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# Diversity-Oriented Synthesis of Substituted Furo[2,3-*b*]pyrazines

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A highly efficient method for the synthesis of diversely substituted furo[2,3-*b*]pyrazines has been elaborated. The $Ag^+$- or iodine-mediated electrophilic cyclization of readily generated 5-chloro-3-substituted ethynyl-1-(4-methoxybenzyl)-pyrazin-2(1*H*)-ones affords substituted furo[2,3-*b*]pyrazines, which undergo various palladium catalyzed reactions to generate a library of difficult to attain diversely substituted furo[2,3-*b*]pyrazines.

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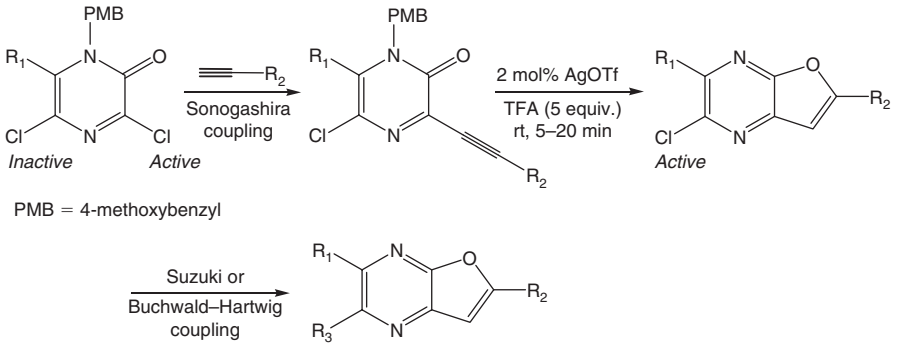
## Introduction

The construction of the furan ring, which is found in many natural and biologically important compounds,[1–3] is attracting considerable attention.[4] Heteroannulation processes for the synthesis of ring-fused furans have been described by the palladium-catalyzed annulation of alkynes.[5,6] Electrophilic cyclization of unsaturated compounds has been proven to be an efficient method for the one-step construction of substituted furans.[7–10] Different methods have been explored for the electrophilic halocyclization of α-alkynyl carbonyl compounds.[7,11] Several syntheses of fused furan moieties like benzo[*b*]furans,[12] furopyridines,[13] and furopyrimidines[14] are reported. The synthesis of furo[2,3-*b*]pyrazines[15] is described by the cyclization of chloroketones.[16] However this method is restricted to the synthesis of 2- or 2,3-disubstituted furo[2,3-*b*]pyrazines. Being oxo-analogues of aloisines, which are known to be selective kinase inhibitors for CDK 1/2/3 and GSK-3 α/β,[17] we were keen to explore the synthesis of diversely substituted furo[2,3-*b*]pyrazines. We have previously elaborated a novel cyclization protocol for the synthesis of furo[2,3-*b*]pyrazines starting from 1-(4-methoxybenzyl)-3,5-dichloropyrazine-2(1*H*)-ones by a $Ag^+$-catalyzed cyclization with concomitant cleavage of the 4-methoxybenzyl (PMB) protecting group (Scheme 1).[18] We now wish to describe a novel approach for the synthesis of this interesting framework by an iodocyclization[19] reaction. We will also comment on the subsequent palladium-catalyzed cross-coupling reactions for the decoration of both generated scaffolds to yield densely substituted furo[2,3-*b*]pyrazines.

## Results and Discussion

Analogously to our previously developed route[18] our sequence starts with a regioselective Sonogashira cross-coupling reaction at the reactive 3-position of the 3,5-dichloropyrazin-2(1*H*)-one **1**[20] to generate the 5-chloro-3-substituted ethynyl-1-(4-methoxybenzyl)-pyrazin-2(1*H*)-ones **3** (Scheme 2 and Table 1).[21] These substrates were further evaluated for the cyclization to 2-chloro or 2-chloro-7-iodo substituted




**Scheme 1.** Synthesis of tri-substituted furo[2,3-*b*]pyrazine.

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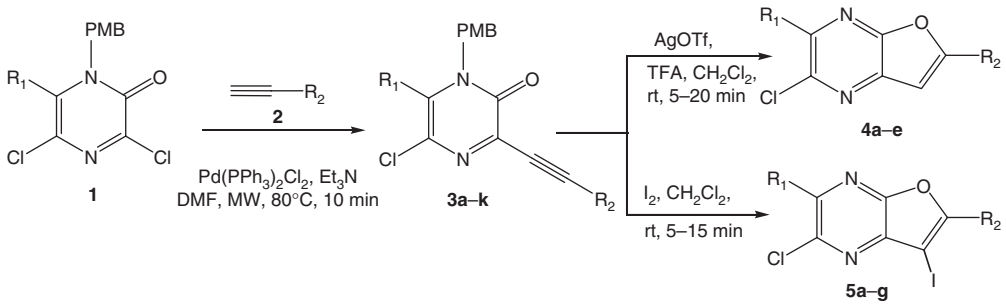
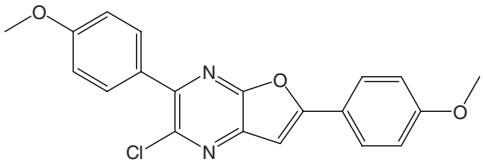
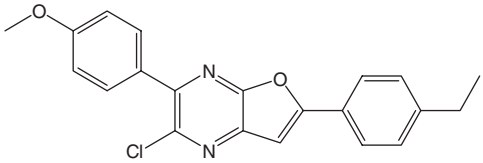
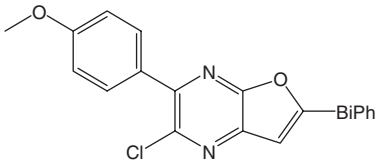
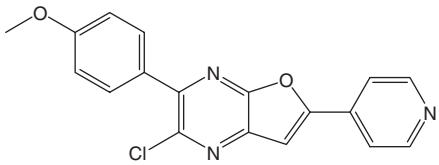
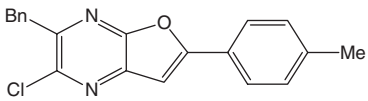
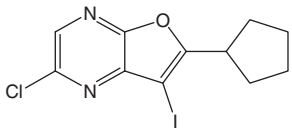
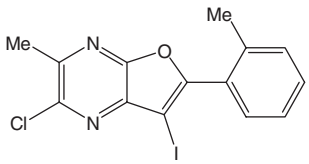


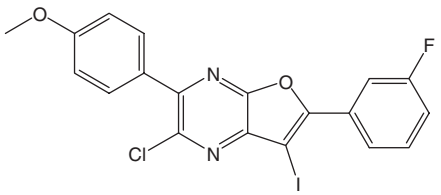
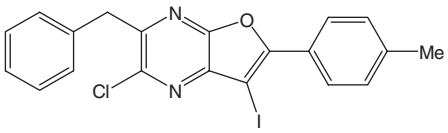
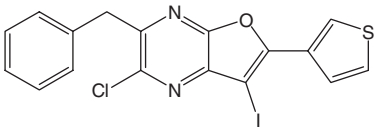
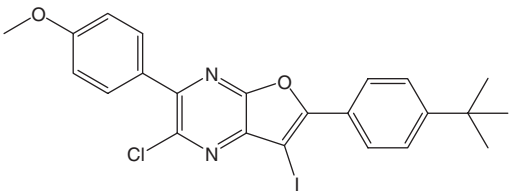
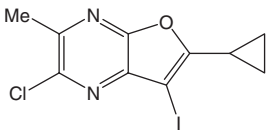

**Scheme 2.** $Ag^{+}$- or $I_2$-mediated cyclization to generate 2-chloro and 2-chloro-7-iodo substituted furo[2,3-*b*]pyrazines. MW, microwave.

**Table 1. Synthesis of substituted 2-chloro and 2-chloro-7-iodo furo[2,3-*b*]pyrazines[A]**

| Entry | **4** or **5** | Product | Cyclization time [min][B] | Yield of **3** [%][C] | Yield of **4** [%][C] | Yield of **5** [%][C] |
|---|---|---|---|---|---|---|
| 1 | **4a** |  | 5 | 99 | 96 | – |
| 2 | **4b** |  | 5 | 92 | 92 | – |
| 3 | **4c** |  | 20 | 83 | 91 | – |
| 4 | **4d** |  | 20 | 85 | 79 | – |
| 5 | **4e** |  | 5 | 99 | 91 | – |
| 6 | **5a** |  | 5 | 82 | – | 76 |
| 7 | **5b** |  | 7 | 94 | – | 86 |

(*Continued*)

**Table 1. (Continued)**

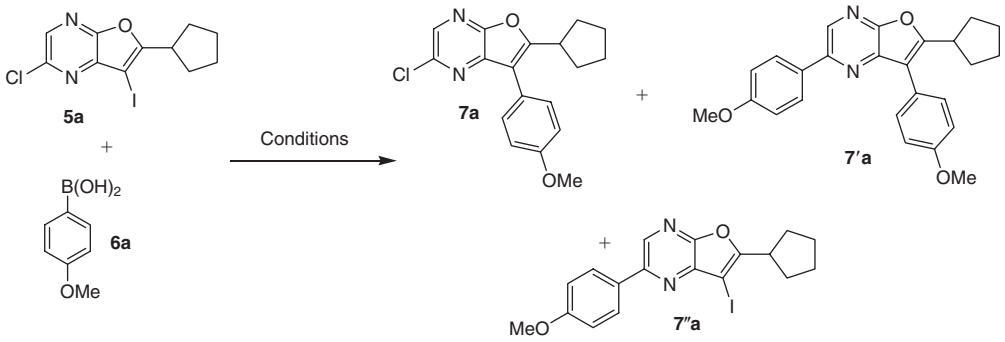
| Entry | **4** or **5** | Product | Cyclization time [min][B] | Yield of **3** [%][C] | Yield of **4** [%][C] | Yield of **5** [%][C] |
|---|---|---|---|---|---|---|
| 8 | **5c** |  | 10 | 99 | – | 88 |
| 9 | **5d** |  | 5 | 99 | – | 91 |
| 10 | **5e** |  | 10 | 88 | – | 96 |
| 11 | **5f** |  | 6 | 96 | – | 96 |
| 11 | **5g** |  | 10 | 84 | – | 68 |

[A]The Sonogashira cross-coupling reaction was run on a 5 mmol scale, using acetylene (1.20 equiv.), $Pd(PPh_3)_2Cl_2$ (1 mol%), and CuI (3 mol%) in DMF/$Et_3N$ (1:1, 20 mL) under microwave irradiation at a maximum power of 80 W and 80°C ceiling temperature for 10 min. Cyclization reactions was run on a 2 mmol scale, using AgOTf (2 mol%), TFA (5.0 equiv.) in DCM (12 mL) at room temperature for the stipulated time. The iodocyclization was run on 2 mmol scale using $I_2$ (2.0 equiv.) in DCM (12 mL) at room temperature for the stipulated time.
[B]Cyclization time as determined by TLC.
[C]Isolated yields (single runs).

furo[2,3-*b*]pyrazines **4** and **5** using $Ag^+$ or $I_2$ respectively. Applying 2 mol% AgOTf in 20% TFA/$CH_2Cl_2$ resulted in smooth formation of the desired compounds **4a**–**e** in 5–20 min at room temperature. For the iodocyclization, compounds **3e**–**k** were reacted with 2.0 equiv. of $I_2$ in dichloromethane to afford the requested compounds **5a**–**g** in 5–15 min at room temperature. These mild and selective procedures provide mono- and di-halo-substituted furo[2,3-*b*]pyrazines, which are susceptible to various transition-metal catalyzed coupling reactions for the decoration of the scaffold (Scheme 2 and Table 1).[18]

We were keen to know whether it should be possible to perform a regioselective Suzuki–Miyaura cross-coupling on the 7-position of the dihalogenated substrates **5**, as a higher reactivity at the site of the iodine could be expected. As a proof of concept the reaction of 2-chloro-6-cyclopentyl-7-iodofuro[2,3-*b*]pyrazine **5a** with *p*-MeO-phenylboronic acid **6a** was investigated applying microwave irradiation (Scheme 3, Table 2, entry 1).[22] The reaction proceeded to full conversion in a mere 20 min to afford the mono-substituted compounds **7a** and **7″a** as well as the di-substituted compound **7′a**. Several attempts were made to obtain regioselective arylation of the 7-position (Table 2). Finally the best conditions for mono arylation were found to be 1.25 equiv. of boronic acid, 1 mol% of $Pd(PPh_3)_4$, 2.0 equiv. of $K_2CO_3$ in 4 mL of *N*,*N*-dimethylformamide (DMF) at a ceiling temperature of 120°C using 200 W maximum power during 20 min, which afforded the required compound **7a** in 91% isolated yield with only trace amounts of **7′a** and **7″a** (Table 2, entry 4).

