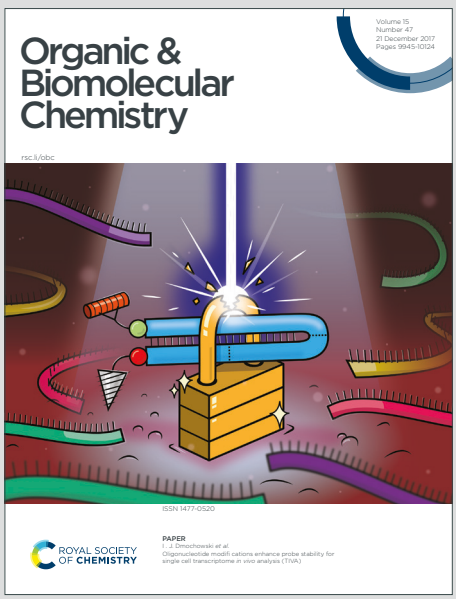
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: A. Sonawane, R. A. Sonawane, K. M. N. Win, M. Ninomiya and M. Koketsu, *Org. Biomol. Chem.*, 2020, DOI: 10.1039/D0OB00375A.



ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/D0OB00375A

Organic and Biomolecular Chemistry

ARTICLE

The *In-Situ* Air Oxidation and Photophysical Studies of Isoquinoline-fused *N*-Heteroacenes

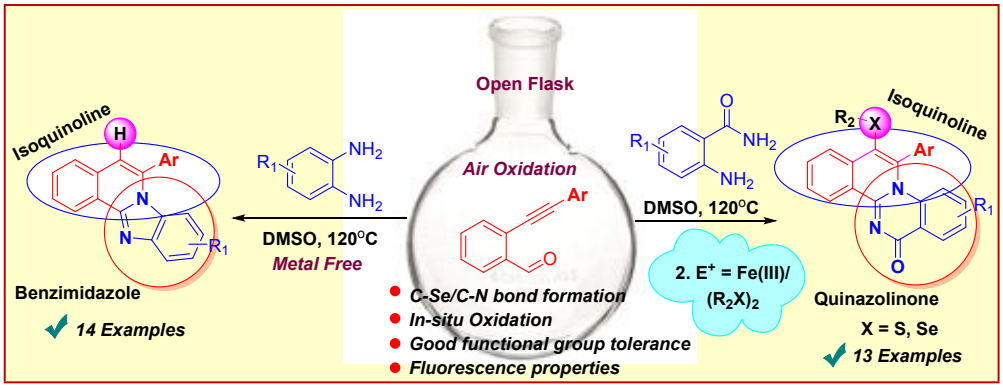
Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Amol D. Sonawane,[a] Rohini A. Sonawane,[a] Khin Myat Noe Win,[a] Masayuki Ninomiya,[a] and Mamoru Koketsu*,[a]

An efficient, metal free and environment friendly synthesis of isoquinoline-fused benzimidazole has been developed *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 $CHCl_3$.



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]. The interesting biological and optical properties of isoquinoline and selenophene-heterocycles encouraged synthetic chemists to develop novel synthetic strategies to access structurally different motifs[8]. Recently, we have successfully synthesized the novel cascade cyclizations resulted into various seleno-fused heteroacenes[9]. 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

[a]Department of Chemistry and Biomolecular Science, Faculty of Engineering, Gifu University, Gifu 501-1193, Japan. Email: koketsu@gifu-u.ac.jp

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 sulfur and selenium-heteroacenes.

