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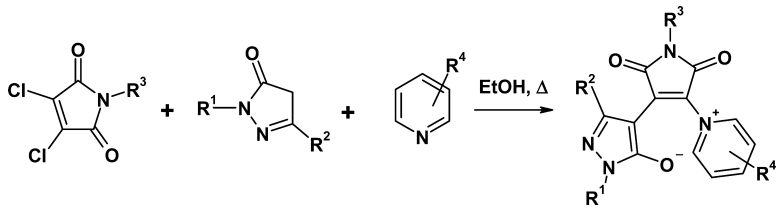
J. Comb. Chem., **2006**, 8 (3), 338-343• DOI: 10.1021/cc0501514 • Publication Date (Web): 19 April 2006



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Solution-Phase Parallel Synthesis of a Pyridinium Pyrazol-3-olate Inner Salt Library Using a Three-Component Reaction

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Received November 18, 2005

We present here the discovery of a novel, versatile, multicomponent reaction leading to various 4-[4-(pyridinium-1-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl]-2*H*-pyrazol-3-olate inner salts. The structure of the unusual zwitterionic inner salts was elucidated, and the scope of the novel reaction was investigated. After rapid optimization, the reaction was adapted to parallel synthesis, and an 800-membered compound library was produced.

Introduction

Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles have been identified from microbial sources, and these sugar-linked alkaloids have showed significant biological activities. For example, Staurosporine (**1** in Figure 1) is a very potent but nonselective kinase inhibitor, including protein kinase C and PKC, and acts as an antitumor agent.[1]

There are lots of efforts to simplify the structure of indolo-[2,3-*a*]-pyrrolo[3,4-*c*]carbazole (**2**) aglycon and identify the minimum active fragment, which could provide drug candidates with high developability value (Scheme 1). During this fragment-based dissection, the indolo[2,3-*a*]-pyrrolo[3,4-*c*]carbazoles turned into bisindolyl maleimides (**3**), which retained mostly the PKC biological activity.

On the basis of the results, intensive research to decorate the indole rings or replace them with other heterocycles began.[2] Pfizer and Roche have recently patented such compounds (**4**[3] and **5**[4]), and their efforts have aimed at improving the selectivity against PKC_{α} isozyme.

Results and Discussion

We followed the same strategy and started our synthetic program from dichloromaleimide, which is the general starting material of these systems.[5] Dichloromaleimides allow realizing the fragment-based strategy, since their Cl atoms could sequentially be substituted with nucleophiles. One fragment can be introduced at one side of the maleimide interface, followed by the addition of the second fragment entering at the opposite side. First, we focused on an indole−pyrazolone replacement on one side. Pyrazolones exhibit several activities, including analgesic, antineoplastic, and antiinflammatory effects; thus, we postulated that pyrazolones linked to maleimide might lead to compounds with interesting combined biological activity as well as improved selectivity.

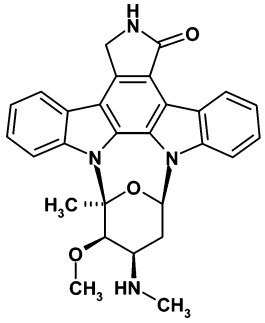

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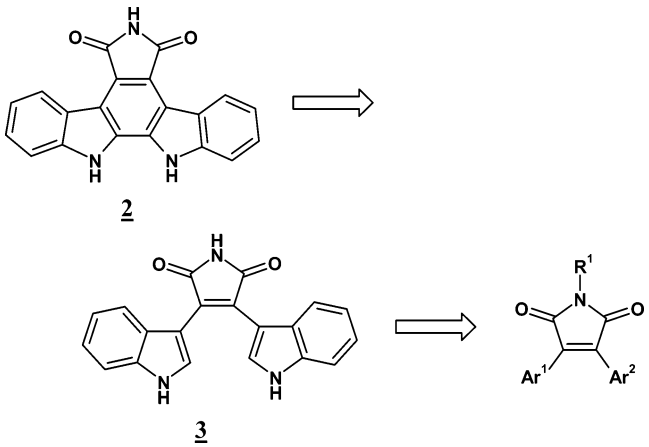
Figure 1. Structure of staurosporine.

