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An Expeditious Route toward Pyrazine-Containing Nucleoside Analogues

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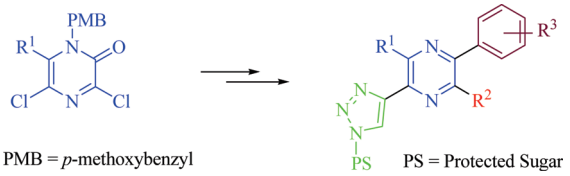

An improved and convenient methodology for the synthesis of asymmetrically substituted pyrazines starting from 3,5-dichloropyrazin-2(1*H*)-ones has been elaborated. Several nucleoside analogues have been synthesized containing the pyrazine core as the organic base coupled with the sugar via a triazole linkage. The beneficial effect of microwave irradiation throughout the sequence has been demonstrated.

Introduction

Nucleosides possess a broad spectrum of biological functions, ranging from their primary role as building blocks in the genetic code to other functions, such as biosynthetic intermediates, energy donors, metabolic regulators, and cofactors in enzymatic processes. Many nucleoside analogues have been developed for screening as antiviral agents, nonradioactive fluorescent labels for DNA, and as anticancer drugs, by variation of the sugar part and/or the heterocyclic base.[1] As a result, nucleosides and their analogues have generated considerable scientific interest in their chemistry and biology.[2] A substantial number of naturally occurring and synthetic nucleosides, many with interesting biological activities, have been prepared via a variety of approaches.[3] Although pyrimidine-like nucleosides have been studied extensively, pyrazine-based nucleosides were still missing from this array until recently.[4] Therefore, we reasoned that it might be worthwhile to investigate the use of substituted pyrazines as alternative organic bases of the nucleoside.

Tri- and tetrasubstituted pyrazines are present in the core structure of a number of important natural as well as synthetic heterocyclic compounds, such as, for example, flavor components in food.[5] Especially, pyrazines substituted with a thioether function are known to possess a nice aroma.

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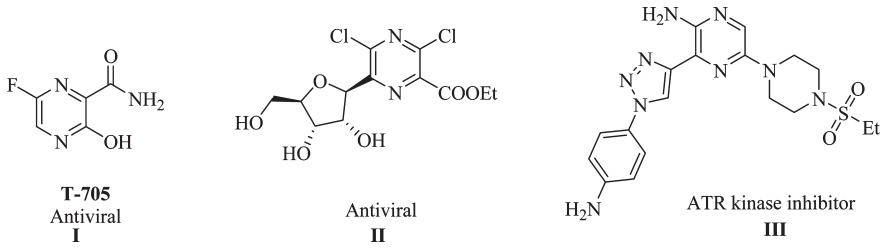

FIGURE 1. Examples of pharmacologically active molecules having a pyrazine core.

Moreover, they are versatile synthetic intermediates.[6] Many substituted pyrazines possess important pharmacological activities, such as antiviral[7] (Figure 1, compounds **I** and **II**), ATR kinase inhibitor[8] (Figure 1, compound **III**), antimutagenic,[9] vascular endothelial growth factor inhibitory activity,[10] or as epithelial sodium channel blockers.[11] Despite their importance, only a limited number of synthetic methodologies are described for the generation of asymmetrically multisubstituted pyrazines.[12]

We have previously explored the application of 3,5-dichloropyrazin-2(1*H*)-ones as attractive starting materials for the synthesis of different heterocyclic compounds.[13] We envisaged that the pyrazinone framework offers a unique gateway for the generation of asymmetrically tri- and tetrasubstituted pyrazines (Scheme 1). The substituent in the C6-position of the pyrazinone is determined by the aldehyde used during its construction,[14] whereas the substituent at the C3-position could be easily introduced via reaction of the imidoyl chloride moiety.[15] The pyrazinone can be converted to the pyrazine-thione by Lawesson's reagent, followed by removal of the *p*-methoxybenzyl group and simultaneous conversion of the thione to the methyl thioether.[16] In the newly generated pyrazines, the chlorine becomes susceptible toward the Sonogashira cross-coupling reaction with trimethylsilylacetylene. After desilylation, affording the corresponding ethynyl pyrazine,[17,3a] a Huisgen [3 + 2] cycloaddition could be performed on this terminal acetylene with a suitable sugar azide.[18] Finally, the methyl thioether group is involved in a Liebeskind−Srogl[19] cross-coupling reaction, giving the asymmetrically substituted pyrazine coupled with a sugar moiety via a triazole linkage.

Results and Discussion

Pyrazin-2(1*H*)-ones **1a**−**c** were alkoxylated at the C3-position using NaH, giving quantitative yields of **2a**−**c** (Scheme 2). Treatment of **1d** with Me_4Sn under Stille conditions provided methylated compound **2d** in 95% yield. All C3-substituted pyrazine-2(1*H*)-ones **2a**−**d** were reacted with Lawesson's reagent in toluene at reflux temperature to afford the corresponding thioamides **3a**−**d** in good yields (Scheme 2).

A mixture of compound **3a** with 5 equiv of methyl iodide and 10 mol % of iodine in toluene was refluxed for 12 h, yielding 72% of the expected methylthioether **4a** together with 20% of *p*-methoxybenzylthioether **5a** as the main byproduct (Table 1, entry 1).[16] The formation of **5a** might be explained by the competitive reaction of the in situ formed *p*-methoxybenzyliodide. During the scale-up of the reaction, we noticed that it was rather difficult to separate the desired methylthioether **4a** from the compound **5a** due to similar polarity. Therefore, efforts were made to make this reaction more selective. However, under microwave irradiation, at a temperature of 130 °C for 30 min applying further the same conditions, the amount of byproduct **5a** increased (Table 1, entry 2). The reaction was rather slow in the absence of iodine, still giving both **4a** and **5a**, with decreased yield

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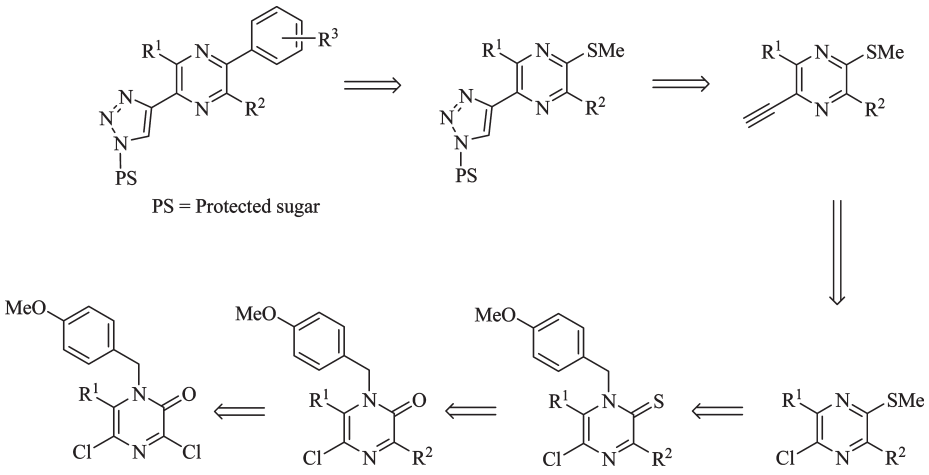
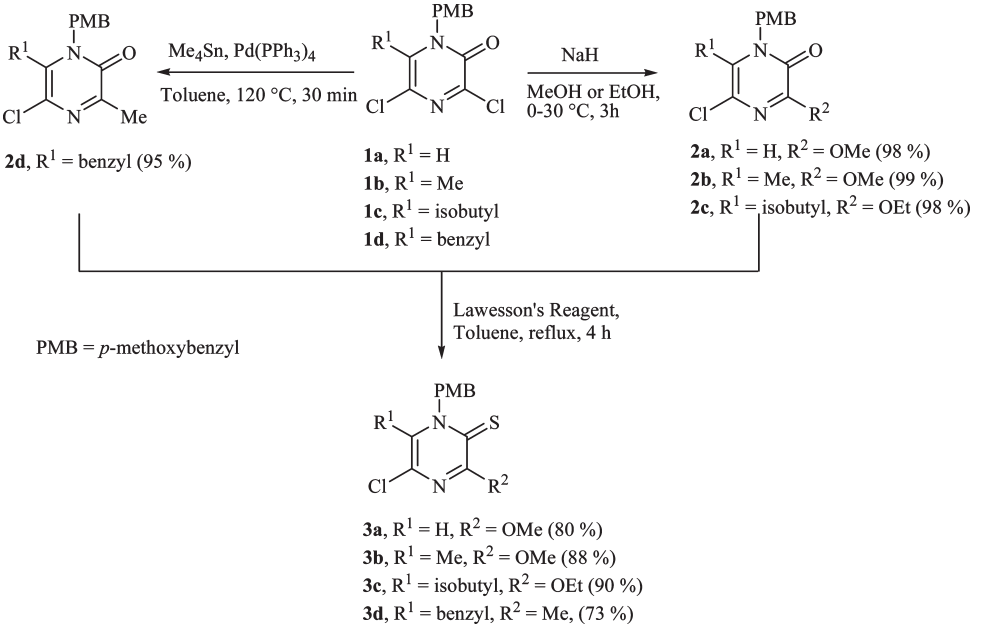
SCHEME 1. Retrosynthetic Analysis for the Generation of Asymmetrically Substituted Pyrazines Coupled with a Sugar Moiety via a Triazole Linkage



