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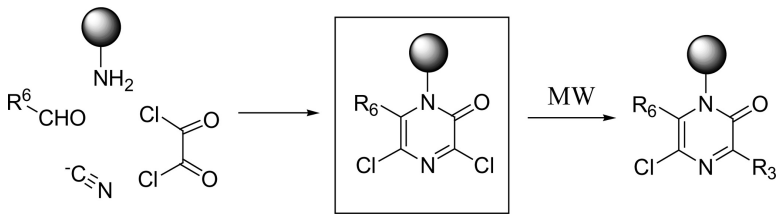

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Solid-Phase Synthesis of the 2(1*H*)-Pyrazinone Scaffold: A New Approach toward Diversely Substituted Heterocycles

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The first solid-phase synthesis of the 2(1*H*)-pyrazinone scaffold is described. The diversity at position C6 of the pyrazinone ring is determined by the choice of the starting aldehyde. Microwave-enhanced transition metal-catalyzed reactions allow easy introduction of a variety of substituents at the C3 position. This opens a way for the generation of libraries of diversely substituted 2(1*H*)-pyrazinones that will be screened for biological activities.

Introduction

Solid-phase synthesis along with high-throughput screening has emerged as a powerful tool for the discovery of novel drug candidates.[1] The synthesis of combinatorial libraries based on so-called "priviledged structures" is of particular interest due to the ability to provide high-affinity ligands for more than one type of receptor, depending on their substitution pattern.[2]

The 2(1*H*)-pyrazinone scaffold can allow the easy introduction of a wide range of pharmacologically active groups with the ability to address the diverse set of biological targets. Fused pyridino pyrazinones[3] **1** and 3-indolyl pyrazinones[4] **2** (Figure 1) can function as corticotropin realizing factor (CRF) receptor antagonists and can be useful for the treatment of various neurological disorders.

Pyrazinones, such as **3**, bearing an alkyl amino substituent at position C3 are known tissue factor VIIa and thrombin inhibitors.[5] Pyrazinones **4** are discovered ligands that bind to a new site on the $GABA_A$/chloride ionophore complex.[6] Pyrazinones, such as **5**, substituted with anilines at position C3 and phenoles at position C5 can be useful in inhibiting HIV replication.[7] A number of pyrazinones with an alkyl group at position N1 and a phenyl group at position C3 shows inhibitory action on platelet aggregation, vasodilating activity, and inhibitory action on liperoxide generation.[8] In addition to their broad physiological activities, 2(1*H*)-pyrazinones can be used as important building blocks in the synthesis of various heterocyclic compounds. Diels−Alder reactions of 2(1*H*)-pyrazinones with ethylene[9] afford bicyclic products that provide access to various scaffolds of pharmaceutical interest, such as bridged analogues of piperazine drugs[10] or β-turn mimics.[11] Recently, we transferred some of these reaction pathways to microwave-enhanced solid-phase chemistry, opening the way for the generation of many biologically interesting structures[12] (Scheme 1).

The separation of the resulting pyridines **8** from pyridones **9** was achieved by applying a traceless-linking concept, whereby pyridones **9** stay on solid support with concomitant release of pyridine **8**. The major drawback of this approach is the limited possibility to generate diversity in the pyrazinone scaffold. Indeed, when the amide nitrogen at N1 serves as a handle for the solid phase, only pyrazinones bearing a hydrogen at position C6 can be attached to the resin in order to avoid unwanted O-alkylation, which proceeds due to steric hindrance.[13] Moreover, the substituent at position C3 must be introduced before linking the pyrazinone scaffold to the solid support, because the sensitive imidoyl chloride moiety would not survive the coupling conditions.

Herein, we report the first solid-phase synthesis of 2(1*H*)-pyrazinones based on the Strecker reaction of the resin-bound amine with an appropriate aldehyde and a cyanide, providing a wide diversity at the C6 position of the pyrazinone ring. Different substituents can be introduced to the C3 position by nucleophilic substitution or by microwave-enhanced transition metal-catalyzed reactions,[14] taking advantage of the sensitive imidoyl chloride moiety. This new solid-phase approach opens a pathway for the generation of a large library of diversely substituted heterocycles with promising biological activities.