Scheme 1. Library Design Based on Fragment-Based Dissection of Indolo[2,3-*a*]-pyrrolo[3,4-*c*]carbazoles



In principle, dichloromaleimides seemed to be a perfect building block for synthetic realization of such a library-building strategy. The first Cl atom could readily be replaced with a variety of, for example, O, N, and S, or even C nucleophiles;[2,6] however, the substitution of the second Cl atom is much more difficult, since its reactivity is strongly affected by the nature of the already incorporated nucleophile, which causes serious limitations to the second group.

This reactivity difference seemed to be ideal for building a small maleimide-based library by adding the desired

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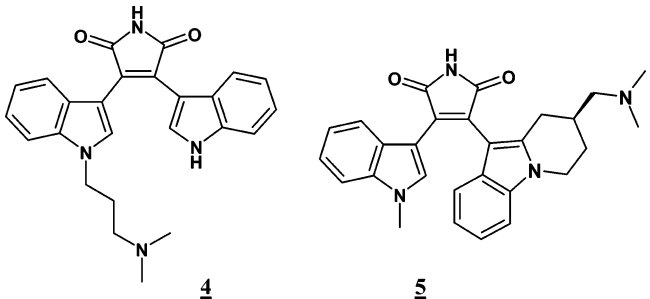
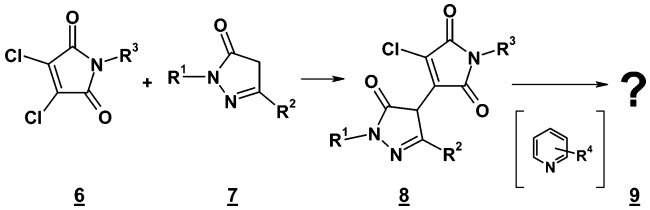
10.1021/cc0501514 CCC: $33.50
Published on Web 04/19/2006



4 **5**

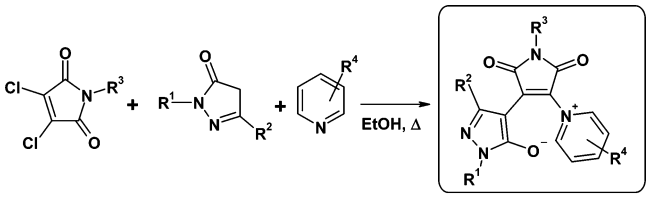
Figure 2. Some typical PKCα antagonists.

Scheme 2. Reaction Scheme of Stepwise Substitution



6 **7** **8** **9**

Scheme 3. Overall Reaction Scheme



6 **7** **10** **9**

fragments stepwise, in a sequential manner. To test our concept, various dichloromaleimides (**6**) were produced from the corresponding anhydrides and amines by using literature methods.[7] The first Cl atom of the various dichloromaleimides was easily reacted with pyrazolones as C nucleophiles under mild conditions. After preparing such intermediates, the reactivity of the second Cl atom was investigated with other nucleophiles in the presence of various organic and inorganic bases. For example, different pyridine ring-containing bases were applied, which led to highly colored crystalline products, which precipitated on cooling from the reaction mixture before addition of any other nucleophiles (Scheme 2).

Structure Elucidation. The crystalline products were analyzed by ^{1}H and ^{13}C NMR spectroscopy, and their molecular compositions were determined by the HRMS method. All the spectral data indicated that pyridine moieties were covalently coupled to the molecules as 1:1 adducts, forming zwitterionic inner salts. To confirm the structure, X-ray analysis was carried out, which unambiguously confirmed the general formula **9** (Scheme 3). To the best of our knowledge, such compounds are not described in the literature; only one publication reported related structures.[8]