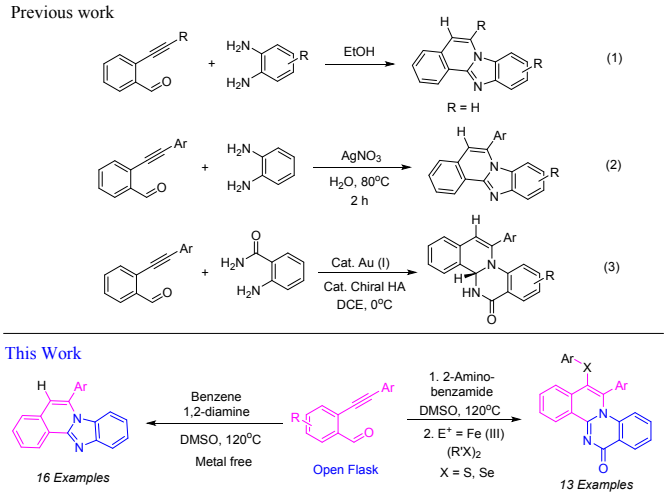
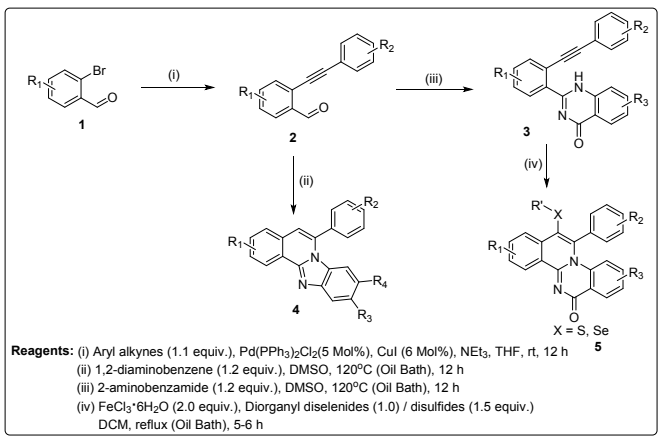


Fig. 1

Result and Discussion

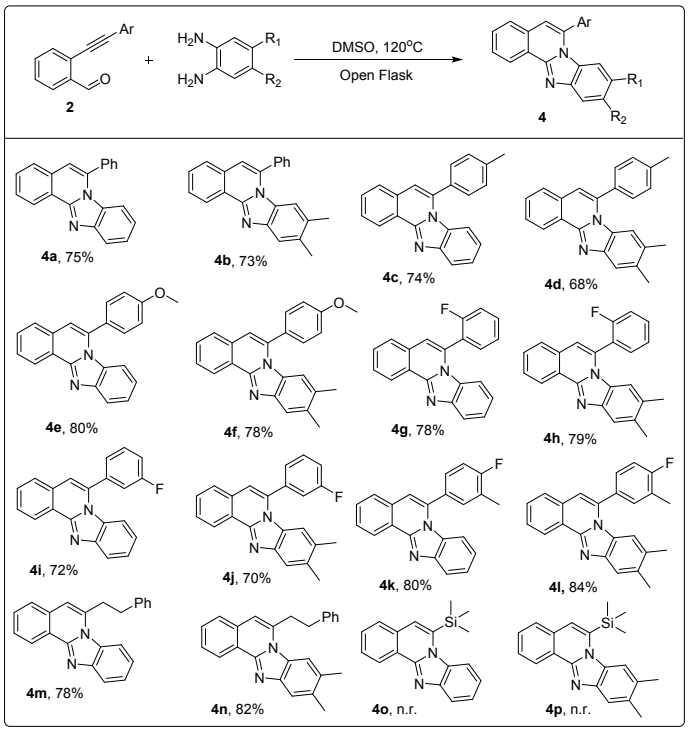
Our investigations were started with the easily available starting materials amines and 2-bromobenzaldehydes **1** which were readily converted to aryl alkynes **2** under Sonogashira coupling conditions, the compounds **1** were alkylated with various aromatic alkynes to afford the corresponding substituted 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**[10] **3**, **4** and **5** were confirmed by the IR, ^{1}H-NMR, ^{13}C-NMR and HRMS spectral analysis.



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**.

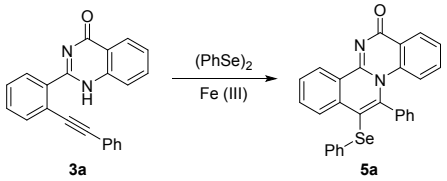


With the standard compound **3a** in hand, we have optimized the synthesis of isoquinoline-based quinazolinone derivative **5a**. We first examined the selenocyclization reaction of aryl alkyne **3a** with 1.5 equiv. of $FeCl_3{\cdot}6H_2O$ and $(PhSe)_2$ (1.5 equiv.) in $CHCl_3$ at room temperature, 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

View Article Online
DOI: 10.1039/D0OB00375A

sulfur and selenium heteroacenes (**Table 3**). Additionally, it was found that the reaction with dibenzyl disulfide $(PhCH_2S)_2$ and dibutyl selenide $(Bu)_2Se$ did not proceed toward the expected products (**5n** and **5o**).