Results and Discussion

For our experiments, we selected the commercially available Wang amide resin due to its stability under the applied reaction conditions and the easy cleavage with TFA−dichloromethane (DCM) mixtures, providing the detached products in moderate to high purities.[12] The solid-phase synthesis of 2(1*H*)-pyrazinones is outlined in Scheme 2

Reaction of the polymer-bound amine **10** with an aldehyde and a cyanide provided α-aminonitrile **11a**−**h**, which was then cyclized to the pyrazinone **12a**−**h**.[15] To evaluate the scope and limitations of this method, we have used a set of (hetero)aromatic and aliphatic aldehydes (Table 1). However, typical aqueous Strecker conditions[16] (inorganic cyanides in aqueous solvents) afforded significantly low yields of aminonitriles **11a**−**h** (the completion of the reaction was determined by the chloranil test,[17] indicating the absence of

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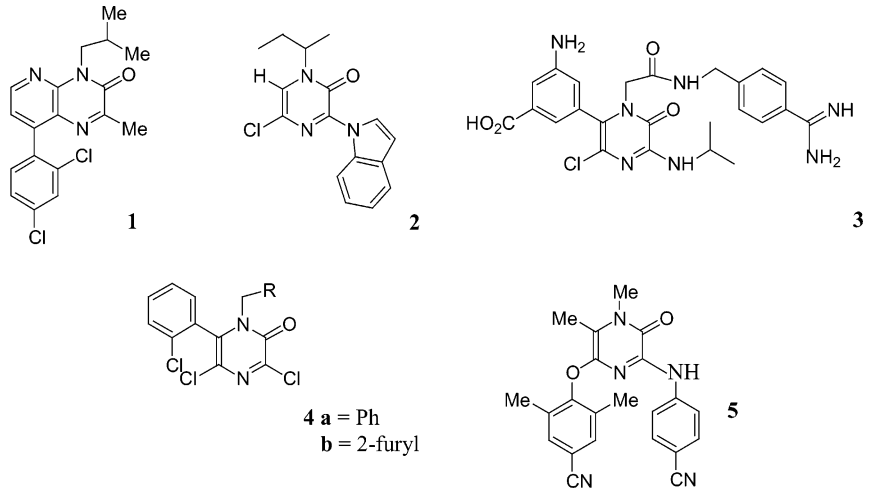
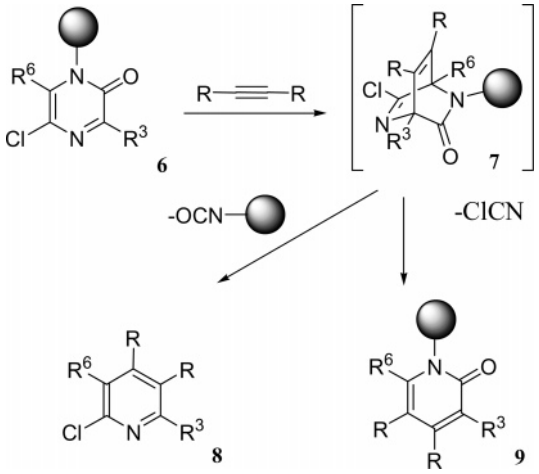


Figure 1. Biologically active 2(1*H*)-pyrazinones.

Scheme 1. Solid-Phase Concept for 2(1*H*)-Pyrazinone Diels−Alder Cycloadditions with Acetylenic Dienophiles



the free amino group). After several attempts to improve the procedure, we ultimately found that the most efficient reaction was performed with trimethylsilyl cyanide (TMSCN) in DCM[18] at room temperature, probably due to higher homogenity of the system and good swelling properties of the resin in this solvent. Subsequent cyclization of the α-aminonitrile salt with an excess of oxalyl chloride in toluene at room temperature afforded 3,5-dichloropyrazinones **12a**−**h**. It should be noted that heating of the reaction mixture at this step may result in decreased yields, probably due to the partial cleavage of the linker. The sensitive imidoyl chloride moiety in the pyrazinones **12a**−**h** underwent addition elimination reaction with in situ-generated sodium methoxide to give compounds **13a**−**h**. Finally, the smooth cleavage from the resin was achieved with a mixture TFA−DCM (1:2) under microwave irradiation to afford pyrazinones **14a**−**h**. The crude products were identified by CI-MS and ^{1}H NMR. The main impurity appeared to be a fragment of the linker, and this could easily be removed by filtration through a plug of silica gel.