SCHEME 2. Synthesis of Pyrazin-2(1*H*)-thiones 3a−d



(Table 1, entry 3). This observation was rather interesting as only salt formation was expected with methyliodide. Clearly, upon heating,[20] the intermediate salt loses *p*-methoxybenzyl iodide, forming **4a**, and the in situ formed *p*-methoxybenzyliodide reacts with an other molecule of starting material **3a** to give **5a**. As it was impossible to minimize the competition between methyl iodide and in situ formed *p*-methoxybenzyl iodide, it was decided to exclude methyl iodide from the reaction mixture. This should result in the sole formation of *p*-methoxybenzylthioether **5a**. As a proof of concept, when **3a** was refluxed in toluene with 10 mol % of I_2, to our satisfaction, only **5a** was formed in 45% yield (Table 1, entry 4). Interestingly, when the solvent was changed to dichloromethane, the yield increased to 65% (Table 1, entry 5). When the reaction was run at rt with 5, 10, 50, and 80 mol % of I_2, respectively, there was not much change in yields, but a dramatic difference in reaction time was observed ranging from 40 to 0.15 h (Table 1, entries 8, 7, 9, and 10). The best condition was obtained when the reaction was carried out with 10 mol % of I_2 in dichloromethane under microwave irradiation at 80 °C and a maximum power of 150 W for 15 min, yielding compound **5a** in 83% yield (Table 1, entry 6).

A plausible mechanism for the transfer of the *p*-methoxybenzyl group is shown in Scheme 3. Iodine first reacts with the sulfur atom of thioamide **3a** to give intermediate **A**. This loses the *p*-methoxybenzyl group to form the unstable intermediates **B** and **C** that directly react with each other to give the *p*-methoxybenzylthioethers **5**, while iodine goes back in the catalytic cycle. It is interesting to note that the reaction, which is rather slow at room temperature, is speeded up under microwave irradiation. To the best of our knowledge, there is no literature precedent about the transfer of a

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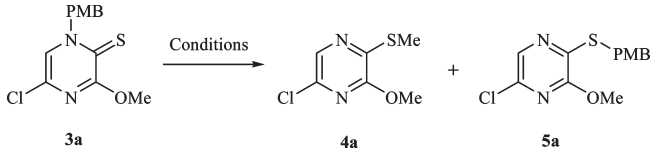
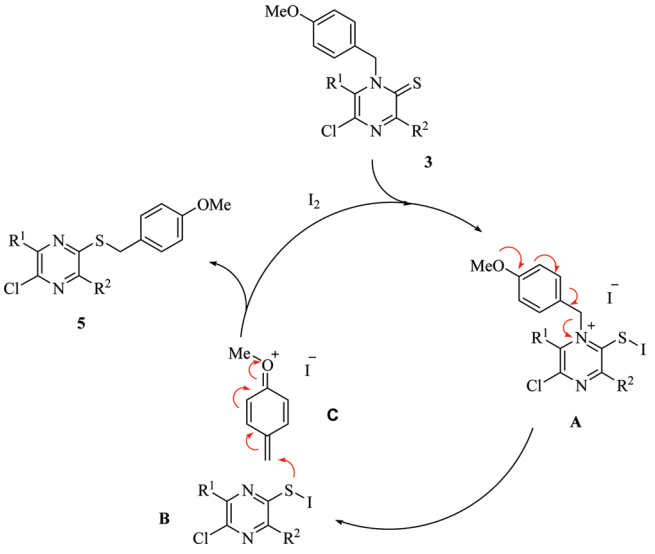
TABLE 1. Optimization Study for Thioether Formation[a]



entry	reagent (equiv)	catalyst (mol %)	solvent	temp	time (h)	yield (%) **4a**:**5a**
1[b]	MeI (5)	I_2 (10)	toluene	reflux	12	72:20
2[c]	MeI (5)	I_2 (10)	toluene	130 °C	0.5	55:30
3	MeI (5)		toluene	reflux	1	40:15
4		I_2 (10)	toluene	reflux	12	0:45
5		I_2 (10)	DCM	reflux	6	0:65
6[d]		I_2 (10)	DCM	80 °C	0.25	0:83
7		I_2 (10)	DCM	rt	24	0:79
8		I_2 (5)	DCM	rt	40	0:73
9		I_2 (50)	DCM	rt	6	0:80
10		I_2 (80)	DCM	rt	0.15	0:85

[a]All the reactions were run on a 0.1 mmol scale of **3a** with conventional heating unless otherwise stated. [b]Scale-up reaction with 5 mmol of **3a** was also done with full conversion, but it was not possible to separate **4a** from **5a** by column chromatography. [c]The reaction mixture was irradiated using a maximum power of 400 W in a multimode microwave apparatus. [d]The reaction mixture was irradiated using a maximum power of 150 W in a multimode microwave apparatus.

SCHEME 3. Plausible Mechanism for the Transfer of the *p*-Methoxybenzyl Group

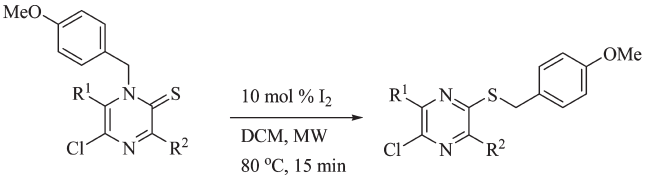


p-methoxybenzyl group from nitrogen to sulfur in a *p*-methoxybenzyl-protected thioamide.

This optimized protocol was applied to convert the pyrazin-2(1*H*)-thiones **3b**−**d** into the corresponding *p*-methoxybenzylthioethers **5b**−**d**, which were obtained in good yields (Scheme 4).

In the newly generated pyrazines **5**, the chlorine atom that was present at the C5-position of the starting pyrazinone is now susceptible for transition-metal-catalyzed cross-coupling reactions. However, to our surprise, all efforts made to perform a Sonogashira reaction met with failure (Table 2). This is in sharp contrast with our previously published work,[16] where the reaction went smoothly when an S-Me group was present instead of an S-PMB group at the C2-position of the pyrazine. Probably, the *p*-methoxybenzylthioether renders the chlorine less susceptible toward nucleophilic substitution by the palladium.

SCHEME 4. Synthesis of *p*-Methoxybenzylthioether Derivatives 5b−d



3b, R^1 = Me, R^2 = OMe
3c, R^1 = isobutyl, R^2 = OEt
3d, R^1 = Benzyl, R^2 = Me

5b, R^1 = Me, R^2 = OMe (88 %)
5c, R^1 = isobutyl, R^2 = OEt (80 %)
5d, R^1 = Benzyl, R^2 = Me (72 %)

Therefore, it seems obvious to substitute first the S-PMB group and then to check the reactivity of chlorine again. It was also interesting to know whether the S-PMB group should be reactive enough under standard Liebiskind−Srogl conditions. When pyrazine **5a** was reacted with boronic acid **8a** in the presence of copper(I)-thiophene-2-carboxylate and $Pd(PPh_3)_4$ in THF under conventional heating as well as under microwave irradiation (Table 3, entries 1−3, 5, and 6), poor to average yields were obtained. As the reaction was rather sluggish, it was assumed that reagents were getting decomposed during the long reaction time at high temperature. To overcome this difficulty, the reagents were added in two portions, and to our satisfaction, the reaction was complete in 1 h under microwave irradiation at 120 °C, yielding **9a** in 84% (Table 3, entry 4).[21]

This optimized protocol was then applied for the conversion of **5a**−**d** to **9b**−**j** in good to excellent yields (Table 4).

Having successfully established the optimized conditions for the pyrazine scaffold, we next explored the scope of the protocol for some other heterocycles bearing an S-PMB group. All starting compounds with a *p*-methoxybenzylthio or benzylthio group were synthesized according to literature procedures[22] from their respective thiol derivative.

