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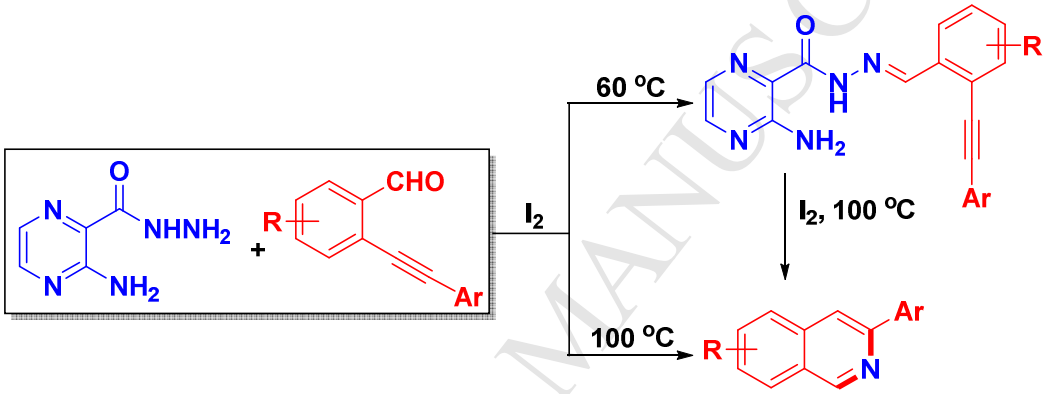

Study on the Iodine-Catalyzed Reaction of 3-Aminopyrazine-2-carbohydrazide and 2-(Arylethynyl)benzaldehydes

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Abstract: At 60 °C in DMSO, the iodine-catalyzed reaction of 3-aminopyrazine-2-carbohydrazide and 2-(arylethynyl)benzaldehydes lead hydrazones. Increasing the reaction temperature to 100 °C, the amino and amido still indicated inactive, only the imine took part in the addition of acetylene bond to give 2-arylisoquinolines in high yields with the cleavage of N-N bond unexpectedly under metal-free conditions.

Keywords: 3-aminopyrazine-2-carbohydrazide, 2-(arylethynyl)benzaldehyde, 2-arylisoquinoline, iodine, metal-free

1. Introduction

Isoquinoline is a very useful heterocyclic skeleton, and the derivatives of which possess various kinds of pharmacological and biological activities, such as anti-telomerase,[1] anti-tobacco mosaic virus,[2] antibacterial,[3] and anti-muscle atrophy activities.[4] *Roxadustat* (FG-4592; Figure 1, left)[5] is a well-known drug based on isoquinoline moiety, and it is an anti-anemic drug which is already used in the phase III clinical trials. Another medicine is the famous *Papaverine*[6] (Figure 1, right) which is also a polysubstituted isoquinoline. It is an opium alkaloid and antispasmodic medication which is used in the treatment of visceral spasm and vasospasm. In view of their biological applications, numerous novel procedures have been reported to synthesize structurally diversified isoquinoline derivatives in recent years.[7]

Of which, utilization of 2-(arylethynyl)benzaldehyde as a reactant is a very efficient method to construct 2-substituted isoquinolines. The nitrogen sources

involve NH_4OAc,[8] NH_4HCO_3,[9] amidine,[10] urea,[11] hydrazine,[12] NH_3,[13] amine[14] and hydroxylamine.[15] However, the catalyst of transition metal salt is essential to this conversion because it is always used to activate carbon-carbon triple bond, such as Cu(I),[10] Cu(II)[11] and Yb(III),[16] especially for Ag(I).[8,9,12,14,15] Therefore, searching for a novel procedure under metal-free conditions is still necessary.

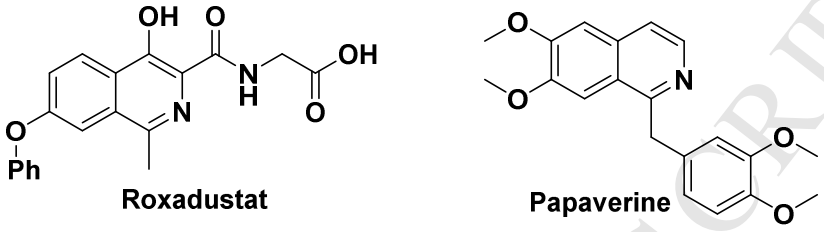
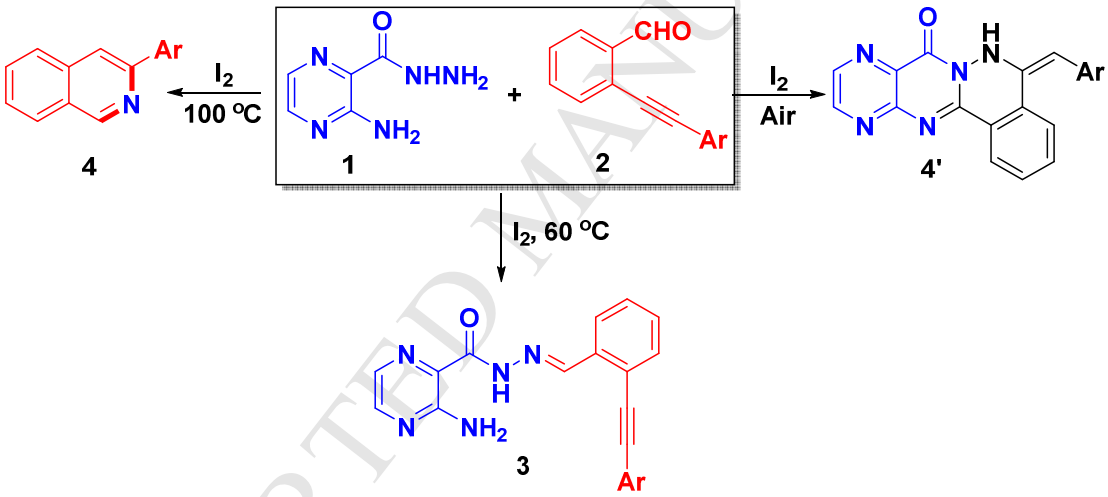


Figure 1. The drugs containing isoquinoline moiety



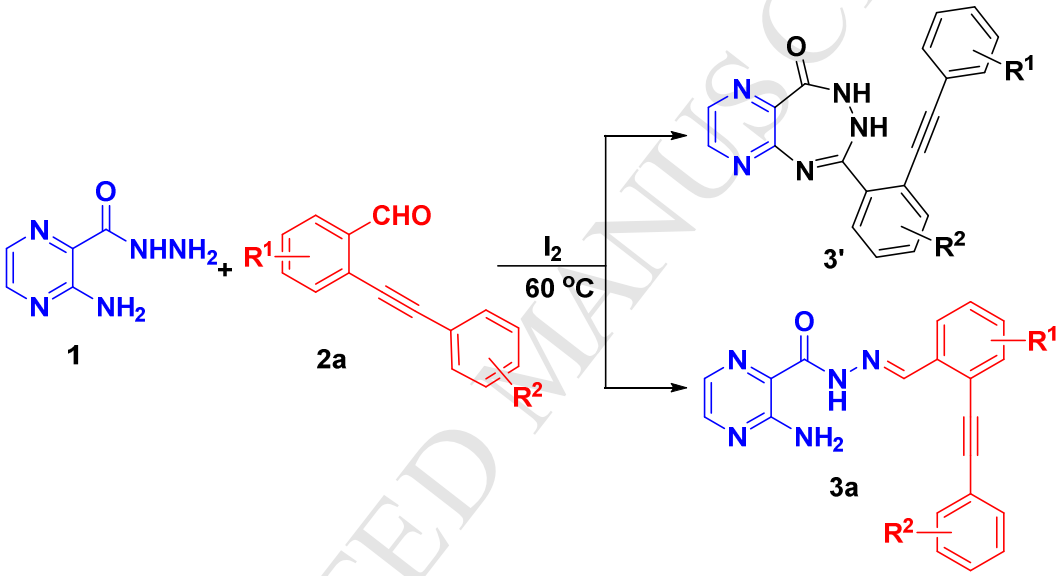
Scheme 1. Our approach to 2-arylisoquinolines

Iodine is a mild Lewis acid which has been used to promote a lot of organic reactions.[17] In our recent study, it was submitted to catalyze the reaction of 3-aminopyrazine-2-carbohydrazide (**1**) and 2-(arylethynyl)benzaldehydes (**2**) in the air. Our intention was to build the fused tetracyclic 5-arylidene-5,6-dihydro-8*H*-phthalazino[1,2-*b*]pteridin-8-ones using three amino groups in the reactant of **1**. However, the amino on pyrazine and the amido group all showed chemical inertness, only the third hydrazine amino group took part in the reaction. It was found that only hydrazones were obtained at 60 °C, while at 100 °C, the subsequent cyclization and

cleavage of N-N bond took place to give 2-arylisoquinolines losing a molecule of 3-amino-*N*-hydroxypyrazine-2-carboxamide unexpectedly (Scheme 1).