Table 1. Solid-Phase Synthesis of 2(1*H*)-Pyrazinones 14[a]

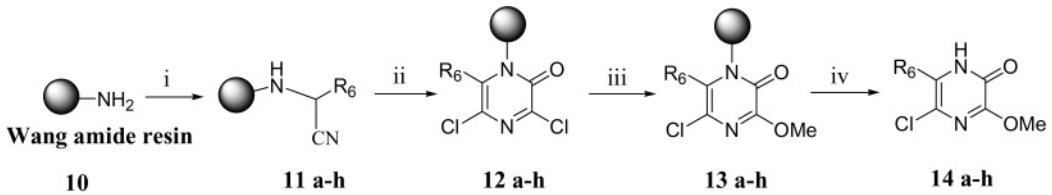
entry	compd	R_6	yield (%)[b]
1	**14a**	phenyl	53
2	**14b**	(4-methoxy)phenyl	67
3	**14c**	(4-carbomethoxy)phenyl	47
4	**14d**	(3,4-methylenedioxy)phenyl	29
5	**14e**	(3,4,5-trimethoxy)phenyl	traces
6	**14f**	2-furyl	14
7	**14g**	H	45
8	**14h**	methyl	20

[a] All reactions were performed on a 0.32-mmol scale based on the loading of Wang amide resin. [b] All yields are isolated yields after purification based on the loading of Wang amide resin (for details, see the Experimental Section).

Benzaldehyde, *p*-anisaldehyde, and *p*-carbomethoxybenzaldehyde (Table 1, entries 1, 2, and 3) provided pyrazinones **14a**−**c** in good yields. The reaction with the acid-sensitive 2-furaldehyde resulted in only 14% of product **14f** (Table 1, entry 6). Trimethoxybenzaldehyde gave almost no desired pyrazinone **14e** (Table 1, entry 5), probably due to its highly electron-rich nature. Acetaldehyde (Table 1, entry 8, 20%) appeared to be less efficient than formaldehyde (Table 1, entry 7, 45%).

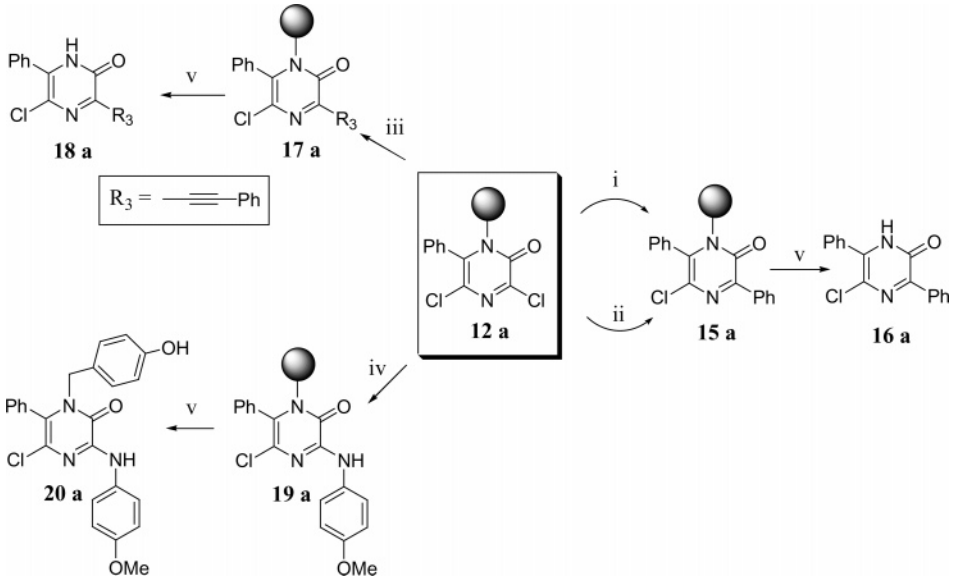
To extend the diversity of the resin-linked pyrazinone system, the imidoyl chloride moiety was investigated for the application of the transition metal-catalyzed reactions that we recently reported in solution phase.[14] As a proof of

Scheme 2. Solid-Phase Synthesis of 2(1*H*)-Pyrazinones **14**



[a] Reagents and conditions: (i) R_6CHO (5 equiv), TMSCN (5 equiv), DCM, r.t., 24 h, repeated once; (ii) 1 M HCl/THF (1:1), r.t., 30 min, then $(COCl)_2$ (3 equiv), toluene, r.t., 3 days; (iii) NaH (5 equiv), MeOH/THF (1:1), r.t., 3 h; (iv) TFA/DCM (1:2), MW, 120° C, 20 min.

Scheme 3. Microwave-Assisted Decoration of 2(1*H*)-Pyrazinone Scaffold[a]



[a] Reagents and conditions: (i) $PhB(OH)_2$ (4 equiv), Na_2CO_3 (5 equiv), $Pd[P(Ph)_3]_4$ (20 mol %), MW, 170° C, 30 min, repeated once; (ii) Ph_4Sn (4 equiv), $Pd[P(Ph)_3]_4$ (20 mol %), DMF, MW, 150° C, 20 min, repeated once; (iii) phenylacetylene (7 equiv), $Pd[P(Ph)_3]_2Cl_2$ (30 mol %), CuI (30 mol %), toluene/TEA (2:1), MW, 120° C, 30 min, repeated once; (iv) *p*-anisidine (5 equiv), Cu wire, CuI, (1 equiv), K_2CO_3 (5 equiv), MW, 175°C, 30 min, repeated once; (v) TFA/DCM (1:2), MW, 120°C, 20 min.

concept, this "scaffold decoration" strategy has been studied using polymer-bound pyrazinone **12a** (Scheme 3).