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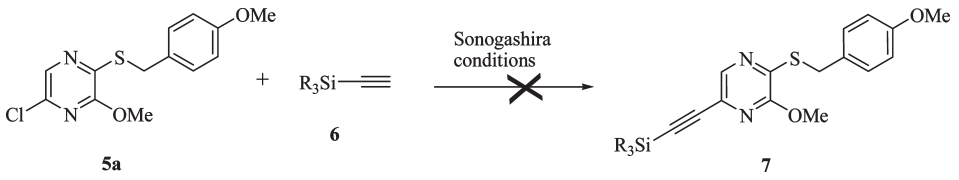
TABLE 2. Attempts for the Sonogashira Cross-Coupling Reaction on Pyrazine 5a[a]

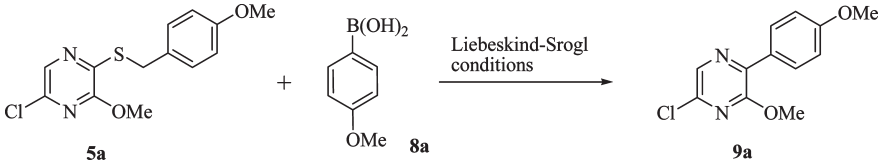


5a **6** **7**

entry	R	Pd catalyst	Cu source	additive (equiv)	yield of **7** (%)
1	Me	$Pd(PPh_3)_2Cl_2$	CuI		[b]
2	Me	$Pd(PPh_3)_2Cl_2$	CuI	TBAI[c] (1.2)	[b]
3	iso-propyl	$Pd(PPh_3)_2Cl_2$	CuI		[b]
4	iso-propyl	$Pd(PPh_3)_2Cl_2$	CuI	TBAI[c] (1.2)	[b]
5	Me	$Pd(OAc)_2$	CuI		[b]
6	Me	$Pd(OAc)_2$	CuI	TBAI[c] (1.2)	[b]

[a]Reactions were run on a 0.1 mmol scale of **5a**, applying silyl acetylene (1.5 equiv), Pd catalyst (5 mol %), and a Cu source (10 mol %) using a mixture of DMF and triethylamine (1:1, 3 mL). The reactions were irradiated for 15 min at a 95 °C ceiling temperature using a maximum power of 75 W in a multimode microwave apparatus. [b]The starting material was recovered. [c]TBAI = tetrabutylammoniumiodide.

TABLE 3. Optimization Study for the Liebeskind−Srogl Cross-Coupling Reaction on the S-PMB Group[a]



5a **8a** **9a**

entry	boronic acid (equiv)	CuTC equiv	$Pd(PPh_3)_4$ mol %	temp °C (MW[b]/ΔT)	time (h)	ratio[c] (**9a**:**5a**)
1	3	3	5	100 (MW)	0.8	40:30
2	5	5	10	120 (MW)	1.3	57:25
3	1.1	1.2	3	100 (MW)	0.8	30:62
4[d]	2 + 1	1.5 + 1	5 + 5	120 (MW)	0.5 + 0.5	84:08
5	3	3	5	reflux (ΔT)	10	30:65
6[d]	2 + 1	1.5 + 1	5 + 5	reflux (ΔT)	4 + 4	45:50

[a]All reactions were run on a 0.2 mmol scale of **5a** in THF in sealed tubes. [b]A maximum power of 500 W in a multimode microwave apparatus was used. [c]Ratio determined by GC-MS. [d]A fresh batch of reagents was added at the stipulated times. CuTC = copper(I)-thiophene-2-carboxylate.

Gratifyingly, applying our optimized protocol, the arylated products **11a−i** were obtained in good to excellent yields (Scheme 5). However, the Liebeskind−Srogl cross-coupling reaction did not proceed in the case of isopropyl boronic acid. Similarly, no reaction occurred when 2-(4-methoxybenxylthio)-1-methyl-1*H*-imidazole **10d** was used (Scheme 5).

As we were able to substitute the S-PMB group of compound **5** by an aryl group in compound **9**, we reinvestigated the reactivity of the chlorine toward the Sonogashira reaction. To our delight, when a mixture of compound **9** with 1.5 equiv of triisopropylsilylacetylene, $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (10 mol %), and TBAI (1.2 equiv) in DMF/TEA (1:1) was irradiated for 20 min at a ceiling temperature of 80 °C, a smooth reaction took place. Subsequent desilylation upon treatment of the crude compound with 1 M tetrabutylammonium fluoride (TBAF) in THF at rt yielded the desired terminal acetylenes **12a−d** (Table 5), which were purified by simple filtration over silica gel.

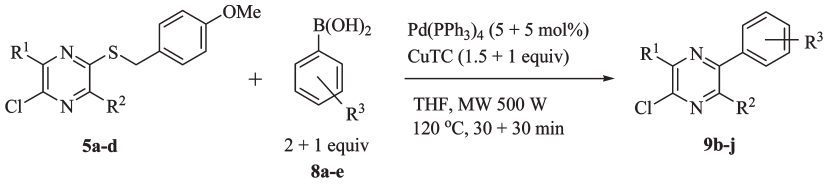
For the final step, all protected sugar azides[23] and the benzyl azide[24] **13a−e** (Figure 2) were synthesized according to literature procedures. The coupling of the azides **13a−d** with the generated pyrazines **12a−d** was then investigated. A mixture of pyrazine **12** with 1.2 equiv of the protected sugar azide **13**, 2 equiv of copper turnings, 5 mol % of $CuSO_4$, and 5 mol % of tris-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-amine ligand (TBTA) in THF/*i*-PrOH/H_2O (3:1:1, 5 mL) was irradiated at a 90 °C ceiling temperature using a maximum power of 200 W for 20 min. The Cu(I)-catalyzed [3 + 2] dipolar cycloaddition reaction occurred with full regioselectivity, resulting in the formation of the corresponding 1,4-disubstituted 1,2,3-triazoles **14a−h** in good yields (Table 6, entries 1−8). Reacting pyrazine **12d** with benzyl azide, applying similar conditions, afforded 1,2,3-triazole compound **14i** in good yield (Table 6, entry 9). Interestingly, when pyrazine **12d** was reacted with TMS-azide, the corresponding desilylated 1,2,3-triazole product **14j** was obtained.

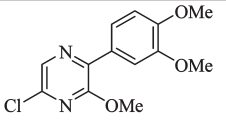
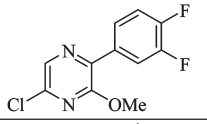
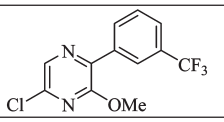
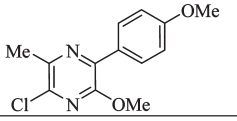
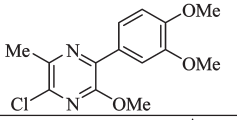
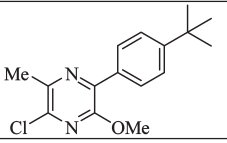
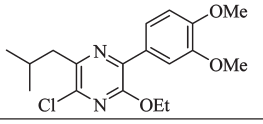
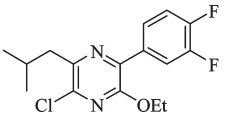
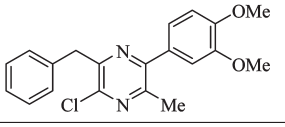
Conclusion

In conclusion, we have developed a new and efficient synthetic procedure for the synthesis of differently substituted ethynyl pyrazines starting from 1-(4-methoxybenzyl)-3,5-dichloropyrazin-2(1*H*)-ones. These newly generated ethynyl pyrazines can easily be coupled, via a triazole linkage, with

(23) (a) Stimac, A.; Kobe, J. *Carbohydr. Res.* **2000**, *324*, 149. (b) Stimac, A.; Kobe, J. *Carbohydr. Res.* **2000**, *329*, 317.
(24) Ankati, H.; Biehl, E. *Tetrahedron Lett.* **2009**, *50*, 4677.

TABLE 4. Liebeskind−Srogl Cross-Coupling Reaction on Pyrazines 5[a]



entry	reactant	R^3	product	structure	yield (%)
1	**5a**	3, 4-diOMe-	**9b**		69
2	**5a**	3, 4-diF-	**9c**		75
3	**5a**	3-CF_3-	**9d**		80
4	**5b**	4-OMe-	**9e**		86
5	**5b**	3, 4-diOMe-	**9f**		93
6	**5b**	4-^{t}Bu-	**9g**		92
7	**5c**	3, 4-diOMe-	**9h**		79
8	**5c**	3, 4-diF-	**9i**		72
9	**5d**	3, 4-diOMe-	**9j**		80