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

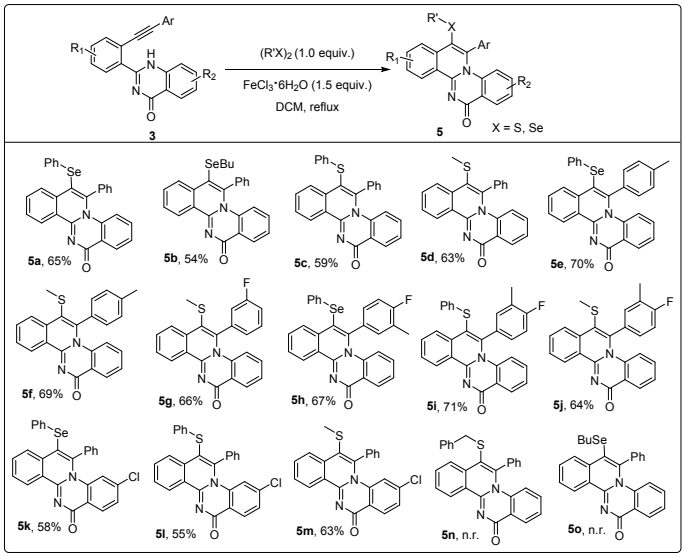


Entry No.	Solvent	E^+ (Eq.)	$(PhSe)_2$ (Eq.)	Time (h)	Temp. (°C)	5a Yield[a] (%)
1	$CHCl_3$	$FeCl_3·6H_2O$ (1.0)	0.5	12	rt	n.r.
2	DCM	$FeCl_3·6H_2O$ (1.0)	0.5	12	reflux	56
3	DCM	$FeCl_3·6H_2O$ (1.5)	2.0	12	reflux	61
4	DCM	$FeCl_3·6H_2O$ (1.5)	1.0	8	reflux	65
5	DCM	$FeCl_3·6H_2O$ (2.5)	2.0	8	reflux	62
6	$CHCl_3$	$FeCl_3$ (2.0)	1.5	12	65	42
7	DCM	$FeCl_3·6H_2O$ (3.5)	3.0	8	reflux	59
8.	DMF	$FeCl_3·6H_2O$ (1.5)	1.0	8	80	n.r.
9.	DMSO	$FeCl_3·6H_2O$ (1.5)	1.0	8	80	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.

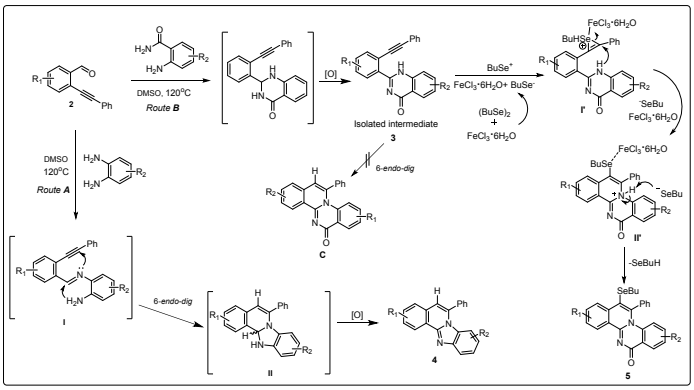
[a]The reaction was performed by addition of diphenyl diselenide (1.0 equiv.) to a solution of $FeCl_3·6H_2O$ (1.5 equiv.) in DCM (4 mL), under an air atmosphere, at room temperature. After 15 min at this temperature, alkyne **3a** (1.0 equiv.) was added. The resulting mixture was refluxed for 8 h. n.r.: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

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** in Scheme 3. *Route **A*** shows the formation of isoquinoline-fused benzimidazole **4**. The reaction 1,2-benezediammine and 2-alkynylbenzaldehyde **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**.

