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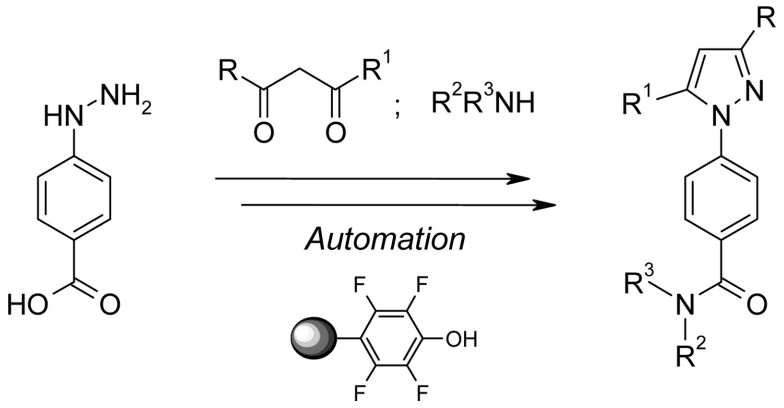

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Fully Automated Polymer-Assisted Synthesis of 1,5-Biaryl Pyrazoles

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The polymer-assisted solution-phase (PASP) synthesis of a 192-member 2-D array of 1,5-biaryl pyrazoles **4**{*1*−*12*,*1*−*16*} is reported. The synthesis was performed in a fully automated manner using a multiprobe top-filtration robot and incorporates a "catch and release" step to afford library compounds directly in high yield and purity.

Introduction

The high-throughput synthesis of large exploratory compound libraries and smaller focused arrays continues to be a key objective within the pharmaceutical industry as a means of both identifying and subsequently optimizing new lead structures for medicinal chemistry programs.[1] Although combinatorial solid-phase methods enable the efficient generation of large numbers of new compound entities,[2] difficulties often associated with solid-phase organic synthesis (SPOS), such as long reaction development and optimization times, the need for large reagent excesses to drive reactions to completion, and the inability to purify intermediate resin-bound intermediates, has refocused attention on developing methods for high-throughput solution-phase synthesis.[3]

Toward this end, polymer-assisted solution-phase (PASP) synthesis has gained considerable popularity.[4] Accordingly, polymer-supported reagents and scavenger resins are utilized to perform synthetic transformations in a sequence of incubations and filtrations. Since the desired compounds remain in solution throughout the synthesis, reaction progress and compound purities may be conveniently monitored at any stage by applying conventional chromatographic techniques. Moreover, there is no need for resin attachment and cleavage steps.

PASP synthesis also allows for the exploitation of a range of in-line purification techniques. For example, reaction byproducts and excess reagents may be removed by scavenging with suitably modified resins.[5] Alternatively, solid-phase extraction may be used to selectively isolate an appropriately functionalized reaction product from solution. The application of resin "catch and release" protocols is particularly powerful in that the reaction product is separated from solution by immobilization onto a resin in an activated form, such that the introduction of a suitably functionalized building block effects simultaneous derivitization and release of a new product back into solution.[6] Importantly, only derivatized material is released from the resin, thereby facilitating the preparation of compounds with intrinsically high purities.

However, although PASP syntheses of a wide range of molecules, from the multistep synthesis of complex natural products[7] to the preparation of druglike compound arrays,[8] have been reported, there are few reports detailing the successful automation of polymer-assisted solution-phase approaches,[9] although the iterative nature of incubation and filtration steps employed is potentially well-suited to such a strategy. This may be attributable in part to the fact that successfully transposing an existing solution-phase synthesis onto an automated platform is not always a trivial task. Changes may be needed in the synthesis itself in order to improve the efficiency of the overall process or to compensate for limitations associated with a particular robotic synthesizer. Simplification and standardization are key attributes likely to lead to successful automation, and this is a particular issue when attempting to automate *multistep* PASP synthesis.

As part of our interest in developing fully automated multistep PASP syntheses of biologically relevant compound arrays for use in drug discovery programs, we now report the fully automated polymer-assisted solution-phase synthesis of a 192-member array of 1,5-biaryl pyrazoles. The complete library synthesis was performed in a single run using a top-filtration robotic synthesizer[10] and after loading the synthesizer with the required starting materials and reagents, did not require any further manual intervention.

Results and Discussion

The 1,5-biaryl pyrazole moiety is found in a number of important pharmaceuticals, such as the selective COX-2 inhibitor Celecoxib **1**[11] and the nonsteroidal antiinflammatory agent Tepoxaline **2**[12] (Figure 1). We therefore decided to investigate the preparation of a prospecting library based upon this druglike scaffold, and to incorporate at least two points of diversity, we targeted an array of pyrazole carboxamides **4**{*x*,*y*}. In particular, we wished to identify a route that could be performed in a fully automated (unat-

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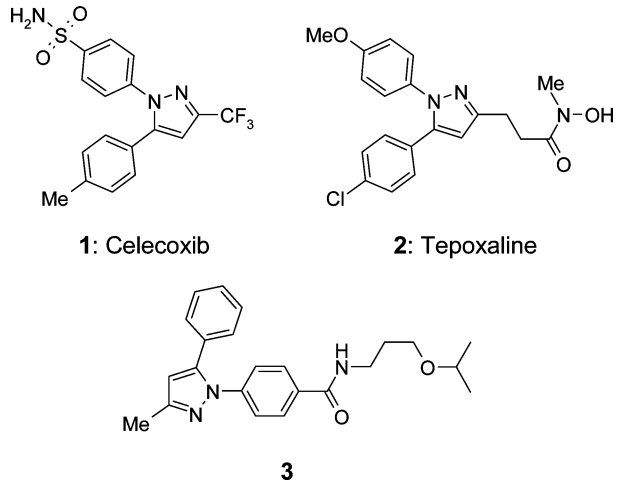
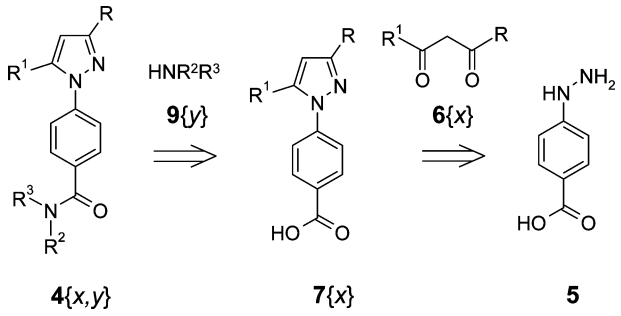


Figure 1. Examples of 1,5-biaryl pyrazoles.