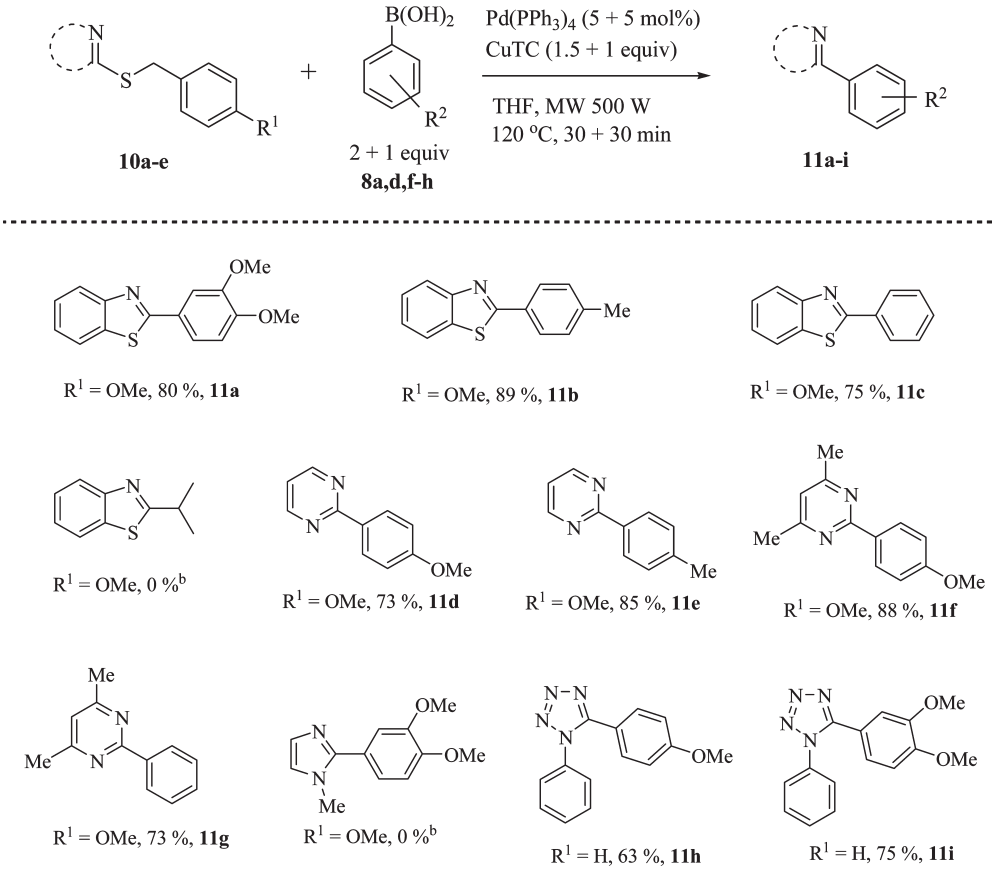
[a]Reactions were run on a 0.5 mmol scale of **5a**−**d**, boronic acids (2 + 1 equiv), $Pd(PPh_3)_4$ (5 + 5 mol %), and CuTC (1.5 + 1 equiv), in THF (4 mL). The mixture was irradiated in a sealed tube at a ceiling temperature of 120 °C and a maximum power of 500 W for 60 min in a multimode microwave apparatus. The reagents were added in two portions as stipulated; the second portion was added at half the reaction time (i.e., 30 min). CuTC = copper(I)-thiophene-2-carboxylate.

sugars applying a regioselective microwave-assisted Cu(I)-catalyzed [3 + 2] dipolar cycloaddition reaction, resulting in the formation of a small library of hitherto unknown nucleoside analogues. The application of microwave irradiation during different steps of the sequence has been shown to be highly valuable for speeding up reactions. We have also demonstrated that our newly optimized Liebeskind−Srogl protocol is applicable for different heterocycles bearing a benzylthio ether functionality.

Experimental Section

General. Proton NMR spectra were recorded on a 300 MHz instrument using $CDCl_3$ and $DMSOd_6$ as solvents unless otherwise stated. The ^1H and ^{13}C chemical shifts are reported

SCHEME 5. Expanding the Scope of the Newly Developed Liebeskind−Srogl Cross-Coupling Procedure for Some Other Heterocycles[a]



[a]All the reactions were run on a 0.5 mmol scale of **10**. [b]Only starting material was recovered.

in parts per million relative to tetramethylsilane as an internal standard. For the mass spectrometry, the ion source temperature was 150−250 °C, as required. High-resolution EI-mass spectra were performed with a resolution of 10 000. For chromatography, analytical TLC plates and 70−230 mesh silica gel were used. All the solvents and chemicals were purchased and used as available.

Microwave Irradiation Experiments. All microwave irradiation experiments were carried out in a multimode Milestone MicroSYNTH microwave reactor (Laboratory Microwave Systems). This apparatus was used in the standard configuration as delivered, including proprietary software. Reactions were carried out in sealed microwave process vials (15, 50 mL), and the temperature control was performed using both external infrared and internal fiber optic sensors. The ramp time (time required to reach the expected temperature) was always between 1 and 2 min and is included in the total reaction time. The reaction mixture was continuously stirred during the reaction. After the irradiation, the reaction vessel was rapidly cooled by air jet cooling to the ambient temperature.

General Procedure for the Preparation of 1a−d. The general procedure for the preparation of **1a−d** is the same as previously described by our group.[25] Data for compounds **1a**,**b**,**d** are in accordance with the previously published work.[25]

1-(4-Methoxybenzyl)-3,5-dichloro-6-isobutylpyrazin-2(1*H*)-one (1c): yellow solid; mp 118−120 °C; yield 44%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, J = 8.49 Hz, 2H), 6.86 (d, J = 8.67 Hz, 2H), 5.30 (s, 2H), 3.78 (s, 3H), 2.70 (d, J = 7.35 Hz, 2H), 2.14−2.03 (m, 1H), 1.05 (d, J = 6.57 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 153.1, 143.8, 138.9, 128.3, 126.2, 124.7, 114.4, 55.3, 49.2, 37.8, 28.8, 22.4; HRMS (EI) calcd for $C_{16}H_{18}Cl_2N_2O_2$ 340.0745, found 340.0753.

General Procedure for the Preparation of 2a−c. The general procedure for the preparation of **2a−c** is the same as previously described by our group. Data for compounds **2a**[16] and **2b**[26] are in accordance with the previously published work.

1-(4-Methoxybenzyl)-5-chloro-3-ethoxy-6-isobutylpyrazin-2(1*H*)-one (2c): white solid; mp 86−88 °C; yield 98%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, J = 8.67 Hz, 2H), 6.84 (d, J = 8.64 Hz, 2H), 5.25 (s, 2H), 4.39 (q, J = 7.14 Hz, 2H), 3.77 (s, 3H), 2.59 (d, J = 7.35 Hz, 2H), 1.99 (m, 1H), 1.46 (t, J = 6.96 Hz, 3H), 1.01 (d, J = 6.60 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 152.9, 151.6, 129.5, 128.2, 127.4, 123.2, 114.2, 63.9, 55.2, 47.6, 37.3, 28.9, 22.3, 14.0; HRMS (EI) calcd for $C_{18}H_{23}ClN_2O_3$ 350.1397, found 350.1389.

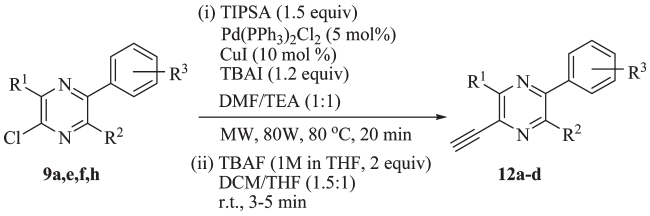
General Procedure for the Preparation of 2d. The general procedure for the preparation of **2d** is the same as previously described by our group.[16]

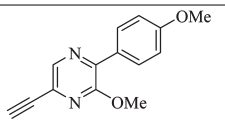
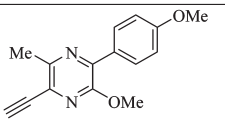
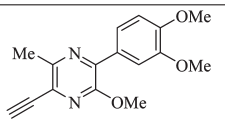
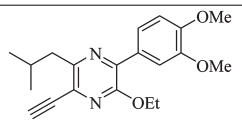
1-(4-Methoxybenzyl)-6-benzyl-5-chloro-3-methylpyrazin-2(1*H*)-one (2d): white solid; mp 152−154 °C; yield 95%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.29 (m, 3H), 7.11 (d, J = 6.78 Hz, 2H), 7.05 (d, J = 8.67 Hz, 2H), 6.87 (d, J = 8.85 Hz, 2H), 5.05 (s, 2H), 4.11 (s, 2H), 3.79 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 156.4, 155.9, 134.7, 134.6, 129.3, 127.8, 127.5 (×2), 127.0, 114.4, 55.3, 47.6, 35.2, 20.9; HRMS (EI) calcd for $C_{20}H_{19}ClN_2O_2$ 354.1135, found 354.1134.

(25) Mehta, V. P.; Modha, S. G.; Ermolate'ev, D.; Van Hecke, K.; Van Meervelt, L.; Van der Eycken, E. V. *Aust. J. Chem.* **2009**, *62*, 27.

(26) Mehta, V. P.; Modha, S. G.; Van der Eycken, E. *J. Org. Chem.* **2008**, *75*, 976.

TABLE 5. Sonogashira Cross-Coupling Reaction of Pyrazines 9a,e,f,h[a]



entry	reactant	product	structure	yield[b] (%)
1	**9a**	**12a**		78
2	**9e**	**12b**		91
3	**9f**	**12c**		80
4	**9h**	**12d**		59

[a]Reactions were run on a 2.0 mmol scale of **9a**,**e**,**f**,**h** in a multimode microwave apparatus. [b]Yields over two steps. TIPSA = triisopropylsilylacetylene, TBAI = tetrabutylammoniumiodide, and TBAF = tetrabutylammoniumfluoride.

General Procedure for the Preparation of 3a−d. The general procedure for the preparation of **3a−d** is the same as previously described by our group.[16] Data for compound **3a** are in accordance with the previously published work.[16]

1-(4-Methoxybenzyl)-5-chloro-3-methoxy-6-methylpyrazine-2(1*H*)-thione (3b): yellow solid; mp 127−129 °C; yield 88%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, J = 8.67 Hz, 2H), 6.84 (d, J = 8.76 Hz, 2H), 6.00 (s, 2H), 4.05 (s, 3H), 3.77 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 159.2, 159.0, 131.0, 129.9, 127.6, 124.9, 114.4, 56.1, 55.3, 17.0; HRMS (EI) calcd for $C_{14}H_{15}ClN_2O_2S$ 310.0543, found 310.0547.

