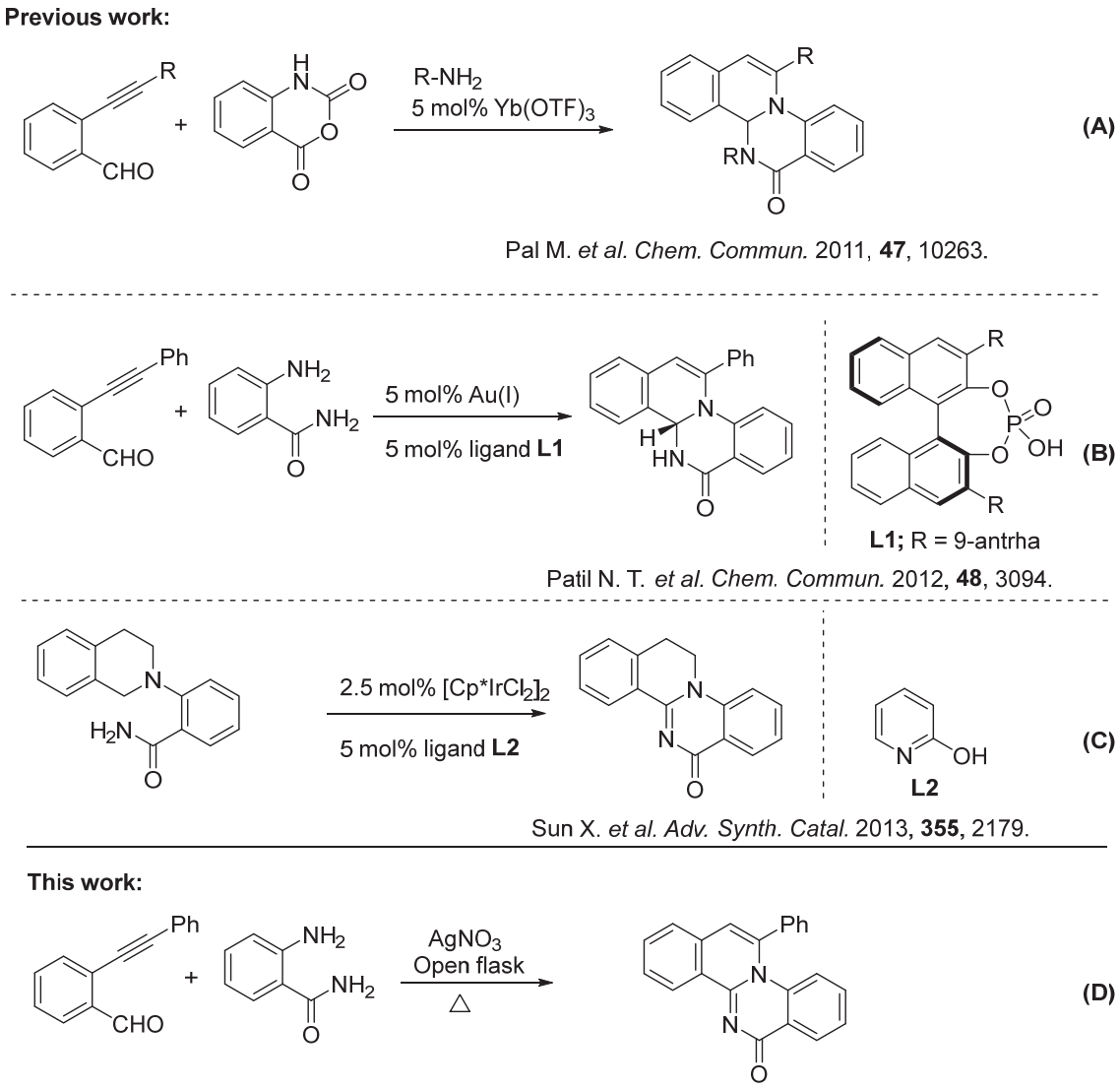


Figure 1. Approaches for the synthesis of quinazolinones

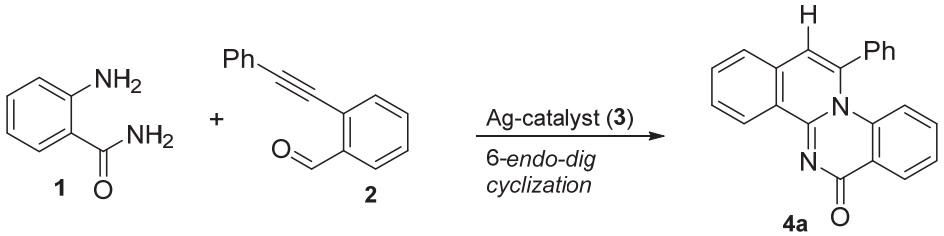
Several reports are available for the synthesis of isoquinoline-fused quinazolinones [12]. Pal M. *et al.* reported the synthesis of fused quinazolinones via one-pot Yb(III)-mediated cascade reaction (**Fig. 1**, **A**) [13]. Further, Patil N. T. *et al.* reported Au(I) catalyzed synthesis of optically pure fused 1,2-dihydroisoquinolines (**B**) [14] and Sun X. *et al.* used the Ir-catalyzed intramolecular acceptorless dehydrogenative cross-coupling of tertiary amines and amides for the synthesis dihydroisoquinoline-fused quinazolinones (**C**) [15]. However, some of these procedures have significant drawbacks such as low yield, longer reaction times, harsh reaction conditions and use of expensive reagents. In an effort to synthesize *N*-fused heterocycles by a

transition-metal-catalyzed C-C functionalization herein we report, the synthesis of isoquinoline-fused quinazolinones *via* $AgNO_3$-catalyzed one-pot cascade cyclization of 2-amino-benzamides and 2-alkynyl benzaldehydes through an oxidation process.

4.2 Result and discussion

In the synthesis of isoquinoline-fused quinazolinones, the fusion of quinazolinone ring may occur in two different ways (linear and angular) for two different types of nitrogen atoms that would lead to the formation of two regioisomers. Both of the isomers should have certain unique pharmacological features. Therefore, a synthetic method, which can exclusively provide single regioisomer instead of a mixture, is highly desirable. With this in mind, we initially began with reaction optimization conditions with 2-aminobenzamide **1a** and 2-(phenylethynyl) benzaldehyde **2a** as a model substrate (Table 1). We initially subjected compounds **1a** and **2a** in equimolar ratio under the oxidative conditions using 30 mol% of AgOTf in DMSO solvent at 100˚C for 5 h (Table 1, entry 1). To our delight, the reaction was very much regioselective and only single regioisomer **4a** was formed (from TLC) as confirmed by NMR in low yield (29%). Next, the yield of the compound **4a** was increased up to 54% with increasing the temperature to 120˚C (entry 2). However, the use of 10 mol% AgOTf in the reaction at this temperature resulted in the decrease in the product yield up to 43% (entry 3). Significant improvement in the yield was observed when 20 mol% of AgOTf used in the reaction and the desired product was isolated in 73% yield (entry 4). On the other hand, use of Ag_2O and $AgPF_6$ catalysts in the reaction afforded desired product **4a** in 9% and 5% yields, respectively (entries 5 and 8). Also, $AgClO_4$ yielded only 33% of product **4a** (entry 6). To improve the yield of the reaction, different solvents were screened with 20 mol% of $AgNO_3$ (entries 7, 11-13) and the best result was obtained when the reaction was carried out in DMSO solvent at 120 ˚C which provided required product **4a** in 89% yield (entry 7). Also, we carried out reaction of 2-aminobenzamide **1a** and 2-(phenylethynyl) benzaldehyde **2a** under nitrogen atmosphere, interestingly we obtained unaromatised product (**B**) [14] in 72 % yield and 13% required product **4a**.

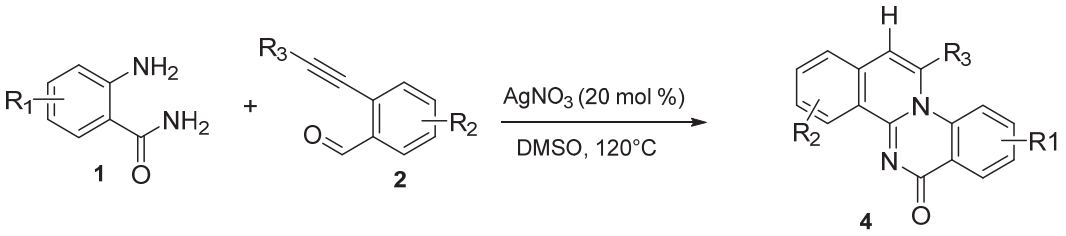
Table 1. Optimization table for 12-phenyl-6H-isoquinolino[2,1-*a*]quinazolin-6-one

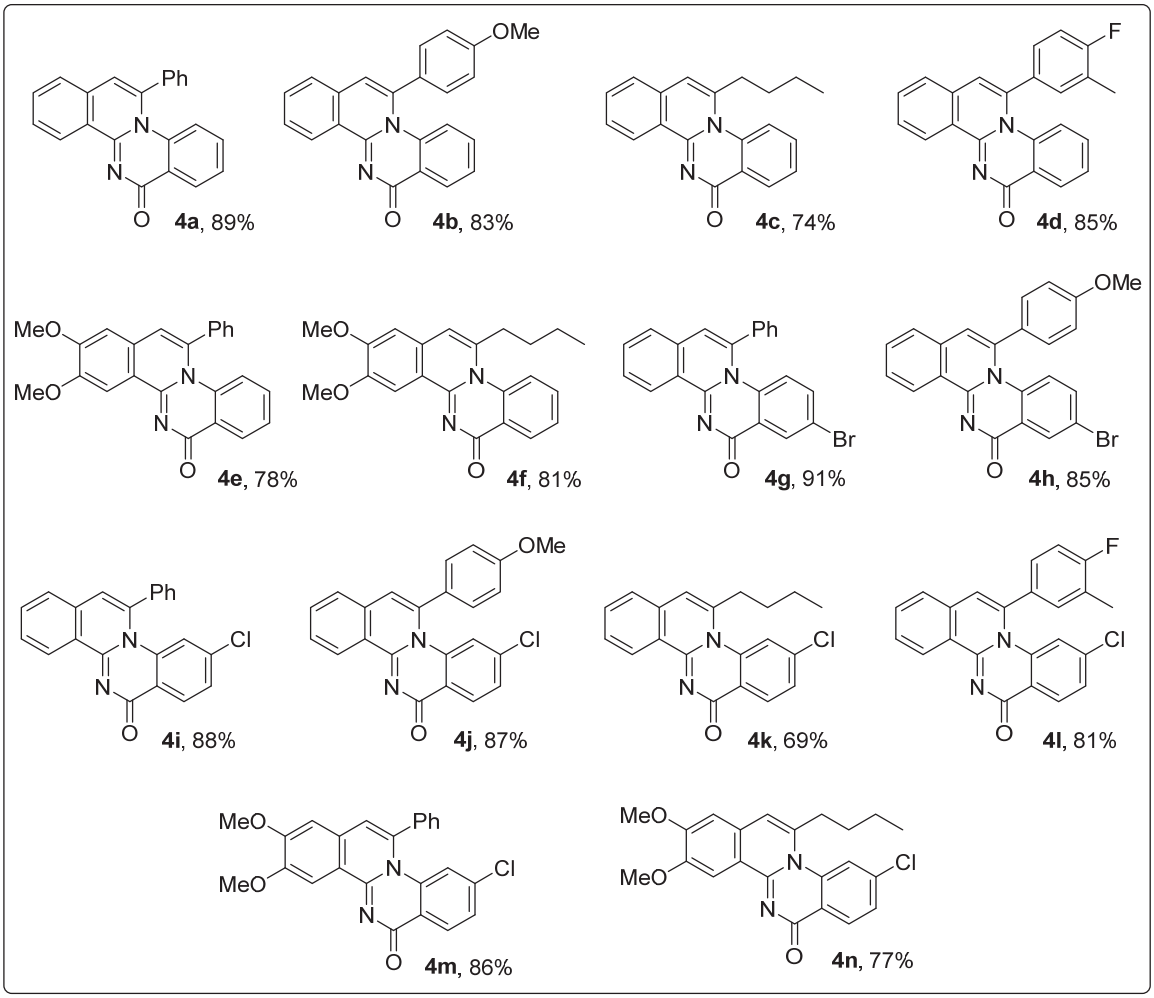


Entry No.	Ag-Catalyst 3 (Mol %)	Solvent	Time (h)	Temp. (°C)	4a Yield (%)[a]
1	AgOTf (30)	DMSO	5	100	29
2	AgOTf (30)	DMSO	4	120	54
3	AgOTf (10)	DMSO	8	120	43
4	AgOTf (20)	DMSO	4	120	73
5	Ag_2O (20)	DMSO	6	120	9
6	$AgClO_4$ (20)	DMSO	6	120	33
7	$AgNO_3$ (02)	DMSO	10	120	77
8	$AgNO_3$ (05)	DMSO	9	120	82
9	$AgNO_3$ (20)	DMSO	6	120	89
10	$AgNO_3$ (20)	DMSO	6	120	13[b]
10	$AgPF_6$ (20)	DMSO	6	120	5
11	$AgNO_3$ (20)	DMF	6	120	42
12	$AgNO_3$ (20)	DMA	6	120	58
13	$AgNO_3$ (20)	Toluene	6	110	34
14	---	DMSO	6	120	n.r.