Suzuki reaction of **12a** was investigated under aqueous and anhydrous reaction conditions. The resin was then subjected to TFA−DCM cleavage, and the crude products were identified by CI-MS analysis. Application of aqueous conditions (aqueous solutions of Na_2CO_3 or Cs_2CO_3 as the base, with $Pd[P(Ph)_3]_4$ as the catalyst, in DMF or DME) afforded mixtures of 3-mono- and 3,5-disubstituted pyrazinones, as detected by CI-MS. All attempts to drive the reaction toward the formation of the disubstituted compound using higher equivalents of reagents or longer reaction times (up to 60 min) were unsuccessful. The best results for compound **16a** were obtained when 20 mol % of Pd catalyst, 4 equiv of phenylboronic acid, and 5 equiv of aqueous Na_2CO_3 were irradiated with 1 equiv of pyrazinone **12a** at 170 °C for 30 min, and in order to get the complete conversion, the whole procedure was repeated once. Alternatively, pyrazinone **16a** was prepared via Stille reaction with 4 equiv of Ph_4Sn, using $Pd[P(Ph)_3]_4$ as the catalyst. Polymer-bound pyrazinone **15a** was extensively washed with a mixture AcOH/DCM (1:5) to remove all Sn impurities. The cleavage from the resin provided compound **16a** in 65% yield on the basis of the loading of the Wang amide resin. Pyrazinone **18a** bearing a phenylalkynyl substituent at position C3, was prepared in 47% yield via Sonogashira reaction with 7 equiv of phenylacetylene in a mixture of toluene/triethylamine (2:1) using $Pd[P(Ph_3)_2]Cl_2$ and CuI as the catalyst system.

Next, we turned our attention to the Ullman coupling of substituted anilines,[19] which can open the way for the construction of libraries of physiologically active compounds.[7] To the best of our knowledge, only one example of an Ullman-type reaction on solid phase has been reported, using the procedure developed by Nicolau for the synthesis of highly substituted diaryl ethers.[20] Polymer-bound pyrazinone **12a** was successfully coupled with *p*-anisidine in toluene in the presence of K_2CO_3 using copper wire and CuI as the catalyst system. Microwave irradiation of the sample without a copper catalyst resulted in the formation of a complex mixture without noticeable traces of desired product (CI-MS analysis of the crude product upon cleavage). It should be noted that the product was cleaved from the resin as its *p*-hydroxybenzyl derivative **20a** under both conventional and microwave-assisted conditions.

In summary, we developed an efficient solid-phase synthesis for the elaboration of variously substituted 2(1*H*)-pyrazinones. The diversity at the C6 position is determined by the choice of the starting aldehyde. Microwave-assisted palladium-catalyzed reactions allow the easy introduction of different substituents at the C3 position of the pyrazinone ring linked with the solid support. Moreover, the N1 hydrogen-substituted pyrazinones generated upon cleavage from the resin, are not directly accessible via the reaction of the corresponding α-aminonitrile with oxalyl chloride. This opens the way for the generation of large libraries of 2(1*H*)-pyrazinone analogues which will be screened for biological activity.

Experimental Section

General Methods. ^1H NMR spectra were recorded on Bruker Avance 300 instrument, using $CDCl_3$ as solvent unless otherwise stated. The ^1H 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 data system. The ion source temperature was 150−250 °C, as required. The low resolution spectra were obtained with a HP5989A MS instrument. For thin-layer chromatography, analytical TLC plates (Alugram SIL G/UV_{254} and 70−230 mesh silicagel (E. M. Merck)) were

used. All reagents purchased from commercial sources were used without further purification.

Microwave Irradiation Experiments. All microwave experiments were carried out in a dedicated CEM-Discover monomode microwave apparatus[21] operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W with utilization of the standard absorbance level of 300 W maximum power. The reactions were carried out in microwave process vials (10 mL) sealed with an aluminum/Teflon crimp top, which can be exposed to 250° C and 20 bar internal pressure. The temperature was measured with an IR sensor on the outer surface of the process vial. After the irradiation period, the reaction vessel was cooled rapidly (60−120 s) to 50 °C via gas jet cooling before the vial was opened.