1-(4-Methoxybenzyl)-5-chloro-3-ethoxy-6-isobutylpyrazine-2(1*H*)-thione (3c): yellow liquid; 90% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (d, J = 8.49 Hz, 2H), 6.84 (d, J = 8.46 Hz, 2H), 5.99 (bs, 2H), 4.46 (q, J = 7.14 Hz, 2H), 3.77 (s, 3H), 2.71 (d, J = 7.14 Hz, 2H), 2.10−1.96 (m, 1H), 1.49 (t, J = 6.99 Hz, 3H), 1.01 (d, J = 6.60 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 158.0, 133.5, 130.2, 130.0, 127.6, 127.2, 125.3, 114.3, 65.0, 55.2, 49.5, 38.1, 29.2, 24.6, 22.3, 15.6, 14.0; HRMS (EI) calcd for $C_{18}H_{23}ClN_2O_2S$ 366.1169, found 366.1156.

1-(4-Methoxybenzyl)-6-benzyl-5-chloro-3-methylpyrazine-2(1*H*)-thione (3d): yellow solid; mp 125−127 °C; yield 73%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.34 (m, 3H), 7.08 (d, J = 6.6 Hz, 2H), 7.00 (d, J = 8.1 Hz, 2H), 6.88 (d, J = 8.07 Hz, 2H), 5.81 (bs, 2H), 4.20 (s, 2H), 3.79 (s, 3H), 2.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 163.8, 159.2, 138.4, 134.3, 134.1, 133.4, 132.3, 132.2, 132.1, 131.5 (×2), 129.4, 128.5, 128.4, 127.7, 127.4, 127.2, 124.9, 114.5, 55.3, 36.0, 26.8; HRMS (EI) calcd for $C_{20}H_{19}ClN_2OS$ 370.0907, found 370.0912.

General Procedure for the Preparation of 5a−d. Thioamide **3** (5 mmol) and iodine (10 mol %) were successively added to dichloromethane (15 mL) in a 50 mL glass vial. The resulting solution was irradiated at an 80 °C ceiling temperature for 15 min using a maximum microwave power of 150 W. After completion of the reaction, the reaction mixture was diluted with 200 mL of ethyl acetate and washed with sodium thiosulfate (5% in water, 100 mL) to remove iodine, followed by water (100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfat and removed under reduced pressure, and the residue was purified by silica gel column chromatography (from 0 to 10% of ethyl acetate in heptane) to afford compounds **5a−d**.

2-(4-Methoxybenzylthio)-5-chloro-3-methoxypyrazine (5a): light yellow solid; mp 79−81 °C; yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.31 (d, J = 8.46 Hz, 2H), 6.82 (d, J = 8.46 Hz, 2H), 4.32 (s, 2H), 4.00 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 155.1, 144.2, 140.0, 133.8, 130.2, 128.9, 113.9, 55.2, 54.7, 32.8; HRMS (EI) calcd for $C_{13}H_{13}ClN_2O_2S$ 296.0386, found 296.0394.

2-(4-Methoxybenzylthio)-5-chloro-3-methoxy-6-methyl-pyrazine (5b): off-white; mp 73−75 °C; yield 88%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, J = 8.67 Hz, 2H), 6.82 (d, J = 8.67 Hz, 2H), 4.32 (s, 2H), 3.96 (s, 3H), 3.78 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 153.5, 142.6, 141.6, 138.4, 130.3, 129.3, 113.8, 55.2, 54.5, 32.8, 20.5; HRMS (EI) calcd for $C_{14}H_{15}ClN_2O_2S$ 310.0543, found 310.0558.

2-(4-Methoxybenzylthio)-5-chloro-3-ethoxy-6-isobutyl-pyrazine (5c): colorless oil; yield 80%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, J = 8.46 Hz, 2H), 6.82 (d, J = 8.46 Hz, 2H), 4.38 (q, J = 6.96 Hz, 2H), 4.32 (s, 2H), 3.77 (s, 3H), 2.71 (d, J = 7.17 Hz, 2H), 2.23−2.12 (m, 1H), 1.39 (t, J = 7.14 Hz, 3H), 0.96 (d, J = 6.57 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 152.9, 144.3, 142.7, 138.6, 130.2, 129.4, 113.8, 63.4, 55.2, 42.1, 32.7, 28.1, 22.4, 14.2; HRMS (EI) calcd for $C_{18}H_{23}ClN_2O_2S$ 366.1169, found 366.115.

2-(4-Methoxybenzylthio)-6-benzyl-5-chloro-3-methyl-pyrazine (5d): colorless oil; yield 72%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.27 (m, 5H), 7.19 (d, J = 8.49 Hz, 2H), 6.77 (d, J = 8.46 Hz, 2H), 4.29 (s, 2H), 4.24 (s, 2H), 3.77 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 152.6, 149.9, 148.6, 142.0, 137.5, 130.1, 129.2, 128.4, 126.6, 113.8, 55.2, 40.3, 33.5, 20.6; HRMS (EI) calcd for $C_{20}H_{19}ClN_2OS$ 370.0907, found 370.0888.

General Procedure for the Preparation of 9a−j. A mixture of pyrazine **5** (0.5 mmol), boronic acid **8** (2 equiv), $Pd(PPh_3)_4$ (5 mol %), and CuTC (1.5 equiv) in THF (4 mL) was irradiated in a 15 mL sealed tube at a ceiling temperature of 120 °C using a maximum power of 500 W for 30 min. After 30 min, a second lot of the above reactants, boronic acid **8** (1 equiv), $Pd(PPh_3)_4$ (5 mol %), and CuTC (1 equiv), was added, and again, the reaction was run for 30 min with the same conditions. After completion of the reaction, the reaction mixture was filtered through Celite and the filtrate was diluted with ethylacetate (200 mL) and washed with water (100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate and distilled under reduced pressure, and the residue was purified by silica gel column chromatography (from 0 to 30% of ethyl acetate in heptane) to afford compounds **9a−j**.

5-Chloro-3-methoxy-2-(4-methoxyphenyl)pyrazines (9a): light yellow solid; mp 69−71 °C; yield 84%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.09 (d, J = 8.85 Hz, 2H), 6.98 (d, J = 8.85 Hz, 2H), 4.06 (s, 3H), 3.97 (s, 3H); HRMS (EI) calcd for $C_{12}H_{11}ClN_2O_2$ 250.0509, found 250.0514.

5-Chloro-3-methoxy-2-(3,4-dimethoxyphenyl)pyrazines (9b): white solid; mp 118−120 °C; yield 69%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.74 (d, J = 8.46 Hz, 1H), 7.65 (s, 1H), 6.95 (d, J = 8.46 Hz, 1H), 4.07 (s, 3H), 3.96−3.94 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 150.2, 148.7, 142.3, 140.5, 134.5, 127.4, 122.2, 111.8, 110.4, 55.9, 54.5; HRMS (EI) calcd for $C_{13}H_{13}ClN_2O_3$ 280.0615, found 280.0578.

5-Chloro-2-(3,4-difluorophenyl)-3-methoxypyrazine (9c): white solid; mp 113−115 °C; yield 75%; ^{1}H NMR (300 MHz, $CDCl_3$)

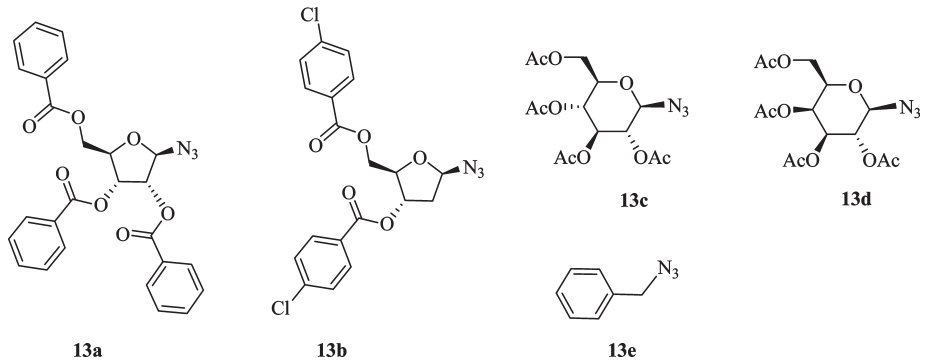
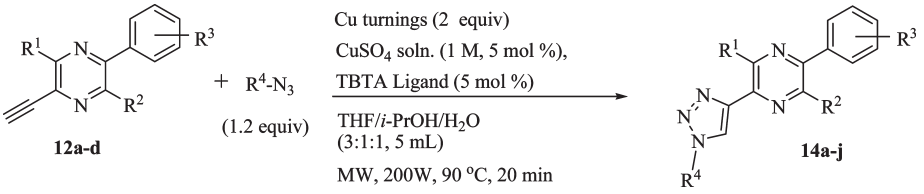


FIGURE 2. Structure of azides **13a**−**e**.