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



*Route **B*** shows the formation of isoquinoline-fused quinazolinone derivatives **5**. The reaction 2-aminobenzamide 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[11]. 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. Plausible mechanism

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 (ε) values of isoquinoline-based benzimidazole (**4a**: λ_{max} = 360 nm, ε = 4,972), (**4e**: λ_{max} = 360 nm, ε = 5,942), (**4i**: λ_{max} = 356 nm, ε = 6,897) and (**4k**: λ_{max} = 359 nm, ε = 4,935) derivatives were almost the same (**Fig. 2a**, **Table 4**). While, In the case of

DOI: 10.1039/D0OB00375A

isoquinoline-fused quinazolinone derivatives **5a**, **5c, 5h** and **5k**, the absorption maximum (λ_{max}) and molar extinction coefficient (ε) values of isoquinoline-fused quinazolinone (**5a**: λ_{max} = 394 nm, ε = 9,262), (**5c**: λ_{max} = 393 nm, ε = 11,688), (**5h**: λ_{max} = 394 nm, ε = 11,549) and (**5k**: λ_{max} = 393 nm, ε = 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).

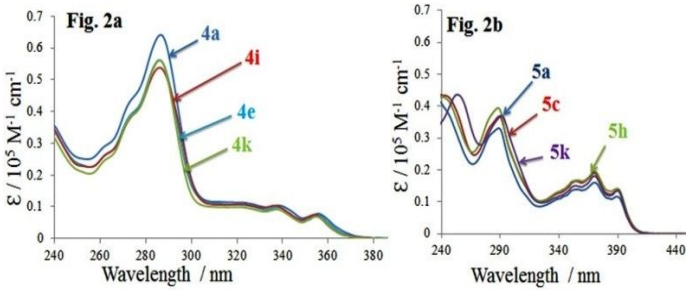


Fig. 2. UV-vis absorption spectra of isoquinoline-fused benzimidazole (**a**) and isoquinoline-fused quinazolinone (**b**) derivatives in $CHCl_3$.

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[12]. 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.

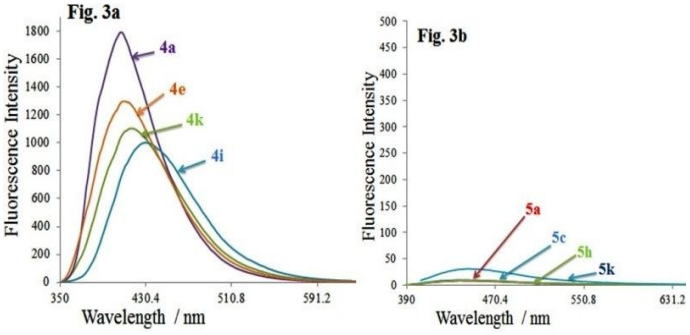


Fig. 3. Fluorescence spectra of isoquinoline-fused benzimidazole (**a**) and isoquinoline-fused quinazolinone (**b**) derivatives in $CHCl_3$.

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

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.

Experimental: General

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.

General procedure and spectral data for the synthesized compounds 2a-2g.

To a solution of 2-bromobenzaldehyde **1a** (350 mg, 2.43 mmol, 1.0 equiv.) in dry THF (10 mL) was added $Pd(PPh_3)_2Cl_2$ (62 mg, 6 mol%), triethylamine (574 mg, 7.29 mmol, 3.0 equiv.), phenyl acetylene (372.50 mg, 3.65 mmol, 1.2 equiv.), and copper(I) iodide (18 mg, 5 mol%) under nitrogen. The

mixture was stirred at room temperature for 15 h. After completion of reaction; the solvent was evaporated under reduced pressure. The residue 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: ethyl acetate (92:8) as the eluent to afford **2a** as brown liquid.

2-(phenylethynyl)benzaldehyde (2a)

Yield: 74%; brown liquid; IR (KBr): 3062, 2216, 1787, 1698, 1592, 1443, 1266, 1070, 817, 756, 689, 517 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.65 (d, *J* = 0.9 Hz, 1H), 7.94-7.96 (m, 1H), 7.64 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.55-7.59 (m, 3H), 7.43-7.47 (m, 1H), 7.38 (dt, *J* = 7.3, 2.9 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 191.8, 136.0, 133.9, 133.3, 131.8, 129.2, 128.7, 128.6, 127.4, 125.0, 122.4, 96.4, 85.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{11}O$ 207.0810; Found 207.0782.