Reaction Piloting. Due to the structural novelty and unknown properties of the inner salts, we initiated a deeper study applying different pyridines while omitting the second nucleophile from the reactions. Since both reaction steps needed nearly identical conditions (they could be performed in alcohol-type solvents at slightly elevated temperature), we attempted a "one-pot" procedure suitable for parallel synthesis. Thus, we mixed all the three components (**6** + **7** + **10**) in 2-propanol and heated the resulting solution to 70 °C. In all cases, the formation of zwitterionic adduct was observed as the major product. Therefore, we concluded that we discovered a versatile, novel three-component reaction (3CR), as shown in Scheme 3. We should note that when we reversed the stepwise addition of the reagents, that is, refluxing maleimide with pyridine in ethanol, no reaction was observed until the pyrazolone component was added. However, after the addition of pyrazolone (**7**) the reaction completed within 15 min, and the product crystallized upon cooling. This finding strongly suggests that the reaction proceeds through intermediate **8**. The elucidation of the exact mechanism was not further examined; rather, that will be the subject of a separate study and publication.

As a next step, we investigated the scope of the reaction by testing a pool of appropriate reagents, and the following conclusions were drawn:

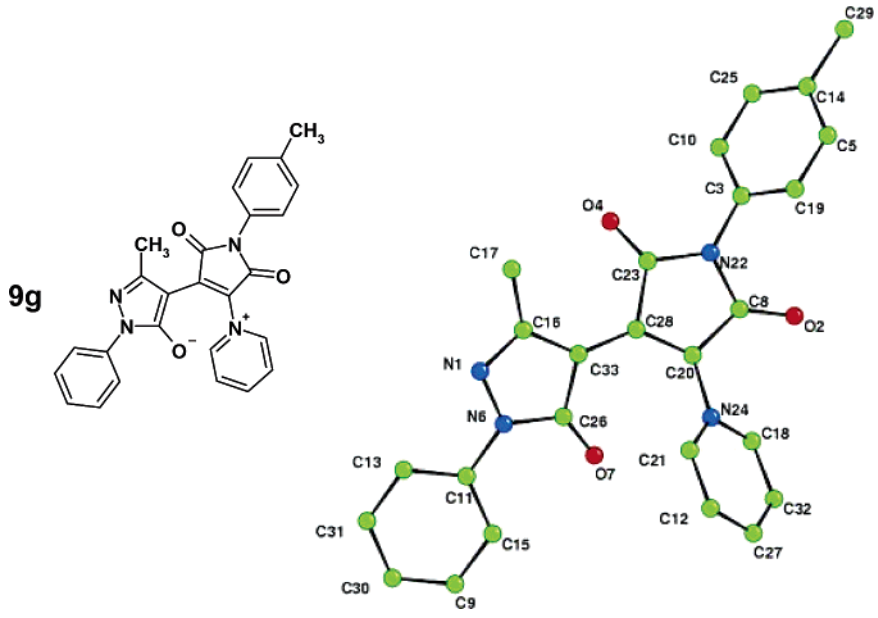
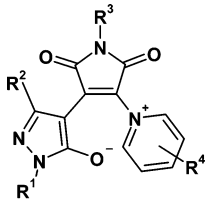


Figure 3. Structure and Ortep plot of **9g**.

Table 1. Representative Examples of **9**



9

compd	R^1	R^2	R^3	R^4	yield, %
9a	Ph	Me	4-Me−Ph	4-Me	87
9b	Ph	Me	*n*Bu	H	75
9c	CH_2Ph	Ph	*n*Bu	H	84
9d	Me	Me	*n*Bu	3-Me	18
9e	Ph	Me	*n*Bu	4-Me	63
9f	CH_2Ph	Ph	*n*Bu	3-Me	86
9g	Ph	Me	4-Me−Ph	H	69

(i) Maleimide-*N*-substitution had little impact on the yield of linear and branched aliphatic or aromatic hydrocarbons; aralkyl groups also worked equally well.

(ii) In the pyrazolone component, R^1 and R^2 could be either aliphatic and aromatic hydrocarbon or aralkyl groups.

(iii) We investigated unsubstituted pyridine, picolines, and short alkyl-substituted pyridines. Most of the reagents gave fairly good chemical yields, except α-picoline, most likely due to steric hindrance.