TABLE 6. Synthesis of Triazoles 14a−j[a]



entry	substrate	azide R^4-N_3	product	yield (%)
1	**12a**	**13a**	**14a**	82
2	**12b**	**13b**	**14b**	69
3	**12b**	**13c**	**14c**	56
4	**12b**	**13d**	**14d**	38
5	**12c**	**13a**	**14e**	92
6	**12c**	**13b**	**14f**	71
7	**12d**	**13a**	**14g**	73
8	**12d**	**13b**	**14h**	63
9	**12d**	**13e**	**14i**	78
10[b]	**12d**	TMS-N_3	**14j** (R^4 = H)	80

[a]All the reactions were run on a 0.1 mmol scale of **12a**−**d** in a multimode microwave apparatus. [b]The protective group (TMS) was cleaved in situ applying the described reaction conditions.

δ 8.23 (s, 1H), 8.01−7.88 (m, 2H), 7.28−7.19 (m, 1H), 4.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 151.7, 151.6, 149.4, 149.3, 148.5, 148.3, 143.7, 138.3, 134.9, 131.7, 131.6, 129.9, 125.4 (×2), 125.3 (×2), 118.3, 118.0, 117.1, 116.9, 113.9, 54.7; HRMS (EI) calcd for $C_{11}H_7ClF_2N_2O$ 256.0215, found 256.0227.

5-Chloro-2-(3-(trifluoromethyl)phenyl)-3-methoxypyrazine (9d): white solid; mp 38−40 °C; yield 80%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.27−8.25 (m, 2H), 7.69 (d, J = 7.53 Hz, 1H), 7.58 (t, J = 7.74 Hz, 1H), 4.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 144.1, 139.1, 135.5, 135.1, 132.1, 130.9, 130.5, 128.7, 126.0, 125.9 (×2), 125.8, 122.2, 54.7; HRMS (EI) calcd for $C_{12}H_8ClF_3N_2O$ 288.0277, found 288.0276.

2-Chloro-6-methoxy-5-(4-methoxyphenyl)-3-methylpyrazine (9e): white solid; mp 71−73 °C; yield 86%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 8.85 Hz, 2H), 6.98 (d, J = 8.85 Hz, 2H), 4.03 (s, 3H), 3.86 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 164.9, 142.1, 140.9, 139.7, 130.4, 127.5, 113.6, 55.3, 54.3, 20.7; HRMS (EI) calcd for $C_{13}H_{13}ClN_2O_2$ 264.0666, found 264.0663.

2-Chloro-6-methoxy-5-(3,4-dimethoxyphenyl)-3-methylpyrazine (9f): light yellow solid; mp 94−96 °C; yield 93%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.46 Hz, 1H), 7.65 (d, J = 1.14 Hz, 1H), 6.94 (d, J = 8.46 Hz, 1H), 4.03 (s, 3H), 3.96 (s, 3H), 3.93 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 150.0, 148.7, 142.1, 139.4, 129.6, 127.6, 122.2, 113.8, 111.9, 110.5, 55.9 (×2), 54.4, 20.7; HRMS (EI) calcd for $C_{14}H_{15}ClN_2O_3$ 294.0771, found 294.0765.

2-(4-*tert*-Butylphenyl)-5-chloro-3-methoxy-6-methylpyrazine (9g): colorless liquid; yield 92%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 8.46 Hz, 2H), 7.48 (d, J = 8.67 Hz, 2H), 4.02 (s, 3H), 2.60 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 152.4, 142.3, 141.4, 140.0, 132.1, 128.6, 125.2, 54.3, 34.7, 31.2, 20.7; HRMS (EI) calcd for $C_{16}H_{19}ClN_2O$ 290.1186, found 290.1186.

2-Chloro-6-ethoxy-3-isobutyl-5-(3,4-dimethoxyphenyl)pyrazine (9h): off-white solid; mp 72−74 °C; yield 79%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82−7.79 (m, 2H), 6.95 (d, J = 8.28 Hz, 1H), 4.47 (q, J = 6.99 Hz, 2H), 3.95−3.94 (m, 6H), 2.80 (d, J = 7.17 Hz, 2H), 2.29−2.20 (m, 1H), 1.47 (t, J = 6.99 Hz, 3H), 1.00 (d, J = 6.57 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 149.9, 148.4, 144.7, 141.0, 138.9, 128.0, 122.2, 112.0, 110.6, 63.1, 55.9, 55.7, 42.1, 28.1, 22.4, 14.4; HRMS (EI) calcd for $C_{18}H_{23}ClN_2O_3$ 350.1397, found 350.1387.

2-Chloro-6-ethoxy-5-(3,4-difluorophenyl)-3-isobutylpyrazine (9i): white solid; yield 72%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07−7.94 (m, 2H), 7.20 (t, J = 8.46 Hz, 1H), 4.49 (q, J = 7.14 Hz, 2H), 2.79 (d, J = 7.14 Hz, 2H), 2.30−2.16 (m, 1H), 1.47 (t, J = 7.17 Hz, 3H), 0.99 (d, J = 6.60 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 152.6, 152.4, 151.7, 151.5, 149.2, 149.1, 148.4, 148.3, 145.2, 142.5, 136.8, 132.3 (×2), 132.1, 125.4 (×2), 125.3 (×2), 118.2, 118.0, 117.0, 116.8, 63.5, 42.1, 29.7, 28.1, 22.4, 14.4; HRMS (EI) calcd for $C_{16}H_{17}ClF_2N_2O$ 326.0997, found 326.1014.

2-Benzyl-3-chloro-6-(3,4-dimethoxyphenyl)-5-methylpyrazine (9j): colorless oil; yield 80%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.21 (m, 6H), 7.18−7.14 (m, 2H), 6.96 (d, J = 7.92 Hz, 1H), 4.32 (s, 2H), 3.94 (s, 3H), 3.91 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.0, 150.4, 149.7, 149.0, 148.8,

144.9, 137.5, 130.0, 129.1, 128.4, 126.6, 121.8, 112.4, 110.7, 55.9 (×2), 40.6, 22.6; HRMS (EI) calcd for $C_{20}H_{19}ClN_2O_2$ 354.1135, found 354.1145.

General Procedure for the Preparation of 10a−e. The general procedures for the synthesis of compounds **10a−d**[27] and **10e**[28] are the same as described in the literature starting from their respective thiols. Data for compounds **10a**,[29] **10b**,[30] and **10e**[28] were in accordance with the already published ones in the literature.

2-(4-Methoxybenzylthio)-4,6-dimethylpyrimidine (10c): white solid; yield 79%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 8.64 Hz, 2H), 6.82 (d, J = 8.67 Hz, 2H), 6.68 (s, 1H), 4.36 (s, 2H), 3.78 (s, 3H), 2.40 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 158.6, 130.2, 130.1, 115.6, 113.7, 55.2, 34.6, 23.8; HRMS (EI) calcd for $C_{14}H_{16}N_2OS$ 260.0983, found 260.0998.

2-(4-Methoxybenzylthio)-1-methyl-1*H*-imidazole (10d): white solid; yield 54%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (s, 1H), 7.05 (d, J = 8.46 Hz, 2H), 6.86 (s, 1H), 6.78 (d, J = 8.64 Hz, 2H), 4.12 (s, 2H), 3.77 (s, 3H), 3.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 140.7, 129.9, 129.8, 129.7, 122.3, 113.8, 55.2, 39.5, 33.1; HRMS (EI) calcd for $C_{12}H_{14}N_2OS$ 234.0827, found 234.0840.

General Procedure for the Preparation of 11a−i. The general procedure for the preparation of **11a−i** is the same as that for **9a−j**. Data for compounds **11a**,[31] **11b**,[32] **11c**,[33] **11d**,[34] **11e**,[35] **11f**,[36] **11g**,[37] and **11h**[38] were in accordance with the published data.

5-(3,4-Dimethoxyphenyl)-1-phenyl-1*H*-tetrazole (11i): white solid; yield 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (m, 3H), 7.43 (dd, J = 1.52, 7.68 Hz, 2H), 7.15 (d, 2.04 Hz, 1H), 7.07 (dd, J = 2.0, 8.3 Hz, 1H), 6.83 (d, J = 8.32 Hz, 1H), 3.89 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 149.1, 134.9, 130.4, 129.8, 125.6, 122.1, 115.7, 111.6, 111.1, 55.9, 55.8; HRMS (EI) calcd for $C_{15}H_{14}N_4O_2$ 282.1117, found 282.1131.

General Procedure for the Preparation of 12a−d. A mixture of pyrazine **9** (2.0 mmol), triisopropylsilylacetylene (1.5 equiv), $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (10 mol %), and tetrabutylammonium iodide (TBAI, 1.2 equiv) in DMF/TEA (1:1, 4 mL) was irradiated in a 15 mL sealed tube at a ceiling temperature of 80 °C using a maximum power of 80 W for 20 min. After completion of the reaction, the reaction mixture was diluted with dichloromethane (200 mL) and washed with water (100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, distilled under reduced pressure. The obtained residue was dissolved in DCM/THF (1.5:1, 5 mL), and TBAF solution in THF (1M, 2 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 3−5 min. After completion of the reaction, solvents were removed under reduced pressure and the residue was directly subjected to flash column chromatography on short silica gel pads (from 0 to 30% ethyl acetate in heptane) to afford the desired terminal acetylenes **12a−d** in good yields.