As our continuous research on the construction of heterocycles catalyzed by iodine,[18] we would like to report the synthesis of 2-arylisoquinoline from an iodine-catalyzed reaction of 3-aminopyrazine-2-carbohydrazide and 2-(arylethynyl) benzaldehydes under metal-free conditions.

2. Results and discussion



Scheme 2. The iodine-catalyzed reaction to hydrazone at 60 °C

As shown in Scheme 1 and 2, in our initial assumption, we planned to build phthalazino[1,2-*b*]pteridin-8-one skeleton promoted by iodine. However, a new compound was obtained at 60°C in the presence of 5 mol% iodine, and twelve protons (see SI) were observed in its ^{1}H NMR when 2-(phenylethynyl)benzaldehyde (**2a**, R^1 = R^2 = H) was submitted to react with **1** in DMSO. Two peaks arriving (see SI) at 86.2 and 95.1 indicated that the triple bond did not attend the reaction initially. According to the NMR data, 5*H*-pyrazino[2,3-*e*][1,2,4]triazepin-5-one (**3′**) was thought to be the cyclation and oxidation product. Subsequently, various kinds of **2** (Table 1) were

tested to react with **1**, and all gave the similar products **3a**-**m** in high yields under the optimized reaction conditions. In our continuous study, a single crystal of **3e** was obtained in $CHCl_3$ solution, and the X-ray diffraction analysis (Figure 2) confirmed that it was the hydrazone (**3e**) that was 3-amino-*N*'-(5-fluoro-2-(phenylethynyl) benzylidene)pyrazine-2-carbohydrazide.

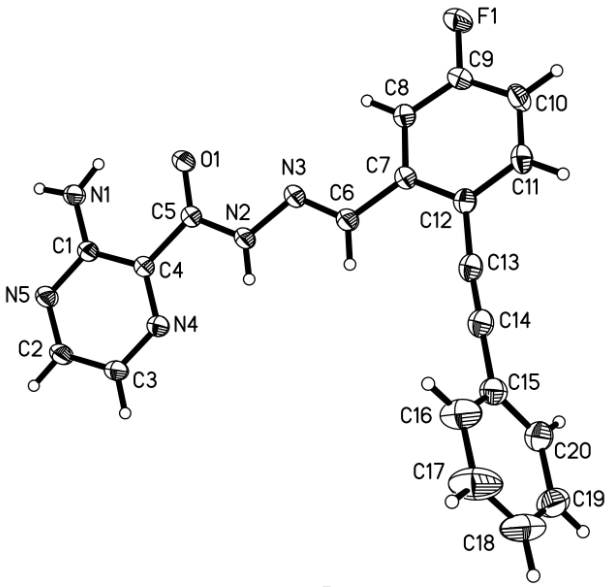


Figure 2. The crystal structure of **3e**

Table 1. The synthetic results for the products **3**

Entry	R^1	R^2	Products	Yields (%)
1	H	H	**3a**	95
2	4-Cl	H	**3b**	97
3	4-F	H	**3c**	93
4	5-Cl	H	**3d**	97
5	5-F	H	**3e**	92
6	5-OCH_3	H	**3f**	93
7	4,5-$(OCH_3)_2$	H	**3g**	90
8	2-Thieny	H	**3h**	91
9	H	3-Cl	**3i**	92
10	H	4-Cl	**3j**	85
11	4-Cl	3-F	**3k**	89
12	4,5-$(OCH_3)_2$	4-Cl	**3l**	88
13	4,5-$(OCH_3)_2$	4-*n*-Pr	**3m**	87

Reaction condition: **1** (77 mg, 0.5 mmol), **2** (0.5 mmol), iodine (7 mg), DMSO (5.0 mL), 60 °C.

In order to promote one of the following reactions: (1) the addition of amino and imine; (2) the coupling between amido and triple bond of carbon; (3) the addition of imine and acetylenic bond, we subsequently changed the reaction temperature, catalyst dosage and solvents in our lab (Table 2). It was found that the third addition of imine and acetylenic bond gradually took place when the reaction increased to 100 °C giving isoquinoline derivatives. Furthermore, the highest yield reached 91% using 10 mol% iodine as a catalyst (Table 2) in the solvent of DMSO.

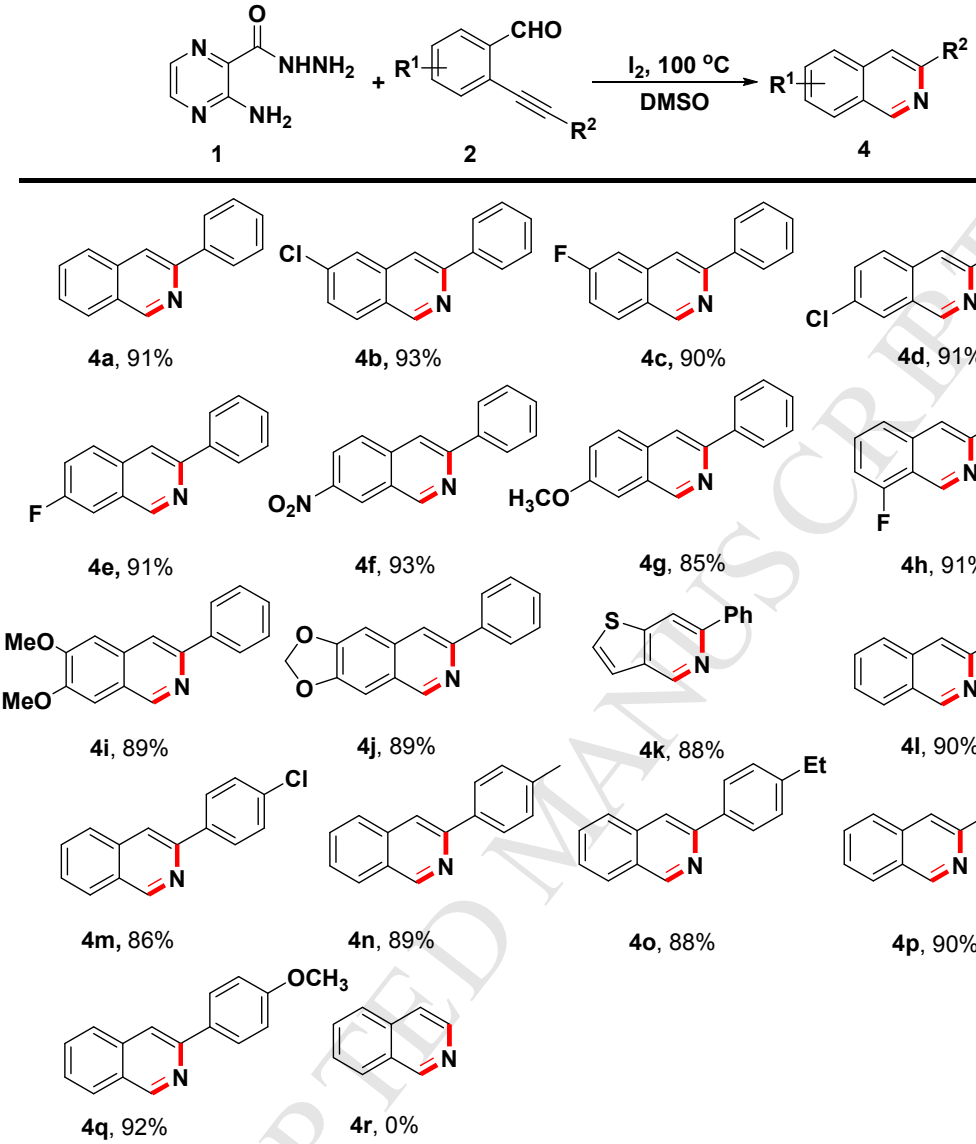
Table 2. The screening of reaction conditions from **1** to **4**