Solid-Phase Synthesis of α-Aminonitriles 11. To a suspension of Wang amide resin (0.4 g, 0.32 mmol, purchased from Advanced ChemTech, Lot No. 19546) in dichloromethane (DCM) (5 mL) were added trimethylsilyl cyanide (TMSCN) (0.21 mL, 1.6 mmol, 5 equiv) and an appropriate aldehyde (see Table 1) (1.6 mmol, 5 equiv). The reaction mixture was gently shaken for 24 h at room temperature. The solvent was then filtered out with a polypropylene frit cartridge, and the resin was washed with DCM (5 mL × 3); MeOH (5 mL × 3); and finally, with DCM (5 mL × 3). The whole procedure was repeated once.

Cyclization of α-Aminonitriles 11 to 2(1*H*)-Pyrazinones 12. To a suspension of resin **11** in THF (2 mL) was added 1 M HCL (2 mL). The reaction vessel was shaken for 30 min at room temperature. The solvent was then filtered out with a polypropylene frit cartridge, and the resin was washed with THF (5 mL × 3) and DCM (5 mL × 3). After drying under vacuum, the resin was suspended in dry toluene (5 mL). Oxalyl chloride (84 μL, 0.96 mmol, 3 equiv) was added carefully to the reaction mixture. The reaction vessel was shaken for 3 days at room temperature. The solvent was then filtered out with a polypropylene frit cartridge, and the resin was washed with toluene (5 mL × 3); MeOH (5 mL × 3); and finally, with DCM (5 mL × 3). The resin **12** was dried under vacuum.

Nucleophilic Substitution of the Imidoyl Chloride Moiety in Pyrazinone 12. To a suspension of polymer-bound pyrazinone **12** in THF (2 mL) was added a solution of NaH (80% suspension in oil, 0.048 g, 1.6 mmol, 5 equiv). The reaction mixture was shaken for 3 h at room temperature. The solvent was then filtered out with a polypropylene frit cartridge and washed with THF (5 mL × 3); THF/1 M HCl (1:1, v:v, 5 mL × 3); THF/H_2O (1:1, v:v, 5 mL × 3); THF (5 mL × 3); MeOH (5 mL × 3); and finally, with DCM (5 mL × 3).

Cleavage of Pyrazinones 14 from Solid Support. The resin **13** was suspended in a mixture of TFA/DCM (1:2, v:v, 3 mL). The reaction vessel was irradiated at 120°C for 20 min (120 W maximum power). The sample was cooled to room temperature. The solvent was then filtered out with a polypropylene frit cartridge and washed with DCM (5 mL × 5). The supernatant was neutralized with an excess of solid K_2CO_3. The resulting mixture was filtered and concentrated, and the solvent was evaporated under reduced pressure. The crude product was loaded onto a short silica gel plug and eluted with DCM/EtOAc (1:1) mixture to afford after concentration in vaccuo pyrazinones **14**.

5-Chloro-3-methoxy-6-phenyl-2(1*H*)-pyrazinone (14a). Yield: 0.04 g (53%). ^{1}H NMR ($CDCl_3$−CD_3OD, 2:1): δ 4.05 (s, 3H), 7.48−7.54 (m, 5H). ^{13}C NMR: 56.8, 123.2, 130.3, 130.5, 130.9, 131.5, 132.9, 153.4, 155.9. MS (CI): *m*/*z* (%) = 237 (100) [MH^+].

5-Chloro-3-methoxy-6-(4-methoxyphenyl)-2(1*H*)-pyrazinone (14b). Yield: 0.057 g (67%). ^{1}H NMR ($CDCl_3$−CD_3OD, 2:1): δ 3.87 (s, 3H), 4.03 (s, 3H), 7.01 (d, 2H, J = 8.8 Hz), 7.48 (d, 2H, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$−CD_3OD, 2:1): 55.2, 55.5, 114.2, 121.5, 123.6, 128.9, 130.9, 152.0, 154.1, 160.9. MS (CI): *m*/*z* (%) = 267 (100) [MH^+].

4-(3-Chloro-5-methoxy-6-oxo-1,6-dihydro-pyrazin-2-yl)-benzoic Acid Methyl Ester (14c). Yield: 0.044 g (47%). ^{1}H NMR ($CDCl_3$−CD_3OD, 2:1): δ 3.97 (s, 3H), 4.05 (s, 3H), 7.67 (d, 2H, J = 8.8 Hz), 8.14 (d, 2H, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$−CD_3OD, 2:1): 54.0, 56.7, 131.2, 131.3 (×2), 131.5, 132.6, 137.7, 153.2, 156.0, 168.5. MS (CI): *m*/*z* (%) = 295 (100) [MH^+].