5-Ethynyl-3-methoxy-2-(4-methoxyphenyl)pyrazine (12a): light yellow solid; yield 78%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.10 (d, J = 8.85 Hz, 2H), 6.99 (d, J = 8.88 Hz, 2H), 4.06 (s, 3H), 3.87 (s, 3H), 3.29 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 156.7, 142.7, 139.6, 131.7, 130.8, 127.7, 113.6, 80.5, 79.8, 55.3, 54.0; HRMS (EI) calcd for $C_{14}H_{12}N_2O_2$ 240.0899, found 240.0897.

2-Ethynyl-6-methoxy-5-(4-methoxyphenyl)-3-methylpyrazine (12b): dark brown solid; mp 128−130 °C; yield 91%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 8.85 Hz, 2H), 6.98 (d, J = 8.85 Hz, 2H), 4.03 (s, 3H), 3.86 (s, 3H), 3.45 (s, 1H), 2.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 155.1, 147.7, 141.5, 130.8, 130.0, 127.9, 113.6, 82.1, 80.9, 55.3, 53.9, 20.9; HRMS (EI) calcd for $C_{15}H_{14}N_2O_2$ 254.1055, found 254.1065.

2-Ethynyl-6-methoxy-5-(3,4-dimethoxyphenyl)-3-methylpyrazine (12c): light brown solid; mp 145−147 °C; yield 80%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (dd, J = 1.71, 8.47 Hz, 1H), 7.71 (d, J = 1.50 Hz, 1H), 6.94 (d, J = 8.46 Hz, 1H), 4.04 (s, 3H), 3.96 (s, 3H), 3.94 (s, 3H), 3.46 (s, 1H), 2.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 150.3, 148.6, 147.7, 141.2, 130.1, 128.0, 122.6, 112.1, 110.5, 82.2, 80.8, 55.9, 53.9, 20.9; HRMS (EI) calcd for $C_{16}H_{16}N_2O_3$ 284.1161, found 284.1170.

2-Ethoxy-6-ethynyl-5-isobutyl-3-(3,4-dimethoxyphenyl)pyrazine (12d): pink solid; mp 108−110 °C; yield 59%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88−7.86 (m, 2H), 6.95 (d, J = 8.28 Hz, 1H), 4.48 (q, J = 6.96 Hz, 2H), 3.95−3.94 (m, 6H), 3.39 (s, 1H), 2.86 (d, J = 7.14 Hz, 2H), 2.31−2.18 (m, 1H), 1.47 (t, J = 7.14 Hz, 3H), 0.99 (d, J = 6.78 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 150.5, 150.2, 148.4, 140.7, 130.2, 128.4, 122.7, 112.3, 110.5, 81.5, 81.0, 62.5, 55.9, 55.7, 42.7, 28.8, 22.4, 14.5; HRMS (EI) calcd for $C_{20}H_{24}N_2O_3$ 340.1787, found 340.1775.

General Procedure for the Preparation of 13a−e. All protected sugar azides[23] **13a−d** and the benzyl azide[24] **13e** were synthesized according to literature procedures.

General Procedure for the Preparation of 14a−j. A mixture of pyrazine **12** (0.1 mmol), azide **13** (1.2 equiv), copper turnings (2 equiv), $CuSO_4$ solution in water (1M, 5 mol %), and tris-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine ligand (TBTA, 5 mol %) in THF/*i*-PrOH/H_2O (3:1:1, 5 mL) was irradiated in a 15 mL sealed tube at a ceiling temperature of 90 °C using a maximum power of 200 W for 20 min. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, distilled under reduced pressure. The obtained residue was subjected to silica gel column chromatography (from 0 to 50% ethyl acetate in heptane) to afford the desired compounds **14a−j**.

(2*R*,3*R*,4*R*,5*R*)-2-(Benzoyloxymethyl)-5-(4-(6-methoxy-5-(4-methoxyphenyl)pyrazin-2-yl)-1*H*-1,2,3-triazol-1-yl)tetrahydrofuran-3,4-diyl Dibenzoate (14a): white solid; mp 77−79 °C; yield 82%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.30 (s, 1H), 8.11 (d, J = 8.49 Hz, 2H), 8.03−7.96 (m, 6H), 7.62−7.34 (m, 9H), 7.00 (d, J = 8.46 Hz, 2H), 6.54 (d, J = 3.03 Hz, 1H), 6.37 (bs, 1H), 6.18 (t, J = 5.25 Hz, 1H), 4.94−4.88 (m, 2H), 4.63 (dd, J = 3.39, 11.97 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 165.1 (×2), 160.5, 156.8, 146.7, 141.9, 138.9, 133.9, 133.7, 133.3, 132.8, 130.6, 129.9, 129.8, 129.6, 129.1, 128.6, 128.5, 128.4, 128.2, 121.5, 113.6, 90.5, 81.4, 75.3, 71.5, 63.5, 55.3, 53.4; MS (ESI^+) calcd for $C_{40}H_{33}N_5O_9$ 727.7, found 750.3 $[M + Na]^+$, 1478.2 $[2M + Na]^+$.

((2*R*,3*S*,5*R*)-3-(4-Chlorobenzoyloxy)-5-(4-(6-methoxy-5-(4-methoxyphenyl)-3-methyl-pyrazin-2-yl)-1*H*-1,2,3-triazol-1-yl)-tetrahydro-furan-2-yl)methyl-4-chlorobenzoate (14b): yellow solid; mp 66−67 °C; yield 69%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.14 (d, J = 8.67 Hz, 2H), 8.01 (d, J = 8.46 Hz, 2H), 7.85 (d, J = 8.46 Hz, 2H), 7.47 (d, J = 8.31 Hz, 2H), 7.31 (d, J = 8.49 Hz,

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2H), 7.00 (d, J = 8.64 Hz, 2H), 6.52 (t, J = 5.85 Hz, 1H), 5.87 (bs, 1H), 4.75−4.69 (m, 2H), 4.54−4.51 (m, 1H), 3.96 (s, 3H), 3.87 (s, 3H), 3.51−3.42 (m, 1H), 2.98−2.89 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 64.9, 160.4, 154.7, 148.3, 142.2, 140.2, 139.8, 136.2, 131.1, 130.9, 130.6, 128.9, 128.2, 127.6, 127.4, 123.2, 113.6, 88.7, 83.5, 74.8, 63.9, 55.3, 53.3, 37.8, 22.4; MS (ESI^+) calcd for $C_{34}H_{29}Cl_2N_5O_7$ 690.5, found 691.2 $[M]^+$, 1403.4 $[2M + Na]^+$.

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(6-methoxy-5-(4-methoxyphenyl)-3-methyl-pyrazin-2-yl)-1*H*-1,2,3-triazol-1-yl)-tetrahydro-2H-pyran-3,4,5-triyl Triacetate (14c): white solid; mp 182−185 °C; yield 56%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.14 (d, J = 8.85 Hz, 2H), 7.00 (d, J = 8.85 Hz, 2H), 5.98 (d, J = 9.42 Hz, 1H), 5.58 (t, J = 9.42 Hz, 1H), 5.46 (t, J = 9.42 Hz, 1H), 5.30 (t, J = 9.78 Hz, 1H), 4.37−4.31 (m, 1H), 4.18 (d, J = 12.63 Hz, 1H), 4.08−4.04 (m, 4H), 3.87 (s, 3H), 2.96 (s, 3H), 2.09 (s, 6H), 2.04 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 169.9, 169.4, 169.0, 160.4, 154.9, 148.5, 142.3, 140.5, 136.0, 130.6, 128.2, 122.3, 113.6, 85.8, 75.2, 70.3, 67.7, 61.6, 55.3, 53.5, 22.4, 20.7, 20.5 (×2), 20.2; MS (ESI^+) calcd for $C_{29}H_{33}N_5O_{11}$ 627.5, found 628.8 $[M]^+$, 1277.8 $[2M + Na]^+$.

(2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-(6-methoxy-5-(4-methoxyphenyl)-3-methyl-pyrazin-2-yl)-1*H*-1,2,3-triazol-1-yl)-tetrahydro-2H-pyran-3,4,5-triyl Triacetate (14d): white solid; mp 81−83 °C; yield 38%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.14 (d, J = 8.85 Hz, 2H), 7.00 (d, J = 8.85 Hz, 2H), 5.93 (d, J = 9.21 Hz, 1H), 5.69 (t, J = 9.78 Hz, 1H), 5.59 (bs, 1H), 5.30 (dd, J = 3.39, 10.33 Hz, 1H), 4.28−4.20 (m, 3H), 4.10 (s, 3H), 3.87 (s, 3H), 2.96 (s, 3H), 2.25 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 170.0, 169.8, 169.2, 160.4, 154.9, 148.4, 142.4, 140.4, 136.2, 130.6, 128.2, 122.3, 113.6, 86.3, 74.2, 70.8, 67.8, 66.8, 61.2, 55.3, 53.6, 22.4, 20.7, 20.6, 20.5, 20.3; MS (ESI^+) calcd for $C_{29}H_{33}N_5O_{11}$ 627.5, found 628.9 $[M]^+$, 1277.6 $[2M + Na]^+$.