Entry	T/°C	Cat./mol%	Solvent	Yields (%)
1	70	5	DMSO	-
2	80	5	DMSO	Trace
3	100	5	DMSO	78
4	110	5	DMSO	76
5	100	10	DMSO	91
6	100	15	DMSO	90
7	100	10	Dioxane	86
8	100	10	Toluene	78
9	100	10	Xylene	76
10	100	10	DMF	87

Reaction condition: **1** (77 mg, 0.5 mmol), **2a** (103 mg, 0.5 mmol), solvent (5.0 mL).

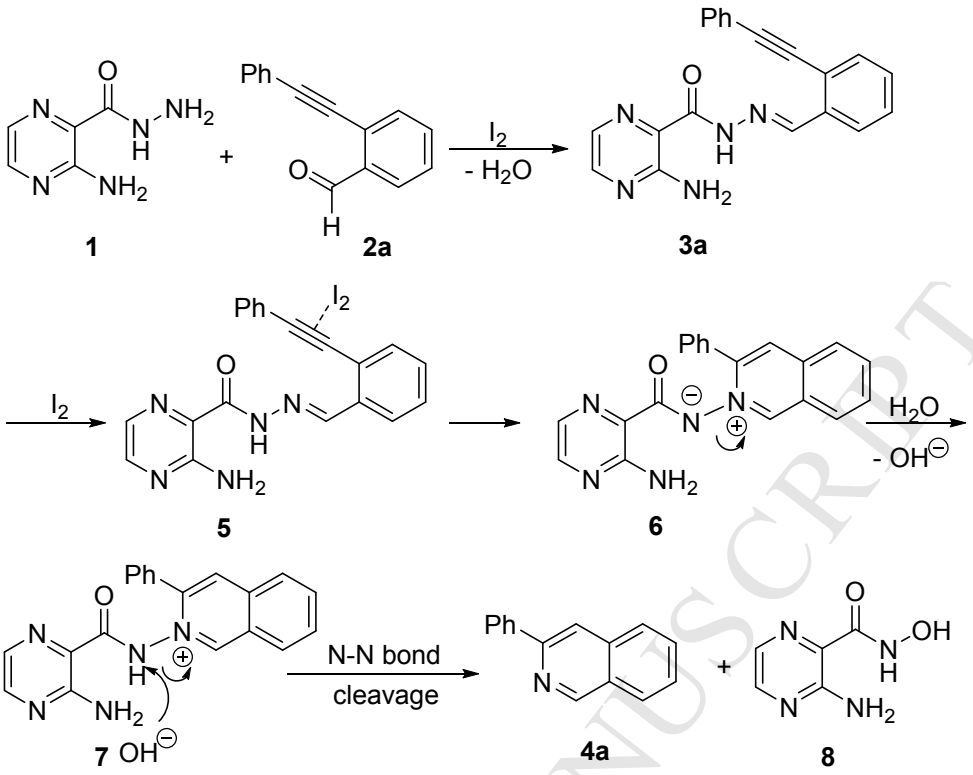
With the optimized reaction conditions in hand, we next investigated the substrate scope of the I_2-catalyzed reaction by varying 2-(arylethynyl)benzaldehydes (Table 3). In general, the reactants **2** with both electron-donating (e.g., H, Ph or Me) and -withdrawing groups (e.g., Cl, F or Br) all reacted smoothly with **1** to give 2-arylisoquinolines in good to excellent yields (**4a-4q**, Table 3, 85-93%). It was worthy to be noted that 2-(phenylethynyl)thiophene-3-carbaldehyde (**2k**) also underwent the same reaction to lead 6-phenylthieno[3,2-*c*]pyridine (**4k**) in 88% yield. However, we failed to give non-substituted isoquinoline (**4r**) when 2-ethynylbenzaldehyde (**2r**) was used as a reactant to react with **1** under the same reaction conditions.

Table 3. The structurally diversified isoquinoline products **4**



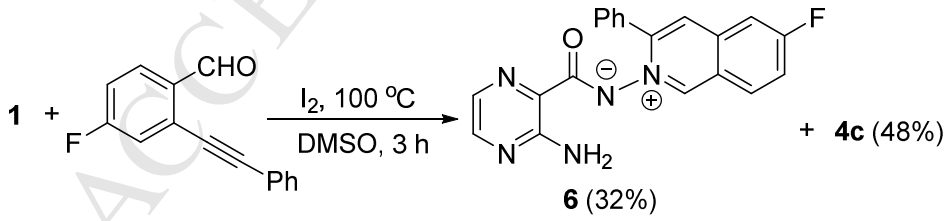
Reaction condition: **1** (77 mg, 0.5 mmol), **2** (0.5 mmol), DMSO (5.0 mL), I_2 (13 mg, 0.05 mmol), 100 °C.

According to the literature[12] and the structure of **4a**, we believe that the iodine activates the acetylenic bond first as a Lewis acid followed by the imine addition to the activated triple bond to produce ylide **6**. In the following step, the nitrogen anion undergoes a protonation from water to yield intermediate **7**. Finally, the key cleavage of N-N bond occurs to give final product **4a**, losing a molecule of 3-amino-*N*-hydroxypyrazine-2-carboxamide (**8**). The possible reaction mechanism is outlined in Scheme 3 as follows (using **4a** as a model).



Scheme 3. The possible reaction mechanism

In order to acquire more insight to the reaction mechanism, one of the intermediate products **6** (R^1 = 6-F, R^2 = Ph) could be isolated in 32% yield by column chromatography when the reaction (Scheme 4) was stopped at about half time (3 h). To our delight, the 3-amino-*N*-hydroxypyrazine-2-carboxamide (**8**) was also obtained (52% yield) successfully in the filtrate which was extracted by ethyl acetate.



Scheme 4. The controlled reaction to **6**

3. Conclusion

In conclusion, we found a temperature-controlled reaction of 3-aminopyrazine-2-carbohydrazide and 2-(arylethynyl)benzaldehydes catalyzed by

iodine. It only gave hydrazones at 60 °C while the amino on pyrazine and amido groups did not participate in this reaction. With the increase of temperature (100 °C) and catalyst dosage (10 mol%), the imine group indicated higher reactivity to provide 2-arylisoquinoline derivatives with satisfied yields.

4. Experimental Section

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Tensor 27 spectrometer in KBr pellet. ^{1}H NMR spectra were obtained from a solution in DMSO-d_6 with Me_4Si as internal standard using a Bruker-400 spectrometer. HRMS analyses were carried out using a Bruker-micro-TOF-Q-MS analyzer. All the starting materials were purchased from Beijing InnoChem Science & Technology Co., Ltd except for 2-(arylethynyl)benzaldehydes which were prepared from the reaction of substituted 2-bromobenzoaldehydes and arynes according to the literature.[19]

4.1 General procedure for the syntheses of (*E*)-3-amino-*N*'-(2-(arylethynyl) benzylidene)pyrazine-2-carbohydrazides 3

3-Aminopyrazine-2-carbohydrazide (77 mg, 0.5 mmol) 2-(arylethynyl)benz-aldehydes (0.5 mmol), iodine (7 mg, 0.025 mmol), and DMSO (5.0 mL) was added into a dry 25 mL flask. The reaction mixture was stirred at 60 °C for 2-6 h until all the **1** was consumed which was monitored by TLC. Water (about 50 mL) was added to the cool mixture, and the pale yellow precipitate formed immediately. The crude product was obtained by filtration and purified by recrystallization from EtOH to give **3**.