[a]Reactions were carried out in open atmosphere; [b]Reaction was carried out under nitrogen atmosphere; n.r.: No reaction

Table 2. Synthesis of 12-alkyl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one derivatives[a,b]

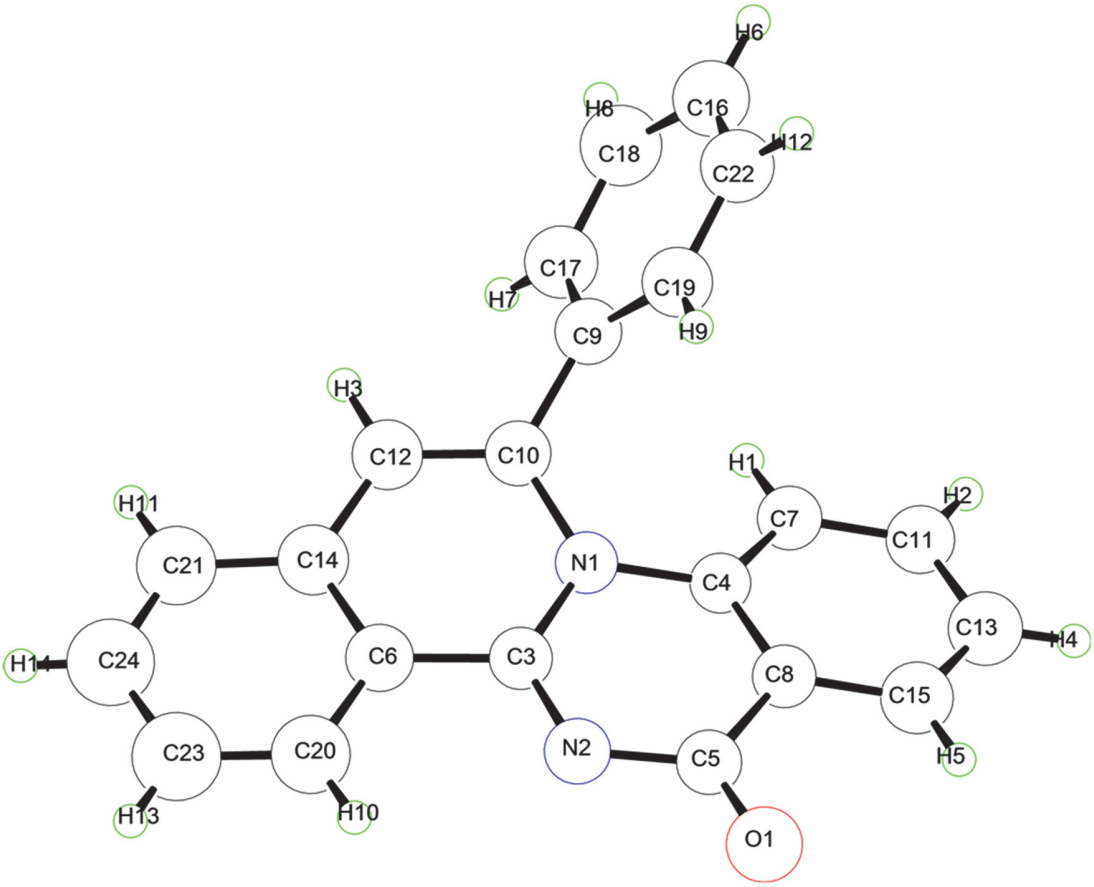




[a]All reactions were conducted with 2-aminobenzamide **1** (0.24 mmol), *O*-akynylaldehyde **2** (0.24 mmol) and 20 mol % of $AgNO_3$-catalyst in DMSO at 120°C unless and otherwise stated. [b]Isolated yields.

Next, to assess the substrate scope and generality of the newly developed $AgNO_3$-catalysed cascade reaction, a variety of *Ortho*-aldehydes bearing different alkynyl-substituents at o-position (**2**) and a range of 2-amino-benzamides (**1**) were employed under the optimized reaction conditions (Table 2). As shown in Table 2, a variety of substituents at the alkynyl part of the substituted benzaldehyde such as aliphatic, aromatic ring containing electron withdrawing halide groups as well as electron donating methoxy groups were well tolerated under the present reaction conditions and afforded the desired isoquinoline-fused quinazolinones **4a-4n** in good to excellent yields (Table 2, 69-91%). Electron donating groups at the aldehydic aromatic ring were also well tolerated. However, the presence of electron-withdrawing halide groups at the 2-amino-

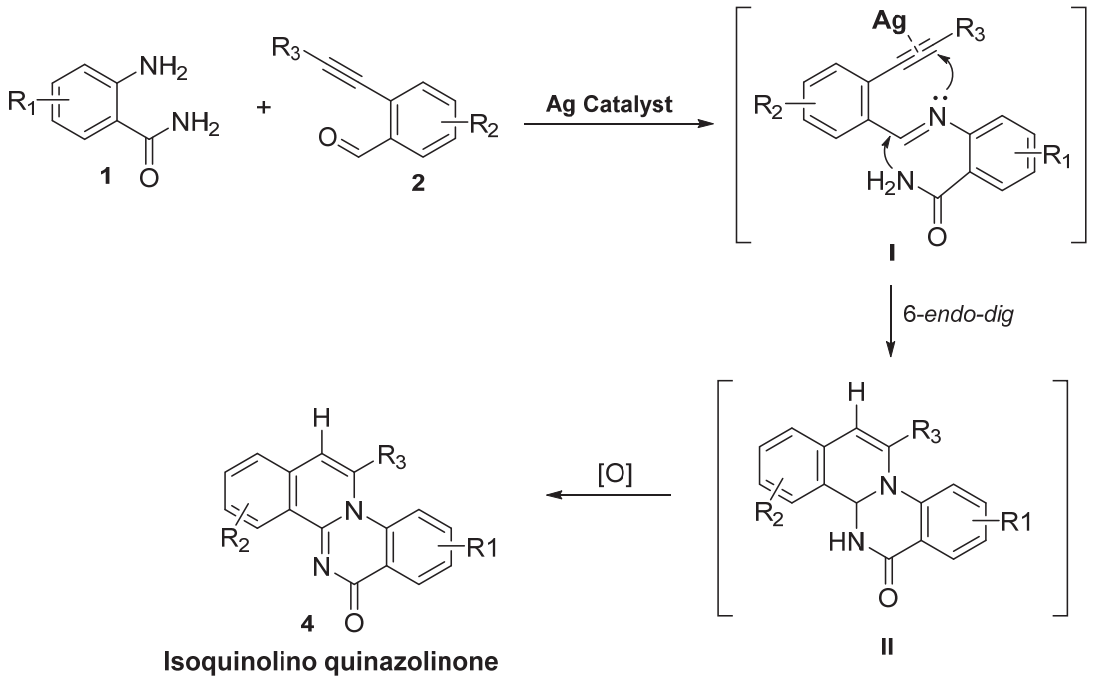
benzamide ring does not make any significant difference in the yield. The synthesized compounds **4a-4n** was characterized by IR, HRMS, ^{1}H and ^{13}C spectral analysis.



4.2.1 Figure 2. X-Ray crystal structure (ORTEP diagram)

Finally, the regioselectivity achieved through Ag(I)-catalysed cascade annulation of 2-amino-benzamides and 2-alkynylbenzaldehydes in the synthesis of isoquinoline-fused benzquinazolinone **4** was confirmed by the X-ray crystallography analysis. The crystal structure of the representative compound 12-phenyl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one **(4a)** was confirmed by the X-ray crystallography analysis (Fig. 2) [16].

4.2.2 Scheme 1 Plausible mechanism for isoquinoline-fused quinazolinones



A plausible mechanism for the formation of isoquinoline-fused quinazolinones **4** is presented in scheme 1. The reaction of 2-amino benzamides **1** and 2-alkynyl benzaldehyde **2** gives rise to imine which is coordinates to Ag catalyst, offering the intermediate **I**. The intermediate **I** on 6-*endo-dig* cyclization *via* protodemetallation deliver intermediate **II**. Finally, the intermediate **II** on *in-situ* oxidation deliver desired isoquinoline-fused quinazolinone derivatives **4** and regenerates silver catalyst for a new catalytic cycle.

4.3 Summary

In summary, we developed a novel $AgNO_3$-catalyzed cascade cyclization of 2-amino benzamides and 2-alkynyl benzaldehydes which underwent *in-situ* oxidation delivers isoquinoline fused quinazolinone derivatives in good to excellent yields. This novel synthetic approach is amenable for the generation of a library of isoquinoline fused quinazolinone analogs. Further expansion of current strategies and evaluation of biological activity is in progress.

4.4 Experimental section

4.4.1 General methods: All solvents and reagents were purchased from the suppliers and used without further purification. IR spectra were recorded on a JASCO FT/IR-460 Plus spectrophotometer. Reactions were monitored by TLC on silica plates using UV-light or Iodine chamber for visualization. Evaporation and condensation were carried out *in vacuo*. NMR

spectra were recorded with JEOL JNM-ECS 400 spectrometers with tetramethylsilane as an internal standard. Chemical shifts δ and coupling constants *J* are given in ppm (parts per million) and Hz (hertz), respectively. The following abbreviations were used as follows: s: singlet, d: doublet, t: triplet and m: multiplet. All known compounds data are inconsistent with the given literature reports. Scale up reactions also performed as per the given general procedure without any deviation. Melting points were measured by a Yanaco micro melting point apparatus.

4.4.2 General procedure and spectral data

General procedure for the synthesis of 2-(phenylethynyl)benzaldehyde (2).

To a solution of bromobenzaldehyde (2.7 mmol, 1 equiv.) in 10 ml THF was added $Pd(PPh_3)_2Cl_2$ (5 mol%) and NEt_3 (8.1 mmol, 3 equiv.); the resulting mixture was stirred and purged with nitrogen gas for 10 min, Further Phenyl acetylene (4.054 mmol, 1.5 equiv.) and CuI (5 mol%) was added. The reaction mixture was further stirred under nitrogen gas at room temperature for 24 h. After completion, the reaction was quenched with sat. NH_4Cl and extracted with ethyl acetate. Organic layer was washed with brine dried over sodium sulphate. The crude residue was purified by silica gel chromatography using ethyl acetate / n-hexane (3:97) as eluents to afford **2**.

General procedure and spectral data for the synthesis of 12-alkyl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4)

To a solution of 2-aminobenzamides **1** (0.24 mmol, 1 equiv.) and 2-alkynylbenzaldehydes **2** (0.24 mmol, 1 equiv.) in 4 ml DMSO, $AgNO_3$ (20 mol %), was added. The resulting mixture was then heated at 120°C for 4 h. After completion of the reaction, the reaction mixture was extracted with ethyl acetate: brine; the crude was purified by silica gel chromatography using acetone/hexane (20:80) as eluents to afford **4**.

The isolated yield and the spectral data for **4a–4n** are as follows:

12-Phenyl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4a)

Yield: 89%; Melting point: 211-213°C; IR (neat): 2999, 1655, 1630, 1599, 1586, 1561, 1479, 1467, 1254, 1179, 1136, 1066, 858, 832, 752, 676, 580, 542 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.69 (d, *J* = 8.1 Hz, 1H), 8.08 (d, *J* = 6.7 Hz, 1H), 7.87 (d, *J* = 4.0 Hz, 2H), 7.71 (q, *J* = 3.9 Hz, 1H), 7.50 (d, *J* = 3.6 Hz, 2H), 7.40-7.46 (m, 5H), 7.31 (t, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 9.0 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 166.44, 153.40, 138.49, 138.23, 136.86, 133.54, 130.44,

129.10, 128.91, 128.70, 127.48, 127.02, 126.79, 126.70, 126.49, 125.30, 122.28, 122.19, 117.16. HRMS (ESI): *m/z* = 323.1184 calcd. For $C_{22}H_{15}N_2O$ found 323.1155 $[M+H]^+$.

12-(4-Methoxyphenyl)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4b)

Yield: 83%; Melting point: 235-236°C; IR (neat): 3067, 2905, 1651, 1626, 1602, 1523, 1510, 1337, 1258, 1023, 831, 822, 772, 762, 544 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ 8.65 (d, *J* = 8.1 Hz, 1H), 8.05 (d, *J* = 6.3 Hz, 1H), 7.82 (d, *J* = 5.4 Hz, 2H), 7.63-7.67 (m, 1H), 7.39-7.45 (m, 3H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.27 (s, 1H), 6.97 (dd, *J* = 14.8, 8.5 Hz, 3H), 3.77 (s, 3H) ^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ 166.43, 159.57, 153.43, 138.40, 138.36, 133.71, 133.44, 130.35, 129.16, 128.90, 128.31, 126.73, 126.60, 126.43, 125.09, 122.20, 122.13, 116.15, 114.44, 55.28; HRMS (ESI): *m/z* = 375.1109 calcd. For $C_{23}H_{16}N_2O_2Na$ found 375.1133 $[M+Na]^+$.

12-Butyl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4c)

Yield: 74%; Melting point: 95-96°C; IR (neat): 2931, 2872, 1647, 1634, 1603, 1592, 1516, 1456, 1343, 1271, 1189, 1114, 1066, 787, 759, 710, 544 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ 8.58 (d, *J* = 8.1 Hz, 1H), 8.14 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 1H), 7.74-7.83 (m, 3H), 7.60-7.66 (m, 2H), 7.27 (s, 1H), 3.12 (t, *J* = 7.6 Hz, 2H), 1.37-1.44 (m, 2H), 1.08-1.16 (m, 2H), 0.72 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ 166.22, 153.40, 140.10, 137.75, 133.76, 133.34, 131.57, 127.89, 127.42, 126.60, 126.53, 126.03, 124.60, 122.32, 121.39, 114.50, 33.67, 30.98, 21.50, 13.48; HRMS (ESI): *m/z* = 303.1497 calcd. For $C_{20}H_{19}N_2O$ found 303.1469 $[M+H]^+$.

12-(4-Fluoro-3-methylphenyl)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4d)

Yield: 85%); Melting point: 86-87°C; IR (neat): 3015, 1651, 1646, 1629, 1519, 1362, 1215, 1157, 1033, 824, 754, 666, 645, 537 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.95 (d, *J* = 8.1 Hz, 1H), 8.33 (d, *J* = 8.1 Hz, 1H), 7.75 (t, *J* = 7.0 Hz, 1H), 7.61 (dd, *J* = 13.0, 7.6 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.22-7.29 (m, 2H), 7.10 (s, 1H), 6.97-7.03 (m, 3H), 2.27 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.03, 162.79, 160.26, 154.24, 138.50, 137.89, 133.57, 132.80, 130.65, 130.32, 130.26, 128.75, 128.20, 127.72, 126.88, 126.54, 126.46, 126.40, 125.99, 122.45, 122.03, 117.53, 116.23, 116.00, 14.76, 14.72; HRMS (ESI): *m/z* = 377.1066 calcd. For $C_{23}H_{15}N_2OFNa$, found 377.1096 $[M+Na]^+$.