Having optimized the conditions, we reacted an array of differently substituted 2-chloro[18] and 2-chloro-7-iodo furo[2,3-*b*]pyrazines **4a**–**c**,**e** and **5a**–**g** with various boronic acids **6a**–**l** that bear electron withdrawing or electron donating groups (Scheme 4, Table 3). The corresponding arylated products **7b**–**j** and **8a**–**d** were obtained in excellent yields regardless of the bulkiness of the $R_1$ and $R_2$-substitutents of the boronic acid. Even when 4-cyano-phenylboronic acid was used the corresponding arylated product was obtained in an excellent 91% yield after 45 min of microwave irradiation (Table 3, entry 9).

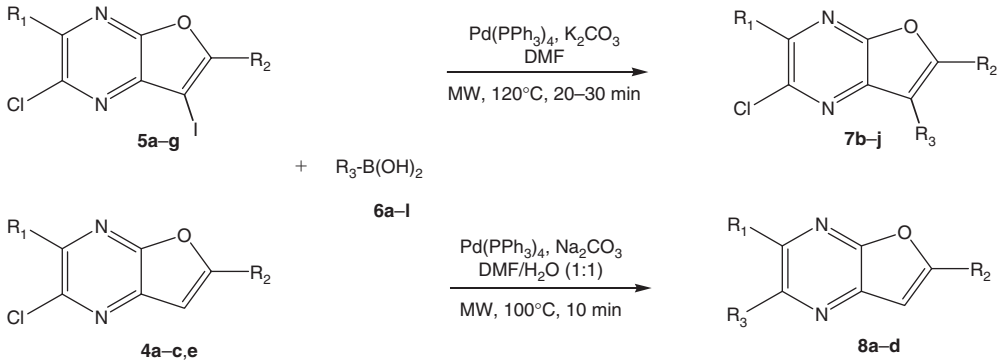



**Scheme 3.** Optimization of the conditions for the regioselective Suzuki–Miyaura cross-coupling reaction.

**Table 2. Optimization of the conditions for the regioselective Suzuki–Miyaura cross-coupling reaction[A]**

| Entry | Boronic acid equiv. | Base (equiv.) | Solvent | Temp. [°C] | Time [min] | Ratio [%] of **7a**/**7′a**/**7″a**/**5a**[B] |
|---|---|---|---|---|---|---|
| 1 | 1.25 | $Na_2CO_3$ (2.0) | DMF:$H_2O$ (1:1) | 100 | 20 | 70:21:8:0 |
| 2 | 1.05 | $Na_2CO_3$ (2.0) | DMF:$H_2O$ (1:1) | 90 | 20 | 60:15:0:15 |
| 3 | 1.25 | $K_2CO_3$ (2.0) | Dioxan:$H_2O$ (1:1) | 110 | 20 | 74:20:0:0 |
| 4 | 1.25 | $K_2CO_3$ (2.0) | DMF | 120 | 10 | 95[C]:4:0:0 |
| 5 | 1.25 | $K_2CO_3$ (2.0) | DMF | 110 | 10 | 85:5:0:10 |

[A]The Suzuki–Miyaura cross-coupling reaction was run on a 0.3 mmol scale of **5a**, using boronic acid **6a** (1.05–1.25 equiv.), $Pd(PPh_3)_4$ (1 mol%), and base (2.0 equiv.) in the indicated solvent (4 mL) under microwave irradiation at a maximum power of 200 W and stipulated temperature for the indicated time.
[B]Ratios were determined by GC-MS analysis.
[C]The isolated yield was 91% (single run).




**Scheme 4.** Microwave (MW)-assisted Suzuki–Miyaura cross-coupling of compounds **4** and **5**.

The structure of compound **8d** was unambiguously assigned by X-ray analysis (Fig. 1).[23]

Having successfully established the protocol for the Suzuki–Miyaura cross-coupling, we were next interested in checking whether Sonogashira cross-coupling[24] could be performed on substrates **4** and **5**. Substrate **4a** was reacted with acetylene (1.3 equiv.) in the presence of tetrabutylammonium iodide (TBAI) (1.2 equiv.) as additive, $Pd(PPh_3)Cl_2$ (5 mol%) and CuI (10 mol%) as catalytic system in DMF/triethylamine (TEA) (1:1, 4 mL) under microwave irradiation at 80 W maximum power and 100°C ceiling temperature for 15 min.[25] Gratifyingly, we obtained the desired alkynylated product **9a** in an excellent yield of 85%. Remarkably, if no TBAI was added; only the starting material was recovered even after 1 h of microwave irradiation. Analogously compounds **9b**,**c** were synthesized in 92% and 96% yield (Table 4, entries 2 and 3). We then investigated whether it should be possible to perform a regioselective Sonogashira cross-coupling reaction on the 7-position of the dihalogenated substrates **5**. However, using the same conditions as for the substrates **4a**–**c**, the reaction turned out to be rather sluggish and resulted in the formation of a complex mixture of compounds. To our satisfaction we found that when TBAI was omitted from the reaction mixture, the conversion proceeded well when **5e** was reacted with 3-ethynylthiophene **2i** (1.05 equiv.) upon microwave irradiation for 7 min at a ceiling temperature of 95°C and a maximum power of 150 W. The monoalkynylated compound **10a** was obtained in 89% yield next to only traces of the dialkynylated product (4%) (Scheme 5, Table 4, entry 4). Similarly compounds **10b**,**c** were regioselectively synthesized applying this protocol (Scheme 5, Table 4, entries 5 and 6).

We then investigated whether the selectively generated 7-substituted 2-chloro furo[2,3-*b*]pyrazines **7** could be further

decorated at their 2-position (Scheme 6). Three different starting compounds **7b**,**d**,**e** were subjected to the optimized Suzuki–Miyaura and Sonogashira conditions for chloro substitution to result in the formation of the corresponding substituted furo[2,3-*b*]pyrazines in good to excellent yields (Table 5).

Finally, we have investigated the Suzuki cross-coupling to generate symmetrically substituted furo[2,3-*b*]pyrazines starting from the 2-chloro-,7-iodo-substituted compound **5g** (Scheme 7). A mixture of this compound together with a large excess of boronic acid **6o** (3.0 equiv.), $Pd(PPh_3)_4$ (5 mol%) and $K_2CO_3$ (5.0 equiv.) in DMF (4 mL) was irradiated for 25 min at 140°C ceiling temperature using 300 W maximum power. The desired disubstituted compound **12a** could be isolated in 93% yield.

## Conclusion

In conclusion we have developed a novel procedure for the generation of difficult to attain diversely substituted furo[2,3-*b*]pyrazines starting from 3,5-dichloropyrazin-2(1*H*)-ones pyrazinones protected with a *p*-methoxybenzylether at their N1 position. The key step of this sequence is a mild, one step $Ag^+$- or iodine-mediated electrophilic cyclization with concomitant cleavage of the protecting *p*-methoxybenzylether. The corresponding compounds were evaluated for selective palladium-catalyzed cross-coupling reactions. The chloro substituent, inactive in the pyrazinone, becomes sensitive to substitution in the generated pyrazines. We have also demonstrated that in the case of the generated 2-chloro,7-iodo furo[2,3-*b*]pyrazines, regioselective Suzuki–Miyaura and Sonogoshira cross-coupling reactions are possible at the 7-position. The application of microwave irradiation during the different steps of the sequence has been shown to be highly valuable for speeding up reactions.

## Experimental

### General Experimental Methods

$^1$H NMR spectra were recorded on a Bruker Avance 300 MHz instrument using $CDCl_3$ as solvent unless otherwise stated. The $^1$H and $^{13}$C chemical shifts are reported in parts per million relative to tetramethylsilane using the residual solvent signal as an internal reference. Mass spectra were recorded by using a Kratos MS50TC and a Kratos Mach III system. The ion source temperature was 150–250°C, as required. High-resolution electron impact (EI) mass spectra were performed with a resolution of 10000. The low-resolution spectra were obtained with a HP5989A MS instrument. For TLC, analytical TLC plates (Alugram SIL G/$UV_{254}$) and 70–230 mesh silica gel (E. M. Merck) were used.

### Microwave Irradiation Experiments

A multimode Milestone MicroSYNTH microwave reactor (Laboratory Microwave Systems) was used in the standard configuration as delivered, including proprietary software. All experiments were carried out in sealed microwave process vials (15, 50 mL). Temperature control was performed using both external infrared and internal fibre optic sensors. After completion of the reaction, the vial was cooled to 25°C with air jet cooling before opening.

### A Typical Procedure for the Preparation of 1-(4-Methoxybenzyl)-3,5-dichloropyrazin-2(1H)-ones **1a–d**

In a 1 L round-bottomed flask $NaHSO_3$ (26.1 g, 0.25 mol) was dissolved in 400 mL water and aldehyde was added dropwise under an argon atmosphere. After stirring for 45 min, a solution of 4-methoxybenzylamine (32 mL, 0.25 mol) in methanol (100 mL) was added dropwise to the reaction mixture and stirring was continued for 2 h at 60°C. NaCN (14.7 g, 0.25 mol) was then added and the reaction mixture was left stirring overnight at 60°C (in a fumehood!). The reaction mixture was cooled to room temperature and extracted with dichloromethane (3 × 300 mL). The organic phases were combined, washed with brine (1 × 200 mL), and then dried for 2 h over $Na_2SO_4$ and concentrated. The residue was dissolved in dry ether (500 mL) and the resulting solution was cooled to 0°C. Dry HCl gas was bubbled through the solution upon vigorous stirring for 20 min and the precipitate was filtered off and dried. The precipitate was then suspended in a 1 L flask in dry toluene (400 mL) and oxalyl chloride (86 mL, 1 mol, 4.0 equiv.) was added dropwise under an argon atmosphere. After stirring for 45 min, triethylamine hydrochloride (52 g, 0.38 mol, 1.5 equiv.) was added in small portions, DMF (2 mL, 25 mmol, 0.1 equiv.) was added and the reaction mixture was kept stirring for 2 days. The reaction mixture was concentrated and the residue was purified by silica gel column chromatography (from 10% to 30% EtOAc in petroleum ether) to afford 3,5-dichloropyrazin-2(1*H*)-one **1** as a white solid.

#### 3,5-Dichloro-1-(4-methoxybenzyl)pyrazin-2(1H)-one (**1a**)

53% yield. $\delta_H$ (300 MHz, $CDCl_3$) 7.29 (d, *J* 7.2, 2H), 7.18 (s, 1H), 6.91 (d, *J* 7.2, 2H), 5.04 (s, 2H), 3.81 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 160. 4, 152.0, 147.4, 130.6, 126.1, 125.5, 124.2, 114.9, 55.5, 53.4. *m*/*z* (HR-MS EI) Found 285.0119. $C_{12}H_{10}Cl_2N_2O_2$ requires 285.0119.