(2*R*,3*R*,4*R*,5*R*)-2-(Benzoyloxymethyl)-5-(4-(5-(3,4-dimethoxyphenyl)-6-methoxy-3-methyl-pyrazin-2-yl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-furan-3,4-diyl Dibenzoate (14e): white solid; mp 83−85 °C; yield 92%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.03−7.96 (m, 6H), 7.82 (d, J = 8.46 Hz, 1H), 7.77 (s, 1H), 7.62−7.55 (m, 2H), 7.50−7.35 (m, 7H), 6.96 (d, J = 8.46 Hz, 1H), 6.54 (d, J = 1.14 Hz, 1H), 6.38 (t, J = 4.14 Hz, 1H), 6.22 (t, J = 5.28 Hz, 1H), 4.96−4.87 (m, 2H), 4.63 (dd, J = 3.96, 12.24 Hz, 1H), 3.99 (s, 3H), 3.95 (s, 3H), 3.90 (s, 3H), 2.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 165.1, 154.7, 150.0, 148.7, 148.3, 142.2, 139.9, 136.2, 13.9, 133.7, 133.3, 129.9, 129.8, 129.6, 129.1, 128.6 (×2), 128.5, 128.4 (×2), 123.3, 122.4, 112.0, 110.5, 90.4, 81.3, 75.4, 71.5, 63.5, 55.9, 53.4, 35.4, 31.8, 26.4, 22.6, 22.5, 14.1; MS (ESI^+) calcd for $C_{42}H_{37}N_5O_{10}$ 771.7, found 772.4 $[M]^+$, 1565.0 $[2M + Na]^+$.

((2*R*,3*S*,5*R*)-3-(4-Chlorobenzoyloxy)-5-(4-(5-(3,4-dimethoxyphenyl)-6-methoxy-3-methyl-pyrazin-2-yl)-1*H*-1,2,3-triazol-1-yl)-tetra-hydrofuran-2-yl)methyl 4-chlorobenzoate (14f): yellow solid; mp 99−101 °C; yield 71%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.01 (d, J = 8.46 Hz, 2H), 7.86−7.81 (m, 3H), 7.78 (s, 1H), 7.47 (d, J = 8.31 Hz, 2H), 7.31 (d, J = 8.46 Hz, 2H), 6.96 (d, J = 8.46 Hz, 1H), 6.52 (t, J = 5.82 Hz, 1H), 5.87 (bs, 1H), 4.76−4.69 (m, 2H), 4.53 (d, J = 7.53 Hz, 1H), 3.99−3.95 (m, 9H), 3.51−3.43 (m, 1H), 3.02−2.89 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 164.9, 154.7, 150.0, 148.7, 148.2, 142.2, 140.3, 139.9, 139.8, 136.3, 131.1, 130.9, 128.9, 128.7, 128.4, 127.6, 127.4, 123.2, 122.4, 112.0, 110.5, 88.7, 83.5, 74.8, 63.9, 55.9, 53.4, 37.8, 35.4, 31.8, 26.4, 26.3, 22.6, 22.4, 14.1; MS (ESI^+) calcd for $C_{35}H_{31}Cl_2N_5O_8$ 720.5, found 721.7 $[M]^+$, 1463.2 $[2M + Na]^+$.

(2*R*,3*R*,4*R*,5*R*)-2-(Benzoyloxymethyl)-5-(4-(5-(3,4-dimethoxyphenyl)-6-ethoxy-3-isobutyl-pyrazin-2-yl)-1*H*-1,2,3-triazol-1-yl)-tetrahydro-furan-3,4-diyl Dibenzoate (14g): light yellow solid; mp 70−72 °C; yield 73%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.03−7.92 (m, 8H), 7.59−7.54 (m, 2H), 7.47−7.32 (m, 7H), 6.97 (d, J = 8.46 Hz, 1H), 6.50 (s, 1H), 6.38 (s, 1H), 6.22 (t, J = 4.89 Hz, 1H), 4.96−4.84 (m, 2H), 4.67−4.63 (m, 1H), 4.35 (t, J = 6.57 Hz, 2H), 3.98−3.95 (m, 6H), 3.41−3.21 (m, 2H), 2.33−2.29 (m, 1H), 1.44 (t, J = 6.03 Hz, 3H), 1.01 (d, J = 6.03 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 165.1, 154.1, 149.8, 148.4 (×2), 145.3, 139.3, 136.2, 133.9, 133.7, 133.3, 129.9, 129.7, 129.1, 128.8, 128.6, 128.5, 128.4, 123.6, 122.4, 112.2, 110.6, 90.4, 81.1, 75.4, 71.5, 63.6, 62.0, 55.9, 55.7, 42.4, 35.4, 30.9, 28.5, 26.4, 22.6, 22.5 (×2), 14.5; MS (ESI^+) calcd for $C_{46}H_{45}N_5O_{10}$ 827.8, found 828.3 $[M]^+$, 1677.1 $[2M + Na]^+$.

((2*R*,3*S*,5*R*)-3-(4-Chlorobenzoyloxy)-5-(4-(5-(3,4-dimethoxyphenyl)-6-ethoxy-3-isobutyl-pyrazin-2-yl)-1*H*-1,2,3-triazol-1-yl-)tetrahydro-furan-2-yl)methyl 4-chlorobenzoate (14h): light yellow solid; mp 59−61 °C; yield 63%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.00 (d, J = 7.74 Hz, 2H), 7.92−7.86 (m, 4H), 7.45 (d, J = 7.92 Hz, 2H), 7.32 (d, J = 7.92 Hz, 2H), 6.98 (d, J = 8.67 Hz, 1H), 6.51 (t, J = 5.64 Hz, 1H), 5.87 (bs, 1H), 4.70−4.67 (m, 2H), 4.57−4.51 (m, 1H), 4.41 (q, 6.39 Hz, 2H), 3.98 (s, 3H), 3.95 (s, 3H), 3.54−3.45 (m, 1H), 3.39−3.21 (m, 2H), 2.95−2.90 (m, 1H), 2.34−2.25 (m, 1H), 1.47 (t, J = 6.96 Hz, 3H), 1.01 (d, J = 6.57 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 164.9, 154.2, 149.8, 148.4 (×2), 145.2, 140.2, 139.8, 138.3, 136.3, 131.1, 128.9, 128.8, 127.7, 127.5, 123.5, 122.4, 112.2, 110.6, 88.7, 83.5, 74.9, 64.0, 62.0, 55.9, 55.7, 42.4, 37.6, 35.4, 31.8, 30.9, 28.5, 26.4, 22.6, 22.5 (×2), 14.6, 14.1; MS (ESI^+) calcd for $C_{39}H_{39}Cl_2N_5O_8$ 776.6, found 777.2 $[M]^+$, 1575.6 $[2M + Na]^+$.

2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-6-ethoxy-3-isobutyl-5-(3,4-dimethoxyphenyl)pyrazine (14i): yellow solid; mp 137−139 °C; yield 78%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.91−7.89 (m, 2H), 7.41−7.33 (m, 5H), 6.96 (d, J = 9.03 Hz, 1H), 5.61 (s, 2H), 4.44 (q, J = 7.23 Hz, 2H), 3.96 (s, 3H), 3.94 (s, 3H), 3.32 (d, J = 6.96 Hz, 2H), 2.33−2.22 (m, 1H), 1.46 (t, J = 6.99 Hz, 3H), 0.99 (d, J = 6.60 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 149.8, 148.4, 148.3, 145.3, 139.0, 136.8, 134.7, 129.1, 128.8, 128.7, 128.0, 124.0, 122.3, 112.2, 110.6, 62.0, 55.9, 55.7, 54.1, 42.5, 28.5, 22.5, 14.5; HRMS (EI) calcd for $C_{27}H_{31}N_5O_3$ 473.2427, found 473.2420.

2-Ethoxy-5-isobutyl-3-(3,4-dimethoxyphenyl)-6-(1*H*-1,2,3-triazol-4-yl)pyrazine (14j): green solid; mp 202−204 °C; yield 80%; ^{1}H NMR (400 MHz, DMSO) δ 15.3 (bs, 1H), 8.38 (bs, 1H), 7.86 (d, J = 1.50 Hz, 1H), 7.82 (dd, J = 1.50, 6.33 Hz, 1H), 7.09 (d, J = 6.42 Hz, 1H), 4.52 (q, J = 5.28 Hz, 2H), 3.83−3.82 (m, 6H), 2.50 (merged in solvent peak, 2H), 2.21−2.13 (m, 1H), 1.44 (t, J = 5.28 Hz, 3H), 0.93 (d, J = 4.92 Hz, 6H); ^{13}C NMR (75 MHz, DMSO) δ 153.8, 149.7, 148.0, 127.8, 121.9, 112.1, 111.2, 61.9, 55.4, 55.2, 54.8, 41.9, 27.8, 22.2, 14.3; HRMS (EI) calcd for $C_{20}H_{25}N_5O_3$ 383.1957, found 383.1973.

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Supporting Information Available: General experimental procedures, spectroscopic and analytical data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.