Scheme 1. Retrosynthetic Analysis of Pyrazole Array 4{*x*,*y*}

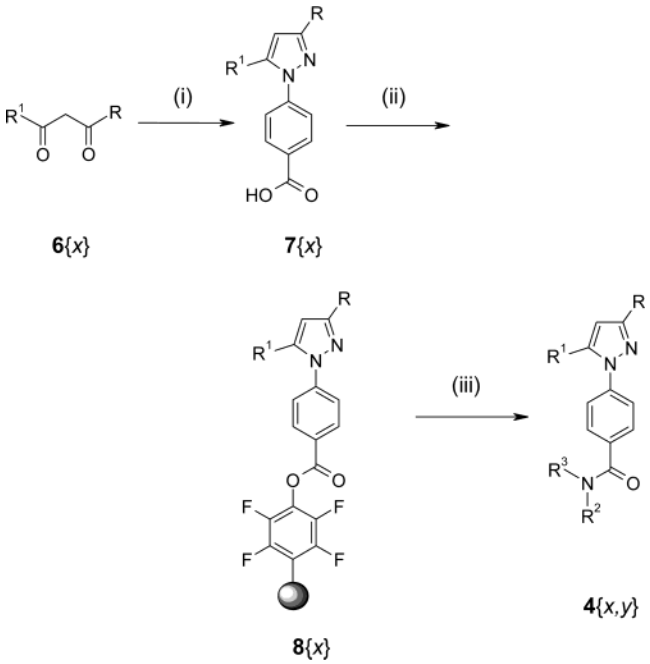


tended) manner using a commercially available robotic synthesizer to deliver compounds with high intrinsic purities suitable for biological evaluation without the need for postsynthesis chromatographic purification.

Manual Synthesis. We anticipated that condensation of a core hydrazine acid **5** with a set of 1,3-diketones **6**{*x*} (Chart 1) would afford the intermediate pyrazole acids **7**{*x*}. A second diversity element could then be incorporated by condensation of the acids **7**{*x*} with a set of amines **9**{*y*} to afford an array of discrete pyrazole carboxamides **4**{*x*,*y*} (Scheme 1). Precedent for this approach is provided by the reported synthesis of the 1,5-biaryl pyrazole **3**,[13] which was prepared in order to demonstrate the use of polymer-supported sequestration enabling reagents (SERs) in solution-phase synthesis.

Initially, we performed a reaction scan condensing the 1,3-diketone **6**{*1*} with phenylhydrazine 4-benzoic acid hydrochloride **5** in a range of solvents (MeOH, CH_2Cl_2, MeCN, $CHCl_3$, DMF, and NMP) in the presence of either polymer-supported diisopropylethylamine (PS-DIPEA) or polymer-supported *N*-methylmorpholine (PS-NMM) at room temperature. Solubility problems were observed with all the solvents except DMF and NMP, leading to low conversion to **7**{*1*}. Moreover, attempts to scavenge unreacted phenylhydrazine **5** by incubation with either polymer-supported isatoic anhydride or Amberlyst H-15 sulfonic acid ion-exchange resin proved to be unreliable. Consequently, we reinvestigated the initial condensation step and found that using triethylamine as base under solution-phase conditions in DMF at room temperature afforded a smooth conversion to the desired product **7**{*1*} in under 6 h, albeit contaminated

Scheme 2. "Capture and Release" PASP Synthesis of 1,5-Biaryl Pyrazoles[a]



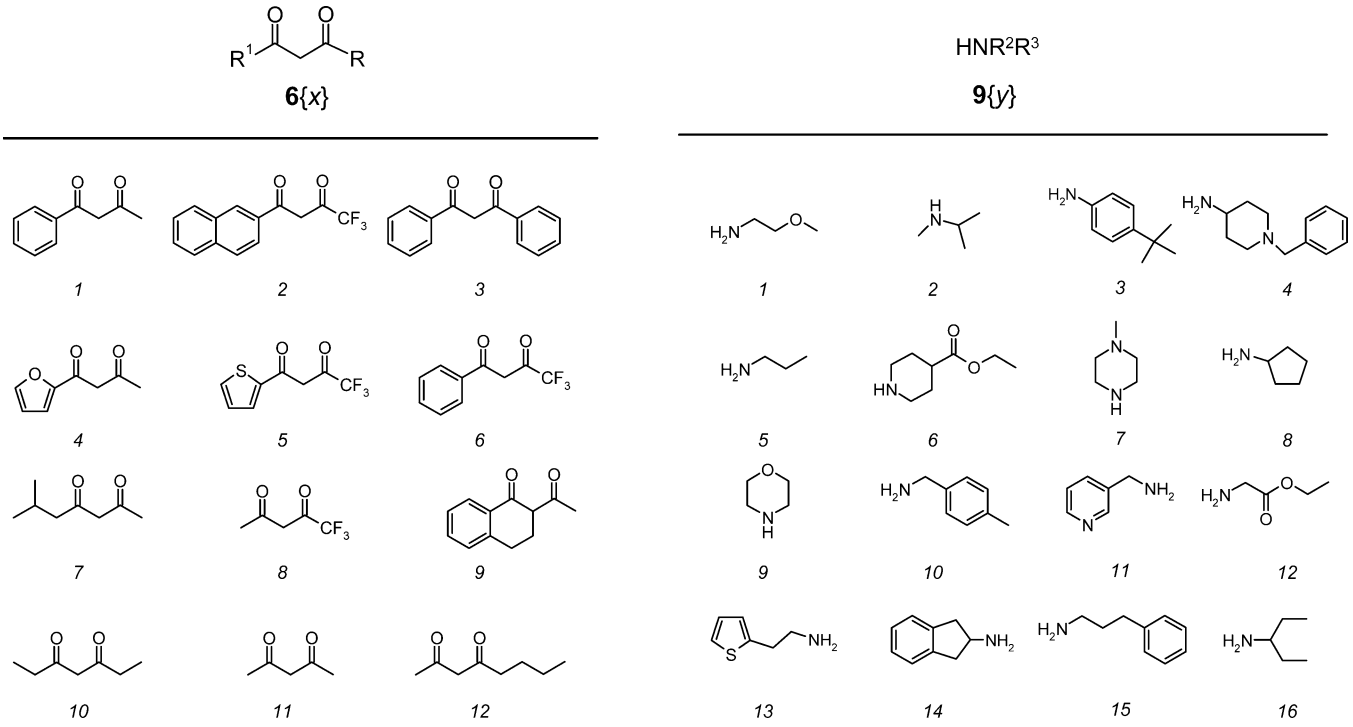
[a] Reagents and conditions: (i) phenylhydrazine 4-benzoic acid hydrochloride **5**, Et_3N, DMF, 80 °C; (ii) DIC, 4-DMAP, PS-TFP, DMF−CH_2Cl_2, rt, 2 h; (iii) R^2R^3NH **9**{*y*}, DMF, 60 °C.