2-(*p*-Tolylethynyl)benzaldehyde (2b)

Yield: 76%; Melting point: 34-35°C; IR (neat): 3026, 2214, 1774, 1693, 1591, 1509, 1388, 1262, 1191, 1018, 816, 758, 633, 519 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.63 (d, *J* = 0.9 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.59-7.61 (m, 1H), 7.54 (td, *J* = 7.6, 1.4 Hz, 1H), 7.38-7.45 (m, 3H), 7.16 (d, *J* = 8.2 Hz, 2H), 2.36 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 191.9, 139.5, 135.9, 133.9, 133.2, 131.8, 129.4, 128.5, 127.3, 127.3, 119.4, 96.8, 84.5, 77.5, 77.20, 76.9, 21.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{13}O$ 221.0966; Found 221.0938.

2-((4-Methoxyphenyl)ethynyl)benzaldehyde (2c)

Yield: 69%; Melting point: 38-39°C; IR (neat): 2837, 2210, 1687, 1592, 1505, 1457, 1288, 1248, 1157, 1025, 812, 670, 537, 521 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.65 (d, *J* = 1.1 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.54-7.58 (m, 1H), 7.50 (dd, *J* = 6.9, 1.8 Hz, 2H), 7.43 (d, *J* = 7.8 Hz, 1H), 6.90 (dd, *J* = 6.6, 2.1 Hz, 2H), 3.84 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 192.0, 160.3, 135.8, 133.9, 133.3, 133.1, 128.3, 127.4, 127.3, 114.5, 114.3, 96.7, 83.9, 77.4, 77.1, 76.8, 55.4; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{12}O_2Na$ 259.0735; Found 259.0714.

2-((2-Fluorophenyl)ethynyl)benzaldehyde (2d)

Yield: 75%; Melting point: 37-38°C; IR (neat): 3055, 2357, 1682, 1592, 1471, 1450, 1262, 1222, 1192, 1099, 823, 796, 692 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.64 (d, *J* = 0.9 Hz, 1H), 7.93 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.63 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.50-7.58 (m, 2H), 7.42-7.46 (m, 1H), 7.31-7.37 (m, 1H), 7.08-7.16 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 191.7, 191.6, 164.1, 161.6, 136.0, 133.8, 133.4, 133.4, 133.3, 131.0, 131.0, 129.1, 127.3, 126.4, 124.3, 124.2, 115.9, 115.8, 115.7, 115.6, 111.2, 111.1, 90.1, 90.0, 89.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{10}OF$ 225.0716; Found 225.0693.

2-((3-Fluorophenyl)ethynyl)benzaldehyde (2e)

Yield: 79%; Sticky; IR (KBr): 3072, 2212, 1776, 1698, 1608, 1593, 1580, 1193, 1122, 943, 872, 786, 761cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.60 (s, 1H), 7.93-7.95 (m, 1H), 7.56-7.64 (m, 2H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.34 (dq, *J* = 4.9, 1.5 Hz, 2H), 7.25 (dd, *J* = 9.4, 2.5 Hz, 1H), 7.06-7.11 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 191.4, 163.7, 161.3, 136.0, 133.9, 133.4, 130.3, 130.2, 129.0, 127.7, 127.7, 127.5, 126.3, 124.3, 124.2, 118.6, 118.4, 116.6, 116.4, 94.9, 94.9, 85.9; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{10}O^{19}F$ 225.0716; Found 225.0688.

2-((4-Fluoro-3-methylphenyl)ethynyl)benzaldehyde (2f)

Yield: 70%; Sticky; IR (KBr): 3036, 1851, 1774, 1693, 1588, 1497, 1448, 1291, 1262, 1230, 1114, 1086, 886, 830, 635, 532 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.62 (s, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.56-7.62 (m, 2H), 7.35-7.46 (m, 3H), 7.01 (t, *J* = 8.9 Hz, 1H), 2.28 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 191.8, 162.7, 160.8, 135.9, 135.0, 135.0, 133.9, 133.2, 131.1, 131.0, 128.7, 127.4, 126.9, 125.7, 125.6, 118.2, 115.7, 115.5, 95.7, 84.4, 14.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{12}OF$ 239.0872; Found 239.0867.