6-Benzo[1,3]dioxol-5-yl-5-chloro-3-methoxy-2(1*H*)-pyrazinone (14d). Yield: 0.026 g (29%). ^{1}H NMR ($CDCl_3$−CD_3OD, 2:1): δ 4.03 (s, 3H), 6.05 (s, 2H), 6.93 (s, 1H), 7.01 (m, 2H). ^{13}C NMR ($CDCl_3$−CD_3OD, 2:1): 56.5, 69.6, 103.4, 110.0, 111.2, 123.1, 125.3, 126.5, 149.5, 150.6, 153.4, 155.6. MS (CI): *m*/*z* (%) = 281 (100) [MH^+].

5-Chloro-6-furan-2-yl-3-methoxy-2(1*H*)-pyrazinone (14f). Yield: 0.01 g (14%). ^{1}H NMR ($CDCl_3$−CD_3OD, 2:1): δ 3.99 (s, 3H), 6.58 (m, 1H), 7.13 (d, 1H, J = 3.7 Hz), 7.61 (d, 1H, J = 1.5 Hz). ^{13}C NMR ($CDCl_3$−CD_3OD, 2:1): 55.3, 112.7, 113.1, 119.8, 120.8, 143.5, 144.1, 151.3, 153.4. MS (CI): *m*/*z* (%) = 227 (100) [MH^+].

5-Chloro-3-methoxy-2(1*H*)-pyrazinone (14g). Yield: 0.023 g (45%). Spectral data were reported earlier.[12]

5-Chloro-3-methoxy-6-methyl-2(1*H*)-pyrazinone (14h). Yield: 0.01 g (20%). ^{1}H NMR ($CDCl_3$−CD_3OD, 2:1): δ 2.25 (s, 3H), 3.97 (s, 3H). ^{13}C NMR ($CDCl_3$−CD_3OD, 2:1): 55.0, 57.8, 125.7, 129.1, 131.4, 132.4. MS (CI): *m*/*z* (%) = 175 (100) [MH^+].

Suzuki Cross-Coupling Reaction of Polymer-Bound Pyrazinone 12a. Pyrazinone **12a** was prepared according to the procedure described above, starting from 0.2 g (0.16 mmol) of Wang amide resin. To a suspension of pyrazinone **12a** in DMF (3 mL) were added phenylboronic acid (0.08 g, 0.65 mmol, 4 equiv), Na_2CO_3 (0.085 g, 0.8 mmol, 5 equiv), and $Pd[P(Ph)_3]_4$ (0.037 g, 0.032 mmol, 20 mol %). The reaction vessel was irradiated at 170 °C for 30 min (200 W maximum power). The reaction mixture was cooled to ambient temperature, and the solvent was then filtered out with a polypropylene frit cartridge. The resin was washed as follows: DMF (5 mL × 3); DMF/H_2O (1:1,v:v, 5 mL × 3); MeOH (5 mL × 3); TFA/DCM (1:9, v:v, 5 mL × 5); and finally. with DCM (5 mL × 3). The whole procedure was repeated once. Pyrazinone **16a** was cleaved from solid support according to the method described above. The crude product was loaded onto a short silica gel plug and eluted with a mixture DCM/EtOAc (95:5). The solvent was

concentrated in vaccuo to provide pyrazinone **16a** (0.021 g, 47%).

Stille Cross-Coupling Reaction of Polymer-Bound Pyrazinone 12a. Pyrazinone **12a** was prepared according to the procedure described above, starting from 0.2 g (0.16 mmol) of Wang amide resin. To a suspension of pyrazinone **12a** in DMF (5 mL) were added tetraphenyl tin (Ph_4Sn) (0.273 g, 0.64 mmol, 4 equiv) and $Pd[P(Ph)_3]_4$ (0.037 g, 0.032 mmol, 20 mol %). The reaction vessel was irradiated at 150° C for 20 min (250 W maximum power). The reaction mixture was cooled to ambient temperature, and the solvent was then filtered out with a polypropylene frit cartridge. The resin was washed as follows: DMF (5 mL × 3); AcOH/DCM (1:5, v:v, 5 mL × 10); MeOH (5 mL × 3); and finally, with DCM (5 mL × 3). The whole procedure was repeated once. Pyrazinone **16a** was cleaved from solid support according to the procedure described above. The crude product was loaded onto a short silica gel plug and eluted with a mixture of DCM/EtOAc (95:5). The solvent was concentrated in vaccuo to provide pyrazinone **16a** (0.029 g, 65%).