with triethylamine hydrochloride. However, when the condensation was attempted with the electron-deficient 1,3-diketone **6**{*2*} and the more hindered diketone **6**{*3*}, the reaction did not go to completion at room temperature, and it was found necessary to increase the temperature to 80 °C to achieve complete conversion. At this stage, rather than attempting to remove the triethylamine hydrochloride contaminant by resin scavenging, we elected to perform a phase switch and "capture" the product acid **7**{*1*} as an activated ester immobilized on polystyrene **8**{*1*} (Scheme 2).

Resin "capture and release" has the added advantage that it facilitates solvent exchange without the added complexity associated with the introduction of evaporation steps. This is of particular significance in automated chemistry, in which it is desirable to reduce operational complexity as much as possible. Both polymer-supported 1-hydroxybenzotriazole (PS-HOBt) and polymer-supported tetrafluorophenol (PS-TFP) were evaluated for their ability to immobilize the acid **8**{*1*}, but more efficient "capture" was observed with PS-TFP. Moreover, PS-TFP has a higher loading, which is also advantageous from the point of view of automation.[14] However, although immobilization of the acid **8**{*1*} could be efficiently accomplished within 2 h at room temperature in the presence of diisopropylcarbodiimide (DIC) and 4-(dimethylamino)pyridine (4-DMAP),[15] the subsequent nucleophilic release process was observed to display a substrate dependence with respect to the amine (Figure 2).

Using a representative set of amines **9**{*1*−*3*}, kinetic studies using automated sampling and HPLC analysis of the reaction mixtures[16] revealed that anilines, such as **9**{*3*}, in particular, were poor nucleophiles. Nevertheless, an acceptable rate of reaction could be obtained for all the monomer combinations by heating to 60 °C for 2 h.

Chart 1. 1,3-Diketone Monomer Set **6**{*x*} and Amine Monomer Set **9**{*y*} Used to Prepare 1,5-Biaryl Pyrazole Array **4**{*x*,*y*}



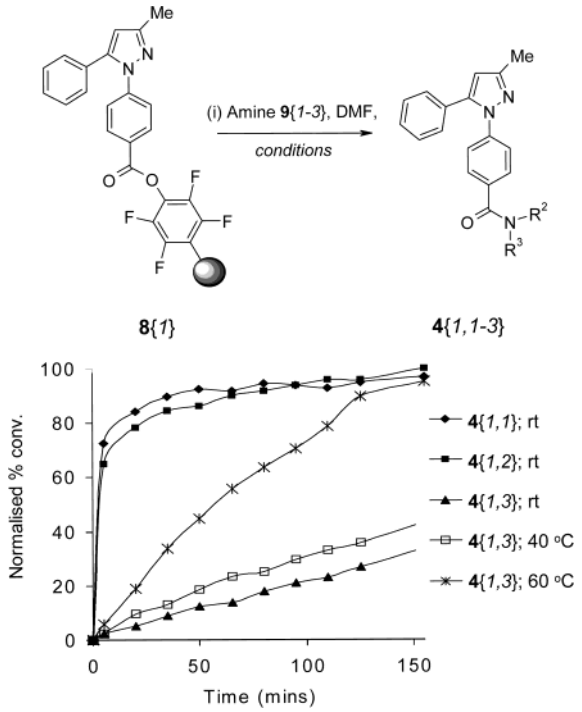


Figure 2. Relative kinetic plots for amine mediated carboxamide "release" from PS-TFP resin.

With a general set of reaction conditions established, we next performed a rehearsal of the array synthesis targeting the nine-member compound array **4**{*2*−*4*,*3*−*5*}, which included several new monomers chosen from the diversity sets **6**{*x*} and **9**{*y*}, to further validate the library synthesis. This study established that, in the case of the trifluoromethyl-substituted 1,3-diketone **6**{*2*}, the more stable hemi-ketal intermediate formed in the pyrazole formation step necessitated a longer reaction time (15 h) to ensure complete dehydration to afford the desired 1,5-biaryl pyrazole acid **7**{*2*}. Under these modified conditions, the desired pyrazoles **4**{*2*−*4*,*3*−*5*} were all obtained in good yield and in high purity according to LC/MS analysis (Table 1). For these monomers, no evidence was observed for the formation of the products derived from the regioisomeric pyrazoles in which R and R^1 are exchanged.[17]

Automated Synthesis. To perform the fully automated array synthesis, we selected a multiprobe, top-filtration robotic synthesizer as the preferred platform. We have previously established that such a device enables the efficient separation of the supernatant solution from polymer-supported reagents.[9] Moreover, the synthesizer is able to efficiently mix the heterogeneous resin suspensions by high speed vortexing. The proposed pyrazole array synthesis is conveniently represented as a flowchart in which, having taken into account all the manipulations required, it is apparent that what is formally only a 3-step synthesis becomes a more complex process when translated onto an automated platform (Figure 3). Accordingly, the robot was programmed to perform the required solution transfers, filtrations, and plate manipulations, and a rehearsal of the automated sequence was performed again, targeting the trial array **4**{*2*−*4*,*3*−*5*} in order to contrast the efficiency of the automated and manual protocols.