2,3-Dimethoxy-12-phenyl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4e)

Yield: 78%; Melting point: 209-211°C; IR (neat): 3061, 1644, 1621, 1602, 1495, 1416, 1368, 1195, 1131, 991, 752, 698, 641, 529, 501 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 12.1

Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 6H), 7.20 (t, *J* = 7.9 Hz, 1H), 7.01 (q, *J* = 8.7 Hz, 3H), 4.09 (s, 3H), 4.05 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.13, 154.63, 153.62, 150.59, 138.61, 137.68, 137.25, 130.43, 129.52, 129.43, 128.96, 127.70, 127.21, 126.68, 122.50, 122.31, 120.11, 117.53, 108.19, 106.56, 56.80, 56.41; HRMS (ESI): *m/z* = 405.1215 calcd. For $C_{24}H_{18}N_2O_3Na$ found 405.1226 $[M+Na]^+$.

12-Butyl-2,3-dimethoxy-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4f)

Yield: 81%; Sticky; IR (neat): 2934, 2961, 1719, 1630, 1604, 1592, 1439, 1398, 1340, 1267, 1226, 1166, 1064, 1032, 998, 878, 862, 771, 755, 664, 644 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 7.6 Hz, 1H), 8.28 (s, 1H), 7.66 (d, *J* = 3.6 Hz, 2H), 7.55-7.60 (m, 1H), 6.94 (d, *J* = 5.8 Hz, 2H), 4.06 (s, 3H), 4.04 (s, 3H), 3.13 (t, *J* = 7.6 Hz, 2H), 1.47-1.54 (m, 2H), 1.17-1.25 (m, 2H), 0.82 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.03, 154.56, 153.76, 150.11, 138.66, 138.30, 131.03, 129.78, 128.10, 127.24, 123.04, 120.72, 119.50, 115.18, 107.99, 105.88, 56.77, 56.37, 34.71, 32.31, 22.23, 13.78; HRMS (ESI): *m/z* = 363.1709 calcd. For $C_{22}H_{23}N_2O_3$ found 363.1679 $[M+H]^+$.

8-Bromo-12-phenyl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4g)

Yield: 91%; Melting point: 218-219°C; IR (neat): 3027, 1772, 1630, 1508, 1482, 1491, 1317, 1250, 1183, 1168, 895, 814, 712, 638, 529 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ 8.69 (d, *J* = 8.1 Hz, 1H), 8.14 (d, *J* = 2.2 Hz, 1H), 7.88 (q, *J* = 1.8 Hz, 2H), 7.69-7.74 (m, 1H), 7.49-7.55 (m, 3H), 7.42-7.45 (m, 4H), 6.91 (d, *J* = 9.4 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ 165.22, 153.56, 138.32, 137.40, 136.57, 133.75, 133.60, 133.02, 129.22, 129.07, 128.82, 128.55, 127.52, 127.07, 126.91, 125.16, 124.64, 123.84, 119.46, 117.40; HRMS (ESI): *m/z* = 401.0289 calcd. For $C_{22}H_{14}N_2OBr$, found 401.0300 $[M+H]^+$.

8-Bromo-12-(4-methoxyphenyl)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4h)

Yield: 85%; Melting point: 254-256°C; IR (neat): 1648, 1628, 1603, 1506, 1478, 1317, 1277, 1248, 1163, 1122, 1026, 890, 833, 813, 793, 618, 540 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ 8.66 (d, *J* = 8.1 Hz, 1H), 8.12 (d, *J* = 2.2 Hz, 1H), 7.86 (dd, *J* = 14.6, 8.3 Hz, 2H), 7.66-7.70 (m, 1H), 7.53 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.46 (d, *J* = 9.0 Hz, 2H), 7.33 (d, *J* = 7.2 Hz, 1H), 6.94-7.00 (m, 3H), 3.79 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ 165.25, 159.70, 153.62, 138.30, 137.56, 133.79, 133.69, 132.99, 129.03, 128.91, 128.50, 126.87, 124.98, 124.54, 123.89, 119.41, 116.43, 114.58, 55.31; HRMS (ESI): *m/z* = 431.0395 calcd. For $C_{23}H_{16}N_2O_2Br$, found 431.0394 $[M+H]^+$.

9-Chloro-12-phenyl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4i)

Yield: 88%; Melting point: 268-270°C; IR (neat): 3170, 3040, 1707, 1646, 1629, 1586, 1509, 1474, 1302, 1067, 869, 843, 832, 756, 705, 681, 547 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.99 (d, *J* = 7.6 Hz, 1H), 8.29 (d, *J* = 8.5 Hz, 1H), 7.77-7.81 (m, 1H), 7.66 (t, *J* = 7.2 Hz, 2H), 7.46 (t, *J* = 3.4 Hz, 3H), 7.36-7.39 (m, 3H), 7.12 (s, 1H), 6.96 (d, *J* = 1.8 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.24, 154.53, 139.20, 138.44, 137.04, 136.31, 133.79, 133.53, 129.61, 129.51, 129.19, 128.96, 128.35, 127.37, 127.21, 126.47, 125.87, 122.12, 120.72, 117.88; HRMS (ESI): *m/z* = 357.0795 calcd. For $C_{22}H_{14}N_2OCl$, found 357.0770 $[M+H]^+$.

9-Chloro-12-(4-methoxyphenyl)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4j)

Yield: 87%; Melting point: 177-178°C; IR (neat): 3066, 3000, 1655, 1630, 1599, 1586, 1479, 1467, 1316, 1254, 1136, 1098, 833, 788, 754, 663, 453 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.93 (d, *J* = 7.6 Hz, 1H), 8.25 (d, *J* = 8.5 Hz, 1H), 7.75 (t, *J* = 7.4 Hz, 1H), 7.60 (t, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 3.86 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.25, 160.48, 154.63, 139.36, 138.34, 136.93, 133.72, 129.13, 128.61, 128.28, 127.29, 126.29, 125.69, 122.09, 120.76, 116.99, 114.96, 55.53; HRMS (ESI): *m/z* = 409.0720 calcd. For $C_{23}H_{15}N_2O_2NaCl$, found 409.0749 $[M+Na]^+$.

12-Butyl-9-chloro-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4k)

Yield: 69%; Brown sticky liquid; IR (neat): 2960, 2873, 1719, 1561, 1479, 1466, 1450, 1423, 1340, 1316, 1266, 1155, 913, 876, 780, 564, 515 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 8.1 Hz, 1H), 8.34 (d, *J* = 8.5 Hz, 1H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.67 (s, 1H), 7.54-7.60 (m, 3H), 7.00 (s, 1H), 3.10 (t, *J* = 7.9 Hz, 2H), 1.50-1.58 (m, 2H), 1.27 (d, *J* = 7.2 Hz, 2H), 0.83-0.90 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.10, 154.62, 139.18, 138.87, 137.60, 133.68, 133.57, 129.63, 128.28, 128.01, 127.78, 125.67, 125.36, 121.21, 120.34, 115.85, 34.34, 32.02, 22.07, 13.64; HRMS (ESI): *m/z* = 337.1108 calcd. For $C_{20}H_{18}N_2OCl$, found 337.1097 $[M+H]^+$.

9-Chloro-12-(4-fluoro-3-methylphenyl)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4l)

Yield: 81%; Brown solid; Melting point: 252-254°C; IR (neat): 3139, 3033, 1637, 1597, 1583, 1511, 1501, 1481, 1444, 1318, 1128, 1120, 833, 809, 772, 754, 611 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.97 (d, *J* = 7.6 Hz, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 7.77-7.81 (m, 1H), 7.65 (t, *J* = 7.2 Hz, 2H), 7.39 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.14 (q, *J* = 2.4 Hz, 1H), 7.05-7.10 (m, 2H), 6.99 (d, *J* = 1.7 Hz, 1H), 2.30 (d, *J* = 1.8 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.23, 162.94, 160.40, 154.50, 139.14, 137.56, 137.05, 133.83, 133.46, 132.17, 132.13, 130.26, 130.21, 129.24, 128.96, 128.31, 127.44, 126.82, 126.63, 126.49, 126.42, 125.80, 121.96, 120.71,

117.73, 116.41, 116.19, 14.73, 14.70; HRMS (ESI): *m/z* = 389.0857 calcd. For $C_{23}H_{15}N_2OFCl$, found 389.0827 $[M+H]^+$.

9-Chloro-2,3-dimethoxy-12-phenyl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (4m)

Yield: 86%; Yellow solid; Melting point: 256-258°C; IR (neat): 3061, 3004, 1619, 1584, 1495, 1454, 1393, 1270, 1220, 1195, 1072, 998, 880, 771, 701, 646, 532 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 7.43-7.45 (m, 3H), 7.34-7.37 (m, 3H), 7.05 (d, *J* = 14.8 Hz, 2H), 6.97 (d, *J* = 1.3 Hz, 1H), 4.09 (s, 3H), 4.05 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.38, 154.92, 153.91, 150.77, 139.32, 137.47, 136.91, 136.62, 129.69, 129.56, 129.38, 129.24, 127.30, 127.25, 122.37, 120.83, 119.95, 117.73, 108.29, 106.66, 56.84, 56.46; HRMS (ESI): *m/z* = 417.1006 calcd. For $C_{24}H_{18}N_2O_3Cl$, found 417.0987 $[M+H]^+$.

12-Butyl-9-chloro-2,3-dimethoxy-6*H*-isoquinolino[2,1 *a*]quinazolin-6-one (4n)

Yield: 77%; Yellow solid; Melting point: 96-97°C; IR (neat): 2959, 2931, 1634, 1603, 1592, 1516, 1481, 1343, 1271, 1155, 962, 935, 760, 710, 622, 473 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.1 Hz, 1H), 8.25 (s, 1H), 7.67 (d, *J* = 1.8 Hz, 1H), 7.54 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.94 (d, *J* = 6.7 Hz, 2H), 4.06 (s, 3H), 4.04 (s, 3H), 3.10 (t, *J* = 7.9 Hz, 2H), 1.51-1.58 (m, 2H), 1.26 (td, *J* = 14.7, 7.5 Hz, 2H), 0.85 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.26, 154.80, 154.05, 150.26, 139.04, 138.22, 137.44, 129.77, 129.73, 127.72, 121.36, 120.57, 119.34, 115.66, 108.05, 105.99, 56.78, 56.41, 34.49, 32.29, 22.19, 13.77; HRMS (ESI): *m/z* = 419.1138 calcd. For $C_{22}H_{21}N_2O_3NaCl$, found 419.1145 $[M+Na]^+$.

4.5 References

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Chapter 5

The *in-situ* air oxidation and photophysical studies of isoquinoline-based *N*-heteroacenes

5.1 Introduction

Among the *N*-heterocycles, isoquinoline-fused benzimidazole and isoquinoline-fused quinazolinone have attracted considerable attention due to their immense and outstanding biological properties [1]. It is also known that many synthetic methods have been developed and documented for their analogs due to their intrinsic anticancer, anti-HIV-1, antiviral, antimicrobial, and antifungal properties [2]. Therefore, molecules containing this motif have attracted considerable attention in medicinal chemistry and much effort has been focused on the synthetic methods of isoquinoline-fused benzimidazole ring system. The commonly used synthetic routes involve cascade cyclization strategies with 2-ethynylbenzaldehydes and benzenediamines or 2-amino benzamide as substrates to give isoquinoline-fused benzimidazole and isoquinoline-fused quinazolinone polycyclic skeletons (**Fig. 1**) [3, 4]. In the literature survey, reports are available towards the construction of isoquinoline-fused benzimidazole heteroacenes in the presence of various expensive Lewis acidic catalysts such as silver, gold, copper, magnesium and rhodium-catalyst [5]. The cascade cyclizations of alkynes *via* diorganyl diselenides are gaining considerable attentions due to novel seleno-heterocycles [6] and further applications in the preparation of physical materials that shows potentially useful optical and fluorescent properties [7]. Recently, we have successfully synthesized the novel cascade cyclizations resulted into various seleno-fused heteroacenes [8]. Herein, we have successfully attempted the two core heterosystems, isoquinoline-fused benzimidazole and isoquinoline-fused quinazolinone in the open flask. Isoquinoline-fused benzimidazoles were achieved by metal free catalyst. The reaction was found to occur in three major steps involving first imine formations, further cyclization, and finally air oxidation. Meanwhile, the isoquinoline-fused quinazolinone heteroacenes were successfully achieved by intramolecular cascade cyclization by Fe(III) catalyst which resulted into various substituted S and Se-heteroacenes.