3-Amino-*N*'-(2-(phenylethynyl)benzylidene)pyrazine-2-carbohydrazide (3a): M.p. 160~161 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.78 (brs., 2H, NH_2), 7.38~7.42 (m, 5H, ArH), 7.56~7.58 (m, 1H, ArH), 7.60~7.62 (m, 2H, ArH), 7.85 (d, J = 1.6 Hz,

1H, ArH), 8.22 (d, *J* = 2.0 Hz, 1H, ArH), 8.28~8.30 (m, 1H, ArH), 8.75 (s, 1H, CH), 10.88 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 86.2, 95.1, 122.8, 123.5, 125.3, 126.1, 128.5, 128.7, 128.8, 130.2, 131.7, 132.7, 134.4, 146.5, 147.5, 155.4, 162.0. IR (KBr): ν 3397, 3313, 2975, 1691, 1666, 1603, 1529, 1478, 1438, 1390, 1350, 1294, 1249, 1150, 1034, 945, 922, 828 cm^{-1}. HRMS (ESI, *m/z*): Calcd for $C_{20}H_{14}N_5O$ [M - H]$^-$ 340.1204, found 340.1183.

3-Amino-*N*'-(4-chloro-2-(phenylethynyl)benzylidene)pyrazine-2-carbohydrazide (3b): M.p. 216~217 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.73 (brs., 2H, NH_2), 7.36 (dd, *J* = 8.4 Hz, *J'* = 1.6 Hz, 1H, ArH), 7.41~7.43 (m, 3H, ArH), 7.56~7.60 (m, 3H, ArH), 7.85 (d, *J* = 1.6 Hz, 1H, ArH), 8.21~8.23 (m, 2H, ArH), 8.68 (s, 1H, CH), 10.89 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 84.9, 96.1, 122.2, 124.8, 125.1, 127.4, 128.6, 129.1, 129.2, 131.70, 131.72, 132.2, 132.9, 136.0, 145.3, 147.6, 155.4, 162.0. IR (KBr): ν 3371, 3166, 3135, 1663, 1618, 1581, 1498, 1453, 1420, 1361, 1321, 1278, 1226, 1166, 1029, 950, 825, 691 cm^{-1}. HRMS (ESI, *m/z*): Calcd for $C_{20}H_{13}ClN_5O$ [M - H]$^-$ 374.0814, found 374.0838.

3-Amino-*N*'-(4-fluoro-2-(phenylethynyl)benzylidene)pyrazine-2-carbohydrazide (3c): M.p. 189~190 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.68 (brs., 2H, NH_2), 7.09~7.14 (m, 1H, ArH), 7.24~7.27 (m, 1H, ArH), 7.41~7.44 (m, 3H, ArH), 7.58~7.62 (m, 2H, ArH), 7.85 (d, *J* = 2.4 Hz, 1H, ArH), 8.23 (d, *J* = 2.0 Hz, 1H, ArH), 8.27~8.30 (m, 1H, ArH), 8.70 (s, 1H, CH), 10.87 (s, 1H, NH). IR (KBr): ν 3400, 3362, 3143, 2972, 1655, 1618, 1513, 1476, 1381, 1289, 1241, 1209, 1132, 1048, 1037, 941, 863, 805 cm^{-1}. HRMS (ESI, *m/z*): Calcd for $C_{20}H_{13}FN_5O$ [M - H]$^-$ 358.1109, found 358.1102.

3-Amino-*N*'-(5-chloro-2-(phenylethynyl)benzylidene)pyrazine-2-carbohydrazide (3d): M.p. 198~199 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.70 (brs., 2H, NH_2), 7.34~7.36 (m, 1H, ArH), 7.40~7.42 (m, 3H, ArH), 7.49 (d, *J* = 8.4 Hz, 1H, ArH), 7.58~7.61 (m, 2H, ArH), 7.85 (d, *J* = 2.0 Hz, 1H, ArH), 8.24 (d, *J* = 2.4 Hz, 1H, ArH), 8.28 (d, *J* = 2.4 Hz, 1H, ArH), 8.69 (s, 1H, CH), 10.92 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 85.3, 95.9, 121.7, 122.4, 125.0, 125.9, 128.6, 129.0, 130.3, 131.66, 131.71, 133.8, 135.1, 135.9, 145.1, 147.7, 155.4, 162.0. IR (KBr): ν 3386, 3312, 3153, 2993, 1690, 1630, 1557, 1505, 1434, 1376, 1304, 1252, 1214, 1172, 1136, 1093, 1036, 1009, 997, 836, 806, 580 cm^{-1}. HRMS (ESI, *m/z*): Calcd for $C_{20}H_{13}ClN_5O$ $[M - H]^-$ 374.0814, found 374.0844.

3-Amino-*N*'-(5-fluoro-2-(phenylethynyl)benzylidene)pyrazine-2-carbohydrazide (3e): M.p. 183~184 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.70 (brs., 2H, NH_2), 7.08~7.12 (m, 1H, ArH), 7.40~7.42 (m, 3H, ArH), 7.53~7.60 (m, 3H, ArH), 7.85 (d, *J* = 1.6 Hz, 1H, ArH), 7.98 (dd, *J* = 8.4 Hz, *J'* = 2.0 Hz, 1H, ArH), 8.23 (d, *J* = 1.2 Hz, 1H, ArH), 8.71 (s, 1H, CH), 10.92 (s, 1H, NH). IR (KBr): ν 3400, 3260, 2958, 2930, 1665, 1612, 1586, 1502, 1439, 1408, 1337, 1247, 1215, 1143, 1094, 1004, 936, 883, 810, 758, 685 cm^{-1}. HRMS (ESI, *m/z*): Calcd for $C_{20}H_{13}FN_5O$ $[M - H]^-$ 358.1109, found 358.1101.

3-Amino-*N*'-(5-methoxy-2-(phenylethynyl)benzylidene)pyrazine-2-carbohydrazide (3f): M.p. 248~249 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.91 (s, 3H, OCH_3), 5.82 (brs., 2H, NH_2), 6.96 (dd, *J* = 8.8 Hz, *J'* = 2.4 Hz, 1H, ArH), 7.38~7.41 (m, 3H, ArH), 7.48 (d, *J* = 8.8 Hz, 1H, ArH), 7.57~7.59 (m, 2H, ArH), 7.75 (d, *J* = 2.4 Hz, 1H, ArH), 7.85 (d, *J* = 1.6 Hz, 1H, ArH), 8.23 (d, *J* = 2.0 Hz, 1H, ArH), 8.74 (s, 1H, CH), 10.90 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 55.7, 86.3, 93.8, 108.7, 116.2, 118.6, 123.1, 125.2, 128.47, 128.51, 131.5, 131.7, 134.0, 135.8, 146.7, 147.6, 155.4,

159.8, 162.0. IR (KBr): ν 3391, 3266, 3148, 3072, 1691, 1627, 1604, 1574, 1556, 1527, 1487, 1429, 1353, 1276, 1138, 1081, 949, 795, 678 cm^{-1}. HRMS (ESI, *m/z*): Calcd for $C_{21}H_{16}N_5O_2$ $[M - H]^-$ 370.1309, found 370.1306.