#### 3,5-Dichloro-1-(4-methoxybenzyl)-6-methyl-pyrazin-2(1H)-one (**1b**)

51% yield. $\delta_H$ (400 MHz, $CDCl_3$) 7.16 (d, *J* 7.1, 2H), 6.86 (d, *J* 7.3, 2H), 5.29 (s, 2H), 3.79 (s, 3H), 2.44 (s, 3H). $\delta_C$ (100 MHz, $CDCl_3$) 159.6, 153.2, 143.7, 136.2, 128.7, 125.9, 123.9, 114.5, 55.4, 49.6, 16.8. DEPT (100 MHz, $CDCl_3$) 128.6, 114.5, 113.8, 55.3, −49.8, 16.9. *m*/*z* (HR-MS EI) Found 298.0279. $C_{13}H_{12}Cl_2N_2O_2$ requires 298.0276.

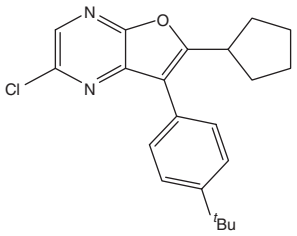
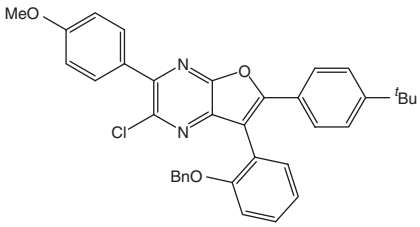
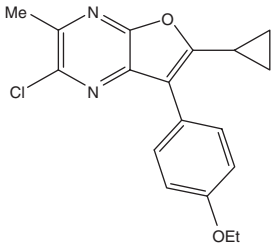
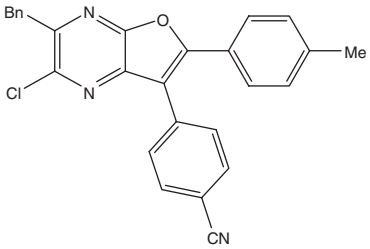
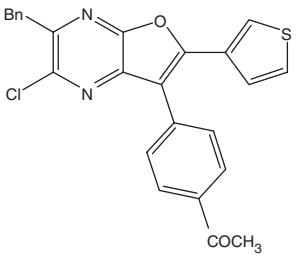
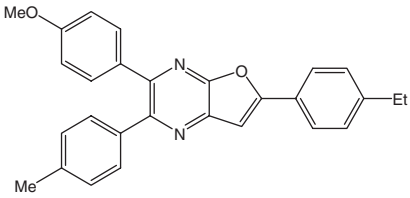
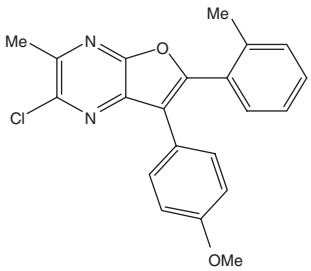
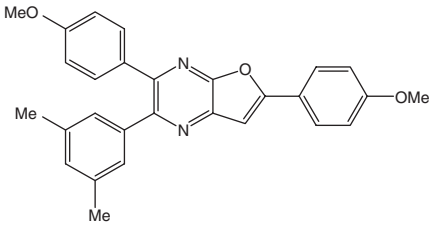
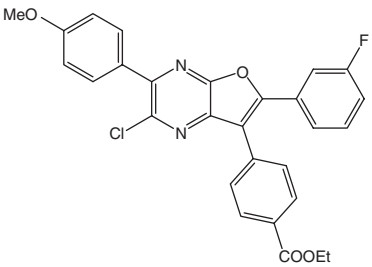
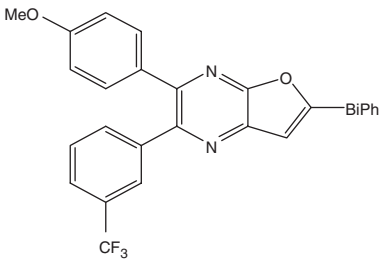
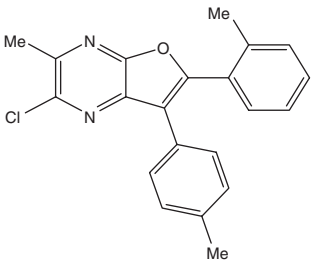
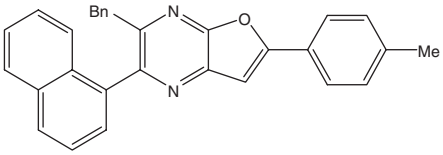
#### 6-Benzyl-3,5-dichloro-1-(4-methoxybenzyl)pyrazin-2(1H)-one (**1c**)

32% yield. $\delta_H$ (300 MHz, $CDCl_3$) 7.40–7.32 (m, 3H), 7.12–7.07 (m, 4H), 6.88 (d, *J* 9.6, 2H), 5.10 (s, 2H), 4.15 (s, 2H), 3.80 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 159.7, 153.4, 145.3, 137.4, 133.9, 129.6, 128.2, 127.9, 127.5, 126.3, 125.4, 114.7, 55.5, 49.3, 32.3. DEPT (75 MHz, $CDCl_3$) 129.9, 128.5, 128.2, 127.8, 115.0, 55.7, −49.6, −35.6. *m*/*z* (HR-MS EI) Found 250.0879. $C_{13}H_{15}ClN_2O$ requires 250.0873; Found 374.0596. $C_{19}H_{16}Cl_2N_2O_2$ requires 374.0589.

#### 3,5-Dichloro-1-(4-methoxybenzyl)-6-(4-methoxyphenyl)pyrazin-2(1H)-one (**1d**)

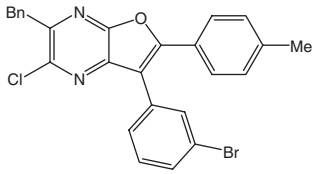
76% yield. $\delta_H$ (400 MHz, $CDCl_3$) 7.04 (d, *J* 7.2, 2H), 6.97 (d, *J* 7.3, 2H), 6.81 (d, *J* 7.2, 2H), 6.72 (d, *J* 7.1, 2H), 5.05 (s, 2H), 3.88 (s, 3H), 3.76 (s, 3H). $\delta_C$ (100 MHz, $CDCl_3$) 161.1, 159.5, 152.9, 145.8 138.6, 130.9, 129.4, 126.9, 124.7, 122.3, 114.5, 113.9, 55.5, 55.3, 50.8. DEPT (100 MHz, $CDCl_3$) 130.9, 129.4, 114.4, 113.8, 55.4, 55.3, −50.7. *m*/*z* (HR-MS EI) Found 390.0549. $C_{19}H_{16}Cl_2N_2O_3$ requires 390.0538.

**Table 3. Microwave-assisted Suzuki–Miyaura cross-coupling of compounds 4[A] and 5[B]**

| Entry | Compd | Product | Yield [%][C] | Entry | Compd | Product | Yield [%][C] |
|---|---|---|---|---|---|---|---|
| 1 | **7b** |  | 78 | 8 | **7i** |  | 89 |
| 2 | **7c** |  | 86 | 9 | **7j**[D] |  | 91 |
| 3 | **7d** |  | 87 | 10 | **8a** |  | 85 |
| 4 | **7e** |  | 89 | 11 | **8b** |  | 90 |
| 5 | **7f** |  | 78 | 12 | **8c** |  | 87 |
| 6 | **7g** |  | 90 | 13 | **8d** |  | 100 |

(*Continued*)

**Table 3. (Continued)**

| Entry | Compd | Product | Yield [%][C] | Entry | Compd | Product | Yield [%][C] |
|---|---|---|---|---|---|---|---|
| 7 | **7h** |  | 79 | | | | |

[A]Reaction conditions for **8a**–**d**: the Suzuki–Miyaura cross-coupling reaction was run on a 0.3 mmol scale of **4a**–**c**,**e**, using boronic acid (1.50 equiv.), $Pd(PPh_3)_4$ (1 mol%), and $Na_2CO_3$ (2.0 equiv.) in DMF/$H_2O$ (1:1, 4 mL), under microwave irradiation at a maximum power of 100 W and 100°C ceiling temperature for 10 min.
[B]Reaction conditions for **7b**–**j**: the Suzuki–Miyaura cross-coupling reaction was run on a 0.3 mmol scale of **5a**–**g**, using boronic acid (1.25 equiv.), $Pd(PPh_3)_4$ (1 mol%), and $K_2CO_3$ (2 equiv.) in DMF (4 mL) under microwave irradiation at a maximum power of 200 W and 120°C ceiling temperature and 20–30 min.
[C]Isolated yields (single runs).
[D]45 min of irradiation was needed.

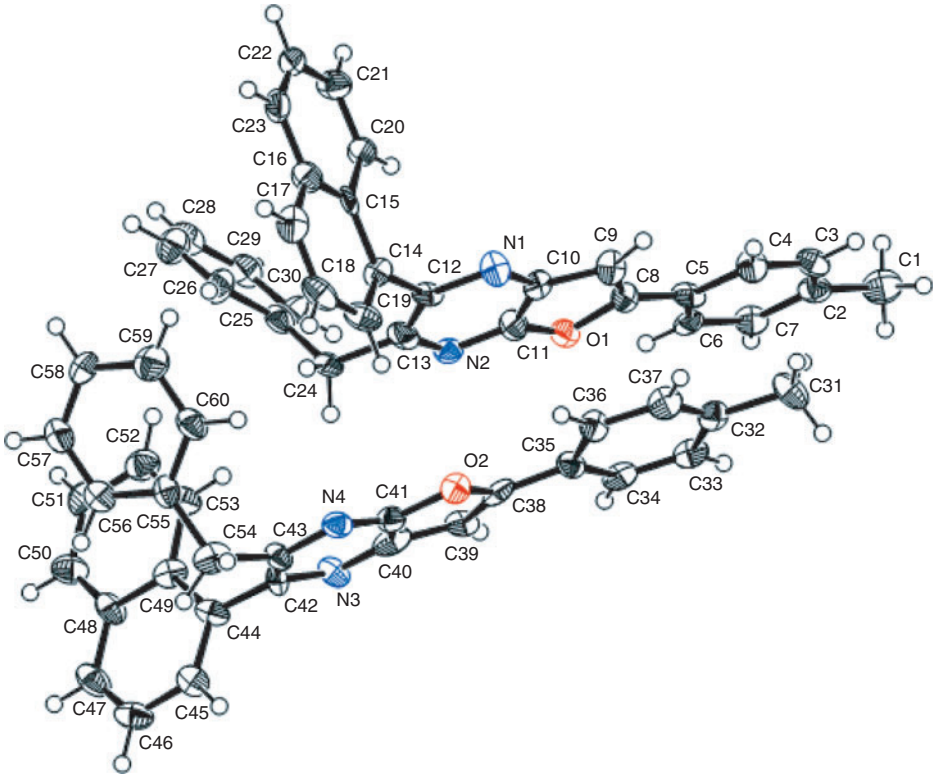


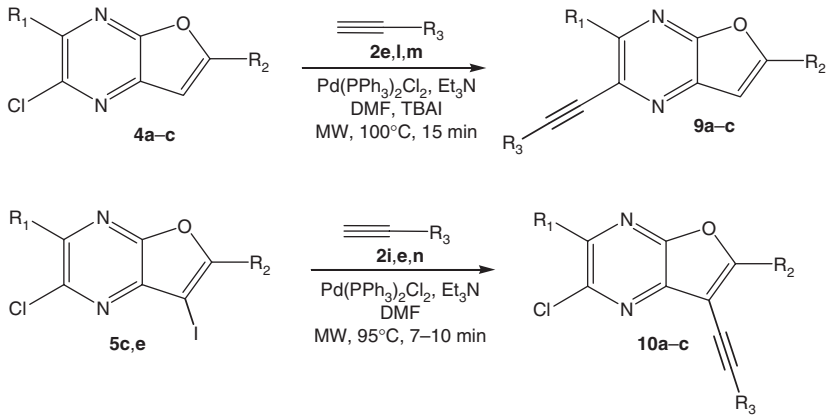

**Fig. 1.** X-Ray crystal structure[23] of **8d**. Thermal ellipsoids at the 50% probability level.

*Sonogashira Coupling Reaction on 1-(4-Methoxybenzyl)-3,5-dichloropyrazin-2(1H)-ones **1a**–**d**. A Typical Procedure*

In a 50 mL microwave vial were successively dissolved in DMF/$Et_3N$ (1:1, 20 mL), pyrazinone **1** (5 mmol), acetylene **2** (6.25–7.5 mmol), $Pd(PPh_3)Cl_2$ (35 mg, 1 mol%), and CuI (28 mg, 3 mol%). The reaction tube was sealed and irradiated in a microwave reactor at a ceiling temperature of 80°C at 80 W maximum power for 10 min. Afterwards the reaction mixture was cooled with an air flow for 15 min, extracted with dichloromethane (2 × 150 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to silica gel column chromatography (from 10% to 30% EtOAc in petroleum ether) to afford compounds **3a**–**k**.