Reassuringly, under full automation, all of the desired products were obtained in good yield[18] and with excellent purities (Table 2).

At this stage, the robot was programmed to prepare the full 192-member (12 × 16) array, commencing with 2 mmol of each 1,3-diketone **6**{*x*} in order to afford 10−20 mg of each array product. From a consideration of the flowchart, it is apparent that the synthesis requires a variety of different reaction block configurations. This choice was, in part, dictated by what was available commercially. However, although in principle, 96-position reaction blocks might have

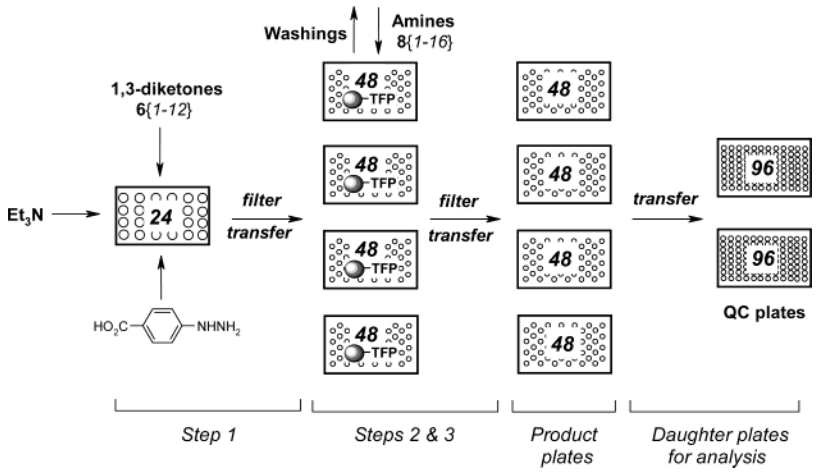


Figure 3. Flowchart for the fully automated PASP synthesis of the 192-member 1,5-biaryl pyrazole array **4**{*1*−*12*,*1*−*16*}.

Table 1. Isolated Yields and HPLC Purities for Trial Manual Compound Array **4**{*2-4*,*3-5*}

amine	% yield[a] (purity)[b]		
9{*y*}	**6** {*2*}	**6** {*3*}	**6** {*4*}
9{*3*}	68 (87)	58 (>97)	62 (94)
9{*4*}	89 (89)	89 (>97)	96 (>97)
9{*5*}	98 (88)	83 (>97)	67 (>97)

[a] By weight. [b] LC/MS purity (220−330 nm).

Table 2. Yields and HPLC Purities for the Automated Trial Array Synthesis **4**{*2-4*,*3-5*}

amine	% yield[a] (purity)[b]		
9{*y*}	**6** {*2*}	**6** {*3*}	**6** {*4*}
9{*3*}	62 (85)	60 (>97)	66 (>97)
9{*4*}	67 (85)	64 (>97)	83 (>97)
9{*5*}	75 (85)	66 (>97)	79 (>97)

[a] By weight. [b] LC/MS purity (220−330 nm).

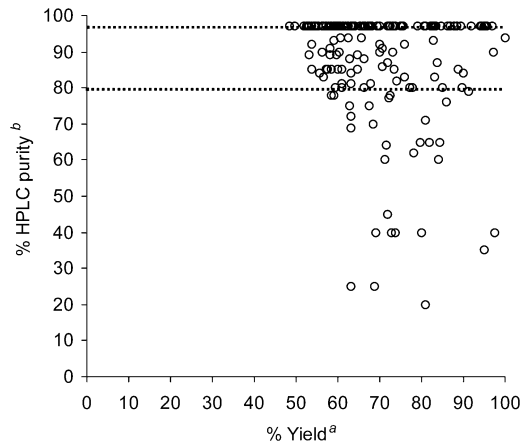


Figure 4. Purity vs yield profile for the auto-PASP 1,5-biaryl pyrazole array **4**{*1*−*12*,*1*−*16*}; [a] Gravimetric yield; [b] Percent peak area by UV (220−330 nm). Thresholds indicated correspond to 97 and 80% LC/MS purities.

been used for the resin-capture stage, the larger vessel sizes in the 48-position blocks promote more efficient vortex mixing of the resin suspensions and were therefore preferred. We also found that it was most convenient to produce quality control (QC) daughter plates containing small quantities of the reaction product solutions, which are then diluted down in situ prior to LC/MS analysis, as part of the automation process. Thus, in a fully automated manner, the set of

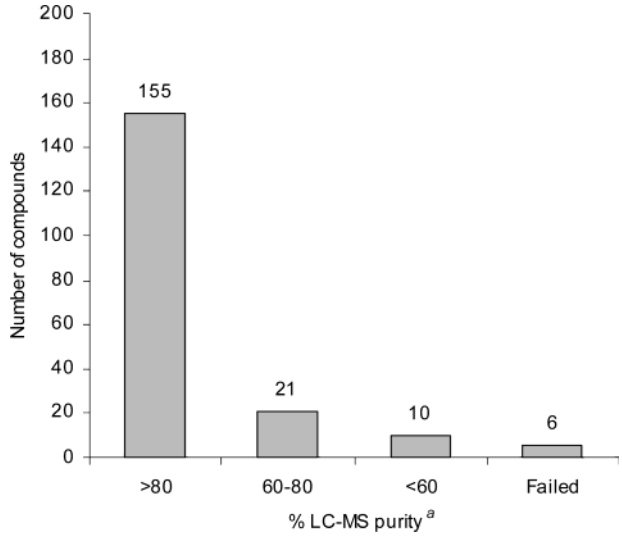


Figure 5. LC/MS purity profile for 1,5-biaryl pyrazole array **4**{*1*−*12*,*1*−*16*}; [a] Percent peak area by UV (220−330 nm).

diketones **6**{*1*−*12*} were converted to the intermediate pyrazole acids **7**{*1*−*12*}, which were split-out in situ and "captured" in 192 individual wells containing polymer-supported tetrafluorophenol. The resulting resins were washed free of contaminants and then treated with DMF solutions of the amines **9**{*1*−*16*} and vortexed at 60 °C for 2 h. The product solutions were transferred by top-filtration into 96-well microtiter product plates prior to parallel solvent evaporation to afford the pyrazole array **4**{*1*−*12*,*1*−*16*} (Figure 4).