5-Chloro-3,6-diphenyl-2(1*H*)-pyrazinone (16a). ^{1}H NMR ($CDCl_3-CD_3OD$, 2:1): δ 7.39 (m, 2H), 7.45 (m, 4H), 7.67 (m, 2H), 8.22 (m, 2H). ^{13}C NMR ($CDCl_3-CD_3OD$, 2:1): 128.3, 128.6, 129.1, 129.2, 129.3, 129.4, 129.6, 130.1, 131.5, 132.5, 135.4, 168.6. MS (CI): *m*/*z* (%) = 283 (100) [MH^+].

Sonogashira Cross-Coupling Reaction of Polymer-Bound Pyrazinone 12a. Pyrazinone **12a** was prepared according to the procedure described above, starting from 0.2 g (0.16 mmol) of Wang amide resin. To a suspension of pyrazinone **12a** in a mixture of toluene/triethylamine (TEA) (2:1, v:v, 3 mL) were added phenylacetylene (0.12 mL, 1.1 mmol, 7 equiv), $Pd[P(Ph)_2]Cl_2$ (0.034 g, 0.048 mmol, 30 mol %), and CuI (0.009 g, 0.047 mmol, 30 mol %). The reaction vessel was irradiated at 120° C for 30 min (100 W maximum power). The reaction mixture was cooled to ambient temperature, and the solvent was then filtered out with a polypropylene frit cartridge. The resin was washed as follows: DMF (5 mL × 3); DMF/H_2O (1:1, v:v, 5 mL × 10); THF/1 M HCl (1:1, v:v, 5 mL × 3); MeOH (5 mL × 3); and finally, with DCM (5 mL × 3). The whole procedure was repeated once. Pyrazinone **18a** was cleaved from solid support according to the method described above. The crude product was loaded onto a short silica gel plug and eluted with DCM. The solvent was concentrated in vaccuo to provide pyrazinone **18a** (0.023 g, 47%).

5-Chloro-6-phenyl-3-phenylethynyl-2(1*H*)-pyrazinone (18a). ^{1}H NMR: δ 7.21 (s, 1H), 7.53 (m, 5H), 7.87 (d, 2H, J = 6.6 Hz), 7.97 (d, 2H, J = 6.6 Hz). ^{13}C NMR: 101.0, 126.2, 128.6, 128.9, 129.6, 129.7, 130.2, 131.2, 137.0, 140.5, 144.0, 145.9, 154.5, 162.3. MS (CI): *m*/*z* (%) = 308 (100) [MH^+].

Ullman Reaction of Polymer-Bound Pyrazinone 12a with Substituted Aniline. Pyrazinone **12a** was prepared according to the procedure described above, starting from 0.1 g (0.08 mmol) of Wang amide resin. To a suspension of pyrazinone **12a** in toluene (3 mL) were added *p*-anisidine (0.05 g, 0.4 mmol, 5 equiv), K_2CO_3 (0.055 g, 0.4 mmol, 5 equiv), copper wire (0.04 g), and CuI (0.015 g, 0.08 mmol, 1 equiv). The reaction vessel was irradiated at 175° C for 30 min (300 W maximum power). The reaction mixture was cooled to ambient temperature, and the solvent was then filtered out with a polypropylene frit cartridge. The resin was washed as follows: DMF (5 mL × 3); DMF/H_2O (1:1, v:v, 5 mL × 10); THF/1 M HCl (1:1, v:v, 5 mL × 3); MeOH (5 mL × 3); and finally, with DCM (5 mL × 3). The whole procedure was repeated once. Pyrazinone **20a** was cleaved from the solid support according to the method described above. The crude product was loaded onto a short silica gel plug and eluted with DCM. The solvent was concentrated in vaccuo to provide pyrazinone **20a** (0.014 g, 40%).

5-Chloro-1-(4-hydroxybenzyl)-6-phenyl-3-(4-methoxyphenyl)amino-2(1*H*)-pyrazinone (20a). ^{1}H NMR: δ 3.83 (s, 3H), 4.99 (s, 2H), 6.66 (d, 2H, J = 8.8 Hz), 6.73 (d, 2H, J = 8.8 Hz), 6.95 (d, 2H, J = 8.8 Hz), 7.15 (d, 2H, J = 5.9 Hz), 7.43 (m, 3H), 7.76 (d, 2H, J = 8.8 Hz). ^{13}C NMR: 49.7, 55.9, 114.7, 115.7, 121.0, 125.5, 126.6, 128.2, 129.0, 129.4, 129.9 (×2), 131.2, 132.1, 146.3, 152.0, 155.5, 156.3. MS (CI): *m*/*z* (%) = 434 (1), 328 (7), 107 (100).