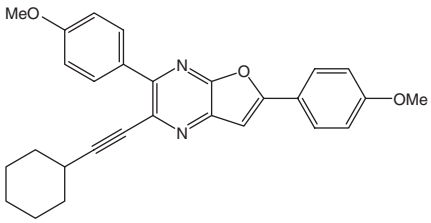
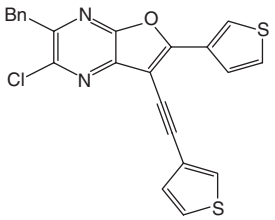
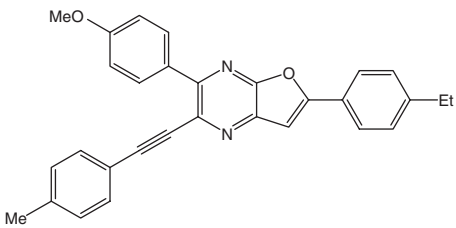
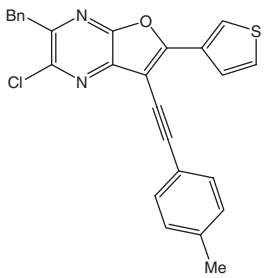
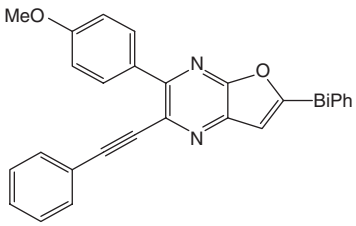
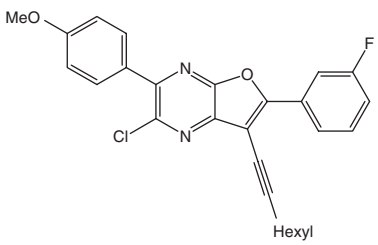
*1-(4-Methoxybenzyl)-5-chloro-6-(4-methoxyphenyl)-3-(2-(4-methoxyphenyl)ethynyl)-pyrazin-2(1H)-one (**3a**)*

99% yield. $\delta_H$ (300 MHz, $CDCl_3$) 7.63 (d, *J* 8.91, 2H), 7.06 (d, *J* 8.79, 2H), 6.96 (d, *J* 8.43, 2H), 6.90 (d, *J* 8.85, 2H), 6.84 (d, *J* 8.49, 2H), 6.73 (d, *J* 8.55, 2H), 5.05 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.76 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 160.9, 159.3, 139.6, 138.1, 134.5, 131.0, 129.3, 127.6, 123.0, 114.3, 113.9, 98.9, 85.3, 55.5, 55.4, 55.3, 49.9. *m/z* (HR-MS EI) Found: 486.1353. $C_{28}H_{23}O_4N_2Cl$ requires 486.1346.




**Scheme 5.** Microwave (MW)-assisted Sonogashira cross-coupling reactions on substrates **4** and **5**.

**Table 4. Evaluation of the microwave-assisted Sonogashira cross-coupling reaction**

| Entry | Compd | Product[A] | Yield [%][C] | Entry | Compd | Product[B] | Yield [%][C] |
|---|---|---|---|---|---|---|---|
| 1 | **9a** |  | 85 | 4 | **10a** |  | 89 (4) |
| 2 | **9b** |  | 92 | 5 | **10b** |  | 86 (5) |
| 3 | **9c** |  | 96 | 6 | **10c** |  | 74 (9) |

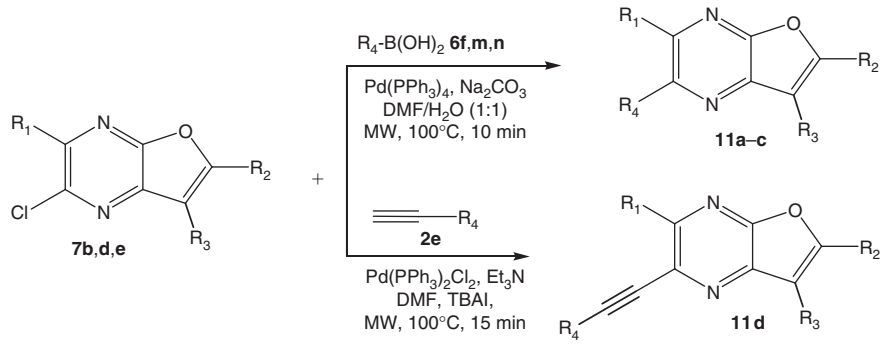
[A]Reaction conditions for **9a**–**c**: the reaction was run on a 0.3 mmol scale of **4a**–**c**, using acetylene (1.3 equiv.), $Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (10 mol%), and tetrabutylammonium iodide (TBAI) (2.0 equiv.), in DMF/$Et_3N$ (1:1, 4 mL) under microwave irradiation at a maximum power of 80 W at 100°C ceiling temperature for 15 min.

[B]Reaction conditions for **10a**–**c**: the reaction was run on a 0.3 mmol scale of **5c**,**e**, using acetylene (1.05 equiv.), $Pd(PPh_3)_2Cl_2$ (1 mol%), and CuI (3 mol%), in DMF/$Et_3N$ (1:1, 4 mL) under microwave irradiation at a maximum power of 80 W and 95°C ceiling temperature for 7–10 min.

[C]Isolated yields (single runs); yields in parenthesis indicate dialkynylated product.

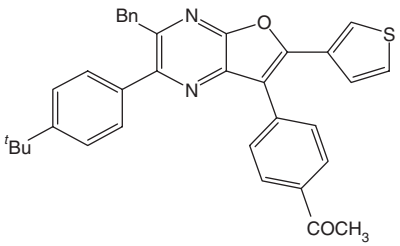
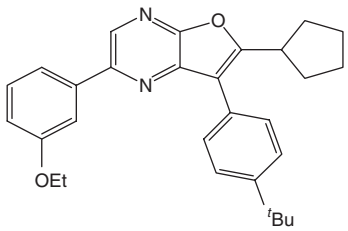
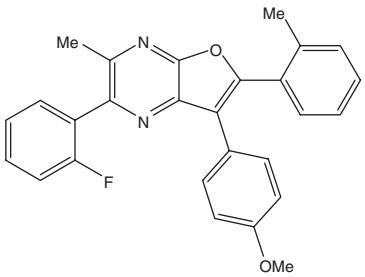
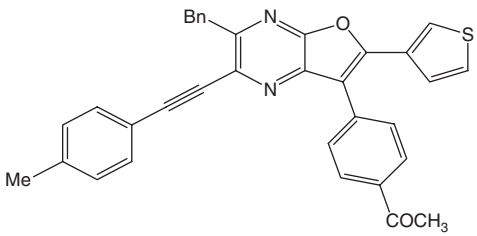
*1-(4-Methoxybenzyl)-5-chloro-3-(2-(4-ethylphenyl) ethynyl)-6-(4-methoxyphenyl)pyrazin-2(1*H*)-one (**3b**)*

92% yield. $\delta_H$ (300 MHz, $CDCl_3$) 7.60 (d, *J* 8.1, 2H), 7.22 (m, 2H), 7.05 (d, *J* 8.4, 2H), 6.95 (d, *J* 8.4, 2H), 6.83 (d, *J* 8.5, 2H), 6.73 (d, *J* 8.5, 2H), 5.06 (s, 2H), 3.88 (s, 3H), 3.77 (s, 3H), 2.66 (m, 2H), 1.25 (t, *J* 15.3, 7.5, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 161.3, 159.7, 156.2, 146.9, 139.8, 138.8, 133.2, 131.3, 129.6, 128.4, 127.9, 127.7, 123.3, 119.1, 114.7, 114.3, 99.0, 85.9,

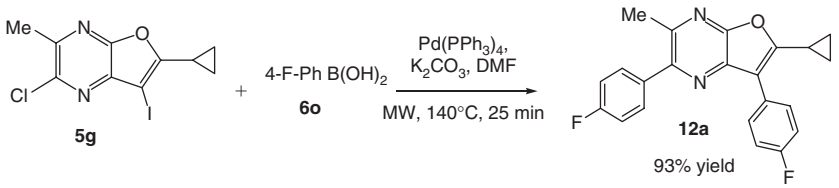



**Scheme 6.** Microwave (MW)-assisted decoration of the 7-substituted 2-chloro furo[2,3-*b*]pyrazines.

**Table 5. Microwave-assisted decoration of the 7-substituted 2-chloro furo[2,3-*b*]pyrazines[A]**

| Entry | Compd | Product | Yield [%][B] |
|---|---|---|---|
| 1 | **11a** |  | 87 |
| 2 | **11b** |  | 92 |
| 3 | **11c** |  | 95 |
| 4 | **11d** |  | 86 |

[A]Reaction conditions for **11a**–**c**: the reaction was run on a 0.3 mmol scale of **7**, using boronic acid (1.5 equiv.), $Pd(PPh_3)_4$ (1 mol%), and $Na_2CO_3$ (2 equiv.) in $DMF/H_2O$ (1:1, 4 mL) under microwave irradiation using a maximum power of 100 W at 100°C ceiling temperature for 10 min; reaction condition for **11d**: the reaction was run on a 0.3 mmol scale of **7**, using acetylene (1.3 equiv.), $Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (10 mol%), and TBAI (1.2 equiv.) as additive, in $DMF/Et_3N$ (1:1, 4 mL) under microwave irradiation using a maximum power of 80 W and 100°C ceiling temperature for 15 min.
[B]Isolated yields (single run).




**Scheme 7.** Suzuki cross-coupling to generate symmetrically substituted furo[2,3-*b*]pyrazines. MW, microwave.

55.8, 55.7, 50.3, 29.4, 15.6. *m/z* (HR-MS EI) Found: 484.1577. $C_{29}H_{25}O_3N_2Cl$ requires 484.1554.

*3-(1,1′-Biphenyl-4-ylethynyl)-5-chloro-1-(4-methoxybenzyl)-6-(4-methoxyphenyl)pyrazin-2(1*H*)-one (**3c**)*

83% yield. $\delta_H$ (300 MHz, $CDCl_3$) 7.75 (d, *J* 8.2, 2H), 7.61 (m, 5H), 7.43 (m, 3H), 7.07 (d, *J* 8.7, 2H), 6.97 (d, *J* 8.8, 2H), 6.84 (d, *J* 8.6, 2H), 6.73 (d, *J* 8.5, 2H), 5.07 (s, 2H), 3.88 (s, 3H), 3.77 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 160.9, 159.3, 155.8, 142.5, 140.0, 139.1, 138.6, 133.1, 132.9, 130.9, 129.2, 128.9, 127.9, 127.6, 127.2, 127.1, 122.8, 120.4, 114.3, 113.9, 98.1, 86.5, 55.4, 55.2, 49.9. *m/z* (HR-MS EI) Found: 532.1549. $C_{33}H_{25}O_3N_2Cl$ requires 532.1554.