Analysis of the resulting compound array by LC/MS revealed that of the 192 compounds targeted, 186 were successfully obtained. The average isolated yield was 70%, and the majority of compounds (155, equivalent to 82%) were >80% pure (Figure 5). Only 6 compounds were not isolated, and an additional 31 compounds required further purification. These compounds typically contained the amine monomers **9**{*13*} and **9**{*14*}, which were generally found to perform badly. The ^{1}H NMR spectrum of a typical array member **4**{*4*,*8*} is shown in Figure 6. Significantly, although the high throughput required the robot to deal with up to 4 blocks simultaneously, the overall run time was only 44 h from start to finish, which included 25 h allocated to automated liquid handling and probe washing protocols.

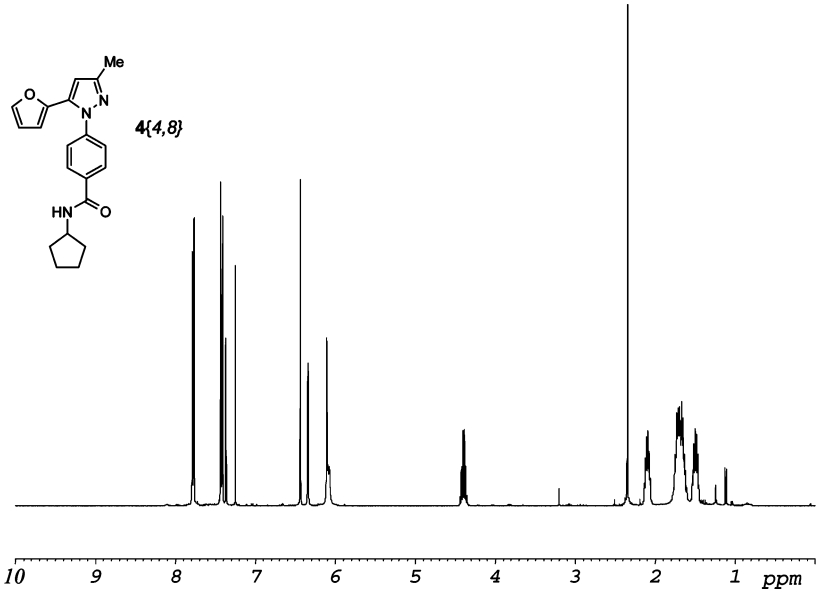


Figure 6. ^{1}H NMR spectrum of representative "crude" array member **4**{*4,8*}.

Conclusion

In summary, we have prepared a 192-member 2-D array of biologically relevant 1,5-biaryl pyrazoles **4**{*1*−*12,1*−*16*} in a fully automated, unattended combinatorial manner by parallel auto-PASP synthesis. The synthesis was performed using a top-filtration robotic synthesizer, and the incorporation of a resin "catch and release" in-line purification step led to compounds in both high yields (average yield = 70%) and purities (average purity = 85%). We are currently developing alternative fully automated polymer-assisted solution-phase (auto-PASP) protocols to facilitate the synthesis of other pharmacophoric motifs. Ultimately, it is envisaged that optimized protocols of this type might be combined in a "plug and play" manner and thereby constitute a new paradigm for highly automated solution-phase library synthesis.

Experimental Section

General Information. All solvents and reagents were used as supplied unless otherwise stated. Analytical high-pressure liquid chromatography (HPLC) was performed under the following conditions. Column: Supelcosil ABZ$^+$PLUS 3.3 cm × 4.6 mm, 3 μm. Eluent A: water, 0.1% TFA; B: acetonitrile 95%, water 5%, TFA 0.05%. Flow rate: 1 mL/min. Detection: UV (diode array, 215, 230, 254 nm). Method: gradient 10−95% B in A over 7 min. Infrared spectra were collected on a FT-IR instrument under attenuated total reflectance (ATR). Liquid chromatography/mass spectra (LC/MS) were recorded under electrospray positive and negative ionization following HPLC. Column: Supelcosil ABZ$^+$PLUS 3.3 cm × 4.6 mm, 3 μm. Eluent A: 10 mM solution of ammonium acetate in water, 0.1% formic acid; B: acetonitrile 95%, water 5%, formic acid 0.05%. Flow rate: 3 mL/min. Detection: UV (diode array, 220−330 nm). Method: gradient 0−100% B in A over 3.5 min. High-resolution mass spectra were obtained in either positive or negative electrospray (ESI) ionization mode using a time-of-flight spectrometer. NMR spectra were recorded at 400 and 500 MHz, respectively, for ^{1}H NMR and at 100 and 125 MHz for ^{13}C NMR (proton decoupled) in the indicated solvent. Chemical shifts (δ) are reported in parts per million (ppm). The following abbreviations are used for multiplicities: s = singlet; d = doublet; t = triplet; m = multiplet; dd = doublet of doublets; br = broad; and coupling constant J values are quoted in Hz.

Note that both the exploratory manual and automated syntheses were performed on the same scale to facilitate transposition of the optimized manual protocol to the automated platform.

Preparation of Pyrazole Amides 4{*x,y*}: General Manual Procedure. The diketone **6**{x} (1.00 mmol) was dissolved in DMF (1.5 mL). A solution of phenylhydrazine-4-benzoic acid hydrochloride **5** (186 mg, 1.00 mmol) in DMF (2.5 mL) and triethylamine (140 μL, 1.00 mmol) were added, and the reaction mixture was stirred at 80 °C for 15 h. The reaction mixture was allowed to cool and then partitioned into eight equal portions (∼0.125 mmol each). Each portion was added to PS-TFP (70 mg, 0.08 mmol) and diluted with CH_2Cl_2 (0.9 mL). To each resin was added diisopropylcarbodiimide (DIC) (12 μL, 0.56 mmol, 4.5 equiv) and 4-(dimethylamino)pyridine (DMAP) (9.8 mg, 0.08 mmol, 0.6 equiv), and the reaction mixtures were vortexed at room temperature for 2 h. The resins were filtered and washed with DMF (3 × 5 mL), CH_2Cl_2 (3 × 5 mL), DMF (3 × 5 mL), CH_2Cl_2 (3 × 5 mL), and DMF (3 × 5 mL). An amine **9**{y} (1 mL of 70 mM solution in DMF, 0.70 μmol, 0.88 equiv) was added to each reaction mixture, and the resulting suspensions were vortexed at 60 °C for 2 h. The reaction mixtures were cooled, and the resins were filtered and washed with DMF (2 × 3 mL). The solvent was removed in vacuo to yield the pyrazole carboxamides **4**{*x,y*}.