2-(4-Phenylbut-1-yn-1-yl)benzaldehyde (2g)

Yield: 75%; Sticky; IR (neat): 3029, 2228, 1852, 1788, 1775, 1697, 1595, 1497, 1477, 1244, 1193, 1030, 823, 761, 699, 637, 507 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.45-7.51 (m, 2H), 7.35 (dt, *J* = 19.9, 7.4 Hz, 3H), 7.26 (t, *J* = 6.9 Hz, 3H), 2.95 (t, *J* = 7.4 Hz, 2H), 2.79 (t, *J* = 7.4 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 192.2, 140.3, 136.1, 133.8, 133.4, 128.6, 128.6, 128.1, 127.7, 127.0, 126.7, 97.1, 34.9, 21.9; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{15}O$ 235.1123; Found 235.1105.

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

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(1*H*)-one (3a)

Yield: 69%; Melting point: 156-158°C; 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: 162-164°C; 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: 150-151°C; 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: 136-137°C; 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(1*H*)-one (3e)

Yield: 43%; Melting point: 152-154°C; 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 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.

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

Yield: 75%; Melting point: 163-165°C; 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: 225-227°C; 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: 148-150°C; 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: 170-172°C; 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: 184-186°C; 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: 216-217°C; 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: 144-146°C; 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: 170-172°C; 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: 162-163°C; 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: 261-262°C; 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: 160-162°C; 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: 212-214°C; 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: 164-166°C; 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: 148-150°C; 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 $(n\text{-BuSe})_2$ (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: 204-205°C; 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 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; ^{77}Se-NMR (75 MHz, $CDCl_3$) δ 193.97; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{28}H_{19}N_2OSe$ 479.0663; Found 479.0639.

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

Yield: 54%; Melting point: 128-130°C; 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 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 319.75; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{26}H_{23}N_2OSe$ 459.0976; Found 459.0952.

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

Yield: 59%; Melting point: 207-208°C; 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)

View Article Online DOI: 10.1039/D0OB00375A

Yield: 63%; Melting point: 180-181°C; 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: 130-132°C; 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: 152-154°C; 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: 184-185°C; 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: 184-186°C; IR (neat): 1688, 1610, 1591, 1557, 1544, 1467, 1346, 1272, 1124, 831, 761, 740,

DOI: 10.1039/D0OB00075A

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: 160-162°C; 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: 179-180°C; 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: 218-220°C; 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: 184-186°C; 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: 262-264°C; 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.

Conflicts of interest

"There are no conflicts to declare".

Acknowledgements

This study was supported by JSPS KAKENHI Grant Number 17550099 (to MK). Author ADS and KMNW are thankful to MEXT: Monbukagakusho for scholarship and also thankful to Daiki Kaneko for help in elemental analysis characterization.

Supporting Information:

Experimental procedures, characterization data for the new compounds, and copies of ^{1}H and ^{13}C-NMR spectra. This material is available free of charge *via* the Internet at http://

References

1. (a) V. Rustagi, R. Tiwari and A. K. Verma, *Eur. J. Org. Chem.,* 2012, **24**, 4590; (b) L. W. Deady, T. Rodemann, G. J. Finlay, B. C. Baguley and W. A. Denny, *Anti-Cancer Drug Des.,* 2000, **15**, 339; (c) S. M. Rida, S. A. M. El-Hawash, H. T. Y. Fahmy, A. A. Hazzaa and M. M. M. El-Meligy, *Arch. Pharmacal. Res.,* 2006, **29**, 826; (d) K. W. Bentley, *Nat. Prod. Rep*., **2006**, *23*, 444; (e) K. W. Bentley, *Nat. Prod. Rep.,* 2005, **22**, 249; (f) M. Chrzanowska and M. D. Rozwadowska, *Chem. Rev.* 2004, **104**, 3341.