*1-(4-Methoxybenzyl)-5-chloro-6-(4-methoxyphenyl)-3-(2-(pyridin-4-yl)ethynyl)pyrazin-2-(1*H*)-one (**3d**)*

85% yield. $\delta_H$ (300 MHz, $CDCl_3$) 8.65 (d, *J* 5.2, 2H), 7.50 (d, *J* 6.0, 2H), 7.07 (d, *J* 8.4, 2H), 6.97 (d, *J* 8.7, 2H), 6.83 (d, *J* 8.6, 2H), 6.74 (d, *J* 8.4, 2H), 5.08 (s, 2H), 3.89 (s, 3H), 3.77 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 161.1, 159.4, 155.7, 149.9, 140.2, 130.7, 129.7, 129.3, 128.6, 128.4, 127.8, 126.9, 126.0, 114.4, 113.9, 93.7, 89.0, 55.5, 55.3, 50.1. *m/z* (HR-MS EI) Found: 457.1208. $C_{26}H_{20}ClN_3O_3$ requires 457.1193.

*1-(4-Methoxybenzyl)-6-benzyl-5-chloro-3-(2-*p*-tolylethynyl)pyrazin-2(1*H*)-one (**3e**)*

99% yield. $\delta_H$ (300 MHz, $CDCl_3$) 7.56 (d, *J* 8.07, 2H), 7.38–7.33 (m, 3H), 7.19–7.10 (m, 6H), 6.88 (d, *J* 8.79, 2H), 5.11 (s, 2H), 4.17 (s, 2H), 3.79 (s, 3H), 2.38 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 159.5, 156.2, 140.4, 138.9, 137.3, 134.3, 132.6, 129.5, 128.3, 127.7, 126.6, 118.5, 114.6, 98.8, 85.3, 55.4, 48.4, 35.6, 21.8. *m/z* (HR-MS EI) Found 454.1464. $C_{28}H_{23}O_2N_2Cl$ requires 454.1448.

*1-(4-Methoxybenzyl)-5-chloro-3-(2-cyclopentylethynyl)pyrazin-2(1*H*)-one (**3f**)*

Yellow solid in 82% yield. $\delta_H$ (300 MHz, $CDCl_3$) 7.28 (d, *J* 9.12, 2H), 7.10 (s, 1H), 6.90 (d, *J* 9.12, 2H), 4.99 (s, 2H), 3.81 (s, 3H), 2.96–2.91 (m, 1H), 2.24–1.99 (m, 2H), 1.78 (s, 4H), 1.60 (s, 2H). $\delta_C$ (75 MHz, $CDCl_3$) 160.1, 155.0, 141.4, 130.5, 126.4, 125.9, 125.4, 114.7, 106.0, 55.4, 52.5, 33.5, 31.0, 25.4. *m/z* (HR-MS EI) Found 342.1141. $C_{19}H_{19}O_2N_2Cl$ requires 342.1135.

*1-(4-Methoxybenzyl)-5-chloro-6-methyl-3-(2-*o*-tolylethynyl)pyrazin-2(1*H*)-one (**3g**)*

Orange solid in 94% yield. mp 144–147°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.61 (d, *J* 7.32, 1H), 7.29–7.16 (m, 5H), 6.87 (d, *J* 8.22, 2H), 5.32 (s, 2H), 3.79 (s, 3H), 2.60 (s, 3H), 2.48 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 159.5, 156.1, 141.7, 137.5, 136.3, 132.9, 129.8, 128.5, 126.8, 126.3, 125.7, 121.5, 114.5, 96.8, 89.4, 55.4, 48.9, 20.8, 17.3. *m/z* (HR-MS EI) Found 378.1141. $C_{22}H_{19}O_2N_2Cl$ requires 378.1135.

*1-(4-Methoxybenzyl)-5-chloro-3-(2-(3-fluorophenyl) ethynyl)-6-(4-methoxyphenyl)pyrazin-2(1*H*)-one (**3h**)*

Yellow solid in 99% yield. mp 142–145°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.46 (d, *J* 7.32, 1H), 7.38–7.32 (q, *J* 5.49, 2.73, 2H), 7.11–7.05 (m, 3H), 6.97 (d, *J* 8.22, 2H), 6.83 (d, *J* 9.03, 2H), 6.72 (d, *J* 9.12, 2H), 5.06 (s, 2H), 3.88 (s, 3H), 3.76 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 163.9, 161.0, 159.4, 155.84, 139.3, 138.7, 130.9, 130.2, 129.3, 128.6, 127.6, 127.2, 123.5, 122.7, 119.5, 117.3, 114.4, 113.9, 96.1, 86.3, 55.5, 50.0. *m/z* (HR-MS EI) Found 474.1154. $C_{27}H_{20}O_3N_2ClF$ requires 474.1146.

*1-(4-Methoxybenzyl)-6-benzyl-5-chloro-3-(2-(thiophen-3-yl)ethynyl)pyrazin-2(1*H*)-one (**3i**)*

88% yield. $\delta_H$ (300 MHz, $CDCl_3$) 7.76 (s, 1H), 7.38–7.30 (m, 5H), 7.14–7.09 (m, 4H), 6.88 (d, *J* 8.94, 2H), 5.11 (s, 2H), 4.17 (s, 2H), 3.79 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 159.5, 156.2, 138.7, 137.5, 134.3, 132.2, 130.3, 129.5, 128.3, 127.6, 126.5, 125.7, 120.8, 114.6, 93.5, 85.5, 55.4, 48.4, 35.6. *m/z* (HR-MS EI) Found 446.0858. $C_{25}H_{19}O_2N_2SCl$ requires 446.0856.

*1-(4-Methoxybenzyl)-3-(2-(4-*tert*-butylphenyl)ethynyl)-5-chloro-6-(4-methoxyphenyl)pyrazin-2(1*H*)-one (**3j**)*

Yellow solid in 96% yield. mp 178–180°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.62 (d, *J* 9.4, 2H), 7.39 (d, *J* 9.1, 2H), 7.05 (d, *J* 9.6, 2H), 6.96 (d, *J* 9.2, 2H), 6.84 (d, *J* 9.3, 2H), 6.73 (d, *J* 9.4, 2H), 5.06 (s, 2H), 3.88 (s, 3H), 3.77 (s, 3H), 1.33 (s, 9H). $\delta_C$ (75 MHz, $CDCl_3$) 160.9, 159.3, 155.9, 153.4, 139.5, 138.4, 132.6, 131.0, 129.5, 129.3, 127.6, 127.4, 125.6, 123.0, 122.3, 118.6, 114.4, 113.9, 98.7, 85.6, 55.5, 55.3, 50.0, 35.1, 31.2. *m/z* (HR-MS EI) Found 512.1867. $C_{31}H_{29}O_3N_2Cl$ requires 512.1867.

*1-(4-Methoxybenzyl)-5-chloro-3-(2-cyclopropylethynyl)-6-methylpyrazin-2(1*H*)-one (**3k**)*

84% yield. $\delta_H$ (300 MHz, $CDCl_3$) 7.17 (d, *J* 8.22, 2H), 6.85 (d, *J* 9.12, 2H), 5.25 (s, 2H), 3.78 (s, 3H), 2.44 (s, 3H), 1.61–1.57 (s, 1H), 0.97–0.93 (m, 4H). $\delta_C$ (75 MHz, $CDCl_3$) 159.4, 156.2, 137.6, 135.5, 128.6, 126.4, 114.4, 103.7, 55.3, 48.8, 17.1, 9.5. *m/z* (HR-MS EI) Found: 328.0982. $C_{18}H_{17}O_2N_2Cl$ requires 328.0979.

### *A Typical Procedure for the Preparation of Furopyrazines **4a**–**e***

In a 25 mL flask pyrazinone **3** (2 mmol) was dissolved in dry dichloromethane (12 mL). AgOTf (11 mg, 2 mol%) and trifluoroacetic acid (0.8 mL, 10 mmol, 5 equiv.) were then added and the reaction mixture was stirred at room temperature for 5–20 min. After reaction completion the solvent was evaporated and the residue was subjected to silica gel column chromatography (from 20% to 50% $CH_2Cl_2$ in petroleum ether) to afford compounds **4a**–**e**.

*2-Chloro-3,6-bis(4-methoxyphenyl)furo[2,3-*b*]pyrazine (**4a**)*

Yellow solid in 96% yield. mp 118–119°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.88 (d, *J* 9.1, 2H), 7.83 (d, *J* 8.2, 2H), 7.04–6.99 (m, 5H), 3.89 (s, 6H). $\delta_C$ (75 MHz, $CDCl_3$) 161.9, 161.7, 160.5, 154.1, 144.5, 143.1, 140.1, 131.4, 129.2, 129.1, 128.9, 127.5, 121.3, 114.7, 114.6, 113.7, 88.9, 55.6, 55.5. *m/z* (HR-MS EI) Found 366.0793. $C_{20}H_{15}O_3N_2Cl$ requires 366.0771.

*2-Chloro-6-(4-ethylphenyl)-3-(4-methoxyphenyl)furo[2,3-*b*]pyrazine (**4b**)*

92% yield. $\delta_H$ (300 MHz, $CDCl_3$) 7.85 (m, 4H), 7.34 (d, *J* 8.1, 2H), 7.12 (s, 1H), 7.03 (d, *J* 8.3, 2H), 3.89 (s, 3H), 2.72 (m, 2H), 1.28 (t, *J* 7.4, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 162.3, 160.8, 154.4, 147.9, 145.2, 143.5, 140.1, 131.7, 129.4, 129.1, 126.5, 126.1, 114.0, 100.3, 55.8, 29.3, 15.7. *m/z* (HR-MS EI) Found 364.0975. $C_{21}H_{17}O_2N_2Cl$ requires 364.0979.

*6-(1,1′-Biphenyl-4-yl)-2-chloro-3-(4-methoxyphenyl)furo[2,3-*b*]pyrazine (**4c**)*

91% yield. $\delta_H$ (300 MHz, $CDCl_3$) 8.03 (d, *J* 9.00, 2H), 7.86 (d, *J* 9.00, 2H), 7.77–7.65 (m, 4H), 7.52–7.47 (m, 3H), 7.21 (s, 1H), 7.05 (d, *J* 9.00, 2H), 3.90 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 161.3, 160.5, 145.2, 143.5, 139.9, 131.3, 129.0, 128.1, 127.8, 127.1, 126.2, 113.7, 100.6, 55.4. *m/z* (HR-MS EI) Found 412.0983. $C_{25}H_{17}O_2N_2Cl$ requires 412.0979.

*2-Chloro-3-(4-methoxyphenyl)-6-pyridin-4-ylfuro[2,3-*b*]pyrazine (**4d**)*

79% yield. $\delta_H$ (300 MHz, $CDCl_3$) 8.84 (br, 2H), 7.89 (m, 4H), 7.48 (s, 1H), 7.05 (d, *J* 8.8, 2H), 3.90 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 160.9, 157.3, 154.4, 149.4, 147.6, 144.4, 138.0, 136.9, 132.1, 131.5, 128.5, 128.4, 119.5, 113.8, 104.9, 55.4. *m/z* (HR-MS EI) Found 337.0621. $C_{18}H_{12}O_2N_3Cl$ requires 337.0618.