To implement the reaction into our parallel synthesis pipeline, we carried out a standard library piloting procedure with designed test reactions to identify the appropriate conditions suitable for most of the building blocks to be applied. The optimal conditions, we found, were mixing the reactants in either ethanolic or 2-propanolic solution, stirring it for few minutes at RT, and heating at ∼70 °C until the reaction went to completion. The products either crystallized on cooling or they were isolated by trituration after evaporation of the solvents and taking up the residue in water. During chemical piloting, we found, the ratio of 1:1:2.5 dichloromaleimide, pyrazolone, and pyridine reagents gave good yields, and the procedure was suitable for robot-assisted parallel synthesis. Seven compounds (**9a**−**g**) were synthesized as a small test library using the above conditions in parallel synthesis (Table 1.). The isolated yields were reasonably good (63−87%), except for **9d** (18%), in which the nonaromatic substituents improve the solubility, which reduces crystallization. (Another portion could be obtained from the mother liquor by chromatographic separation). All of these novel chemical entities were thoroughly analyzed by HPLC, IR, ^{1}H and ^{13}C NMR, and HRMS methods that proved both the purity and the structural identity.

Product Properties. The obtained zwitterionic compounds were highly colored in crystalline form (from deep purple to black) due to the multiply conjugated electronic character. The crystals were fairly soluble in common organic solvents (e.g., $CHCl_3$, EtOH), which revealed their actual color (red-, violet-, purple-, or dark blue). Their UV/vis spectra showed significant absorption in both the UV and the visible regions. We found that the products, even in solution, were not sensitive to light. They can be stored for months in their crystalline form under ambient conditions in the air without any detectable decomposition.

Parallelization and Library Synthesis. After characterization of the products and parameter optimization in the testing phase, we carried out the parallel synthesis with a large pool of in-house-synthesized pyrazolone and maleimide reagents. As a result, we obtained an ∼800-membered library (after QC control on a HT LC/MS platform). The typical amount was 10−30 mg for each compound. The overall diversity of the library is demonstrated in Table 2, displaying the substitution variations around the central core.

Table 3 shows examples of the 800-membered library together with their purities. Its substitution pattern covers the major functional groups and building blocks obtained during the library's production.

Summary

A novel, versatile, three-component reaction was discovered, which leads to unusual zwitterionic inner salts. The reaction is suitable for the generation of a library with high structural and functional diversity. After rapid optimization, the reaction was adapted to parallel synthesis, and a medium-sized compound library was produced. The compounds can be equally interesting for both pharmaceutical research and the color industry. Further transformations of the products are under investigation, including complete or partial saturation of the pyridinium salt into piperidine or dihydropyridine moieties. The results will be the subject of a separate paper.

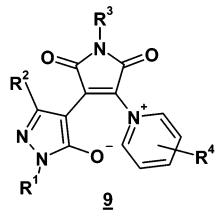
Experimental Section

Materials and General Methods. The melting points were measured with a Boetius apparatus, and the data are not corrected. Thin-layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60 F_{254}). The ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian Inova (400 MHz) spectrometer with TMS as an internal reference. IR spectra were measured on a Nicolet FTIR Magna 750 spectrophotometer. For HPLC runs, a Waters 1525 high-pressure binary HPLC pump integrated with an in-house-developed autosampler based on a Cavro RSP 9452 (Cavro Scientific Inst., Inc.) robotic workstation was used. The column type used was LiChroCART 30-4 Purospher Star RP-18, endcapped, 3 μm (Merck). The relative purity determination was based on 220- or 254-nm wavelength (MUX-UV 2488 detector, Waters Corp.). MS data were collected on a ZQ2000 MS instrument (Micromass-Waters Corp.) with ESI interface integrated with MUX (Waters Corp.). HRMS experiments were performed on a Micromass LCT spectrometer using an electrospray interface with a lock-mass sign of tetrabutylammonium ion. The UV/vis spectra were recorded on an Agilent 8453 DAD spectrophotometer in a 1-mm quartz cuvette using spectroscopic grade dichloromethane as solvent.

All solvents and reagents were obtained from commercial sources and were used without purification.