3-Amino-*N*'-(4,5-dimethoxy-2-(phenylethynyl)benzylidene)pyrazine-2-carbohydrazide (3g): M.p. 204~205 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ_H 3.95 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 5.84 (brs., 2H, NH_2), 7.01 (s, 1H, ArH), 7.40~7.41 (m, 3H, ArH), 7.59~7.61 (m, 2H, ArH), 7.72 (s, 1H, ArH), 7.85 (d, *J* = 2.4 Hz, 1H, ArH), 8.22 (d, *J* = 2.4 Hz, 1H, ArH), 8.68 (s, 1H, CH), 10.82 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 56.1, 56.3, 86.3, 93.9, 107.5, 114.0, 117.0, 122.9, 125.3, 128.1, 128.5, 128.6, 131.6, 131.7, 146.9, 147.4, 149.9, 150.9, 155.4, 161.8. IR (KBr): ν 3414, 3312, 3258, 3190, 3143, 1677, 1650, 1641, 1613, 1530, 1505, 1492, 1468, 1434, 1421, 1351, 1259, 1236, 1200, 1155, 1130, 1083, 1001, 982, 929, 880, 750, 687 cm^{-1}. HRMS (ESI, *m/z*): Calcd for $C_{22}H_{18}N_5O_3$ $[M - H]^-$ 400.1415, found 400.1440.

3-Amino-*N*'-((3-(phenylethynyl)thiophen-2-yl)methylene)pyrazine-2-carbohydrazide (3h): M.p. 213~214 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ_H 5.76 (brs., 2H, NH_2), 7.13~7.14 (m, 1H, ArH), 7.36~7.40 (m, 4H, ArH), 7.56~7.59 (m, 2H, ArH), 7.82~7.83 (m, 1H, ArH), 8.21~8.22 (m, 1H, ArH), 8.66 (s, 1H, CH), 10.82 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 82.6, 94.7, 122.6, 124.9, 125.2, 128.3, 128.5, 128.8, 130.3, 131.6, 140.3, 142.1, 147.5, 155.4, 161.7. IR (KBr): ν 3478, 3400, 3251, 2360, 2342, 1656, 1652, 1606, 1562, 1515, 1490, 1470, 1434, 1397, 1359, 1237, 1209, 1090, 1065, 1035, 1014, 940, 849, 830, 757 cm^{-1}. HRMS (ESI, *m/z*): Calcd for $C_{18}H_{12}N_5OS$ $[M - H]^-$ 346.0768, found 346.0782.

3-Amino-*N*'-(2-((3-chlorophenyl)ethynyl)benzylidene)pyrazine-2-carbohydrazide (3i): M.p. 195~196 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ_H 5.91 (brs., 2H, NH_2),

7.32~7.62 (m, 7H, ArH), 7.86 (d, *J* = 2.4 Hz, 1H, ArH), 8.23 (d, *J* = 2.4 Hz, 1H, ArH), 8.27~8.29 (m, 7H, ArH), 8.76 (s, 1H, CH), 10.89 (s, 1H, NH). IR (KBr): ν 3432, 3337, 3292, 1624, 1592, 1558, 1505, 1466, 1444, 1357, 1212, 1147, 1089, 1003, 954, 891, 777, 752, 675 cm^{-1}. HRMS (ESI, *m/z*): Calcd for $C_{20}H_{13}ClN_5O$ $[M - H]^-$ 374.0814, found 374.0837.

3-Amino-*N*'-(2-((4-chlorophenyl)ethynyl)benzylidene)pyrazine-2-carbohydrazide (3j): M.p. 212~213 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ_H 5.72 (brs., 2H, NH_2), 7.37~7.42 (m, 4H, ArH), 7.52~7.57 (m, 3H, ArH), 7.85 (d, *J* = 2.4 Hz, 1H, ArH), 8.23 (d, *J* = 2.4 Hz, 1H, ArH), 8.27~8.29 (m, 1H, ArH), 8.73 (s, 1H, CH), 10.88 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 87.2, 93.9, 121.2, 123.1, 125.2, 126.2, 128.86, 128.92, 130.2, 131.7, 132.7, 132.9, 134.4, 134.9, 146.3, 147.6, 155.4, 162.0. IR (KBr): ν 3400, 3333, 3295, 3195, 3156, 1664, 1628, 1598, 1584, 1549, 1524, 1502, 1468, 1441, 1360, 1290, 1246, 1208, 1143, 1102, 1081, 1001, 953, 876, 823, 750, 687 cm^{-1}. HRMS (ESI, *m/z*): Calcd for $C_{20}H_{13}ClN_5O$ $[M - H]^-$ 374.0814, found 374.0839.

3-Amino-*N*'-(4-chloro-2-((3-fluorophenyl)ethynyl)benzylidene)pyrazine-2-carbohydrazide (3k): M.p. 194~195 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ_H 5.80 (brs., 2H, NH_2), 7.09~7.14 (m, 1H, ArH), 7.30 (dd, *J* = 8.8 Hz, *J'* = 2.4 Hz, 1H, ArH), 7.35~7.39 (m, 3H, ArH), 7.49 (d, *J* = 8.4 Hz, 1H, ArH), 7.86 (d, *J* = 2.0 Hz, 1H, ArH), 8.24 (d, *J* = 2.4 Hz, 1H, ArH), 8.28 (d, *J* = 2.0 Hz, 1H, ArH), 8.69 (s, 1H, CH), 10.93 (s, 1H, NH). IR (KBr): ν 3478, 3350, 3226, 3102, 1651, 1600, 1546, 1527, 1510, 1454, 1431, 1327, 1284, 1236, 1202, 1145, 1066, 1027, 945, 932, 861, 837, 810, 753, 738, 692 cm^{-1}. HRMS (ESI, *m/z*): Calcd for $C_{20}H_{12}ClFN_5O$ $[M - H]^-$ 392.0720, found 392.0714.

3-Amino-*N*'-(2-((4-chlorophenyl)ethynyl)-4,5-dimethoxybenzylidene)pyrazine-2-carbohydrazide (3l): M.p. 212~213 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ_H 3.94 (s,

3H, OCH_3), 4.01 (s, 3H, OCH_3), 5.92 (brs., 2H, NH_2), 6.99 (s, 1H, ArH), 7.36~7.38 (m, 2H, ArH), 7.51~7.53 (m, 2H, ArH), 7.72 (s, 1H, ArH), 7.84 (d, *J* = 2.0 Hz, 1H, ArH), 8.22 (d, *J* = 2.4 Hz, 1H, ArH), 8.66 (s, 1H, CH), 10.84 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 56.1, 56.3, 87.3, 92.7, 107.5, 114.0, 116.5, 121.4, 125.3, 128.3, 128.9, 131.7, 132.8, 134.7, 146.7, 147.5, 150.1, 150.9, 155.4, 161.9. IR (KBr): ν 3460, 3408, 1687, 1592, 1556, 1506, 1467, 1450, 1438, 1409, 1377, 1335, 1250, 1215, 1171, 1141, 1094, 1070, 1002, 938, 856, 756 cm^{-1}. HRMS (ESI, *m/z*): Calcd for $C_{22}H_{17}ClN_5O_3$ $[M - H]^-$ 434.1025, found 434.1014.

3-Amino-*N*'-(4,5-dimethoxy-2-((4-propylphenyl)ethynyl)benzylidene)pyrazine-2-carbohydrazide (3m): M.p. 193~194 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 0.96 (t, *J* = 7.2 Hz, 3H, CH_3), 1.66~1.70 (m, 2H, CH_2), 2.63 (t, *J* = 7.2 Hz, 2H, CH_2), 3.94 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 5.88 (brs., 2H, NH_2), 7.00 (s, 1H, ArH), 7.20~7.22 (m, 2H, ArH), 7.49~7.51 (m, 2H, ArH), 7.70 (s, 1H, ArH), 7.84 (d, *J* = 2.4 Hz, 1H, ArH), 8.21 (d, *J* = 2.4 Hz, 1H, ArH), 8.68 (s, 1H, CH), 10.82 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 13.8, 24.4, 38.0, 56.1, 56.3, 85.6, 94.1, 107.4, 114.0, 117.2, 120.0, 125.3, 128.0, 128.7, 131.5, 131.7, 143.7, 147.0, 147.4, 149.8, 150.9, 155.4, 161.8. IR (KBr): ν 3400, 3343, 3197, 1659, 1651, 1608, 1548, 1531, 1504, 1494, 1462, 1441, 1408, 1360, 1237, 1202, 1145, 1108, 1083, 949, 754, 688 cm^{-1}. HRMS (ESI, *m/z*): Calcd for $C_{25}H_{24}N_5O_3$ $[M - H]^-$ 442.1884, found 442.1889.