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References and Notes

(1) For the recent review, see: Dolle, R. E. *J. Comb. Chem.* **2003**, *5*, 693−753.
(2) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893−930.
(3) Sielecki-Dzurdz, T. M.; Arvanitis, A. G.; Dzierba, C. D. PCT/US 03/30570; WO 04/031189, 2002; *Chem. Abstr.* **2004**, *140*, 321385.
(4) Arvanitis, A.; Gilligan, P.; Hartz, R. PCT/US 02/15493; WO 02/092090, 2002; *Chem. Abstr.* **2002**, *137*, 370110.
(5) (a) Parlow, J. J.; Case, B. L.; Dice, T. A.; Fenton, R. L.; Hayes, M. J.; Jones, D. E.; Neumann, W. L.; Wood, R. S.; Lachance, R. M.; Girard, T. J.; Nicholson, N. S.; Clare, M.; Stegeman, R. A.; Stevens, A. M.; Stallings, W. C.; Kurumbail, R. G.; South, M. S. *J. Med. Chem.* **2003**, *46*, 4050−4062. (b) Sanderson, P.; Lyle, T.; Dorsey, B.; Varsolona, R. PCT/US 97/06744; WO 97/40024, 1997; *Chem. Abstr.* **1997**, 127, 248015.
(6) Im, H. K.; Im, W. B.; Judge, T. M.; Gammill, R. B.; Hamilton, B. J.; Carter, D. B.; Pregenzer, J. F. *Mol. Pharm.* **1993**, *44*, 468−472.
(7) Janssen, P. A. J.; Van Aken, K. J. A.; Lewi, P. J.; Koymans, L. M. H.; De Jonge, M. R.; Heeres, J.; Daeyaert, F. F. D.; Hoornaert, G. J. C.; Compernolle, F. J. C.; Kilonda, A. PCT/US 02-EP2806; WO 02/078708, 2002; *Chem. Abstr.* **2002**, *137*, 294978.
(8) Yaso, M.; Suzuki, Y.; Shibata, K.; Hayashi, E. Jpn. Kokai Tokkyo Koho JP 62,198,671, 1987; *Chem. Abstr.* **1988**, *108*, 167500.
(9) Kaval, N.; Dehaen, W.; Kappe, C. O.; Van der Eycken, E. *Org. Biomol. Chem.* **2004**, *2*, 154−156.
(10) Loosen, P. K.; Khorasani, M. F.; Toppet, S. M.; Hoornaert, G. J. *Tetrahedron* **1991**, *47*, 9269−9278.
(11) De Borggraeve, W. M.; Rombouts, F. J. R.; Van der Eycken, E. V.; Toppet, S. M.; Hoornaert, G. J. *Tetrahedron Lett.* **2001**, *42*, 4693−5695.
(12) Kaval, N.; Van Der Eycken, J.; Caroen, J.; Dehaen, W.; Strohmeier, G. A.; Kappe, C. O.; Van Der Eycken, E. *J. Comb. Chem.* **2003**, *5*, 560−568.

(13) Rombouts, F. J. R. Ph.D. Thesis, KULeuven, 2002**.**
(14) Kaval, N.; Bisztray, K.; Dehaen, W.; Kappe, C. O.; Van der Eycken, E. *Mol. Diversity* **2003**, *7*, 125−134.
(15) Vekemans, J.; Pollers-Wieërs, C.; Hoornaert, G. *J. Heterocycl. Chem.* **1983**, *20*, 919−923.
(16) (a) Taylor, H. M.; Hauser, C. R. *Org. Synth., Coll.* **1973**, *5*, 437. (b) Corson, B. B.; Dodge, R. A.; Harris, S. A.; Yeaw, J. S. *Org. Synth., Coll.* **1932**, *1*, 336.
(17) Vojkovsky, T. *Pept. Res.* **1995**, *8*, 236.
(18) Leblanc, J.-P.; Gibson, H. W. *Tetrahedron Lett.* **1992**, *33*, 6295−6298.
(19) Moser, P.; Sallman, A.; Wiesenberg, I. *J. Med. Chem.* **1990**, *33*, 2358−2368.
(20) Knepper, K.; Lormann, M. E. P.; Brase, S. *J. Comb. Chem.* **2004**, *6*, 460-463.
(21) CEM-Discover, CEM Corporation, P.O. Box 200, Matthews, NC 28106. For a detailed description of the monomode microwave apparatus, see: Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2001**, *3*, 624−630.

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