2. (a) B. W. Yang, P. D. Q. Dao, N. S. Yoon and C. S. Cho, *J. Organometallic Chem.,* 2017, **851**, 136; (b) G. Dyker, W. Stirner and G. Henkel, *Eur. J. Org. Chem.,* 2000, **2000**, 1433; (c) N. Okamoto, K. Sakurai, M. Ishikura, K. Takeda and R. Yanada, *Tetrahedron Lett.,* 2009, **50**, 4167; (d) H. -C. Ouyang, R. -Y. Tang, P. Zhong, X. -G. Zhang and J. -H. Li, *J. Org. Chem.,* 2011, **76**, 223; (e) S. Nandi, S. Samanta, S. Jana and J. K. Ray, *Tetrahedron Lett.,* 2010, **51**, 5294; (f) M. Sun, H. Wu, J. Zheng and W. Bao, *Adv. Synth. Catal.,* 2012, **354**, 835; (g) J. Peng, G.

Shang, C. Chen, Z. Miao and B. Li, *J. Org. Chem.,* 2013, **78**, 1242; (h) J. Jie, H. Li, S. Wu, Q. Chai, H. Wang and X. Yang, *RSC Adv.,* 2017, **7**, 20548.

3. (a) M. Mishra, D. Twardy, C. Ellstrom, K. A. Wheeler, R. Dembinski and B. Torok, *Green Chem.,* 2019, **21**, 99; (b) H. Xie, Q. Xing, Z. Shan, F. Xiao and G.-J. Deng, *Adv. Synth. Catal.,* 2019, **361**, 1896; (c) V. Rustagi, T. Aggarwal and A. K. Verma, *Green Chem.,* 2011, **13**, 1640.
4. (a) N. T. Patil, A. K. Mutyala, A. Konala and R. B. Tella, *Chem. Commun.,* 2012, **48**, 3094; (b) A. D. Sonawane, Y. B. Shaikh, D. R. Garud and M. Koketsu, *Synthesis*, 2019, **51**, 500-507.
5. (a) Z. Chen, X. Yang and J. Wu, *Chem. Commun.,* 2009, 3469; (b) X. Yu and J. Wu, *J. Comb. Chem.,* 2010, **12**, 238; (c) R. Yanada, S. Obika, H. Kono and Y. Takemoto, *Angew. Chem.* 2006, **118**, 3906; (d) Y.-H. Zhao, Y. Li, T. Guo, Z. Tang, K. Deng and G. Zhao, *Synthetic Commun.,* 2016, 355; (e) H.-C. Ouyang, R.-Y. Tang, P. Zhong, X.-G. Zhang and J.-H. Li, *J. Org. Chem.,* 2011, **76**, 223; (f) K. Gao and J. Wu, *J. Org. Chem.,* 2007, **72**, 8611; (g) V. P. Reddy, T. Iwasaki and N. Kambe, *Org. Biomol. Chem.,* 2013, **11**, 2249; (h) R. Yang, X. Wu, S. Sun, J. -T. Yu and J. Cheng, *Synthesis*, 2018, **50**, 3487; (i) N. T. Patil, A. K. Mutyala, P. G. V. V. Lakshmi, P. V. K. Raju and B. Sridhar, *Eur. J. Org. Chem.,* 2010, 1999; (j) N. Asao, K. Iso and Y. S. Salprima, *Org. Lett.,* 2006, **8**, 4149.
6. (a) A. C. G Tales, J. A. G. Kazmirski, D. F. Back and G. Zeni, *J. Org. Chem.,* 2019, **84**, 14113; (b) F. N. Bilheri, A. L. Stein and G. Zeni, *Adv. Synth. Catal.,* 2015, 357, 1221; (c) F. N. Bilheri, R. P. Pistoia, D. F. Back and G. Zeni, *Adv. Synth. Catal.,* 2017, 359, 4208; (d) T. A. C. Goulart, D. F. Back and G. Zeni, *Adv. Synth. Catal.,* 2017, **359**, 1901; (e) A. M. S. Recchi, D. F. Back and G. Zeni, *J. Org. Chem.,* 2017, **82**, 2713; (f) T. Prochnow, D. F. Back and G. Zeni, *Adv. Synth. Catal.,* 2016, **358**, 1119; (g) T. B. Grimaldi, G. Lutz, D. F. Back and G. Zeni, *Org. Biomol. Chem.,* 2016, **14**, 10415; (h) R. M. Gay, F. Manarin, C. C. Schneider, D. A. Barancelli, M. D. Costa and G. Zeni, *J. Org. Chem.,* 2010, **75**, 5701; (i) K. K. Casola, D. F. Back and G. Zeni, *J. Org. Chem.,* 2015, **80**, 7702.