All the pyrazolones (**7**)[9] and the dichloromaleimides[7] were produced according to the literature. The target compounds (**9a**−**g**) were prepared according to the general procedure

Table 2. Diversity Elements of the Library



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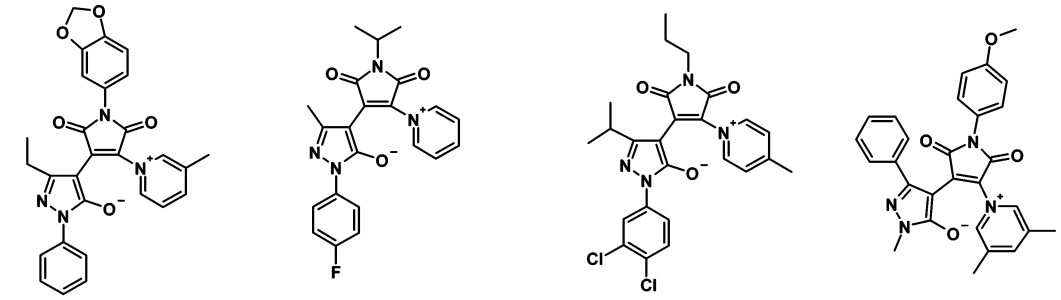
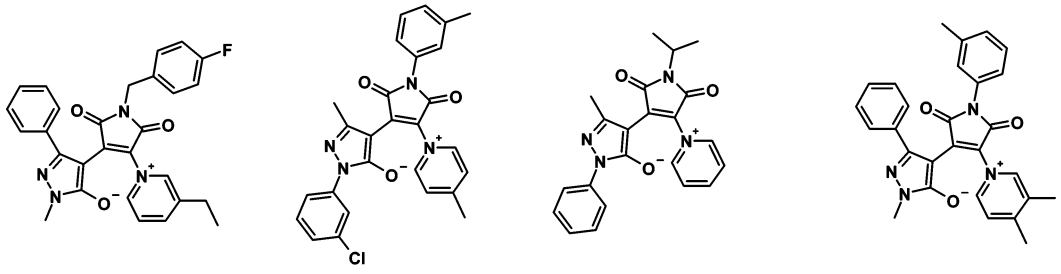
Variable groups	Substituents
R^1	CH_3-, CH_2-, Cl, CH_3, CH_3, Cl, Cl, CH_3, CH_3, F, Cl
R^2	CH_3-, C_2H_5-, $^nC_3H_7$-, $^iC_3H_7$-
R^3	$^iC_3H_7$-, $^nC_3H_7$-, $^nC_4H_9$-, $^iC_4H_9$-, $CH_3O(CH_2)_2$-, CH_2-, F, CH_3, O, O, CH_2-, CH_3, OMe, F, F, Cl, F
R^4	H, 3-Me, 4-Me, 3-Et, 4-Et, 3,4-Me_2, 3,5-Me_2

Table 3. Some Representative Library Compounds Together with Their HPLC Purity



HPLC: 88% HPLC: 89% HPLC: 88% HPLC: 94%



HPLC: 99% HPLC: 95% HPLC: 96% HPLC: 99%

described below; the library elements, on a semiautomated robotic platform.

5-Methyl-4-[4-(4-methylpyridinium-1-yl)-2,5-dioxo-1-p-tolyl-2,5-dihydro-1*H*-pyrrol-3-yl]-2-phenyl-2*H*-pyrazol-3-olate Inner Salt (9a). 3,4-Dichloro-1-*p*-tolylpyrrole-2,5-dione (1.79 g; 7 mmol) and 5-methyl-2-phenyl-2,4-dihydropyrazol-3-one (1.22 g; 7 mmol) were suspended in 2-propanol (15 mL). 4-Methylpyridine (1.66 mL; 17.5 mmol) was added, and the mixture was stirred and refluxed for 30 min. The solvent was evaporated, and the residue was crystallized with water. The product was filtered off; washed with water and ether; and finally, dried in a vacuum desiccator over P_2O_5/KOH. Yield 2.76 g (87%), dark-brown crystals. mp: 214.5−217.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 2.58 (s, 3H), 2.62 (s, 3H), 7.07 (t, 1H, J = 8.0 Hz), 7.30 (t, 2H, J = 8.0 Hz), 7.35 (s, 4H), 7.58 (d, 2H, J = 7.0 Hz), 7.82 (d, 2H, J = 8.0 Hz), 8.47 (d, 2H, J = 7.0 Hz). HR-MS (ES) 451.1786 found, 451.177