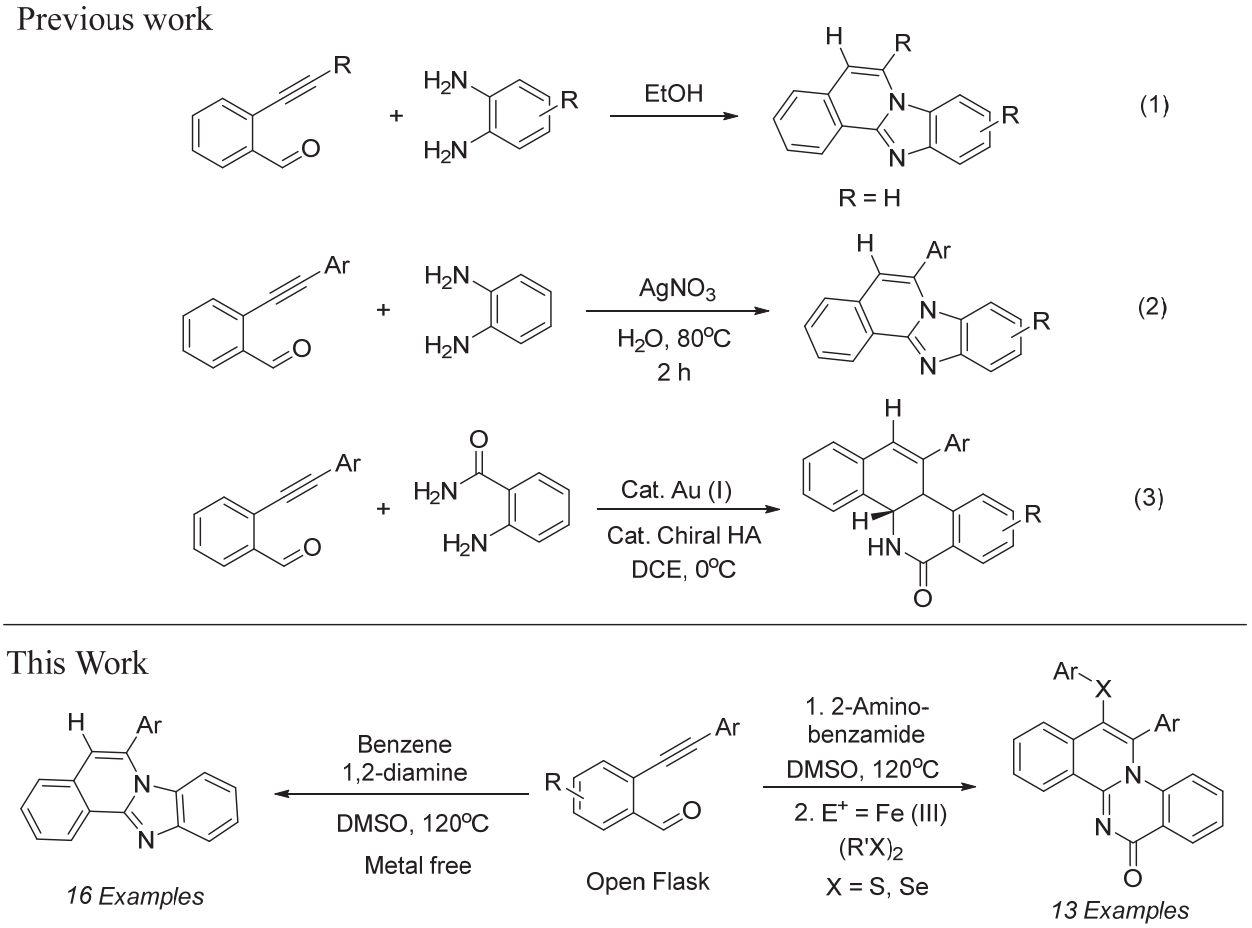
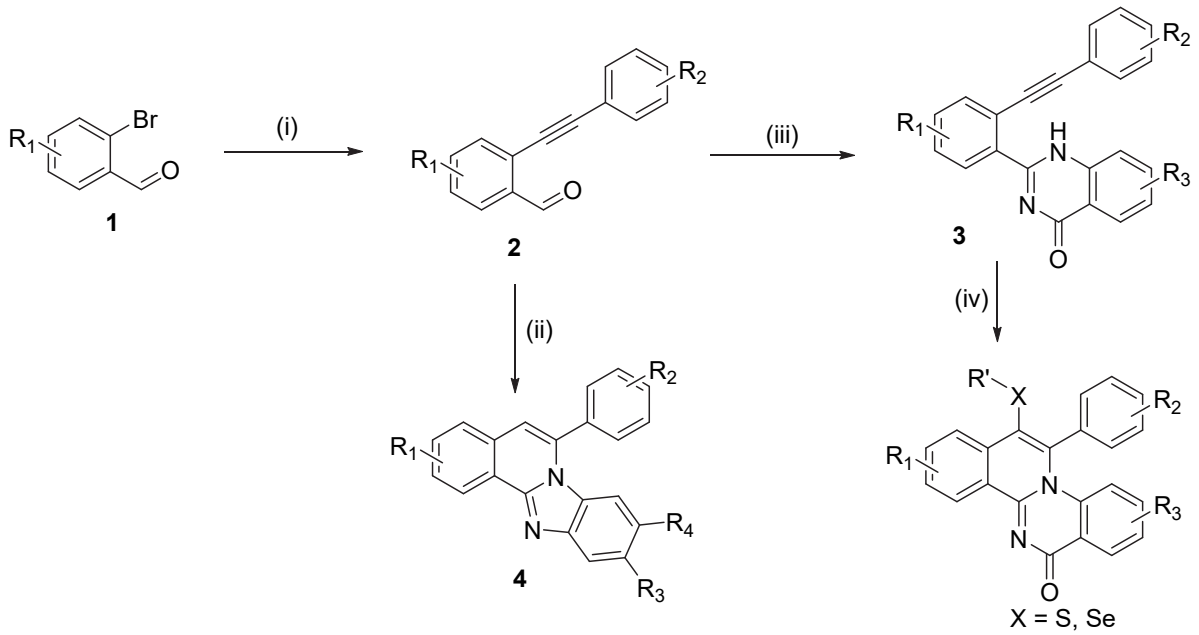


Fig. 1

5.2 Result and Discussion

Our investigations were started with the easily available starting materials amines and 2-bromobenzaldehydes (**1**) which were readily converted to aryl alkynes (**2**) under Sonogashira coupling conditions, the compounds (**1**) were alkylated with various aromatic alkynes to afford the corresponding substituted aryl alkynes (**2**) in 60-70% yields. Further, compounds (**2**) were successfully converted to intermediate (**3**) by reacting with substituted 2-amino benzamides in DMSO solvent at 120°C in open atmosphere. At the same time, if compounds (**2**) were treated with substituted 1,2-diamine benzenes which resulted into the cyclized products (**4**) with good yields under the same reaction conditions. Further, compound (**3**) in hand was successfully transformed to the substituted sulfur and selenium-heterocycles (**5**) in the presence of disulfide and diselenide respectively *via* Fe(III) catalyst (**Scheme 1**). The structures of (**2**) [9] (**3**), (**4**) and (**5**) were confirmed by the IR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectral analysis.

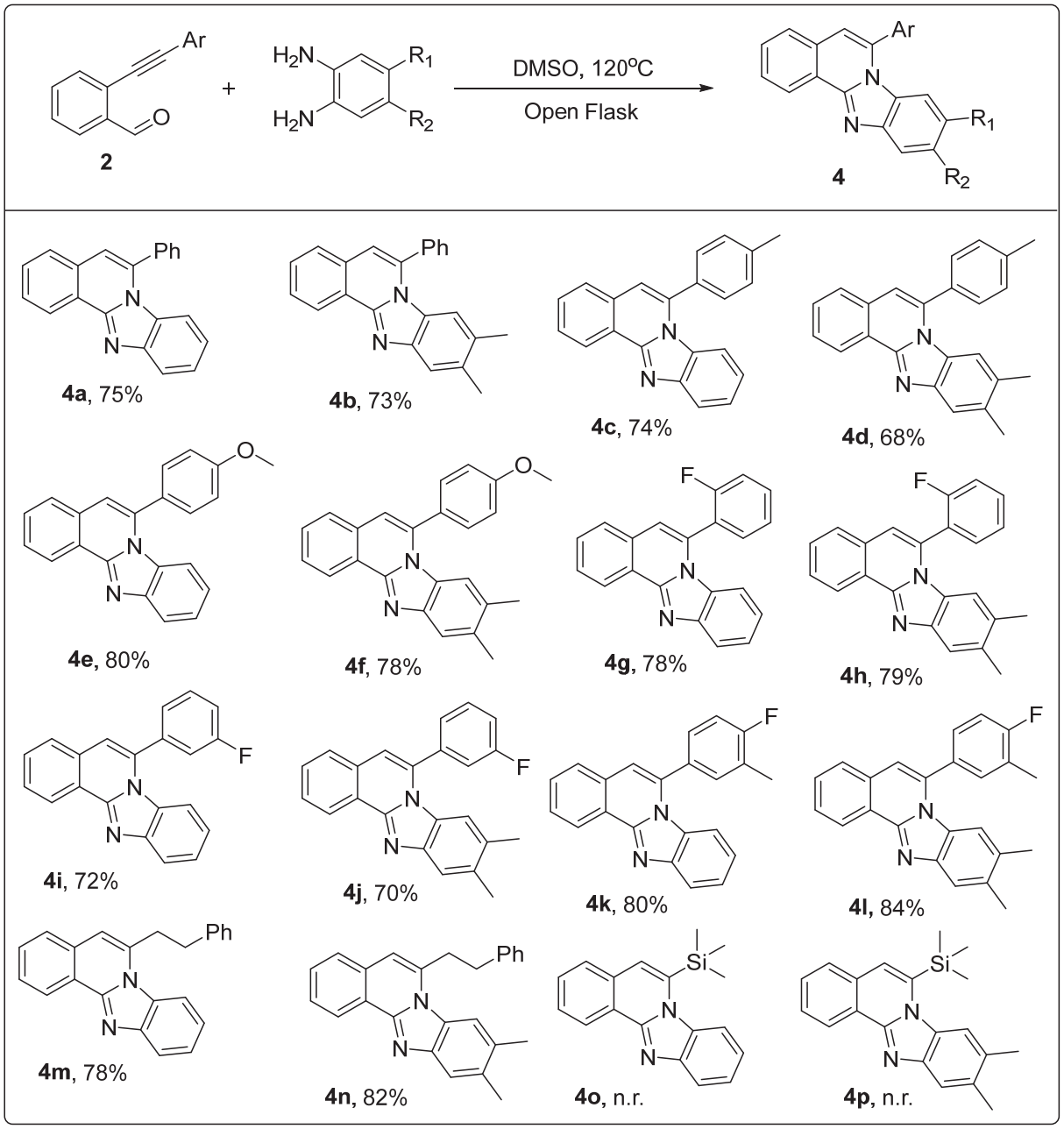


Reagents: (i) Aryl alkynes (1.1 equiv.), $Pd(PPh_3)_2Cl_2$(5 Mol%), CuI (6 Mol%), NEt_3, THF, rt, 12 h
(ii) 1,2-diamine benzene (1.2 equiv.), DMSO, 120°C (Oil Bath), 12 h
(iii) 2-amino benzamide (1.2 equiv.), DMSO, 120°C (Oil Bath), 12 h
(iv) $FeCl_3 \cdot 6H_2O$ (2.0 equiv.), Diorganyl diselenides (1.0) / disulfides (1.5 equiv.)
DCM, reflux (Oil Bath), 5-6 h

Scheme 1. Synthesis of isoquinoline-fused benzimidazole (**4**) and isoquinoline-based quinazolinone (**5**) heteroacenes

Table 1 shows the variety of substrate scopes for isoquinoline-fused benzimidazole derivatives. The reactions are facile for electron-donating as well as electron withdrawing substituents, on the controversy reaction did not proceeded for the substituted TMS-alkyne which did not resulted into the product (**4o**) and (**4p**) respectively. All the reactions were carried out in open flask at 120°C in DMSO solvent, the yield of reaction drastically decreased under the nitrogen atmosphere.

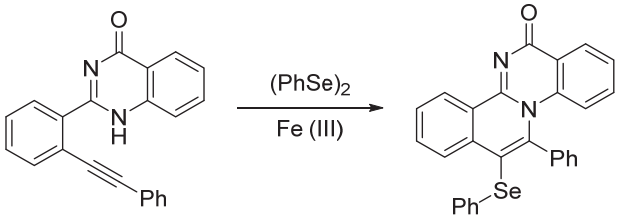
Table 1. Substrate scopes for Isoquinoline-fused benzimidazole derivatives **(4)**.



With the standard compound **3a** in hand, we have optimized the synthesis of isoquinoline-based quinazolinone derivative **5a**. We first examined the selenocyclization reaction of aryl alkyne **3a** with 1.5 equiv. of $FeCl_3 \cdot 6H_2O$ and $(PhSe)_2$ (1.5 equiv.) in DCM at room temperature, the reaction did not proceeded and the starting 3a was isolated by column chromatography. Further, the reaction was carried out with 1.0 equiv. of $FeCl_3 \cdot 6H_2O$ and $(PhSe)_2$ (0.5 equiv.) in DCM under reflux conditions. Interestingly, the reaction resulted in the formation of 12-phenyl-13-(phenylselanyl)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one derivative **5a** in 56% yield. To

improve the yield of cyclization product, different reaction conditions were screened (**Table 2**, entries 1-12). The best result was obtained, when the selenocyclization reaction was carried out using 1.5 equiv. of $FeCl_3 \cdot 6H_2O$ and $(PhSe)_2$ (1.0 equiv.) in DCM under reflux conditions to afford desired 12-phenyl-13-(phenylselanyl)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one derivative **5a** in 65% yield (**Table 2**, entry 4). With the standard conditions in hands, we have successfully synthesized various substituted sulfur and selenium heteroacenes (**Table 3**). Additionally, it was found that the reaction did not proceed when treated with $(PhCH_2S)_2$ (**5n**) and dibutyl selenide $(Bu)_2Se$ (**5o**).

Table 2. Optimization Table for synthesis of 12-phenyl-13-(phenylselanyl)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (**5a**)