*3-Benzyl-2-chloro-6-*p*-tolylfuro[2,3-*b*]pyrazine (**4e**)*

White solid in 91% yield. mp 214–216°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.80 (d, *J* 9.0, 2H), 7.38 (d, *J* 8.3, 2H), 7.33–7.22 (m, 5H), 7.05 (s, 1H), 4.37 (s, 2H), 2.42 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 161.6, 154.0, 146.5, 144.7, 141.3, 140.2, 137.6, 131.4, 129.9, 128.7, 126.9, 125.9, 125.7, 99.8, 42.3, 21.7 *m/z* (HR-MS EI) Found 334.0858. $C_{20}H_{15}ON_2Cl$ requires 334.0873.

### *A Typical Procedure for the Preparation of Furopyrazines **5a–g***

In a 25 mL flask pyrazinone **3** (2 mmol) was dissolved in dry dichloromethane (12 mL). $I_2$ (2.0 equiv.) was then added and the reaction mixture was stirred at room temperature for 5–15 min. After reaction completion the solvent was evaporated and the residue was subjected to silica gel column chromatography (from 5% to 10% $CH_2Cl_2$ in petroleum ether) to afford compounds **5a–g**.

*2-Chloro-6-cyclopentyl-7-iodofuro[2,3-*b*]pyrazine (**5a**)*

White solid in 76% yield. mp 128–131°C. $\delta_H$ (300 MHz, $CDCl_3$) 8.17 (s, 1H), 3.56–3.45 (m, 1H), 2.13–2.07 (m, 2H), 1.93 (s, 4H), 1.76 (s, 2H). $\delta_C$ (75 MHz, $CDCl_3$) 169.2, 153.4, 142.2, 136.8, 62.2, 39.5, 31.7, 26.2. *m/z* (HR-MS EI) Found 347.9547. $C_{11}H_{10}ON_2ICl$ requires 347.9526.

*2-Chloro-7-iodo-3-methyl-6-*o*-tolylfuro[2,3-*b*]pyrazine (**5b**)*

Yellow solid in 86% yield. mp 158–161°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.61 (d, *J* 7.32, 1H), 7.45 (m, 1H), 7.34 (m, 2H), 2.77 (s, 3H), 2.41 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 160.9, 153.3, 147.3, 145.7, 139.8, 138.4, 131.1, 128.2, 125.8, 64.6, 22.6, 20.6. *m/z* (HR-MS EI) Found 383.9522. $C_{14}H_{10}ON_2ICl$ requires 383.9526.

*2-Chloro-6-(3-fluorophenyl)-7-iodo-3-(4-methoxyphenyl)furo[2,3-*b*]pyrazine (**5c**)*

Light yellow solid in 88% yield. mp 210–214°C. $\delta_H$ (300 MHz, $CDCl_3$) 8.13 (d, *J* 8.22, 1H), 8.03 (d, *J* 10.05, 1H), 7.85 (d, *J* 8.22, 2H), 7.53 (m, 1H), 7.24 (d, *J* 2.73, 1H), 7.03 (d, *J* 8.22, 2H), 3.89 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 160.9, 156.4, 144.5, 131.6, 130.7, 128.4, 123.6, 118.2, 117.1, 114.9, 114.6, 113.8, 55.5. *m/z* (HR-MS EI) Found 479.9565. $C_{19}H_{11}O_2N_2IClF$ requires 479.9538.

*3-Benzyl-2-chloro-7-iodo-6-*p*-tolylfuro[2,3-*b*]pyrazine (**5d**)*

Yellow solid in 91% yield. mp 157–159°C. $\delta_H$ (300 MHz, $CDCl_3$) 8.16 (d, *J* 9.15, 2H), 7.37–7.26 (m, 7H), 4.40 (s, 2H), 2.44 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 158.0, 152.8, 148.5, 145.5, 141.6, 141.2, 137.3, 129.6, 129.4, 128.7, 127.9, 126.9, 125.8, 59.7, 41.2, 21.7. *m/z* (HR-MS EI) Found 459.9829. $C_{20}H_{14}ON_2ICl$ requires 459.9839.

*3-Benzyl-2-chloro-7-iodo-6-(thiophen-3-yl)furo[2,3-*b*]pyrazine (**5e**)*

Yellow solid in 96% yield. mp 168–171°C. $\delta_H$ (300 MHz, $CDCl_3$) 8.40 (d, *J* 1.83, 1H), 7.98 (d, *J* 5.49, 7H), 7.50–7.48 (m, 1H), 7.37–7.23 (m, 5H), 4.40 (s, 2H). $\delta_C$ (75 MHz, $CDCl_3$) 155.3, 152.5, 148.5, 145.6, 141.0, 137.2, 130.1, 129.1, 128.7, 127.8, 126.9, 126.2, 59.6, 41.2. *m/z* (HR-MS EI) Found 451.9242. $C_{17}H_{10}ON_2SICl$ requires 451.9247.

*6-(4-*tert*-Butylphenyl)-2-chloro-7-iodo-3-(4-methoxyphenyl)furo[2,3-*b*]pyrazine (**5f**)*

Yellow solid in 96% yield. mp 146–150°C. $\delta_H$ (300 MHz, $CDCl_3$) 8.26 (d, *J* 9.12, 2H), 7.85 (d, *J* 9.12, 2H), 7.58 (d, *J* 8.22, 1H), 7.03 (d, *J* 9.15, 5H), 3.89 (s, 3H), 1.38 (s, 9H). $\delta_C$ (75 MHz, $CDCl_3$) 160.7, 158.4, 154.8, 152.9, 146.9, 144.1, 141.0, 131.5, 128.7, 127.8, 125.9, 113.8, 59.8, 55.5, 35.2, 31.2. *m/z* (HR-MS EI) Found 518.0268. $C_{23}H_{20}O_2N_2ICl$ requires 518.0258.

*2-Chloro-6-cyclopropyl-7-iodo-3-methylfuro[2,3-*b*]pyrazine (**5g**)*

Yellow solid in 68% yield. mp 82–85°C. $\delta_H$ (300 MHz, $CDCl_3$) 2.69 (s, 3H), 2.34–2.25 (m, 1H), 1.31–1.19 (m, 4H). $\delta_C$ (75 MHz, $CDCl_3$) 164.9, 152.2, 145.1, 140.2, 130.1, 114.3, 60.7, 22.3, 11.0, 9.4. *m/z* (HR-MS EI) Found 333.9363. $C_{10}H_8ON_2ICl$ requires 333.9370.

### *A Typical Procedure for Selective Suzuki–Miyaura Reaction on Compounds **5a–g***

In a 15 mL microwave vial were successively dissolved in DMF (4 mL) furopyrazine **5a–g** (0.3 mmol), boronic acid **6a**,**f–l** (0.375 mmol, 1.25 equiv.), $Pd(PPh_3)_4$ (3 mg, 1 mol%), and $K_2CO_3$ (82 mg, 2 equiv.). The reaction tube was sealed and irradiated at a ceiling temperature of 120°C at 100 W maximum power for 10–30 min. After the reaction the mixture was cooled

with an air flow for 15 min, extracted with dichloromethane (2 × 50 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to silica gel chromatography (from 5% to 20% EtOAC in heptane) to afford compounds **7a**–**j**.

*2-Chloro-6-cyclopentyl-7-(4-methoxyphenyl)furo [2,3-*b*]pyrazine (**7a**)*

Yellow oil in 91% yield. $\delta_H$ (300 MHz, $CDCl_3$) 8.16 (s, 1H), 7.54 (d, *J* 9.15, 2H), 7.04 (d, *J* 9.15, 2H), 3.86 (s, 3H), 3.55–3.50 (m, 1H), 2.05–1.94 (m, 6H), 1.74–1.68 (m, 2H). $\delta_C$ (75 MHz, $CDCl_3$) 164.8, 159.4, 153.4, 145.1, 140.9, 135.4, 130.4, 121.6, 115.7, 114.5, 55.4, 37.7, 32.4, 26.4. *m*/*z* (HR-MS EI) Found 328.0987. $C_{18}H_{17}O_2N_2Cl$ requires 328.0979.

*7-(4-*tert*-Butylphenyl)-2-chloro-6-cyclopentylfuro [2,3-*b*]pyrazine (**7b**)*

White solid in 78% yield. mp 97–99°C. $\delta_H$ (300 MHz, $CDCl_3$) 8.17 (s, 1H), 7.57–7.50 (m, 4H), 3.59–3.53 (m, 1H), 2.06–1.94 (m, 6H), 1.75–1.71 (m, 2H), 1.36 (s, 9H). $\delta_C$ (75 MHz, $CDCl_3$) 165.2, 153.5, 151.1, 145.2, 140.9, 135.5, 128.9, 126.4, 126.0, 116.0, 37.8, 34.8, 32.5, 31.4, 26.4. *m*/*z* (HR-MS EI) Found 354.1506. $C_{21}H_{23}ON_2Cl$ requires 354.1499.

*2-Chloro-6-cyclopropyl-7-(4-ethoxyphenyl)-3-methylfuro[2,3-*b*]pyrazine (**7c**)*

White solid in 86% yield. mp 82–85°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.71 (d, *J* 8.22, 2H), 7.03 (d, *J* 9.12, 2H), 4.12–4.05 (q, 2H), 2.68 (s, 3H), 2.35–2.33 (m, 1H), 1.45 (t, *J* 13.71, 6.39, 3H), 1.29–1.26 (m, 4H). $\delta_C$ (75 MHz, $CDCl_3$) 160.3, 158.6, 152.5, 144.3, 143.6, 138.9, 130.1, 121.9, 115.0, 63.6, 22.4, 14.9, 9.5, 8.9. *m*/*z* (HR-MS EI) Found 328.0987. $C_{18}H_{17}O_2N_2Cl$ requires 328.0979.

*1-(4-(3-Benzyl-2-chloro-6-(thiophen-3-yl)furo [2,3-*b*]pyrazin-7-yl)phenyl)ethanone (**7d**)*

White solid in 87% yield. mp 209–214°C. $\delta_H$ (300 MHz, $CDCl_3$) 8.08 (d, *J* 8.22, 2H), 7.84 (d, *J* 2.76, 1H), 7.75 (d, *J* 8.22, 2H), 7.40–7.23 (m, 7H), 4.40 (s, 2H), 2.66 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 197.7, 153.2, 152.9, 147.7, 145.2, 139.0, 137.4, 137.0, 134.4, 130.1, 129.2, 128.7, 127.0, 126.9 126.0, 114.5, 41.4, 29.8, 26.8. *m*/*z* (HR-MS EI) Found 444.0691. $C_{25}H_{17}O_2N_2SCl$ requires 444.0699.

*2-Chloro-7-(4-methoxyphenyl)-3-methyl-6-o-tolylfuro[2,3-*b*]pyrazine (**7e**)*

White solid in 89% yield. mp 136–140°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.53 (d, *J* 8.22, 2H), 7.44 (d, *J* 8.19, 1H), 7.38 (d, *J* 7.32, 1H), 7.32–7.23 (m, 2H), 6.88 (d, *J* 9.15, 2H), 3.80 (s, 3H), 2.76 (s, 3H), 2.22 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 159.4, 155.8, 153.7, 145.6, 144.7, 138.1, 131.1, 130.9, 130.4, 129.8, 129.4, 126.1, 122.1, 117.0, 114.3, 55.3, 22.7, 20.3. *m*/*z* (HR-MS EI) Found 364.0984. $C_{21}H_{17}O_2N_2Cl$ requires 364.0979.

*Ethyl 4-(2-Chloro-6-(3-fluorophenyl)-3-(4-methoxyphenyl)furo[2,3-*b*]pyrazin-7-yl)benzoate (**7f**)*

White solid in 78% yield. mp 163–167°C. $\delta_H$ (300 MHz, $CDCl_3$) 8.18 (d, *J* 7.29, 2H), 7.87 (d, *J* 9.12, 2H), 7.73 (d, *J* 8.22, 2H), 7.52–7.45 (m, 2H), 7.39–7.32 (q, 1H), 7.16–7.10 (m, 1H), 7.04 (d, *J* 9.12, 2H), 4.46–4.39 (q, 2H), 3.89 (s, 3H), 1.45–1.40 (t, *J* 14.61, 7.29, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 166.3, 164.5, 161.2, 160.8, 154.8, 153.5, 146.8, 144.0, 138.3, 133.8, 131.5, 130.9, 130.6, 129.7, 128.8, 123.6, 117.8, 116.7, 114.9, 113.3, 61.3, 55.5, 14.5. *m*/*z* (HR-MS EI) Found 502.1089. $C_{28}H_{20}O_4N_2ClF$ requires 502.1096.