calcd for $C_{27}H_{23}N_4O_3^+$. IR (KBr): 1755 m (ν_s N(C═O)$_2$), 1699 vs (ν_{as} N(C═O)$_2$), 1635 vs (ν C−O$^-$), 1561 s (pyridine ring), 1514 vs and 1390 vs and 1198 m (skeletal vibr.). HPLC purity (254 nm): 99%.

5-Methyl-4-[4-(pyridinium-1-yl)-2,5-dioxo-1-butyl-2,5-dihydro-1*H*-pyrrol-3-yl]-2-phenyl-2*H*-pyrazol-3-olate Inner Salt (9b). The experimental procedure was similar to that described for compound **9a**. Yield: 2.10 g (75%), dark-brown crystals. mp: 204−209 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, 3H, J = 6.0 Hz), 1.40 (h, 2H, J = 6.0 Hz), 1.65 (p, 2H, J = 6.0 Hz), 2.58 (s, 3H), 3.62 (t, 2H, J = 6.0 Hz), 7.05 (t, 1H, J = 7.5 Hz), 7.29 (t, 2H, J = 7.5 Hz), 7.75 (t, 2H, J = 7.0 Hz), 7.85 (d, 2H, J = 7.5 Hz), 8.08 (t, 1H, J = 7.0 Hz), 8.47 (d, 2H, J = 7.0 Hz). HR-MS (ES) 403.1772 found, 403.177calcd for $C_{23}H_{23}N_4O_3^+$. IR (KBr): 1755 m (ν_s N(C═O)$_2$), 1694 vs (ν_{as} N(C═O)$_2$), 1639 s (ν C−O$^-$), 1556 s (pyridine ring), 1510 s and 1403 vs and 1138 m (skeletal vibr.). HPLC purity (254 nm): 95%.

5-Phenyl-4-[4-(pyridinium-1-yl)-2,5-dioxo-1-butyl-2,5-dihydro-1*H*-pyrrol-3-yl]-2-benzyl-2*H*-pyrazol-3-olate Inner Salt (9c). The experimental procedure was similar to that described for compound **9a**. Yield: 2.82 g (84%), black crystals. mp: 137−142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, 3H, J = 5.8 Hz), 1.26 (h, 2H, J = 5.8 Hz), 1.50 (p, 2H, J = 5.8 Hz), 3.50 (t, 2H, J = 5.8 Hz), 5.00 (s, 2H), 7.15−7.35 (m, 8H), 7.50 (d, 2H, J = 8.0 Hz), 7.74 (t, 2H, J = 6.0 Hz), 8.05 (t, 1H, J = 6.0 Hz), 8.58 (d, 2H, J = 6.0 Hz). HR-MS (ES) 479.2077 found, 479.2083 calcd for $C_{29}H_{28}N_4O_3^+$. IR (KBr): 1754 m (ν_s N(C═O)$_2$), 1695 vs (ν_{as} N(C═O)$_2$), 1637 vs (ν C−O$^-$), 1554 s (pyridine ring), 1476 s and 1400 vs and 1091 m (skeletal vibr.). UV/vis (λ): 433 (ϵ = 6285), 551 (ϵ = 5426). HPLC purity (254 nm): 100%.