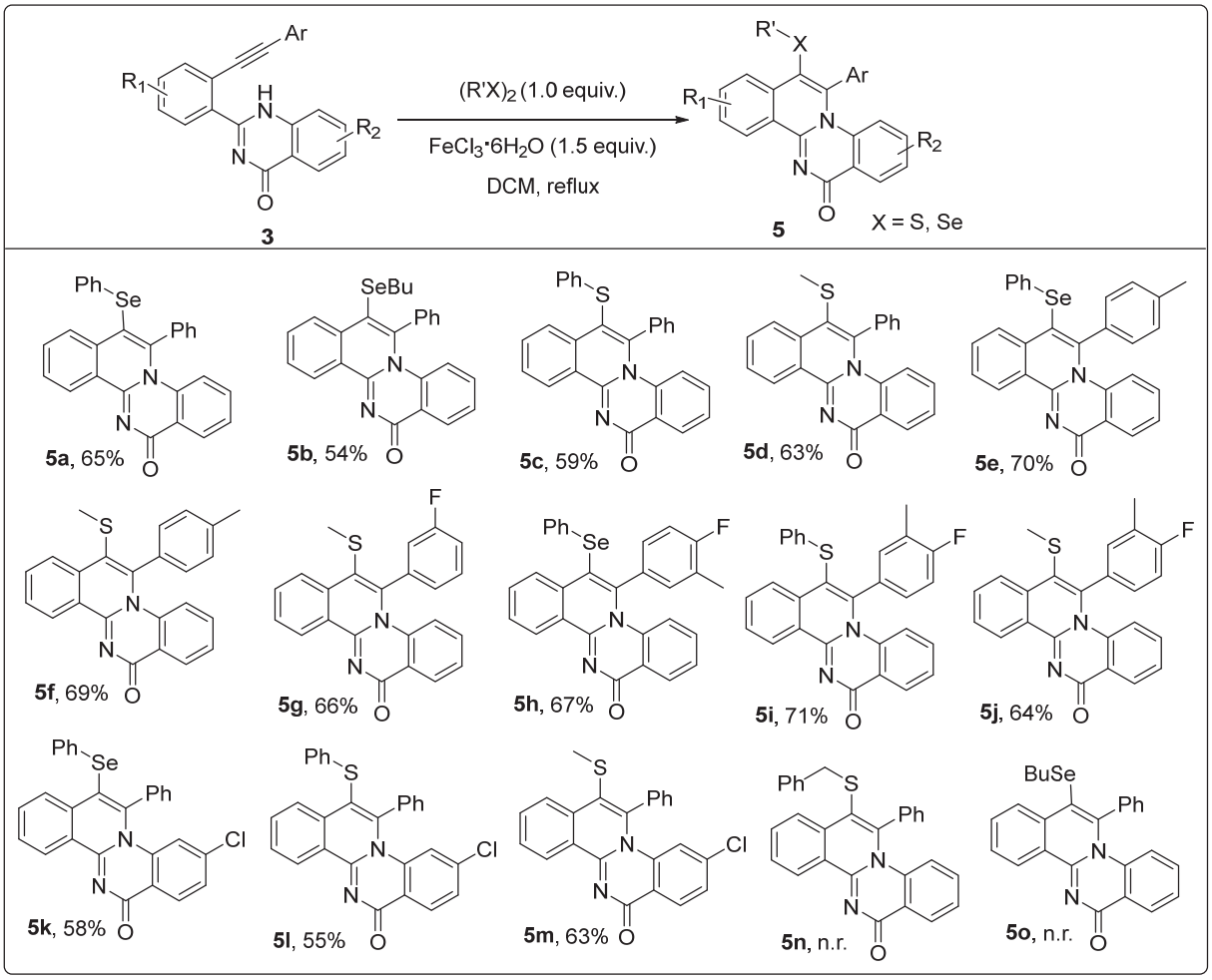


3a **5a**

Entry No.	Solvent	E^+ (Eq.)	$(PhSe)_2$ (Eq.)	Time (h)	Temp. (ºC)	Yield (%)[a] 5a
1	$CHCl_3$	$FeCl_3 \cdot 6H_2O$ (1.0)	0.5	12	rt	n.r.
2	DCM	$FeCl_3 \cdot 6H_2O$ (1.0)	0.5	12	reflux	56
3	DCM	$FeCl_3 \cdot 6H_2O$ (1.5)	2.0	12	reflux	61
4	DCM	$FeCl_3 \cdot 6H_2O$ (1.5)	1.0	8	reflux	65
5	DCM	$FeCl_3 \cdot 6H_2O$ (2.5)	2.0	8	reflux	62
6	$CHCl_3$	$FeCl_3$ (2.0)	1.5	12	65	42
7	DCM	$FeCl_3 \cdot 6H_2O$ (3.5)	3.0	8	reflux	59
8	DMF	$FeCl_3 \cdot 6H_2O$ (1.5)	1.0	8	80ºC	n.r.
9	DMSO	$FeCl_3 \cdot 6H_2O$ (1.5)	1.0	8	80ºC	n.r.
10	DCM	CuI (0.1)/I_2 (1.0)	1.0	12	reflux	n.r.
11	DCM	$CuCl_2$ (0.1)	1.0	12	reflux	n.r.
12	DCM	CuI(0.1)/NIS (1.0)	1.0	12	reflux	n.r.
13	DCM	---	1.0	12	reflux	n.r.

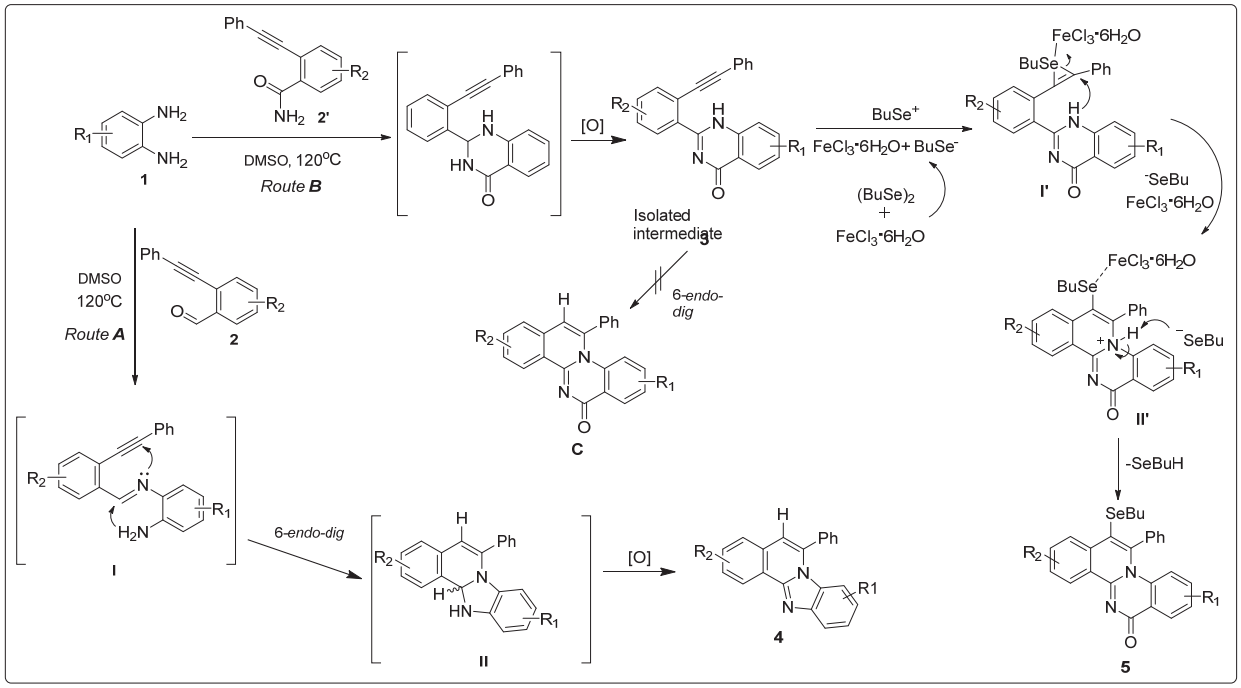
[a]The reaction was performed by addition of diphenyl diselenide (1.0 equiv.) to a solution of $FeCl_3 \cdot 6H_2O$ (1.5 equiv.) in DCM (4 mL), under an air atmosphere, at room temperature. After 15 min at this temperature, alkyne **3a** (1.0 equiv.) was added. The resulting mixture was refluxed for 8 h. n.r.: No reaction.

Table 3. Substrate scopes for synthesis of isoquinoline-fused quinazolinone derivatives (**5**).



In this study, we have hypothesized the plausible reaction mechanism for the synthesis of isoquinoline-fused benzimidazole (**4**) as well as the novel cascade cyclization for the synthesis of isoquinoline-fused quinazolinone (**5**). *Route **A*** shows the formation of isoquinoline-fused benzimidazole **4**. The reaction 1,2-benezediammine (**1**) and 2-alkynyl benzaldehyde (**2**) gives rise to imine which results into the formation of intermediate **I**. The intermediate **I** on 6-*endo-dig* cyclization delivers intermediate **II**. Finally, the intermediate **II** on *in-situ* oxidation delivers the desire isoquinoline-fused benzimidazole derivatives (**4**). *Route **B*** shows the formation of

isoquinoline-fused quinazolinone derivatives (**5**). The reaction 1,2-benezediammine (**1**) with 2-alkynyl benzamide (**2'**) does not resulted into the cyclized product **C**, instead we isolated the intermediate **3**. Further, the intermediate **3** was cyclized *via* novel cascade cyclization pathway. In the first step, iron salt reacts with dibutyl diselenide promoting the cleavage of Se-Se bond to give an organoselenyl cation and an organoselenyl anion [10]. The Fe(III) coordinates with one selenium atom from dibutyl diselenide, which results in the intermediate **I'**, further the nucleophilic anti-attack on activated seleniranium ion **I'** takes place by internal amine as nucleophile results into the intermediate cyclized product **II'**. Finally, the cascade cyclized product (**5**) was successfully achieved in good yields (**Scheme 3**).



5.2.1 Scheme 3. Plausible mechanism

5.3 Photophysical study

The UV-vis absorption spectra of **4a**, **4e**, **4i**, **4k, 5a**, **5c**, **5h** and **5k** in DCM are shown in Fig. 2. In the isoquinoline-fused benzimidazole derivatives **4a**, **4e**, **4i** and **4k**, the absorption maximum (λ_{max}) and molar extinction coefficient ($\mathcal{E}$) values of isoquinoline-based benzimidazole (**4a**: λ_{max} = 360 nm, $\mathcal{E}$ = 4,972), (**4e**: λ_{max} = 360 nm, $\mathcal{E}$ = 5,942), (**4i**: λ_{max} = 356 nm, $\mathcal{E}$ = 6,897) and

(**4k**: λ_{max} = 359 nm, $\mathcal{E}$ = 4,935) derivatives were almost the same (**Fig. 2a**, Table 4). While, In the case of isoquinoline-fused quinazolinone derivatives **5a**, **5c, 5h** and **5k**, the absorption maximum (λ_{max}) and molar extinction coefficient ($\mathcal{E}$) values of isoquinoline-fused quinazolinone (**5a**: λ_{max} = 394 nm, $\mathcal{E}$ = 9,262), (**5c**: λ_{max} = 393 nm, $\mathcal{E}$ = 11,688), (**5h**: λ_{max} = 394 nm, $\mathcal{E}$ = 11,549) and (**5k**: λ_{max} = 393 nm, $\mathcal{E}$ = 11,845) derivatives were almost the same (**Fig. 2b**, Table 4). The isoquinoline-fused benzimidazole derivatives **4a**, **4e**, **4i** and **4k** have higher absorbance maxima (λ_{max} = 393-394 nm) than the isoquinoline-fused quinazolinone derivatives **5a**, **5c**, **5h** and **5k** (λ_{max} = 356-360 nm).

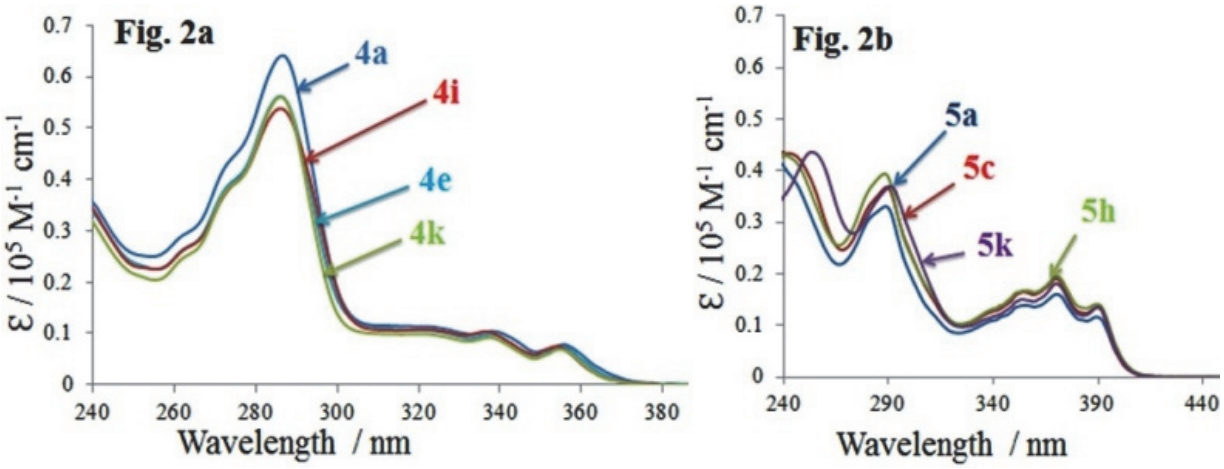


Fig. 2. UV-vis absorption spectra of isoquinoline-fused benzimidazole (**a**) and isoquinoline-fused quinazolinone (**b**) derivatives in $CHCl_3$.

The fluorescence spectra of **4a**, **4e**, **4i**, **4k 5a**, **5c**, **5h** and **5k** in DCM are shown in **Fig. 3**. The fluorescence maximum (F_{max}) and Stokes shift values were in the range of 403 to 444 nm and 43 to 78 nm, respectively (Table 4). The fluorescence quantum yield (ϕ_f) values obtained for isoquinoline-based benzimidazole were (ϕ_f: 0.370-0.471), while the fluorescence quantum yield (ϕ_f) values obtained for isoquinoline-based quinazolinone derivatives (**5**) were relatively low (ϕ_f: 0.063-0.135) probably because of heavy atom effect [11]. Interestingly, the fluorescence spectra of isoquinoline-fused benzimidazole **4a**, **4e**, **4i** and **4k** (**Fig. 3a**) showed the higher fluorescence than the isoquinoline-fused quinazolinone derivatives **5a, 5c**, **5h** and **5k** (**Fig. 3b**) because of the heavy atom effect.

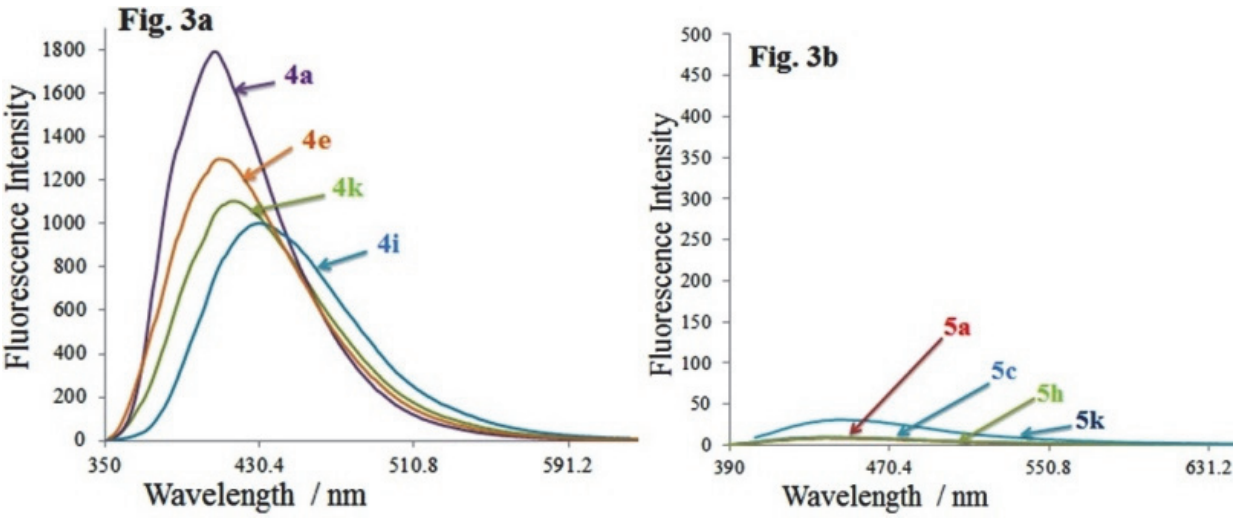


Fig. 3. Fluorescence spectra of isoquinoline-fused benzimidazole (**a**) and isoquinoline-fused quinazolinone (**b**) derivatives in $CHCl_3$.