*2-Chloro-3-methyl-6-o-tolyl-7-p-tolylfuro [2,3-*b*]pyrazine (**7g**)*

White solid in 90% yield. mp 97–99°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.48–7.39 (m, 4H), 7.36–7.22 (m, 2H), 7.15 (d, *J* 7.32, 2H), 2.76 (s, 3H), 2.34 (s, 3H), 2.22 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 156.2, 153.7, 145.7, 144.8, 138.1, 137.9, 131.1, 130.4, 129.5, 128.5, 126.8, 126.1, 117.4, 22.7, 21.4, 20.3. *m*/*z* (HR-MS EI) Found 348.1013. $C_{21}H_{17}ON_2Cl$ requires 348.1029.

*3-Benzyl-7-(3-bromophenyl)-2-chloro-6-p-tolylfuro [2,3-*b*]pyrazine (**7h**)*

79% yield. $\delta_H$ (300 MHz, $CDCl_3$) 7.73 (s, 1H), 7.62–7.49 (m, 4H), 7.39–7.28 (m, 5H), 7.26–7.18 (m, 3H), 4.40 (s, 2H), 2.39 (s, 3H). *m*/*z* (HR-MS EI) Found 488.0303. $C_{26}H_{18}ON_2BrCl$ requires 488.0291.

*7-(2-(Benzyloxy)phenyl)-6-(4-*tert*-butylphenyl)-2-chloro-3-(4-methoxyphenyl)furo[2,3-*b*]pyrazine (**7i**)*

White solid in 89% yield. mp 61–65°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.83 (d, *J* 9.12, 2H), 7.67 (d, *J* 8.22, 2H), 7.50–7.35 (m, 4H), 7.17–7.13 (m, 3H), 7.11–7.00 (m, 6H), 4.96 (s, 2H), 3.87 (s, 3H), 1.31 (s, 9H). $\delta_C$ (75 MHz, $CDCl_3$) 207.0, 160.4, 156.9, 156.6, 153.5, 153.3, 145.0, 143.1, 140.1, 136.6, 132.1, 131.3, 130.2, 129.3, 128.2, 127.6, 127.3, 127.0, 126.8, 125.6, 121.4, 119.1, 113.6, 113.0, 55.4, 34.9, 31.1. *m*/*z* (HR-MS EI) Found 574.2027. $C_{36}H_{31}O_3N_2Cl$ requires 574.2023.

*4-(3-benzyl-2-chloro-6-p-tolylfuro[2,3-*b*]pyrazin-7-yl)benzonitrile (**7j**)*

White solid in 91% yield. mp 158–162°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.74 (m, 4H), 7.58 (d, *J* 8.22, 2H), 7.38 (d, *J* 7.32, 2H), 7.33–7.21 (m, 5H), 4.46 (s, 2H), 2.41 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 157.2, 153.4, 148.0, 145.1, 141.6, 138.6, 137.3, 134.8, 132.7, 130.2, 129.8, 129.1, 128.7, 128.0, 126.9, 125.6, 118.7, 114.0, 111.9, 41.3, 21.6. *m*/*z* (HR-MS EI) Found 435.1132. $C_{27}H_{18}ON_3Cl$ requires 435.1138.

### *A Typical Procedure for the Preparation of Furopyrazines **8a**–**d***

In a 15 mL microwave vial were successively dissolved in DMF/$H_2O$ (1:1, 4 mL) furopyrazine **4a**–**c**,**e** (0.3 mmol), boronic acid **6b**–**e** (0.45 mmol, 1.50 equiv.), $Pd(PPh_3)_4$ (3 mg, 1 mol%), and $Na_2CO_3$ (64 mg, 2 equiv.). The reaction tube was sealed and irradiated at a ceiling temperature of 100°C at 100 W maximum power for 10 min. After the reaction the mixture was cooled with an air flow for 15 min, extracted with dichloromethane (2 × 50 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to silica gel flash chromatography (from 10% to 50% $CH_2Cl_2$ in petroleum ether) to afford compounds **8a**–**d**.

*6-(4-Ethylphenyl)-3-(4-methoxyphenyl)-2-p-tolylfuro-[2,3-*b*]pyrazine (**8a**)*

Light yellow solid in 85% yield. mp 172–175°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.89 (d, *J* 8.22, 2H), 7.43 (d, *J* 9.12, 2H), 7.36–7.33 (m, 4H), 7.20 (s, 1H), 7.14 (d, *J* 8.22, 2H), 6.83 (d, *J* 8.22, 2H), 3.81 (s, 3H), 2.76–2.68 (m, 2H), 2.36 (s, 3H), 1.31–1.26 (t, *J* 14.61, 7.29, 3H). $\delta_C$ (75 MHz, $CDCl_3$)

160.7, 159.8, 154.4, 150.3, 147.1, 146.0, 139.9, 138.0, 137.0, 131.5, 129.8, 128.7, 126.7, 125.7, 113.7, 100.6, 55.3, 29.0, 21.4, 15.5. *m/z* (HR-MS EI) Found 420.1821. $C_{28}H_{24}O_2N_2Cl$ requires 420.1838.

*2-(3,5-Dimethylphenyl)-3,6-bis(4-methoxyphenyl)furo-[2,3-*b*]pyrazine (**8b**)*

Yellow solid in 90% yield. mp 72–75°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.92 (d, *J* 9.15, 2H), 7.43 (d, *J* 9.12, 2H), 7.11 (s, 1H), 7.05–6.96 (m, 5H), 6.82 (d, *J* 9.12, 2H), 3.89 (s, 3H), 3.81 (s, 3H), 2.26 (s, 6H). $\delta_C$ (75 MHz, $CDCl_3$) 161.4, 160.6, 159.7, 154.4, 150.4, 145.6, 140.0, 137.9, 131.5, 129.8, 129.4, 128.8, 128.0, 127.7, 127.3, 121.9, 114.6, 113.5, 99.6, 55.5, 21.4. *m/z* (HR-MS EI) Found 436.1793. $C_{28}H_{24}O_3N_2$ requires 436.1787.

*6-(Biphenyl-4-yl)-3-(4-methoxyphenyl)-2-(3-(trifluoromethyl)phenyl)furo[2,3-*b*]pyrazine (**8c**)*

Yellow solid in 87% yield. mp 150–153°C. $\delta_H$ (300 MHz, $CDCl_3$) 8.06 (d, *J* 8.22, 2H), 7.84 (s, 1H), 7.76 (d, *J* 8.22, 2H), 7.67 (d, *J* 7.32, 2H), 7.60 (d, *J* 7.29, 2H), 7.51–7.37 (m, 7H), 7.31 (s, 1H), 6.85 (d, *J* 8.22, 2H), 3.82 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 160.7, 160.1, 148.7, 146.5, 143.3, 140.6, 140.0, 133.4, 131.6, 130.8, 130.5, 129.1, 128.7, 128.1, 127.2, 126.9, 126.2, 124.9, 113.9, 101.2, 55.4. *m/z* (HR-MS EI) Found 522.1566. $C_{32}H_{21}O_2N_2F_3$ requires 522.1555.

*3-Benzyl-2-(naphthalen-1-yl)-6-*p*-tolylfuro[2,3-*b*]pyrazine (**8d**)*

100% yield. $\delta_H$ (300 MHz, $CDCl_3$) 7.89 (m, 4H), 7.52 (m, 2H), 7.35 (m, 5H), 7.16 (s, 1H), 7.10 (m, 3H), 6.90 (m, 2H), 3.95 (m, 2H), 2.44 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 160.6, 154.6, 150.5, 148.4, 140.0, 136.2, 133.7, 131.9, 129.8, 128.9, 128.4, 128.2, 127.7, 126.6, 126.2, 126.1, 125.3, 100.5, 41.3, 21.6. *m/z* (HR-MS EI) Found 426.1735. $C_{30}H_{22}ON_2$ requires 426.1732.

*Sonogashira Coupling Reaction on Substituted 2-Chloro-furo[2,3-*b*]pyrazine **4a**–**c**. A Typical Procedure*

In a 15 mL microwave vial were successively dissolved in DMF/$Et_3N$ (1:1, 4 mL) pyrazine **4a**–**c** (0.3 mmol), acetylene **2e**,**l**,**m** (0.375 mmol, 1.25 equiv.), $Pd(PPh_3)Cl_2$ (17 mg, 5 mol%), and CuI (5.7 mg, 10 mol%). The reaction tube was sealed and irradiated in a microwave reactor at a ceiling temperature of 100°C at 80 W maximum power for 15 min. After the reaction the mixture was cooled with an air flow for 15 min, extracted with dichloromethane (2 × 150 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to silica gel column chromatography (from 10% to 30% EtOAc in heptane) to afford compounds **9a**–**c**.

*2-(2-Cyclohexylethynyl)-3,6-bis(4-methoxyphenyl)furo[2,3-*b*]pyrazine (**9a**)*

Yellow solid in 85% yield. mp 140–143°C. $\delta_H$ (300 MHz, $CDCl_3$) 8.09 (d, *J* 9.15, 2H), 7.89 (d, *J* 8.22, 2H), 7.03–6.98 (m, 5H), 3.89 (s, 6H), 2.66–2.62 (m, 1H), 1.88–1.86 (m, 2H), 1.73–1.70 (m, 2H), 1.56–1.52 (m, 6H). $\delta_C$ (75 MHz, $CDCl_3$) 161.4, 160.4, 153.6, 148.3, 139.9, 133.9, 131.1, 129.9, 129.1, 128.7, 127.3, 121.5, 114.5, 114.0, 113.3, 99.1, 79.7, 55.4, 31.9, 29.9, 25.8, 24.9. *m/z* (HR-MS EI) Found 438.1964. $C_{28}H_{26}O_3N_2$ requires 438.1943.

*6-(4-Ethylphenyl)-3-(4-methoxyphenyl)-2-(2-*p*-tolylethynyl)furo[2,3-*b*]pyrazine (**9b**)*

Yellow solid in 92% yield. mp 156–159°C. $\delta_H$ (300 MHz, $CDCl_3$) 8.17 (d, *J* 8.22, 2H), 7.89 (d, *J* 8.22, 2H), 7.43 (d, *J* 8.22, 2H), 7.35 (d, *J* 8.22, 2H), 7.16 (d, *J* 8.22, 2H), 7.05 (d, *J* 8.22, 2H), 3.91 (s, 3H), 2.77–2.69 (m, 2H), 2.37 (s, 3H), 1.31–1.26 (t, *J* 15.54, 7.32, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 161.4, 160.6, 149.0, 147.3, 139.9, 133.6, 131.7, 131.1, 129.2, 128.6, 126.2, 125.7, 119.2, 113.4, 100.1, 93.1, 55.4, 28.9, 21.6, 15.3. *m/z* (HR-MS EI) Found 444.1841. $C_{30}H_{24}O_2N_2$ requires 444.1838.