2,5-Dimethyl-4-[4-(3-methyl-pyridinium-1-yl)-2,5-dioxo-1-butyl-2,5-dihydro-1*H*-pyrrol-3-yl]-2*H*-pyrazol-3-olate Inner Salt (9d). The experimental procedure was similar to that described for compound **9a**. Yield: 0.45 g (18%), black crystals. mp: 186−193 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, 3H, J = 5.6 Hz), 1.18 (h, 2H, J = 5.6 Hz), 1.62 (p, 2H, J = 5.6 Hz), 2.50 (s, 3H), 2.53 (s, 3H), 3.31 (s, 3H), 3.61 (t, 2H, J = 5.6 Hz), 7.64 (t, 1H, J = 8.0 Hz), 7.90 (d, 1H, J = 8.0 Hz). 8.23 (d, 1H, J = 8.0 Hz), 8.24 (s, 1H). HR-MS (ES) 355.1772 found, 355.177 calcd for $C_{19}H_{23}N_4O_3^+$. IR (KBr): 1738 m (ν_s N(C═O)$_2$), 1683 vs (ν_{as} N(C═O)$_2$), 1632 vs (ν C−O$^-$), 1556 s (pyridine ring), 1496 s and 1403 vs and 1119 s (skeletal vibr.). HPLC purity (254 nm): 92%.

5-Methyl-4-[4-(4-methyl-pyridinium-1-yl)-2,5-dioxo-1-butyl-2,5-dihydro-1*H*-pyrrol-3-yl]-2-phenyl-2*H*-pyrazol-3-olate Inner Salt (9e). The experimental procedure was similar to that described for compound **9a**. Yield: 1,84 g (63%), brown crystals. mp: 214.5−215 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, 3H, J = 6.0 Hz), 1.39 (h, 2H, J = 6.0 Hz), 1.63 (p, 2H, J = 6.0 Hz), 2.56 (s, 3H), 2.62 (s, 3H), 3.62 (t, 2H, J = 6.0 Hz), 7.03 (t, 1H, J = 8.2 Hz), 7.29 (t, 2H, J = 8.2 Hz), 7.55 (d, 2H, J = 6.0 Hz), 7.83 (d, 2H, J = 8.2 Hz), 8.37 (d, 2H, J = 6.0 Hz). HR-MS (ES) 417.1924 found, 417.1927 calcd for $C_{24}H_{25}N_4O_3^+$. IR (KBr): 1752 m (ν_s N(C═O)$_2$), 1691 vs (ν_{as} N(C═O)$_2$), 1634 vs (ν C−O$^-$), 1564 s (pyridine ring), 1515 s and 1402 vs and 1142 m (skeletal vibr.). UV/vis (λ): 431 (ϵ = 6887), 537(ϵ = 8419). HPLC purity (254 nm): 99%.

5-Phenyl-4-[4-(3-methylpyridinium-1-yl)-2,5-dioxo-1-butyl-2,5-dihydro-1*H*-pyrrol-3-yl]-2-benzyl-2*H*-pyrazol-3-olate Inner Salt (9f). The experimental procedure was similar to that described for compound **9a**. Yield: 2.95 g (86%), claret crystals. mp: 197.5−203 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, J = 6.0 Hz), 1.27 (h, 2H, J = 6.0 Hz), 1.54 (p, 2H, J = 6.0 Hz), 2.45 (s, 3H), 3.50 (t, 2H, J = 6.0 Hz), 5.05 (s, 2H), 7.16−7.41 (m, 8H), 7.43 (d, 2H, J = 8.2 Hz), 7.68 (t, 1H, J = 8.0 Hz), 7.95 (d, 1H, J = 8.0 Hz), 8.41 (s, 1H), 8.60 (d, 1H, J = 8.0 Hz). HR-MS (ES) 493.2238 found, 493.224 calcd for $C_{30}H_{29}N_4O_3^+$. IR (KBr): 1754 m (ν_s N(C═O)$_2$), 1696 vs (ν_{as} N(C═O)$_2$), 1637 vs (ν C−O$^-$), 1555 s (pyridine ring), 1494 m and 1401 s and 1097 m (skeletal vibr.). HPLC purity (254 nm): 92%.