Table 4. Optical properties in DCM

Compound	λ_{max} (ε) / nm	F_{max} / nm	Stokes shift / nm	ϕ_f^b
4a	286 (56,187), 329 (9,629), 344 (7,396), 360 (4,972)	403	43	0.370
4e	287 (64,085), 342 (9,458), 360 (5,942)	406	46	0.427
4i	286 (53,804), 327 (10,279), 341 (8,847), 356 (6,897)	434	78	0.327
4k	286 (56,023), 328 (9,093), 343 (7,251), 359 (4,935)	412	53	0.471
5a	289 (33,068), 356 (13,856), 375 (13,987), 394 (9,262)	440	46	0.135
5c	289 (36,841), 357 (16,264), 374 (17,138), 393 (11,688)	437	44	0.123
5h	289 (39,269), 355 (16,742), 374 (17,882), 394 (11,549)	439	45	0.074
5k	291 (37,042), 357 (14,838), 374 (16,352), 393 (11,845)	444	51	0.063

[a]Measured at a concentration of 1.0×10^{-5} mol dm^{-3}. [b]Measured using an integrating sphere method.

5.4 Conclusion

In conclusion, we have successfully developed an efficient, metal free and environment friendly pathway for the synthesis of isoquinoline-fused benzimidazole and also successfully achieved the isoquinoline-fused quinazolinone heteroacenes *via* Fe(III) catalyst. The synthesized isoquinoline-fused benzimidazole and isoquinoline-fused quinazolinone derivatives showed λ_{max}, F_{max} and ϕ_f values in the range from 356-394 nm, 403-444 nm and 0.063-0.471, respectively in

$CHCl_3$. We believed that this methodology provides a novel pathway for the synthesis of isoquinoline- fused benzimidazole and isoquinoline-fused quinazolinone heteroacenes. Also, the DFT mechanistic studies and biological evaluation for such novel heterocycles are in progress.

5.5 Experimental section

5.5.1 General methods

All solvents and reagents were purchased from the suppliers and used without further purification. IR spectra were recorded on a JASCO FT/IR-460 Plus spectrophotometer. Reactions were monitored by TLC on silica plates using UV-light chamber for visualization. Evaporation and condensation were carried out *in vacuo*. NMR spectra were recorded with JEOL JNM-ECS 400 spectrometers with tetramethylsilane as an internal standard. Chemical shifts δ and coupling constants *J* are given in ppm (parts per million) and Hz (hertz) respectively. The following abbreviations were used as follows: s: singlet, d: doublet, t: triplet, m: multiplet. All known compounds data are in consistent with the given literature reports. Melting points were measured by a Yanaco micromelting point apparatus. The HRMS were recorded with the Acquity XEVO QTof MS analyzer. UV-vis spectra were taken on a Hitachi U4100 spectrophotometer. Fluorescence spectra were measured on a FP-8600 spectrofluorometer. Fluorescence quantum yields were recorded on a Quantaurus-QY.

5.5.2 General procedure and spectral data

To a solution of 2-(phenylethynyl)benzaldehyde **2a** (0.100 g, 5.91 mmol, 1.0 equiv.) in DMSO solvent (4 mL) was added 2-aminobenzamide (0.105 g, 1.3 equiv.), the resulting reaction mixture was heated at 120°C in open flast. After completion of reaction; the reaction mixture was extracted with ethyl acetate and the organic phase was washed successively with water and brine. The organic layer was dried over Na_2SO_4. The resulting crude product was purified by column chromatography using *n*-hexane: acetone (90:10) as the eluent to afford **3a** as white solid.

2-(2-(Phenylethynyl)phenyl)quinazolin-4(1H)-one (3a)

Yield: 69%; Melting point: 156-158ºC; IR (neat): 3180, 1673, 1598, 1557, 1466, 1303, 1219, 1149, 948, 813, 756, 692, 615, 518 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.94 (s, 1H), 8.32-8.34 (m, 1H), 8.25-8.27 (m, 1H), 7.76-7.84 (m, 2H), 7.66-7.69 (m, 1H), 7.60 (td, *J* = 3.8, 2.0 Hz, 2H), 7.48-7.52 (m, 3H), 7.34-7.36 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.9, 151.4, 149.4, 134.8,

133.9, 133.5, 131.8, 131.0, 130.3, 129.3, 129.2, 128.7, 128.2, 127.1, 126.6, 121.8, 121.3, 120.6, 97.0, 86.8; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{14}N_2ONa$ 345.1004; Found 345.0977.

2-(2-(p-Tolylethynyl)phenyl)quinazolin-4(1H)-one (3b)

Yield: 66%; Melting point: 162-164ºC; IR (neat): 3130, 1673, 1593, 1557, 1466, 1448, 1302, 1148, 1110, 949, 879, 819, 743, 729, 701, 615, 510 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.05 (s, 1H), 8.33 (d, *J* = 7.8 Hz, 1H), 8.24-8.27 (m, 1H), 7.75-7.83 (m, 2H), 7.63-7.66 (m, 1H), 7.46-7.51 (m, 5H), 7.13 (d, *J* = 8.2 Hz, 2H), 2.33 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.0, 151.5, 149.4, 139.6, 134.7, 133.8, 133.4, 131.7, 131.0, 130.2, 129.4, 129.0, 128.1, 127.0, 126.6, 121.4, 120.9, 118.8, 97.3, 86.3, 21.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{17}N_2O$ 337.1341; Found 337.1317.

2-(2-((3-Fluorophenyl)ethynyl)phenyl)quinazolin-4(1H)-one (3c)

Yield: 41%; Melting point: 150-151ºC; IR (neat): 3067, 1661, 1605, 1578, 1438, 1202, 1148, 944, 866, 846, 760, 748, 695, 531 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.92 (s, 1H), 8.32-8.34 (m, 1H), 8.22 (q, *J* = 3.1 Hz, 1H), 7.77-7.84 (m, 2H), 7.67-7.69 (m, 1H), 7.49-7.54 (m, 3H), 7.36 (dd, *J* = 6.4, 1.4 Hz, 1H), 7.30 (td, *J* = 7.9, 5.6 Hz, 1H), 7.23-7.26 (m, 1H), 7.04 (td, *J* = 8.1, 2.1 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.7, 162.0, 161.2, 151.3, 149.3, 134.9, 134.0, 131.0, 130.4, 130.3, 130.2, 129.5, 128.1, 127.8, 127.7, 127.2, 126.6, 123.8, 123.7, 121.3, 120.3, 118.6, 118.4, 116.8, 116.5, 95.2, 87.6; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{14}N_2O^{19}F$ 341.1090; Found 341.1081.

2-(2-((4-Fluoro-3-methylphenyl)ethynyl)phenyl)quinazolin-4(1H)-one (3d)

Yield: 57%; Melting point: 136-137ºC; IR (neat): 3069, 1661, 1606, 1578, 1588, 1438, 1426, 1202, 1148, 1107, 944, 866, 846, 780, 765, 748, 674, 531 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.87 (s, 1H), 8.34 (d, *J* = 8.0 Hz, 1H), 8.29-8.30 (m, 1H), 7.78-7.85 (m, 2H), 7.66-7.67 (m, 1H), 7.52 (t, *J* = 4.6 Hz, 3H), 7.40-7.44 (m, 2H), 6.98 (t, *J* = 8.9 Hz, 1H), 2.26 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.9, 151.4, 149.4, 135.1, 135.1, 134.8, 133.8, 133.45, 131.3, 131.2, 131.1, 130.3, 129.2, 128.2, 127.1, 126.6, 125.6, 121.4, 120.6, 117.5, 115.8, 115.6, 96.3, 86.2, 14.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{16}N_2OF$ 355.1247; Found 355.1241.

7-Chloro-2-(2-(phenylethynyl)phenyl)quinazolin-4(1H)-one (3e)

Yield: 43%; Melting point: 152-154ºC; IR (neat): 3323, 1700, 1598, 1556, 1491, 1431, 1420, 1219, 1139, 1099, 1072, 910, 746, 682, 691, 639 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.10 (s, 1H), 8.22-8.26 (m, 2H), 7.79 (d, *J* = 2.3 Hz, 1H), 7.66 (q, *J* = 3.1 Hz, 1H), 7.58 (q, *J* = 3.2 Hz, 2H), 7.48-7.52 (m, 2H), 7.43 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.34 (t, *J* = 3.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.3, 152.5, 150.3, 141.0, 134.0, 133.0, 131.8, 131.3, 130.3, 129.4, 129.2, 128.7, 128.0, 127.6, 121.7, 120.7, 119.8, 97.2, 86.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{14}N_2OCl$ 357.0795; Found 357.0794.

General procedure and spectral data for the synthesized compounds 4a-4n.

To a solution of 2-(phenylethynyl)benzaldehyde **2a** (0.100 g, 5.91 mmol, 1.0 equiv.) in DMSO solvent (4 mL) was added 1,2-diaminebenzene (0.083 g, 7.69 mmol, 1.3 equiv.), the resulting reaction mixture was heated at 120ºC in open flast. After completion of reaction; the reaction mixture was extracted with ethyl acetate and the organic phase was washed successively with water and brine. The organic layer was dried over Na_2SO_4. The resulting crude product was purified by column chromatography using *n*-hexane: acetone (90:10) as the eluent to afford **3a** as white solid.

6-Phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (4a)

Yield: 75%; Melting point: 163-165ºC; IR (neat): 1640, 1525, 1494, 1448, 1330, 1310, 1219, 1118, 833, 737, 699, 650, 547, 486 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.87-8.89 (m, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.57-7.68 (m, 8H), 7.37 (t, *J* = 7.1 Hz, 1H), 6.99 (t, *J* = 7.8 Hz, 1H), 6.87 (s, 1H), 6.48 (d, *J* = 8.7 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.4, 144.3, 137.6, 134.7, 131.7, 130.8, 130.2, 130.0, 129.5, 129.1, 128.0, 126.7, 125.2, 124.3, 123.01, 121.3, 119.8, 114.2, 112.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{15}N_2$ 295.1235; Found 295.1218.

9,10-Dimethyl-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (4b)

Yield: 73%; Melting point: 225-227ºC; IR (neat): 1637, 1527, 1494, 1453, 1397, 1299, 998, 962, 847, 836, 762, 748, 654, 640, 538 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 9.6 Hz, 1H), 7.73 (s, 1H), 7.67-7.69 (m, 1H), 7.61-7.65 (m, 3H), 7.58 (d, *J* = 4.6 Hz, 4H), 6.85 (s, 1H), 6.19 (s, 1H), 2.37 (s, 3H), 2.12 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.78, 143.0, 137.6, 134.9, 133.4, 131.5, 130.4, 129.8, 129.8, 129.5, 129.2, 128.9, 127.8, 126.7, 125.0, 123.1, 119.6, 114.3,

112.1, 20.8, 20.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{19}N_2$ 323.1548; Found 323.1541.

6-(*p*-Tolyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (4c)

Yield: 74%; Melting point: 148-150ºC; IR (neat): 1639, 1529, 1508, 1447, 1329, 1310, 1112, 1014, 844, 823, 752, 662, 609, 494 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.88-8.90 (m, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.65-7.70 (m, 3H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.39 (dd, *J* = 7.3, 5.0 Hz, 3H), 7.02 (t, *J* = 7.8 Hz, 1H), 6.87 (s, 1H), 6.56 (d, *J* = 8.2 Hz, 1H), 2.53 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.4, 144.19, 140.1, 137.7, 131.8, 131.8, 130.8, 130.2, 129.7, 129.3, 127.9, 126.7, 125.2, 124.3, 122.9, 121.3, 119.7, 114.3, 112.7, 21.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{17}N_2$ 309.1392; Found 309.1363.

9,10-Dimethyl-6-(p-tolyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (4d)

Yield: 68%; Melting point: 170-172ºC; IR (neat): 1636, 1531, 1510, 1463, 1454, 1372, 1300, 1219, 1022, 999, 866, 847, 840, 812, 749, 664, 539 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.84 (t, *J* = 4.6 Hz, 1H), 7.73 (s, 1H), 7.62-7.70 (m, 3H), 7.47 (d, *J* = 7.8 Hz, 2H), 7.39 (d, *J* = 7.8 Hz, 2H), 6.84 (s, 1H), 6.30 (s, 1H), 2.54 (s, 3H), 2.38 (s, 3H), 2.15 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.8, 143.0, 139.9, 137.7, 133.4, 132.0, 131.6, 130.3, 129.8, 129.5, 129.4, 129.3, 127.7, 126.6, 125.0, 123.1, 119.6, 114.4, 112.1, 21.6, 20.9, 20.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{21}N_2$ 337.1705; Found 337.1679.

6-(4-Methoxyphenyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (4e)

Yield: 80%; Melting point: 184-186ºC; IR (neat): 1643, 1607, 1527, 1507, 1448, 1328, 1312, 1246, 1178, 1122, 1109, 1017, 831, 813, 740, 610, 482 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.87 (t, *J* = 4.6 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.64-7.69 (m, 3H), 7.49 (dd, *J* = 6.6, 2.1 Hz, 2H), 7.39 (t, *J* = 7.1 Hz, 1H), 7.09 (dd, *J* = 6.6, 2.1 Hz, 2H), 7.00-7.04 (m, 1H), 6.86 (s, 1H), 6.59 (d, *J* = 8.2 Hz, 1H), 3.94 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.8, 148.4, 144.3, 137.5, 131.8, 130.9, 130.8, 130.2, 127.8, 127.1, 126.7, 125.2, 124.2, 122.9, 121.3, 119.7, 114.39, 114.3, 112.7, 77.5, 77.2, 76.8, 55.6; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{17}N_2O$ 325.1341; Found 325.1329.