4.3 General procedure for the syntheses of 2-arylisoquinoline derivatives 4

3-Aminopyrazine-2-carbohydrazide (**1**, 77 mg, 0.5 mmol) 2-(arylethynyl) benzaldehydes **2** (0.5 mmol), iodine (13 mg, 0.05 mmol), and DMSO (5.0 mL) was added into a dry 25 mL flask. The reaction mixture was stirred at 100 °C for 4-10 h until all the **1** and intermediate product hydrazone were consumed which was monitored by TLC. The separation and purification of the products **4** were the same to

those of **3**. In the process of **4a**, the filtrate was extracted with ethyl acetate (30 mL × 3). The organic layer was combined and dried by anhydrous Na_2SO_4. The ethyl acetate was recovered by rotary evaporation, and the residue was purified by column chromatography using ethyl acetate and petroleum ether (2:1) as an eluant to give 3-amino-*N*-hydroxypyrazine-2-carboxamide (**8**) in 52% yield.

3-Phenylisoquinoline (4a): M.p. 104~105 °C (Lit.[20] 103~104 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.39~7.44 (m, 1H, ArH), 7.49~7.59 (m, 3H, ArH), 7.66~7.70 (m, 1H, ArH), 7.86 (d, J = 8.0 Hz, 1H, ArH), 7.98 (d, J = 8.4 Hz, 1H, ArH), 8.06 (s, 1H, ArH), 8.11~8.14 (m, 2H, ArH), 9.33 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 116.5, 126.9, 127.0, 127.1, 127.6, 127.8, 128.5, 128.8, 130.5, 136.7, 139.6, 151.3, 152.4. IR (KBr): ν 2912, 1625, 1585, 1562, 1515, 1489, 1332, 1279, 1196, 1139, 1131, 1035, 960, 944, 884, 742, 713, 680 cm^{-1}. HRMS (APCI, *m/z*): Calcd for $C_{15}H_{12}N$ $[M + H]^+$ 206.0964, found 206.0973.

3-Amino-*N*-hydroxypyrazine-2-carboxamide (**8**): M.p. 198-200 °C (Lit.[21] 196 °C), ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 7.42 (brs, 3H, NH_2 + OH), 7.76 (d, J = 2.4 Hz, 1H, ArH), 8.17 (d, J = 2.4 Hz, 1H, ArH), 9.43 (brs, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 126.3, 131.3, 146.8, 155.1, 163.6.

6-Chloro-3-phenylisoquinoline (4b): M.p. 143~144 °C (Lit.[22] 140~141 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.41~7.45 (m, 1H, ArH), 7.50~7.54 (m, 3H, ArH), 7.84(d, J = 2.0 Hz, 1H, ArH), 7.92(d, J = 8.8 Hz, 1H, ArH), 7.96 (s, 1H, ArH), 8.09~8.12 (m, 2H, ArH), 9.30 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 115.5, 125.7, 125.9, 127.1, 128.1, 128.9, 129.2, 136.8, 137.4, 139.1, 152.2, 152.4. IR (KBr): ν 3058, 2924, 1597, 1563, 1479, 1451, 1383, 1271, 1071, 1020, 966, 944, 896, 817,

760, 690, 677 cm^{-1}. HRMS (APCI, *m/z*): Calcd for $C_{15}H_{11}ClN$ $[M + H]^+$ 240.0575, found 240.0585.

6-Fluoro-3-phenylisoquinoline (4c): M.p. 110~111 °C (Lit.[23] 108~110 °C); ^1H NMR ($CDCl_3$, 400 MHz): δ_H 7.31~7.36 (m, 1H, ArH), 7.41~7.53 (m, 4H, ArH), 7.97~8.01 (m, 2H, ArH), 8.09~8.12 (m, 2H, ArH), 9.30 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 110.2 (d, $J_{(F-C)}$ = 20.8 Hz), 116.0 (d, $J_{(F-C)}$ = 5.4 Hz), 117.6 (d, $J_{(F-C)}$ = 25.6 Hz), 124.9, 127.1, 128.8, 128.9, 130.6(d, $J_{(F-C)}$ = 9.9 Hz), 138.1 (d, $J_{(F-C)}$ = 10.5 Hz), 139.2, 152.06, 152.14, 163.4 (d, $J_{(F-C)}$ = 250.8 Hz). IR (KBr): ν 3049, 3030, 1625, 1162, 1585, 1562, 1515, 1488, 1372, 1332, 1279, 1212, 1184, 1139, 1131, 1111, 1035, 1015, 960, 944, 884, 742, 713 cm^{-1}. HRMS (APCI, *m/z*): Calcd for $C_{15}H_{11}FN$ $[M + H]^+$ 224.0870, found 224.0886.

7-Chloro-3-phenylisoquinoline (4d): M.p. 106~107 °C (Lit.[22] 108~110 °C); ^1H NMR ($CDCl_3$, 400 MHz): δ_H 7.44~7.47 (m, 1H, ArH), 7.52~7.56 (m, 2H, ArH), 7.65 (dd, *J* = 8.8 Hz, *J'* = 1.6 Hz, 1H, ArH), 7.84 (d, *J* = 8.8 Hz, 1H, ArH), 7.99 (s, 1H, ArH), 8.07 (s, 1H, ArH), 8.13~8.15 (m, 2H, ArH), 9.29 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 116.1, 126.3, 127.0, 128.1, 128.6, 128.8, 128.9, 131.6, 132.5, 134.9, 139.2, 151.4, 151.7. IR (KBr): ν 3057, 3028, 1583, 1569, 1497, 1448, 1348, 1274, 1212, 1078, 947, 921, 882, 814, 782, 761, 689 cm^{-1}. HRMS (APCI, *m/z*): Calcd for $C_{15}H_{11}ClN$ $[M + H]^+$ 240.0575, found 240.0585.

7-Fluoro-3-phenylisoquinoline (4e): M.p. 108~109 °C (Lit.[24] 136~138 °C); ^1H NMR ($CDCl_3$, 400 MHz): δ_H 7.40~7.44 (m, 1H, ArH), 7.45~7.53 (m, 3H, ArH), 7.59 (dd, *J* = 8.8 Hz, *J'* = 2.4 Hz, 1H, ArH), 7.88 (dd, *J* = 9.2 Hz, *J'* = 5.2 Hz, 1H, ArH), 8.05 (s, 1H, ArH), 8.09~8.12 (m, 2H, ArH), 9.29 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 110.6 (d, $J_{(F-C)}$ = 20.5 Hz), 116.3 (d, $J_{(F-C)}$ = 1.5 Hz), 121.2 (d, $J_{(F-C)}$ = 25.5

Hz), 126.9, 128.2 (d, $J_{(F-C)}$ = 8.3 Hz), 128.6, 128.8, 129.6 (d, $J_{(F-C)}$ = 8.4 Hz), 133.7 (d, $J_{(F-C)}$ = 0.5 Hz), 139.3, 151.0 (d, $J_{(F-C)}$ = 2.8 Hz), 151.6 (d, $J_{(F-C)}$ = 5.5 Hz), 160.8 (d, $J_{(F-C)}$ = 247.8 Hz). IR (KBr): ν 3056, 3045, 1574, 1500, 1492, 1452, 1389, 1358, 1280, 1223, 1181, 1138, 1020, 966, 909, 859, 814, 780, 767, 690 cm^{-1}. HRMS (APCI, *m/z*): Calcd for $C_{15}H_{11}FN$ $[M + H]^+$ 224.0870, found 224.0888.