7. (a) J. Hollinger, A. A. Jahnke, N. Coombs and D. S. Seferos, *J. Am. Chem. Soc.,* 2010, **132**, 8546; (b) A. Gupta and B. L. Flynn, *Org. Lett.,* 2017, **19**, 1939; (c) D. Meng, D. Sun, C. Zhong, T. Liu, B. Fan, L. Huo, Y. Li, W. Jiang, H. Choi, T. Kim, J. Y. Kim, Y. Sun, Z. Wang and A. J. Heeger, *J. Am. Chem. Soc.,* 2016, **138**, 375; (d) A. A. Jahnke, B. Djukic, T. M. McCormick, E. B. Domingo, C. Hellmann, Y. Lee and D. S. Seferos, *J. Am. Chem. Soc.,* 2013, **135**, 951; (e) T. Yamamoto and K. Takimiya, *J. Am. Chem. Soc.,* 2007, **129**, 2224; (f) K. Takimiya, Y. Kunugi, Y. Konda, H. Ebata, Y. Toyoshima and T. Otsubo, *J. Am. Chem. Soc.,* 2006, **128**, 3044; (g) R. S. Singh, R. K. Gupta, R. P. Paitandi, M. Dubey, G. Sharma, B. Koch and D. S. Pandey, *Chem. Commun.,* 2015, **51**, 9125.
8. For review's see: (a) B. Godoi, R. F. Schumacher and G. Zeni, *Chem. Rev.,* 2011, **111**, 2937; (b) T. Aggarwal, S. Kumar and A. K. Verma, *Org. Biomol. Chem.,* 2016, **14**, 7639; (c) A. D. Sonawane and M. Koketsu, *Curr. Org. Chem.* 2019, **23**, 3206; (d) B. Banerjee and M. Koketsu, *Coord. Chem. Rev.,* 2017, **339**, 104; (e) M. Ninomiya, D. R. Garud and M. Koketsu, *Coord. Chem. Rev.,* 2011, **255**, 2968.
9. (a) A. D. Sonawane, Y. Kubota and M. Koketsu, *J. Org. Chem.,* 2019, **84**, 8602; (b) K. M. N. Win, A. D. Sonawane and M. Koketsu, *Org. Biomol. Chem.,* 2019, **17**, 9039.
10. (a) A. D. Sonawane, D. R. Garud, T. Udagawa and M. Koketsu, *Org. Biomol. Chem.,* 2018, **16**, 245; (b) A. D. Sonawane, D. R. Garud, T. Udagawa, Y. Kubota and M. Koketsu, *New J. Chem.,* 2018, **42**, 15315.
11. (a) J. S. S. Neto, B. A. Iglesias, D. F. Back and G. Zeni, *Adv. Synth. Catal.,* 2016, **358**, 3572; (b) L. Yu, L. Ren, R. Yi, Y. Wu, T. Chen and R. Guo, *J. Organomet. Chem.,* 2011, **696**, 2228.
12. (a) S. K. Lower and M. A. El-Sayed, *Chem. Rev*., 1966, **66**, 199; (b) A. Gorman, J. Killoran, C. OShea, T. Kenna, W. M. Gallagher and D. F. OShea, *J. Am. Chem. Soc*., 2004, **126**, 10619; (c) B. Lv, X. Shen, J. Xiao, J. Duan, X. Wang and Y. Yi, *Chem. Asian J.,* 2015, 10, 2677.

View Article Online DOI: 10.1039/D0OB00375A

View Article Online
DOI: 10.1039/D0OB00375A