6-(4-Methoxyphenyl)-9,10-dimethylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (4f)

Yield: 78%; Melting point: 216-217ºC; IR (neat): 1634, 1574, 1531, 1509, 1452, 1395, 1290, 1251, 1178, 1024, 999, 844, 835, 813, 762, 624, 543 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.82-8.84 (m, 1H), 7.73 (s, 1H), 7.60-7.67 (m, 3H), 7.49 (dd, *J* = 6.6, 2.1 Hz, 2H), 7.08 (d, *J* = 9.2 Hz, 2H), 6.81 (s, 1H), 6.34 (s, 1H), 3.94 (s, 3H), 2.37 (s, 3H), 2.16 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.8, 147.8, 143.0, 137.4, 133.4, 131.6, 130.8, 130.3, 129.7, 129.3, 127.6, 127.3, 126.6, 125.0, 123.0, 119.6, 114.4, 114.2, 112.3, 55.6, 20.9, 20.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{21}N_2O$ 353.1654; Found 353.1646.

6-(2-Fluorophenyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (4g)

Yield: 78%; Melting point: 144-146ºC; IR (neat): 1605, 1581, 1528, 1487, 1453, 1298, 1210, 1165, 1002, 879, 831, 767, 774, 710, 698, 520, 482 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.90 (dd, *J* = 7.6, 1.6 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.55-7.73 (m, 5H), 7.36-7.42 (m, 2H), 7.31 (t, *J* = 8.7 Hz, 1H), 7.05 (td, *J* = 7.9, 1.2 Hz, 1H), 6.97 (s, 1H), 6.55 (d, *J* = 8.7 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.0, 159.5, 148.2, 144.2, 132.3, 131.8, 131.5, 131.3, 130.9, 130.2, 128.3, 126.9, 125.2, 125.0, 124.5, 124.6, 123.3, 122.8, 122.6, 121.9, 119.9, 116.6, 116.4, 116.3, 116.2, 113.9, 113.8, 112.9; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{14}N_2F$ 313.1141; Found 313.1129.

6-(2-Fluorophenyl)-9,10-dimethylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (4h)

Yield: 79%; Melting point: 170-172ºC; IR (neat): 1643, 1530, 1492, 1452, 1398, 1311, 1237, 1103, 995, 866, 799, 841, 749, 654, 482 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.85-8.87 (m, 1H), 7.74 (s, 1H), 7.61-7.70 (m, 4H), 7.56 (td, *J* = 7.4, 1.5 Hz, 1H), 7.36-7.40 (m, 1H), 7.30 (t, *J* = 8.7 Hz, 1H), 6.92 (s, 1H), 6.25 (s, 1H), 2.37 (s, 3H), 2.14 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.0, 159.5, 147.6, 142.9, 133.5, 132.1, 131.9, 131.4, 131.1, 130.86, 129.8, 129.3, 128.1, 126.8, 125.0, 125.0, 123.4, 123.0, 122.8, 119.8, 119.8, 116.4, 116.3, 116.2, 116.1, 113.3, 113.2, 113.0, 112.9, 21.0, 20.6, 20.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{18}N_2F$ 341.1454; Found 341.1440.

6-(3-Fluorophenyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (4i)

Yield: 72%; Melting point: 162-163ºC; IR (neat): 1614, 1581, 1526, 1484, 1449, 1319, 1332, 1146, 1123, 1014, 908, 884, 835, 792, 730, 648, 520, 479 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.87-8.90 (m, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.67-7.73 (m, 3H), 7.55-7.60 (m, 1H), 7.41 (td, *J* =

7.7, 1.1 Hz, 2H), 7.32-7.36 (m, 2H), 7.03-7.07 (m, 1H), 6.91 (s, 1H), 6.55 (d, *J* = 8.2 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.1, 161.7, 148.3, 144.3, 136.6, 136.6, 136.1, 131.4, 130.9, 130.8, 130.5, 130.3, 128.3, 126.9, 125.4, 125.4, 125.2, 124.4, 123.1, 121.6, 120.0, 117.2, 117.0, 116.9, 116.7, 113.9, 113.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{14}N_2{}^{19}F$ 313.1141; Found 313.1111.

6-(3-Fluorophenyl)-9,10-dimethylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (4j)

Yield: 70%; Melting point: 261-262ºC; IR (neat): 1643, 1605, 1581, 1528, 1486, 1452, 1431, 1314, 1210, 1002, 879, 831, 797, 745, 710, 618, 520, 482 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.83-8.85 (m, 1H), 7.74 (s, 1H), 7.64-7.71 (m, 3H), 7.54-7.58 (m, 1H), 7.32-7.40 (m, 3H), 6.86 (s, 1H), 6.27 (s, 1H), 2.38 (s, 3H), 2.16 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.1, 161.6, 147.7, 143.0, 136.8, 136.7, 136.0, 133.6, 131.2, 130.7, 130.7, 130.6, 129.9, 129.0, 128.1, 126.8, 125.4, 125.4, 125.0, 123.2, 119.8, 117.0, 116.9, 116.8, 116.7, 114.0, 112.5, 20.9, 20.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{18}N_2{}^{19}F$ 341.1454; Found 341.1438.

6-(4-Fluoro-3-methylphenyl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (4k)

Yield: 80%; Melting point: 160-162ºC; IR (neat): 1637, 1527, 1503, 1447, 1333, 1318, 1247, 1232, 1127, 825, 758, 735, 728, 548, 528, 480 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.88 (t, *J* = 4.6 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.66-7.71 (m, 3H), 7.38-7.44 (m, 3H), 7.22 (t, *J* = 8.6 Hz, 1H), 7.04 (t, *J* = 7.7 Hz, 1H), 6.86 (s, 1H), 6.54 (d, *J* = 8.0 Hz, 1H), 2.39 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.2, 161.2, 148.4, 144.3, 136.8, 132.7, 132.7, 131.6, 130.7, 130.5, 130.3, 128.7, 128.7, 128.0, 126.7, 126.1, 126.0, 125.2, 124.3, 123.0, 121.4, 119.9, 115.9, 115.7, 114.1, 112.8, 14.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{16}N_2F$ 327.1298; Found 327.1279.

6-(4-Fluoro-3-methylphenyl)-9,10-dimethylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (4l)

Yield: 84%; Melting point: 212-214ºC; IR (neat): 1635, 1592, 1499, 1450, 1380, 1229, 1203, 1166, 1124, 1023, 995, 856, 833, 825, 746, 698, 654, 481 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.83 (dd, *J* = 5.7, 3.4 Hz, 1H), 7.74 (s, 1H), 7.62-7.69 (m, 3H), 7.43 (d, *J* = 7.3 Hz, 1H), 7.39 (dd, *J* = 8.2, 5.0 Hz, 1H), 7.20-7.25 (m, 1H), 6.82 (s, 1H), 6.30 (s, 1H), 2.40 (d, *J* = 1.8 Hz, 3H), 2.38 (s, 3H), 2.18 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.4, 161.0, 147.8, 143.0, 136.7, 133.5, 132.7, 132.7, 131.4, 130.6, 130.5, 129.8, 129.2, 128.8, 128.7, 127.9, 126.6, 125.9, 125.7, 125.0,

123.1, 119.8, 119.7, 115.7, 114.3, 114.1, 112.4, 112.3, 20.9, 20.6, 20.5, 14.7, 14.7, 14.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{20}N_2F$ 355.1611; Found 355.1592.

6-Phenethylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (4m)

Yield: 78%; Melting point: 164-166ºC; IR (neat): 1644, 1610, 1600, 1559, 1526, 1450, 1427, 1350, 1018, 834, 774, 752, 744, 728, 699, 591, 505 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.82 (t, J = 4.3 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.58-7.61 (m, 3H), 7.49 (t, J = 7.7 Hz, 1H), 7.24-7.37 (m, 6H), 6.71 (s, 1H), 3.57 (t, J = 8.0 Hz, 2H), 3.19 (t, J = 8.0 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 148.6, 144.4, 140.1, 138.1, 131.6, 130.7, 130.1, 128.9, 128.5, 127.4, 126.7, 126.1, 125.1, 124.3, 122.5, 122.0, 120.2, 114.3, 110.0, 35.0, 33.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{19}N_2$ 323.1548; Found 323.1532.

9,10-Dimethyl-6-phenethylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (4n)

Yield: 82%; Melting point: 148-150ºC; IR (neat): 1645, 1530, 1455, 1437, 1334, 1265, 1197, 906, 858, 825, 773, 745, 697, 585, 506, 461 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.77-8.78 (m, 1H), 7.77 (s, 1H), 7.70 (s, 1H), 7.55-7.58 (m, 3H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.28 (q, *J* = 6.7 Hz, 3H), 6.65 (s, 1H), 3.51 (t, *J* = 8.3 Hz, 2H), 3.15 (t, *J* = 8.0 Hz, 2H), 2.43 (s, 3H), 2.40 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 148.0, 143.1, 140.2, 138.0, 133.4, 131.4, 131.1, 129.6, 129.1, 128.9, 128.5, 127.2, 126.7, 126.0, 124.9, 122.6, 120.0, 114.3, 109.7, 34.9, 33.9, 21.0, 20.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{23}N_2$ 351.1861; Found 351.1852.

General procedure and spectral data for the synthesized compounds 5a-5m.

To a solution of 2-(2-(phenylethynyl)phenyl)quinazolin-4(1H)-one **3a** (0.100 g, 5.91 mmol, 1.0 equiv.) in DCM solvent (4 mL) was added (n-BuSe)$_2$ (0.083 g, 7.69 mmol, 1.0 equiv.) and $FeCl_3 \cdot 6H_2O$ (1.5 equiv.), the resulting reaction mixture was refluxed for 8 h. After completion of reaction; the reaction mixture was extracted with DCM, the organic phase was washed successively with water and brine. The organic layer was dried over Na_2SO_4. The resulting crude product was purified by column chromatography using *n*-hexane: ethyl acetate (95:05) as the eluent to afford **5a** as white solid.

12-Phenyl-13-(phenylselanyl)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (5a)

Yield: 65%; Melting point: 204-205ºC; IR (neat): 1700, 1602, 1589, 1557, 1540, 1480, 1463, 1336, 1257, 1134, 1003, 761, 738, 693, 676, 573, 535 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.03 (dd, *J* = 8.2, 0.9 Hz, 1H), 8.43 (d, *J* = 7.3 Hz, 1H), 8.10-8.12 (m, 1H), 7.75-7.85 (m, 3H), 7.64-7.68 (m, 1H), 7.37-7.41 (m, 4H), 7.32 (q, *J* = 3.2 Hz, 2H), 2.46 (t, *J* = 7.3 Hz, 2H), 1.19-1.27 (m, 2H), 1.06 (q, *J* = 7.3 Hz, 2H), 0.68 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.9, 147.5, 146.8, 141.4, 139.2, 134.6, 133.7, 132.5, 129.21, 129.2, 128.7, 127.9, 127.9, 127.4, 127.3, 127.2, 126.9, 125.9, 120.5, 118.8, 31.8, 28.9, 22.6, 13.4; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 193.97; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{26}H_{23}N_2OSe$ 459.0976; Found 459.0952.

13-(Butylselanyl)-12-phenyl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (5b)

Yield: 54%; Melting point: 128-130ºC; IR (neat): 1700, 1650, 1608, 1591, 1156, 1509, 1439, 1324, 1291, 1159, 1141, 1076, 1023, 816, 755, 740, 715, 683, 590, 535, 491 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.99-9.01 (m, 1H), 8.20-8.22 (m, 1H), 8.12 (d, *J* = 7.3 Hz, 1H), 7.79-7.85 (m, 2H), 7.58-7.60 (m, 2H), 7.34-7.41 (m, 4H), 7.29 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.09 (s, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.0, 147.5, 146.8, 142.9, 139.0, 134.8, 133.7, 132.6, 132.6, 129.7, 129.3, 128.9, 128.6, 128.2, 128.1, 127.4, 127.4, 127.3, 127.0, 126.4, 126.0, 120.5, 118.7; 77Se-NMR (75 MHz, $CDCl_3$) δ 319.75; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{28}H_{19}N_2OSe$ 479.0663; Found 479.0639.

12-Phenyl-13-(phenylthio)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (5c)

Yield: 59%; Melting point: 207-208ºC; IR (neat): 1690, 1604, 1592, 1545, 1467, 1340, 1291, 1272, 1146, 1136, 1067, 763, 743, 727, 705, 690, 681, 598, 543, 492 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.01-9.03 (m, 1H), 8.11-8.15 (m, 2H), 7.78-7.85 (m, 2H), 7.58-7.63 (m, 2H), 7.30-7.41 (m, 6H), 7.13 (dd, *J* = 8.2, 6.9 Hz, 2H), 6.99-7.07 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.0, 147.3, 146.7, 143.8, 137.4, 137.3, 134.9, 133.2, 132.6, 129.1, 129.0, 128.3, 128.2, 128.2, 127.5, 127.4, 127.3, 127.0, 126.9, 126.8, 126.1, 125.6, 120.5, 118.9, 77.5, 77.3, 77.1, 76.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{28}H_{19}N_2OS$ 431.1218; Found 431.1197.

13-(Methylthio)-12-phenyl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (5d)

Yield: 63%; Melting point: 180-181ºC; IR (neat): 1702, 1604, 1588, 1557, 1538, 1465, 1443, 1321, 1288, 1135, 1007, 759, 717, 696, 680, 653, 598, 576, 538 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.03 (d, *J* = 7.3 Hz, 1H), 8.40 (d, *J* = 8.7 Hz, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.78-7.83

(m, 3H), 7.66 (t, *J* = 7.1 Hz, 1H), 7.43 (t, *J* = 3.2 Hz, 3H), 7.35-7.40 (m, 3H), 1.98 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.9, 147.2, 146.8, 141.9, 137.7, 134.7, 132.9, 132.6, 128.8, 128.75, 128.2, 128.0, 127.6, 127.4, 127.3, 126.9, 126.5, 125.9, 122.6, 120.4, 19.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{17}N_2OS$ 369.1062; Found 369.1041.

13-(Phenylselanyl)-12-(p-tolyl)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (5e)

Yield: 70%; Melting point: 130-132ºC; IR (neat): 1688, 1609, 1589, 1542, 1507, 1463, 1304, 1219, 1136, 1185, 955, 811, 733, 673, 668, 642, 537 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.97-9.00 (m, 1H), 8.17-8.20 (m, 1H), 8.13 (d, J = 7.8 Hz, 1H), 7.78-7.85 (m, 2H), 7.56-7.58 (m, 2H), 7.39 (td, J = 7.4, 1.5 Hz, 1H), 7.18 (dd, J = 13.1, 8.5 Hz, 4H), 7.07-7.10 (m, 5H), 2.40 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.1, 147.6, 146.77, 143.0, 137.9, 136.1, 134.7, 133.7, 132.7, 132.5, 129.6, 129.3, 128.8, 128.5, 128.3, 128.0, 127.4, 127.2, 126.9, 126.4, 126.0, 120.5, 118.7, 77.5, 21.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{21}N_2OSe$ 493.0819; Found 493.0796.