5-Methyl-4-[4-(pyridinium-1-yl)-2,5-dioxo-1-*p*-tolyl-2,5-dihydro-1*H*-pyrrol-3-yl]-2-phenyl-2*H*-pyrazol-3-olate Inner Salt (9g). The experimental procedure was similar to that described for compound **9a**. Yield: 1.80 g (69%), black crystals. mp: 243.5−245 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.58 (s, 3H), 7.05 (t, 1H, J = 7.2 Hz), 7.37−7.18 (m, 6H), 7.78 (t, 2H, J = 5.7 Hz), 7.85 (d, 2H, J = 7.9 Hz), 8.11 (t, 1H, J = 5.7 Hz), 8.55 (d, 2H, J = 5.7 Hz). ^{13}C NMR ($CDCl_3$): 167.1, 165.9, 165.3, 148.3. 143.6, 141.1, 139.7, 138.5, 130.9, 130.2, 129.4, 129.0, 126.8, 125.6, 124.3, 119.4, 110.9, 99.1, 21.6, 18.5. HR-MS (ES) 437.1615 found, 437.1613 calcd for $C_{26}H_{21}N_4O_3^+$. IR (KBr): 1760 m (ν_s N(C═O)$_2$), 1695 vs (ν_{as} N(C═O)$_2$), 1640 vs (ν C−O$^-$), 1555 s (pyridine ring), 1512 s and 1388 vs and 1128 m (skeletal vibr.). HPLC purity (254 nm): 100%.

HT Parallel Synthesis: Parallel Reactors. The reactor unit was a 6 × 8 matrix-arranged block equipped with heating and stirring. The reaction vessels were labeled, screw-capped 4-mL sample vials with PTFE-coated plastic caps. As a liquid dispenser, Cavro robotic equipment was used.

General Procedure for the Robot-Assisted Parallel Library Production: (1) Preparation of Stock Solutions. c = 0.25 mol/L stock solution was prepared from the appropriate pyrazolone in ethanol. c = 0.25 mol/L stock solution was prepared from the maleimide in ethanol. The appropriate pyridine derivative was used in neat form. If the corresponding pyrazolone was poorly soluble in ethanol, it was added as a solid.

First, 1.0 mL (0.25 mmol) from the pyrazolone stock solution, then 1 mL (0.25 mmol) from the maleimide stock solution, were dispensed into the vials. Then 0.625 mmol from the appropriate pyridine was added to them. The vials were capped and stirred at 80 °C for 4 h. The reaction was monitored by TLC with an eluent mixture of 1,2-dichloroethane/ethanol 5:1. If the reaction was not complete, an additional 0.5 mL (0.125 mmol) of maleimide solution and 0.125 mmol of base were added. The stirring and heating was continued for an additional 2 h.

(2) Workup. The vials were decapped, and the solvent was evaporated, then 1−2 mL of water was added to the vials. The precipitated solid was filtered off and washed with water. If no precipitation occurred, the aqueous phase was

extracted with chloroform. After phase separation, the organic layer was evaporated to dryness.

Quality Assurance and Evaluation

A multilevel quality control guaranteed the identity and purity of the final products. During the production stage, all of the intermediates (**6**, **7**) were subjected to 100% HPLC/MS and NMR analysis. The accepted purity limit for the last intermediates before the MC3 step was ≥95% (both HPLC and NMR).

For the last step, only a selected portion (3−4%) of the final product (**9**) set was characterized by ^{1}H NMR methods. Total coverage purity checking of the final products was performed by HPLC/MS with the minimum limit of ≥85%.

In the case of the subjected compound library, out of 882 MC3 launched, 404 final products met the above purity limit with the described workup procedure. Another 259 products with purity level between 46 and 85% can be subjected to preparative HPLC purification, and the remaining part of the reactions was considered as fully unsuccessful (HPLC 0−46%).

Acknowledgment. We are grateful to Prof. Mark Bradley (University of Edinburgh) for performing the X-ray analysis in his lab. The authors are indebted to Mária Kajtár Peredy and József Kovács for recording and elucidating the NMR spectra and Richard Lágner for analytical investigations. We thank Peter Baranyai for the UV/vis measurements. The authors are also thankful to János Gerencsér for his support and advice.

Supporting Information Available. Experimental data and structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC0501514