*6-(Biphenyl-4-yl)-3-(4-methoxyphenyl)-2-(phenylethynyl)furo[2,3-*b*]pyrazine (**9c**)*

Yellow solid in 96% yield. mp 191–194°C. $\delta_H$ (300 MHz, $CDCl_3$) 8.16 (d, *J* 9.15, 2H), 8.04 (d, *J* 8.22, 2H), 7.75 (d, *J* 9.15, 2H), 7.66 (d, *J* 7.32, 2H), 7.55–7.46 (m, 4H), 7.42–7.36 (m, 4H), 7.24 (s, 1H), 7.07 (d, *J* 8.22, 2H), 3.91 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 160.9, 154.1, 149.5, 143.3, 140.0, 133.7, 131.9, 131.3, 129.7, 129.2, 128.5, 128.1, 127.8, 127.6, 127.1, 126.2, 122.4, 113.6, 101.0, 93.0, 88.4, 55.5. *m/z* (HR-MS EI) Found 478.1671. $C_{33}H_{22}O_2N_2$ requires 478.1681.

*A Typical Procedure for Selective Sonogashira Coupling Reaction on Dihalo-Substituted Furo[2,3-*b*]pyrazine **5c**,**e***

In a 15 mL microwave vial were successively dissolved in DMF/$Et_3N$ (1:1, 4 mL) pyrazine **5c**,**e** (0.3 mmol), acetylene **2i**,**e**,**n** (0.315 mmol, 1.05 equiv.), $Pd(PPh_3)Cl_2$ (3.4 mg, 1 mol%), and CuI (2.0 mg, 3 mol%). The reaction tube was sealed and irradiated in a microwave reactor at a ceiling temperature of 95°C at 80 W maximum power for 7–10 min. After reaction the mixture was cooled with an air flow for 15 min, extracted with dichloromethane (2 × 150 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to silica gel column chromatography (from 5% to 10% EtOAc in heptane) to afford compounds **10a**–**c**.

*3-Benzyl-2-chloro-6-(thiophen-3-yl)-7-(2-(thiophen-3-yl)ethynyl)furo[2,3-*b*]pyrazine (**10a**)*

Yellow solid in 89% yield. mp 140–144°C. $\delta_H$ (300 MHz, $CDCl_3$) 8.32 (d, *J* 1.83, 1H), 7.97 (d, *J* 5.49, 1H), 7.66 (d, *J* 4.0, 1H), 7.48–7.45 (m, 2H), 7.35–7.28 (m, 6H), 4.39 (s, 2H). $\delta_C$ (75 MHz, $CDCl_3$) 155.4, 152.6, 148.8, 145.2, 141.3, 137.4, 130.6, 129.2, 128.7, 128.2, 127.8, 126.9, 126.2, 125.8, 125.9, 116.0, 89.0, 77.8, 41.2. *m/z* (HR-MS EI) Found 432.0145. $C_{23}H_{13}ON_2S_2Cl$ requires 432.0158.

*3-Benzyl-2-chloro-6-(thiophen-3-yl)-7-(2-*p*-tolylethynyl)furo[2,3-*b*]pyrazine (**10b**)*

Yellow solid in 86% yield. mp 121–125°C. $\delta_H$ (300 MHz, $CDCl_3$) 8.33 (s, 1H), 7.98 (d, *J* 5.49, 1H), 7.53 (d, *J* 8.22, 2H), 7.47–7.43 (m, 1H), 7.37–7.19 (m, 7H), 4.39 (s, 2H), 2.39 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 157.8, 153.0, 147.9, 145.3, 139.4, 138.4, 137.3, 132.0, 130.5, 129.4, 128.7, 126.9, 125.7, 119.5, 98.8, 98.3, 41.3, 21.7. *m/z* (HR-MS EI) Found 440.0746. $C_{26}H_{17}ON_2SCl$ requires 440.0750.

*2-Chloro-6-(3-fluorophenyl)-3-(4-methoxyphenyl)-7-(oct-1-ynyl)furo[2,3-*b*]pyrazine (**10c**)*

Yellow solid in 74% yield. mp 97–100°C. $\delta_H$ (300 MHz, $CDCl_3$) 8.14 (m, 2H), 7.85 (d, *J* 8.19, 2H), 7.52–7.47 (m, 1H), 7.21–7.15 (m, 1H), 7.03 (d, *J* 9.15, 2H), 3.89 (s, 3H), 2.66–2.61 (t, *J* 13.71, 7.32, 2H), 1.79–1.69 (m, 2H), 1.57–1.54 (m, 2H),

1.37–1.35 (m, 4H), 0.94–0.89 (t, *J* 13.71, 6.39, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 164.5, 161.2, 160.8, 158.9, 152.9, 147.0, 144.1, 139.0, 131.5, 130.5, 128.7, 122.2, 117.6, 113.8, 113.2, 102.3, 69.1, 55.5, 31.4, 28.9, 28.4, 22.6, 20.3, 14.1. *m/z* (HR-MS EI) Found 462.1516. $C_{27}H_{24}O_2N_2ClF$ requires 462.1510.

### *A Typical Procedure for the Preparation of Furopyrazines **11a–c***

In a 15 mL microwave vial were successively dissolved in DMF/$H_2O$ (1:1, 4 mL) furopyrazine **7b**,**d**,**e** (0.3 mmol), boronic acid **6f**,**m**,**n** (0.45 mmol, 1.50 equiv.), $Pd(PPh_3)_4$ (3 mg, 1 mol%), and $Na_2CO_3$ (64 mg, 2 equiv.). The reaction tube was sealed and irradiated at a ceiling temperature of 100°C at 100 W maximum power for 10 min. After the reaction the mixture was cooled with an air flow for 15 min, extracted with dichloromethane (2 × 50 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to silica gel flash chromatography (from 10% to 30% $CH_2Cl_2$ in petroleum ether) to afford compounds **11a**–**c**.

#### *1-(4-(3-Benzyl-2-(4-*tert*-butylphenyl)-6-(thiophen-3-yl)furo[2,3-*b*]pyrazin-7-yl)phenyl)ethanone (**11a**)*

White solid in 87% yield. mp 149–152°C. $\delta_H$ (300 MHz, $CDCl_3$) 8.04 (d, *J* 8.22, 2H), 7.84–7.80 (m, 3H), 7.44–7.43 (m, 4H), 7.31 (s, 2H), 7.24–7.10 (m, 5H), 4.33 (s, 2H), 2.63 (s, 3H), 1.36 (s, 9H). $\delta_C$ (75 MHz, $CDCl_3$) 197.8, 153.5, 152.2, 151.6, 148.0, 139.4, 136.6, 135.3, 130.5, 129.3, 128.9, 126.7, 126.4, 125.4, 115.0, 41.2, 34.8, 31.5, 26.8. *m/z* (HR-MS EI) Found 542.2029. $C_{35}H_{30}O_2N_2S$ requires 542.2028.

#### *7-(4-*tert*-Butylphenyl)-6-cyclopentyl-2-(3-ethoxyphenyl)furo[2,3-*b*]pyrazine (**11b**)*

White solid in 92% yield. mp 102–104°C. $\delta_H$ (300 MHz, $CDCl_3$) 8.60 (s, 1H), 7.70 (d, *J* 8.22, 2H), 7.61–7.53 (m, 4H), 7.41–7.36 (t, *J* 16.44, 8.22, 1H), 6.98 (d, *J* 9.12, 1H), 4.15–4.08 (m, 2H), 3.67–3.56 (m, 1H), 2.11–1.96 (m, 6H), 1.74–1.72 (m, 2H), 1.47–1.39 (m, 12H). $\delta_C$ (75 MHz, $CDCl_3$) 161.4, 160.6, 149.0, 147.3, 139.9, 133.6, 131.7, 131.1, 129.2, 128.6, 126.2, 125.7, 119.2, 113.4, 100.1, 93.1, 55.4, 28.9, 21.6, 15.3. *m/z* (HR-MS EI) Found 440.2461. $C_{29}H_{32}O_2N_2$ requires 440.2464.

#### *2-(2-Fluorophenyl)-7-(4-methoxyphenyl)-3-methyl-6-*o*-tolylfuro[2,3-*b*]pyrazine (**11c**)*

95% yield. $\delta_H$ (300 MHz, $CDCl_3$) 7.61 (m, 10H), 6.84 (d, *J* 8.22, 2H), 3.77 (s, 3H), 2.60 (s, 3H), 2.26 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 161.7, 159.1, 158.4, 154.9, 154.4, 146.9, 146.1, 138.1, 132.0, 131.0, 130.5, 129.9, 127.6, 126.1, 124.4, 122.7, 117.3, 115.9, 114.2, 55.2, 22.2, 20.3. *m/z* (HR-MS EI) Found 542.2035. $C_{27}H_{21}O_2N_2F$ requires 542.2028.

### *A Typical Sonogashira Coupling for **11d***

In a 15 mL microwave vial were successively dissolved in DMF/$Et_3N$ (1:1, 4 mL) pyrazine **7d** (0.3 mmol), acetylene **2e** (0.39 mmol, 1.3 equiv.), $Pd(PPh_3)Cl_2$ (17 mg, 5 mol%), and CuI (5.7 mg, 10 mol%). The reaction tube was sealed, and irradiated in a microwave reactor at a ceiling temperature of 100°C at 80 W maximum power for 15 min. After the reaction the mixture was cooled with an air flow for 15 min, extracted with dichloromethane (2 × 150 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to silica gel column chromatography (from 10% to 30% EtOAc in heptane) to afford 1-(4-(3-benzyl-6-(thiophen-3-yl)-2-(2-*p*-tolylethynyl)furo[2,3-*b*]pyrazin-7-yl)phenyl) ethanone (**11d**) as a light yellow solid in 86% yield. mp 210–215°C. $\delta_H$ (300 MHz, $CDCl_3$) 8.08 (d, *J* 8.22, 2H), 7.79–7.76 (m, 3H), 7.50–7.44 (m, 4H), 7.33–7.12 (m, 8H), 4.54 (s, 2H), 2.66 (s, 3H), 2.39 (s, 3H). $\delta_C$ (75 MHz, $CDCl_3$) 197.8, 152.9, 152.4 139.7, 139.3, 138.5, 136.9, 136.1, 134.8, 131.9, 130.3, 129.4, 128.7, 126.9, 126.0, 119.1, 114.7, 94.8, 86.5, 41.9, 26.8, 21.7. *m/z* (HR-MS EI) Found 524.1551. $C_{34}H_{24}O_2N_2S$ requires 524.1558.

### *Disubstituted Suzuki Cross-Coupling. A Typical Procedure*

In a 15 mL microwave vial were successively dissolved in DMF (4 mL) furopyrazine **5g** (0.3 mmol), boronic acid **6o** (0.9 mmol, 3.0 equiv.), $Pd(PPh_3)_4$ (16 mg, 5 mol%), and $K_2CO_3$ (166 mg, 5 equiv.). The reaction tube was sealed and irradiated at a ceiling temperature of 140°C at 300 W maximum power for 25 min. After the reaction the mixture was cooled with an air flow for 15 min, extracted with dichloromethane (2 × 50 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to silica gel flash chromatography (from 0% to 5% EtOAc in heptane) to afford 6-cyclopropyl-2,7-bis(4-fluorophenyl)-3-methylfuro[2,3-*b*]-pyrazine (**12a**) as a white solid in 93% yield. mp 81–84°C. $\delta_H$ (300 MHz, $CDCl_3$) 7.86–7.81 (m, 2H), 7.58–7.54 (m, 2H), 7.20–7.13 (m, 4H), 2.64 (s, 3H), 2.37–2.32 (m, 1H), 1.35–1.13 (m, 4H). $\delta_C$ (75 MHz, $CDCl_3$) 164.5, 163.9, 161.2, 160.6, 159.8, 152.8, 149.5, 143.9, 138.6, 135.6, 131.4, 130.7, 126.3, 116.0, 115.5, 115.1, 23.3, 9.5, 8.8. *m/z* (HR-MS EI) Found 362.1225. $C_{22}H_{16}ON_2F_2$ requires 362.1231.

## Accessory Publication

General experimental methods and spectroscopic and analytical data for compounds are available from the journal's website.

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