7-Nitro-3-phenylisoquinoline (4f): M.p. 106~107 °C (Lit.[23] 105~107 °C); ^1H NMR ($CDCl_3$, 400 MHz): δ_H 7.46~7.56 (m, 3H, ArH), 8.01 (d, *J* = 8.8 Hz, 1H, ArH), 8.16~8.18 (m, 3H, ArH), 8.45 (dd, *J* = 8.8 Hz, *J'* = 2.0 Hz, 1H, ArH), 8.95 (d, *J* = 2.0 Hz, 1H, ArH), 9.52 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 116.4, 126.9, 127.3, 127.6, 127.8, 128.2, 128.9, 130.7, 134.6, 136.6, 138.0, 150.0, 152.5. IR (KBr): ν 3085, 2919, 1628, 1589, 1519, 1484, 1444, 1400, 1343, 1275, 1214, 1085, 959, 924, 830, 822, 789, 786, 765, 691 cm^{-1}. HRMS (APCI, *m/z*): Calcd for $C_{15}H_{11}N_2O_2$ $[M + H]^+$ 251.0815, found 251.0822.

7-Methoxy-3-phenylisoquinoline (4g): M.p. 164~165 °C (Lit.[25] 158~159 °C); ^1H NMR ($CDCl_3$, 400 MHz): δ_H 3.96 (s, 3H, OCH_3), 7.24~7.26 (m, 1H, ArH), 7.35 (dd, *J* = 8.8 Hz, *J'* = 2.8 Hz, 1H, ArH), 7.37~7.42 (m, 1H, ArH), 7.48~7.52 (m, 2H, ArH), 7.77 (d, *J* = 8.8 Hz, 1H, ArH), 8.00 (s, 1H, ArH), 8.09~8.11 (m, 2H, ArH), 9.24 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 55.5, 104.7, 116.4, 123.8, 126.7, 128.2, 128.5, 128.8, 128.9, 132.3, 139.7, 149.7, 150.9, 158.4. IR (KBr): ν 2997, 2967, 1622, 1590, 1492, 1410, 1388, 1359, 1269, 1235, 1202, 1159, 1025, 957, 910, 880, 846, 826, 797, 695 cm^{-1}. HRMS (APCI, *m/z*): Calcd for $C_{16}H_{14}NO$ $[M + H]^+$ 236.1070, found 236.1074.

8-Fluoro-3-phenylisoquinoline (4h): M.p. 99~100 °C (Lit.[26] 99~100 °C); ^1H NMR ($CDCl_3$, 400 MHz): δ_H 7.45~7.49 (m, 2H, ArH), 7.57~7.61 (m, 1H, ArH),

7.68~7.72 (m, 1H, ArH), 7.86 (d, *J* = 8.4 Hz, 1H, ArH), 7.98 (d, *J* = 8.4 Hz, 1H, ArH), 8.03 (s, 1H, ArH), 8.05~8.08 (m, 2H, ArH), 9.31 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 110.8 (d, $J_{(F-C)}$ = 19.0 Hz), 115.8 (d, $J_{(F-C)}$ = 2.9 Hz), 118.1 (d, $J_{(F-C)}$ = 15.5 Hz), 122.8 (d, $J_{(F-C)}$ = 4.3 Hz), 127.1, 128.8, 130.8 (d, $J_{(F-C)}$ = 8.5 Hz), 138.1 (d, $J_{(F-C)}$ = 3.6 Hz), 139.2, 146.2 (d, $J_{(F-C)}$ = 4.6 Hz), 152.3 (d, $J_{(F-C)}$ = 0.9 Hz), 159.3 (d, $J_{(F-C)}$ = 254.7 Hz). IR (KBr): ν 3057, 2954, 2924, 1625, 1561, 1492, 1458, 1438, 1402, 1329, 1277, 1216, 1200, 1141, 1090, 1010, 961, 942, 886, 833, 750, 738, 714, 655 cm^{-1}. HRMS (APCI, *m/z*): Calcd for $C_{15}H_{11}FN$ $[M + H]^+$ 224.0870, found 224.0885.

6,7-Dimethoxy-3-phenylisoquinoline (4i): M.p. 127~128 °C (Lit.[24] 129~131 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.04 (s, 6H, $2OCH_3$), 7.12 (s, 1H, ArH), 7.22 (s, 1H, ArH), 7.38~7.41 (m, 1H, ArH), 7.47~7.51 (m, 2H, ArH), 7.93 (s, 1H, ArH), 8.07~8.09 (m, 2H, ArH), 9.12 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 56.08, 56.11, 105.0, 105.3, 115.5, 123.8, 126.8, 128.2, 128.7, 133.3, 133.9, 149.8, 150.28, 150.30, 153.2. IR (KBr): ν 2995, 1621, 1594, 1577, 1505, 1477, 1363, 1270, 1241, 1148, 1024, 1005, 834, 845, 752, 689, 652 cm^{-1}. HRMS (APCI, *m/z*): Calcd for $C_{17}H_{16}NO_2$ $[M + H]^+$ 266.1176, found 266.1167.

7-Phenyl-[1,3]dioxolo[4,5-*g*]isoquinoline (4j): M.p. 135~136 °C (Lit.[24] 135~137 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.10 (s, 2H, OCH_2), 7.12 (s, 1H, ArH), 7.21 (s, 1H, ArH), 7.37~7.41 (m, 1H, ArH), 7.47~7.51 (m, 2H, ArH), 7.90 (s, 1H, ArH), 8.06~8.08 (m, 2H, ArH), 9.06 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 101.6, 102.8, 103.1, 116.3, 125.0, 126.8, 128.3, 128.7, 135.1, 139.7, 148.3, 150.2, 150.6, 151.1. IR (KBr): ν 2955, 2900, 1600, 1483, 1459, 1441, 1262, 1233, 1159, 1088, 1048, 963, 921, 885, 851, 778, 755, 705 cm^{-1}. HRMS (APCI, *m/z*): Calcd for $C_{16}H_{12}NO_2$ $[M + H]^+$ 250.0863, found 250.0878.

6-Phenylthieno[3,2-*c*]pyridine (4k): M.p. 73~74°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.39~7.43 (m, 2H, ArH), 7.48~7.51 (m, 2H, ArH), 7.72 (d, J = 5.2 Hz, 1H, ArH), 8.04~8.07 (m, 2H, ArH), 8.12 (d, J = 0.8 Hz, 1H, ArH), 9.22 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 114.5, 123.3, 127.0, 128.5, 128.8, 132.4, 135.1, 139.7, 144.3, 146.0, 151.9. IR (KBr): ν 3080, 3052, 1585, 1532, 1476, 1435, 1393, 1296, 1238, 1188, 1178, 1074, 1033, 1016, 898, 869, 760, 689, 645 cm^{-1}. HRMS (APCI, *m/z*): Calcd for $C_{13}H_{10}NS$ $[M + H]^+$ 212.0528, found 212.0548.

3-(3-Chlorophenyl)isoquinoline (4l): M.p. 103~104 °C (Lit.[22] 99~100 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.37~7.45 (m, 2H, ArH), 7.59~7.63 (m, 1H, ArH), 7.69~7.73 (m, 1H, ArH), 7.88 (d, J = 8.0 Hz, 1H, ArH), 7.99~8.01 (m, 2H, ArH), 8.05 (s, 1H, ArH), 8.14~8.15 (m, 1H, ArH), 9.33 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 116.8, 125.0, 127.0, 127.1, 127.4, 127.6, 128.0, 128.5, 130.0, 130.7, 134.9, 136.5, 141.4, 149.7, 152.5. IR (KBr): ν 2955, 2923, 1589, 1564, 1490, 1485, 1472, 1443, 1410, 1386, 1323, 1281, 1214, 1202, 1141, 1091, 1079, 1038, 996, 961, 798, 748, 696, 673 cm^{-1}. HRMS (APCI, *m/z*): Calcd for $C_{15}H_{11}ClN$ $[M + H]^+$ 240.0575, found 240.0578.