Preparation of Pyrazole Amides 4{*x,y*}: General Automated Procedure for 192-Member Array. *Step 1.* Dispense solutions of phenylhydrazine-4-benzoic acid hydrochloride **5** (2 mL of 0.5 mM, 1.00 mmol), the diketone **6**{x} (1.5 mL of 0.67 mM, 1.00 mmol), and triethylamine

(140 μL in 360 μL DMF, 1.00 mmol) into 12 × 8 mL reaction vessels in a 24-position reactor block.

Step 2. Repeat step 1 to fill the remaining 12 vessels with identical reaction mixtures.

Step 3. Vortex reaction block at 80 °C for 15 h.

Step 4. Allow reaction block to cool, then add CH_2Cl_2 (2 mL) to all reaction vessels.

Step 5. Partition each of the 24 reaction mixtures into eight equal portions and dispense each aliquot into a new reaction vessel (4 × 48-position reactor blocks) containing PS-TFP (70 mg, 0.08 mmol).

Step 6. Dilute each reaction vessel with CH_2Cl_2 (0.9 mL).

Step 7. Dispense solutions of DIC (140 μL of 3.75 M, 0.53 mmol) and DMAP (100 μL of 0.82 M, 0.08 mmol) into each of the 192 reaction vessels.

Step 8. Vortex reaction vessels at room temperature for 2 h.

Step 9. Drain resins and wash to waste with CH_2Cl_2, DMF, CH_2Cl_2, and DMF (3 × 3 mL).

Step 10. Dispense solutions of amines **9**{*y*} (1 mL of 60 mM solution in DMF, 0.06 mmol, 0.75 equiv) to appropriate reaction vessels.

Step 11. Vortex reaction blocks at 60 °C for 2 h.

Step 12. Drain resins and wash with DMF (1 mL) to new vials (192).

Step 13. Prepare QC plates; dispense aliquots (0.2 mL) into 96-well microtiter plates, and dilute each well with MeCN (0.5 mL).

Step 14. Remove solvents from bulk samples by parallel centrifugal evaporation in vacuo to afford pyrazoles **4**{*1*−*12*,*1*−*16*}.

Full characterization for 20 representative examples follows; LC/MS data for all 192 compounds is included in the Supporting Information provided.

4{***1,5***}. Cream solid (10.2 mg, 53%). HPLC: t_R = 4.81 min (98%, 254 nm). IR: ν_{MAX}/cm^{-1} 3268, 2963, 1628, 1509. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (d, J = 8 Hz, 2H), 7.30 (m, 5H), 7.20 (m, 2H), 6.30 (s, 1H), 6.11 (brs, 1H), 3.40 (m, 2H), 2.37 (s, 3H), 1.63 (m, 2H), 0.97 (t, J = 7, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c 166.7, 150.1, 143.9, 142.4, 132.9, 130.5, 128.7, 128.6, 128.4, 127.5, 124.6, 108.6, 41.8, 22.9, 13.6, 11.4. LC/MS (ESI): t_R = 3.13 min (*m*/*z* 320 [MH]$^+$). HRMS: $C_{20}H_{21}N_3O$ requires (MH)$^+$ 320.1763, found 320.1763.

4{***1,8***}. Cream solid (10.3 mg, 50%). HPLC: t_R = 5.33 min (95%, 254 nm). IR: ν_{MAX}/cm^{-1} 3257, 2950, 1628, 1509. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.67 (d, J = 8 Hz, 2H), 7.30 (m, 5H), 7.19 (m, 2H), 6.30 (s, 1H), 6.00 (brs, 1H), 4.37 (m, 1H), 2.37 (s, 3H), 2.08 (m, 2H), 1.75−1.60 (m, 4H), 1.47 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c 166.3, 150.1, 143.9, 142.4, 133.0, 130.5, 128.7, 128.6, 128.4, 127.5, 124.5, 108.6, 51.8, 33.2, 23.8, 13.6. LC/MS (ESI): t_R = 3.32 min (*m*/*z* 346 [MH]$^+$). HRMS: $C_{22}H_{23}N_3O$ requires (MH)$^+$ 346.1919, found 346.1911.

4{***2,4***}. Pale yellow glass (15.7 mg, 47%). HPLC: t_R = 4.90 min (94%, 254 nm). IR: ν_{MAX}/cm^{-1} 3277, 2940, 1639. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.75 (m, 6H), 7.54 (m, 2H), 7.39 (d, J = 8 Hz, 2H), 7.36 (m, 5H), 7.71 (dd, J = 8, 2 Hz, 1H), 6.85 (s, 1H), 6.45 (brm, 1H), 4.05 (brm, 1H), 3.75 (s, 2H), 3.10 (brm, 2H), 2.37 (brm, 2H), 2.02 (brm, 2H), 1.83 (brm, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c 165.7, 144.9, 143.8 (quartet), 141.6, 134.1, 133.9, 133.1, 132.9, 130.0, 128.7, 128.6, 128.5, 128.3, 128.2, 128.0, 127.8, 127.3, 127.0, 126.2, 125.7, 125.1, 121.1 (quartet), 106.5, 61.8, 51.7, 46.2, 30.6; LC/MS (ESI): t_R = 2.76 min (*m*/*z* 555 [MH]$^+$). HRMS: $C_{33}H_{29}N_4OF_3$ requires (MH)$^+$ 555.2372, found 555.2364.