13-(Methylthio)-12-(p-tolyl)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (5f)

Yield: 69%; Melting point: 152-154ºC; IR (neat): 1699, 1608, 1589, 1556, 1508, 1464, 1289, 1262, 1137, 974, 869, 817, 758, 697, 681, 650, 458 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.02 (d, *J* = 8.2 Hz, 1H), 8.39 (d, *J* = 8.2 Hz, 1H), 8.12 (d, *J* = 8.2 Hz, 1H), 7.76-7.83 (m, 3H), 7.63-7.67 (m, 1H), 7.38 (td, *J* = 7.3, 1.4 Hz, 1H), 7.22-7.27 (m, 4H), 2.44 (s, 3H), 1.99 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.0, 147.3, 146.8, 142.0, 137.7, 134.7, 134.6, 133.0, 132.5, 128.7, 128.6, 128.2, 127.6, 127.3, 126.9, 126.5, 125.9, 122.5, 120.5, 21.7, 19.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{19}N_2OS$ 383.1218; Found 383.1191.

12-(3-Fluorophenyl)-13-(methylthio)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (5g)

Yield: 66%; Melting point: 184-185ºC; IR (neat): 1704, 1607, 1591, 1557, 1540, 1467, 1339, 1292, 1272, 1187, 1127, 949, 918, 799, 782, 694, 681, 674, 537 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.04 (d, *J* = 7.8 Hz, 1H), 8.40 (d, *J* = 8.7 Hz, 1H), 8.10-8.12 (m, 1H), 7.78-7.84 (m, 3H), 7.66-7.70 (m, 1H), 7.35-7.42 (m, 2H), 7.11 (ddd, *J* = 17.1, 7.7, 1.9 Hz, 3H), 2.01 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.8, 160.7, 147.0, 146.7, 140.4, 139.7, 139.7, 134.8, 132.7, 132.6, 129.1, 128.8, 128.7, 128.3, 127.6, 127.3, 127.0, 126.6, 126.1, 124.6, 124.6, 123.0, 120.2, 116.2, 115.9, 115.0, 114.8, 19.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{16}N_2OFS$ 387.0967; Found 387.0946.

12-(4-Fluoro-3-methylphenyl)-13-(phenylselanyl)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (5h)

Yield: 67%; Melting point: 184-186ºC; IR (neat): 1688, 1610, 1591, 1557, 1544, 1467, 1346, 1272, 1124, 831, 761, 740, 730, 691, 677, 541, 473 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.00-9.02 (m, 1H), 8.23-8.25 (m, 1H), 8.12-8.15 (m, 1H), 7.80-7.86 (m, 2H), 7.59-7.64 (m, 2H), 7.40-7.44 (m, 1H), 7.04-7.12 (m, 7H), 6.98 (t, *J* = 8.7 Hz, 1H), 2.23 (d, *J* = 1.8 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.2, 161.1, 159.7, 147.4, 146.7, 142.1, 134.9, 134.7, 133.7, 132.7, 132.6, 131.8, 131.7, 129.8, 129.6, 129.4, 129.3, 129.0, 128.0, 127.6, 127.4, 127.3, 127.0, 126.4, 126.2, 126.0, 124.1, 123.9, 120.4, 119.2, 14.8; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 320.52; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{20}N_2OFSe$ 511.0725; Found 511.0711.

12-(4-Fluoro-3-methylphenyl)-13-(phenylthio)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (5i)

Yield: 71%; Melting point: 160-162ºC; IR (neat): 1686, 1610, 1590, 1557, 1542, 1476, 1466, 1277, 1221, 1220, 1094, 832, 807, 771, 753, 760, 734, 695, 684, 541, 484 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.01-9.04 (m, 1H), 8.13-8.18 (m, 2H), 7.81-7.87 (m, 2H), 7.61-7.66 (m, 2H), 7.41-7.45 (m, 1H), 7.15 (t, *J* = 7.3 Hz, 2H), 7.07 (t, *J* = 7.3 Hz, 3H), 6.95-7.00 (m, 3H), 2.22 (d, *J* = 1.8 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.2, 161.01, 147.2, 146.7, 143.0, 137.3, 134.9, 133.2, 133.0, 132.6, 131.5, 129.2, 129.1, 128.2, 127.3, 127.0, 126.9, 126.8, 126.7, 126.1, 125.7, 124.1, 124.0, 120.4, 119.3, 14.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{20}N_2OFS$ 463.1280; Found 463.1288.

12-(4-fluoro-3-methylphenyl)-13-(methylthio)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (5j)

Yield: 64%; Melting point: 179-180ºC; IR (neat): 1688, 1655, 1639, 1589, 1554, 1541, 1481, 1337, 1285, 1272, 1135, 925, 762, 689, 678, 642, 647, 474 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.04 (d, *J* = 8.2 Hz, 1H), 8.40 (d, *J* = 8.2 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.79-7.85 (m, 3H), 7.68 (t, *J* = 8.2 Hz, 1H), 7.39-7.43 (m, 1H), 7.13-7.18 (m, 2H), 7.05 (t, *J* = 8.7 Hz, 1H), 2.32 (d, *J* = 1.8 Hz, 3H), 2.00 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.1, 161.0, 159.6, 147.16, 146.8, 141.1, 134.8, 133.2, 132.8, 132.6, 131.9, 131.8, 128.9, 128.2, 127.8, 127.6, 127.3, 127.0, 126.6, 126.0, 124.0, 123.9, 122.9, 120.4, 18.9, 14.9; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{18}N_2OFS$ 401.1124; Found 401.1124.

9-Chloro-12-phenyl-13-(phenylselanyl)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (5k)

Yield: 58%; Melting point: 218-220ºC; IR (neat): 1698, 1603, 1586, 1569, 1533, 1465, 1314, 1069, 928, 859, 764, 731, 717, 695, 686, 467, 460 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.97-8.99 (m, 1H), 8.23 (d, *J* = 9.2 Hz, 1H), 8.04 (d, *J* = 8.7 Hz, 1H), 7.83 (d, *J* = 1.8 Hz, 1H), 7.60-7.63 (m, 2H), 7.26-7.40 (m, 7H), 7.10 (s, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.4, 148.5, 147.7, 142.7, 141.0, 138.8, 133.8, 132.9, 132.5, 129.7, 129.4, 129.4, 129.1, 128.9, 128.6, 128.2, 127.8, 127.5, 127.4, 126.6, 126.5, 126.4, 119.2, 118.7; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 320.67; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{28}H_{17}N_2ONaClSe$ 535.0092; Found 535.0067.

9-Chloro-12-phenyl-13-(phenylthio)-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (5l)

Yield: 55%; Melting point: 184-186ºC; IR (neat): 1700, 1605, 1570, 1556, 1537, 1466, 1287, 1261, 1142, 1070, 939, 860, 737, 687, 673, 575, 462 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.99-9.01 (m, 1H), 8.15-8.17 (m, 1H), 8.04 (d, *J* = 8.7 Hz, 1H), 7.84 (d, *J* = 2.3 Hz, 1H), 7.61-7.66 (m, 2H), 7.29-7.39 (m, 6H), 7.12-7.16 (m, 2H), 7.04-7.08 (m, 1H), 6.99-7.01 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.4, 148.3, 147.6, 143.6, 141.1, 137.2, 137.1, 133.4, 133.0, 129.1, 128.9, 128.3, 127.9, 127.5, 127.5, 127.0, 126.8, 126.7, 126.4, 125.7, 119.4, 118.7; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{28}H_{17}N_2ONaSCl$ 487.0648; Found 487.0651.

9-Chloro-13-(methylthio)-12-phenyl-6*H*-isoquinolino[2,1-*a*]quinazolin-6-one (5m)

Yield: 63%; Melting point: 262-264ºC; IR (neat): 1646, 1614, 1598, 1586, 1501, 1430, 1314, 1289, 1134, 1099, 867, 836, 733, 694, 666, 582, 459 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.99 (d, *J* = 8.2 Hz, 1H), 8.43 (d, *J* = 7.8 Hz, 1H), 8.19 (d, *J* = 8.2 Hz, 1H), 7.88-7.92 (m, 1H), 7.70 (t, *J* = 7.1 Hz, 1H), 7.39-7.47 (m, 5H), 7.29 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.00 (d, *J* = 2.0 Hz, 1H), 1.94 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.3, 154.0, 141.3, 139.9, 137.3, 135.4, 134.1, 134.0, 131.2, 129.8, 129.3, 128.9, 128.5, 127.3, 126.9, 126.6, 122.6, 122.1, 121.0, 18.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{16}N_2OSCl$ 403.0672; Found 403.0669.

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Sincerely,

Amol D. Sonawane

Curriculum Vitae

Amol was born on 2nd June 1990 in Andarsul, Taluka Yeola, District Nashik and Maharashtra, India. He completed the Elementary School, High School, Junior and Senior High School in Nashik District. He completed his bachelor degree (B.Sc. Chemistry) in 2011 from S. M. Sr. College, Yeola, Nashik (Affiliated to Pune University, India).

Amol received his M.Sc. (Organic Chemistry) degree in 2013 from H.P.T. Arts and R.Y.K. Science College, Nashik (Affiliated to Pune University, India). After master degree he joined National Chemical Laboratory (NCL) Pune, Maharashtra as project assistant during the period 2013-2015. Further, in 2016 he joined Indian Institute of Science Education and Research (IISER-P) Pune as JRF fellow. At present from 2016, he is studying for a Ph. D. in the area of 'Cascade cyclization and photophysical properties of quinoline/ isoquinoline-fused heteroacenes' under the supervision of Professor Mamoru Koketsu at Department of Chemistry and Biomolecular Science, Faculty of Engineering, Gifu University, Japan. His Ph. D. study was financially supported by Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan, (Monbukagakusho scholarship). During his study in Gifu University, he got a chance to attend scientific meeting to present his research work and published his research output as listed below.

List of Publications

[1] Amol D. Sonawane, Dinesh R. Garud, Taro Udagawa and Mamoru Koketsu. "Synthesis of thieno [2,3-*b*]quinoline and selenopheno[2,3-*b*]quinoline derivatives *via* iodocyclization reaction and DFT mechanistic study"(*Org. Biomol. Chem.,* **2018**, *16*, 245-255)

https://pubs.rsc.org/en/content/articlelanding/2018/ob/c7ob02523h#!divAbstract

[2] Amol D. Sonawane, Dinesh R. Garud, Taro Udagawa, Yasuhiro Kubota and Mamoru Koketsu. "Synthesis of thieno[2,3-*c*]acridine and furo[2,3-*c*]acridine derivatives *via* iodocyclization reaction, fluorescence properties and DFT mechanistic study" (*New J. Chem.,* **2018**, *42*, 15315-15324)

https://pubs.rsc.org/en/content/articlelanding/2018/nj/c8nj03511c#!divAbstract

[3] Amol D. Sonawane, Yasuhiro Kubota and Mamoru Koketsu. "Iron-promoted intramolecular cascade cyclization for the synthesis of selenophene-fused, quinoline-based heteroacenes" (*J. Org. Chem.,* **2019**, *84*, 8602-8614)

https://pubs.acs.org/doi/abs/10.1021/acs.joc.9b01061

[4] Amol D. Sonawane, Yunnus B. Shaikh, Dinesh R. Garud, Mamoru Koketsu. "Synthesis of isoquinoline-fused benzquinazolinone through Ag (I)-catalysed cascade annulation of 2-amino-benzamides and 2-alkynylbenzaldehydes" (*Synthesis,* **2019**, *51*, 500-507)

https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0037-1610910

[5] Amol D. Sonawane, Rohini A. Sonawane, Khin Myat Noe Win, Yasuhiro Kubota and Mamoru Koketsu. "The highly efficient air oxidation and photophysical studies of isoquinoline-based *N*-heteroacenes" (*Manuscript under review*)

Following Publication is not included in this thesis

[1] Khin Myat Noe Win, Amol D. Sonawane and Mamoru Koketsu. "Iodine mediated *in situ* generation of R-Se-I: Application towards the construction of pyrano[4,3-*b*]quinoline heterocycles and fluorescence properties" (*Org. Biomol. Chem.,* **2019**, *17*, 9039-9049)

https://pubs.rsc.org/en/content/articlelanding/2019/ob/c9ob01648a#!divAbstract

Book Chapter and Review Papers

[1] Amol D. Sonawane and Mamoru Koketsu. “Organic Selenium Chemistry” A book chapter, De Gruyter publisher, Germany. “Chapter 2: Synthesis of organoselenium scaffolds through radical formation” (**2019**, *Ahead of Print,* DOI:10.1515/9783110625110-002)

[2] Amol D. Sonawane and Mamoru Koketsu. “Organic Selenium Chemistry” A book chapter, De Gruyter publisher, Germany. “Chapter 3: Role of isoselenocyanates for the synthesis of selenium-containing heterocycles” (**2019**, *Ahead of Print,* DOI: 10.1515/9783110625110-003)

[3] Amol D. Sonawane and Mamoru Koketsu. “Recent advances on C-Se bond forming reactions at low and room temperature” (*Curr. Org. Chem.,* **2019**, review article, accepted manuscript, DOI : 10.2174/1385272823666191209111934)

[4] Amol D. Sonawane and Mamoru Koketsu. "*1,3-Selenazoles*" A book chapter, Elsevier Publisher; (**2020-2021**, *Comprehensive Heterocyclic Chemistry-IV (CHEC-IV)*, *Submitted Manuscript*)

[5] Amol D. Sonawane and Mamoru Koketsu. “Organocatalyzed bioactive Se-scaffolds” (*Curr. Green Chem.,* **2020**, *Review article*, *under preparation*)

List of Presentations

[1] Attended international conference “*6th Asian Network for Natural and Unnatural Materials (ANNUM VI)-2018*” as oral speaker at Nagaragawa Convention Centre and Gifu University Satellite Campus, Gifu, JAPAN on July 27th and 28th 2018.

[2] Attended international conference “*27th International Society of Heterocyclic Chemistry Congress*” as flash presenter and poster presentation at ROHM Theatre Kyoto & Miyakomesse, Kyoto, JAPAN on Sept. 1 to Sept. 7th 2019.