3-(4-Chlorophenyl)isoquinoline (4m): M.p. 141~143 °C (Lit.[22] 140~142); ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.18~7.22 (m, 1H, ArH), 7.41~7.46 (m, 1H, ArH), 7.50~7.54 (m, 2H, ArH), 7.59~7.66 (m, 2H, ArH), 8.06 (s, 1H, ArH), 8.11~8.14 (m, 2H, ArH), 9.61 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 116.4, 126.9, 127.3, 127.6, 127.8, 128.2, 128.9, 130.7, 134.6, 136.6, 138.0, 150.1, 152.5. IR (KBr): ν 2955, 2924, 1564, 1484, 1443, 1410, 1339, 1323, 1281, 1213, 1202, 1141, 1091, 1079, 1037, 1015, 961, 943, 898, 877, 854, 798, 748, 696, 673 cm^{-1}. HRMS (APCI, *m/z*): Calcd for $C_{15}H_{11}ClN$ $[M + H]^+$ 240.0575, found 240.0595.

3-(*p*-Tolyl)isoquinoline (4n): M.p. 97~98 °C (Lit.[22] 94~96 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 2.42 (s, 3H, CH_3), 7.30~7.32 (m, 2H, ArH), 7.53~7.57 (m, 1H, ArH), 7.65~7.69 (m, 1H, ArH), 7.84 (d, J = 8.4 Hz, 1H, ArH), 7.96 (dd, J = 8.0 Hz, J' = 0.4 Hz, 1H, ArH), 8.01~8.04 (m, 3H, ArH), 9.32 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 21.3, 116.0, 126.8, 127.5, 127.6, 129.5, 130.4, 136.7, 136.8, 138.4, 151.3, 152.3. IR (KBr): ν 3061, 1636, 1591, 1574, 1450, 1434, 1351, 1280, 1256, 1218, 1194, 1083, 1049, 1030, 905, 894, 866, 795, 778, 689, 677 cm^{-1}. HRMS (APCI, *m/z*): Calcd for $C_{16}H_{14}N$ $[M + H]^+$ 220.1121, found 220.1131.

3-(4-Ethylphenyl)isoquinoline (4o): M.p. 89~90 °C (Lit.[27] 85~87 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 1.29 (t, J = 7.6 Hz, 3H, CH_3), 2.72 (q, J = 7.6 Hz, 2H, OCH_2), 7.33~7.35 (m, 2H, ArH), 7.53~7.57 (m, 1H, ArH), 7.65~7.68 (m, 1H, ArH), 7.84 (d, J = 8.0 Hz, 1H, ArH), 7.96 (d, J = 8.4 Hz, 1H, ArH), 8.03~8.06 (m, 3H, ArH), 9.32 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 15.6, 28.7, 116.0, 126.9, 127.0, 127.6, 127.7, 128.3, 130.4, 136.7, 137.1, 144.8, 151.4, 152.3. IR (KBr): ν 2961, 2927, 1743, 1623, 1611, 1584, 1510, 1485, 1445, 1436, 1279, 1186, 1141, 1016, 965, 941, 888, 759 cm^{-1}. HRMS (APCI, *m/z*): Calcd for $C_{17}H_{16}N$ $[M + H]^+$ 234.1277, found 234.1290.

3-(4-*n*-Propylphenyl)isoquinoline (4p): M.p. 68~69 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 0.98 (t, J = 7.2 Hz, 3H, CH_3), 1.66~1.75 (m, 2H, CH_2), 2.66 (t, J = 7.2 Hz, 2H, CH_2), 7.31~7.33 (m, 2H, ArH), 7.54~7.58 (m, 1H, ArH), 7.66~7.70 (m, 1H, ArH), 7.86 (d, J = 8.0 Hz, 1H, ArH), 7.98 (d, J = 8.0 Hz, 1H, ArH), 8.03~8.05 (m, 3H, ArH), 9.32 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 13.9, 24.5, 37.8, 116.1, 126.9, 127.57, 127.64, 129.0, 130.5, 136.7, 137.0, 143.3, 151.4, 152.3. IR (KBr): ν 3000, 2955, 1742, 1624, 1588, 1565, 1511, 1488, 1447, 1438, 1376, 1329, 1280, 1208,

1195, 1142, 1133, 1017, 962, 941, 887, 839, 806, 748, 683 cm^{-1}. HRMS (APCI, *m/z*): Calcd for $C_{18}H_{18}N$ $[M + H]^+$ 248.1434, found 248.1442.

3-(4-Methoxyphenyl)isoquinoline (4q): M.p. 105~106 °C (Lit.[25] 102~103 °C); ^1H NMR ($CDCl_3$, 400 MHz): δ_H 3.88 (s, 3H, OCH_3), 7.03~7.05 (m, 2H, ArH), 7.53~7.56 (m, 1H, ArH), 7.65~7.68 (m, 1H, ArH), 7.83 (d, J = 8.4 Hz, 1H, ArH), 7.95~7.98 (m, 2H, ArH), 8.07~8.09 (m, 2H, ArH), 9.30 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 55.4, 114.2, 115.4, 126.7, 126.8, 127.4, 127.6, 128.2, 130.5, 132.3, 136.8, 151.1, 152.3, 160.1. IR (KBr): ν 3059, 2963, 1740, 1625, 1514, 1491, 1455, 1442, 1345, 1282, 1271, 1196, 1174, 1111, 1039, 1024, 961, 943, 881, 830, 818, 747, 725, 679 cm^{-1}. HRMS (APCI, *m/z*): Calcd for $C_{16}H_{14}NO$ $[M + H]^+$ 236.1070, found 236.1068.

4.4 General procedure for the syntheses of ylide 6

3-Aminopyrazine-2-carbohydrazide (**1**, 77 mg, 0.5 mmol) 4-fluoro-2-(phenyl ethynyl)benzaldehyde (**2c**, 112 mg, 0.5 mmol), iodine (13 mg, 0.05 mmol), and DMSO (5.0 mL) was added into a dry 25 mL flask. The reaction mixture was stirred at 100 °C for 3 h. The cooled mixture was poured into 100 mL water which was extracted with ethyl acetate (50 mL × 3). The organic layer was combined and dried by anhydrous Na_2SO_4. The ethyl acetate was recovered by rotary evaporation, and the residue was purified by column chromatography using ethyl acetate and petroleum ether (1:1) as an eluant to give **4c**, **6** in 48% and 32% yields, respectively.

(3-Aminopyrazine-2-carbonyl)(6-fluoro-3-phenylisoquinolin-2-ium-2-yl)amide (**6**): M.p. 245~246 °C; ^1H NMR (DMSO-d_6, 400 MHz): δ_H 7.15 (s, 2H, NH_2), 7.44~7.46 (m, 3H, ArH), 7.64~7.71 (m, 3H, ArH), 7.91 (s, 2H, ArH), 8.10 (d, J = 9.2 Hz, 1H, ArH), 8.50~8.54 (m, 2H, ArH), 9.87 (s, 1H, ArH). ^{13}C NMR (DMSO-d_6, 100

MHz): δ_C 111.5 (d, $J_{(F-C)}$ = 22.0 Hz), 121.5 (d, $J_{(F-C)}$ = 27.1 Hz), 125.0, 126.1 (d, $J_{(F-C)}$ = 5.3 Hz), 128.6, 129.1, 129.8, 130.3, 131.5, 132.0, 133.1 (d, $J_{(F-C)}$ = 9.8 Hz), 137.7 (d, $J_{(F-C)}$ = 9.5 Hz), 146.6, 148.8, 155.3, 165.4 (d, $J_{(F-C)}$ = 253.8 Hz), 167.4, 169.7. HRMS (APCI, *m/z*): Calcd for $C_{20}H_{15}FN_5O$ $[M + H]^+$ 360.1255, found 360.1248.

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