4{***3,5***}. Pale yellow powder (15.2 mg, 66%). HPLC: t_R = 6.18 min (99%, 254 nm). IR: ν_{MAX}/cm^{-1} 3351, 2935, 1626. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.90 (d, J = 8 Hz, 2H), 7.72 (d, J = 8 Hz, 2H), 7.42 (m, 4H), 7.34 (m, 4H), 7.27 (m, 2H), 6.84 (s, 1H), 6.10 (brs, 1H), 3.41 (q, J = 7 Hz, 2H), 1.63 (quin, J = 7 Hz, 2H), 0.98 (t, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c 166.7, 152.5, 144.6, 142.4, 133.3, 132.7, 130.3, 128.8, 128.7, 128.6, 128.2, 127.6, 125.8, 124.8, 106.0, 41.8, 22.9, 11.4. LC/MS (ESI): t_R = 3.44 min (*m*/*z* 382 [MH]$^+$). HRMS: $C_{25}H_{23}N_3O$ requires (MH)$^+$ 382.1919, found 382.1915.

4{***3,13***}. Orange gum (26.2 mg, 97%). HPLC: t_R = 6.52 min (98%, 254 nm). IR: ν_{MAX}/cm^{-1} 3297, 2927, 1636, 1504. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.90 (m, 2H), 7.68 (d, J = 8 Hz, 2H), 7.45−7.24 (m, 10H), 7. 18 (dd, J = 5,2, 1H), 6.96 (dd, J = 5,4, 1H), 6.87 (dd, J = 4,2, 1H), 6.82 (s, 1H), 6.22 (brs, 1H), 3.74 (q, J = 6, 2H), 3.15 (t, J = 6, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c 166.6, 152.5, 144.6, 142.5, 141.5, 133.0, 132.7, 130.3, 128.8, 128.7 (×2), 128.6, 128.2, 127.6, 127.2, 125.8, 125.5, 124.8, 124.1, 106.0, 41.3, 29.9. LC/MS (ESI): t_R = 3.66 min (*m*/*z* 450 [MH]$^+$). HRMS: $C_{28}H_{23}N_3OS$ requires (MH)$^+$ 450.1640, found 450.1639.

4{***3,16***}. Orange gum (22.4 mg, 91%). HPLC: t_R = 6.53 min (97%, 254 nm). IR: ν_{MAX}/cm^{-1} 3297, 2927, 1626, 1507. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.91 (m, 2H), 7.73 (d, J = 8 Hz, 2H), 7.45−7.26 (m, 10H), 6.82 (s, 1H), 5.79 (brs, 1H), 4.00 (m, 1H), 1.65 (m, 2H), 1.49 (m, 2H), 0.94 (t, J = 7, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c 166.4, 152.5, 144.6, 142.4, 133.5, 132.8, 130.4, 128.8, 128.7 (×2), 128.6, 128.2, 127.5, 125.8, 124.7, 106.0, 52.6, 27.5, 10.3. LC/MS (ESI): t_R = 3.68 min (*m*/*z* 410 [MH]$^+$). HRMS: $C_{27}H_{27}N_3O$ requires (MH)$^+$ 410.2232, found 410.2235.

4{***4,3***}. Brown gum (19.8 mg, 83%). HPLC: t_R = 6.38 min (99%, 254 nm). IR: ν_{MAX}/cm^{-1} 3285, 2962, 1647, 1606, 1514. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.99 (m, 3H), 7.55 (d, J = 8 Hz, 2H), 7.47 (d, J = 8 Hz, 2H), 7.38 (m, 3H), 6.46 (s, 1H), 6.37 (dd, J = 4,2 Hz, 1H), 2.36 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c 164.8, 150.2, 147.8, 144.0, 142.8 (×2), 135.1, 134.7, 134.0, 127.8, 125.9, 125.1, 120.1, 111.3, 109.5, 107.5, 34.4, 31.3 13.5. LC/MS (ESI): t_R = 3.74 min (*m*/*z* 400 [MH]$^+$). HRMS: $C_{25}H_{24}N_3O_2$ requires (MH)$^+$ 400.2025, found 400.2028.

4{***5,10***}. Pale yellow solid (16.2 mg, 61%). HPLC: t_R = 6.36 min (98%, 254 nm). IR: ν_{MAX}/cm^{-1} 3309, 1638, 1132. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.81 (d, J = 8 Hz, 2H), 7.45 (d, J = 8 Hz, 2H), 7.35 (dd, J = 5,2 Hz, 1H), 7.25 (m, 2H), 7.17 (d, J = 8 Hz, 2H), 6.97 (dd, J = 5,4 Hz, 1H), 6.85 (dd, J = 4,2 Hz, 1H), 6.79 (s, 1H), 6.35 (brs, 1H), 4.60 (d, J = 6 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c 166.0, 143.7 (q), 141.2, 138.6, 137.6, 134.8, 134.7, 129.5, 129.2, 128.5, 128.1, 127.9 (×2), 127.7, 126.0, 120.9 (q),

106.2 (d), 44.1, 21.1. LC/MS (ESI): t_R = 3.72 min (*m*/*z* 442 $[MH]^+$). HRMS $C_{23}H_{18}N_3OF_3S$ requires $(MH)^+$ 442.1201, found 442.1193.

4{***7,1***}**.** Yellow gum (10.0 mg, 53%). HPLC: t_R = 3.99 min (98%, 254 nm). IR: ν_{MAX}/cm^{-1} 3314, 2956, 1640, 1609, 1507. ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.85 (d, *J* = 8 Hz, 2H), 7.46 (d, *J* = 8 Hz, 2H), 6.56 (brs, 1H), 6.01 (s, 1H), 3.66 (m, 2H), 3.57 (t, *J* = 5 Hz, 2H), 3.39 (s, 3H), 2.51 (d, *J* = 7 Hz, 2H), 2.30 (s, 3H), 1.79 (m, 1H), 0.85 (d, *J* = 7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c 1665.6, 149.5, 143.8, 142.6, 133.1, 127.9, 125.1, 106.9, 71.1, 58.8, 39.8, 35.3, 28.4, 22.4, 13.5. LC/MS (ESI): t_R = 2.92 min (*m*/*z* 316 $[MH]^+$). HRMS: $C_{18}H_{25}N_3O_2$ requires $(MH)^+$ 316.2025, found 316.2016.

4{***7,4***}**.** Cream solid (12.8 mg, 50%). HPLC: t_R = 3.74 min (99%, 254 nm). IR: ν_{MAX}/cm^{-1} 3242, 2955, 1627, 1508. ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.81 (d, *J* = 8, 2H), 7.45 (d, *J* = 8 Hz, 2H), 7.31 (m, 4H), 7.25 (m, 1H), 6.02 (br, 2H), 4.02 (m, 1H), 3.52 (s, 2H), 2.86 (br, 2H), 2.50 (d, *J* = 7, 2H), 2.30 (s, 3H), 2.19 (brm, 2H), 2.02 (br, 2H), 1.78 (m, 1H), 1.58 (brm, 2H), 0.85 (d, *J* = 7, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c 164.9, 148.5, 142.7, 141.5, 137.1, 132.3, 128.1, 127.2, 126.7, 126.0, 124.0, 105.8, 61.9, 51.2, 46.1, 34.2, 31.2, 27.3, 21.3, 12.5. LC/MS (ESI): t_R = 2.50 min (*m*/*z* 431 $[MH]^+$). HRMS: $C_{27}H_{34}N_4O$ requires $(MH)^+$ 431.2811, found 431.2805.

4{***7,9***}**.** Orange gum (14.5 mg, 74%). HPLC: t_R = 4.07 min (98%, 254 nm). IR: ν_{MAX}/cm^{-1} 2958, 1625, 1114. ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.46 (m, 4H), 6.01 (s, 1H), 3.90−3.40 (brs, 8H), 2.50 (d, *J* = 7 Hz, 2H), 2.29 (s, 3H), 1.82 (m, 1H), 0.86 (d, *J* = 7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c 169.7, 149.4, 143.8, 141.4, 134.2, 128.0, 125.5, 106.6, 66.8, 48.3, 42.6, 35.2, 28.4, 23.5, 22.4, 13.5. LC/MS (ESI): t_R = 2.89 min (*m*/*z* 328 $[MH]^+$). HRMS: $C_{19}H_{25}N_3O_2$ requires $(MH)^+$ 328.2025, found 328.2023.

4{***9,2***}**.** Orange gum (9.9 mg, 56%). HPLC: t_R = 5.18 min (95%, 254 nm). IR: ν_{MAX}/cm^{-1} 2973, 1607, 748. ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.54 (d, *J* = 8 Hz, 2H), 7.44 (brs, 2H), 7.28 (brd, 1H), 7.14 (dt, *J* = 7, 2 Hz, 1H), 7.03 (brt, 1H), 6.94 (brs, 1H), 4.95 (brs, 0.33H), 3.96 (brs, 0.66H), 3.00−2.76 (br, 5H), 2.65 (m, 2H), 2.30 (s, 3H), 1.25−1.09 (brs, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c 170.8, 146.6, 141.5, 138.1, 137.0, 136.3, 128.5, 128.0, 127.5, 127.2, 126.8, 126.5, 125.3, 125.1, 123.3, 119.1, 49.9 and 44.7 (rotamers), 30.8, 30.5, 26.0 and 23.5 (rotamers), 20.3, 19.3, 11.7. LC/MS (ESI): t_R = 3.30 min (*m*/*z* 360 $[MH]^+$). HRMS: $C_{23}H_{25}N_3O$ requires $(MH)^+$ 360.2076, found 360.2067.

4{***9,7***}**.** Orange gum (17.6 mg, 76%). HPLC: t_R = 3.41 min (95%, 254 nm). IR: ν_{MAX}/cm^{-1} 2938, 1624. ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.50 (d, *J* = 8 Hz, 2H), 7.48 (d, *J* = 8 Hz, 2H), 7.28 (d, *J* = 7 Hz, 1H), 7.14 (dt, *J* = 7,2 Hz, 1H), 7.02 (dt, *J* = 8,2 Hz, 1H), 6.92 (d, *J* = 8 Hz, 1H), 3.81 (brs, 2H), 3.46 (brs, 2H), 2.97 (m, 2H), 2.65 (m, 2H), 2.55−2.28 (brs, 4H), 2.32 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c 169.6, 146.7, 141.9, 138.1, 137.1, 134.7, 128.6, 128.1, 127.5, 126.7, 126.5, 125.2, 123.2, 119.3, 55.2, 54.7, 47.6, 46.0, 42.1, 30.5, 19.2, 11.7. LC/MS (ESI): t_R = 2.37 min (*m*/*z* 387 $[MH]^+$). HRMS $C_{24}H_{26}N_4O$ requires $(MH)^+$ 387.2185, found 387.2185.

4{***10,2***}**.** Orange gum (8.7 mg, 48%). HPLC: t_R = 4.36 min (95%, 254 nm). IR: ν_{MAX}/cm^{-1} 2970, 1623, 1608. ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.44 (m, 4H), 6.06 (s, 1H), 4.94 (brs, 0.3H), 3.95 (brs, 0.7H), 2.94 (brs, 0.7H), 2.88 (brs, 0.3H), 2.66 (m, 4H), 1.30−1.08 (brs, 12H), ^{13}C NMR (125 MHz, $CDCl_3$) δ_c 170.8, 155.4, 145.9, 140.7, 136.1, 127.7, 127.0, 125.2, 124.9, 103.7, 49.9 and 44.6 (rotamers), 26.0 and 23.4 (rotamers), 21.5, 20.3 and 19.3 (rotamers), 19.8, 13.9 and 13.2 (rotamers). LC/MS (ESI): t_R = 3.04 min (*m*/*z* 300 $[MH]^+$). HRMS: $C_{18}H_{25}N_3O$ requires $(MH)^+$ 300.2076, found 300.2070.

4{***10,7***}**.** Orange gum (17.3 mg, 88%). HPLC: t_R = 2.93 min (95%, 254 nm). IR: ν_{MAX}/cm^{-1} 1630, 1607. ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.47 (m, 4H), 6.06 (s, 1H), 3.80 (brs, 2H), 3.45 (brs, 2H), 2.67 (m, 4H), 2.48 (brs, 2H), 2.34 (br, 2H), 2.31 (s, 3H), 1.24 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c 169.6, 155.5, 145.9, 134.5, 127.9, 124.9, 103.9, 55.2, 54.7, 47.6, 46.0, 42.1, 21.5, 19.9, 13.8, 13.2. LC/MS (ESI): t_R = 3.45 min (*m*/*z* 327 $[MH]^+$). HRMS: $C_{19}H_{26}N_4O$ requires $(MH)^+$ 327.2185, found 372.2179.

4{***10,9***}**.** Orange gum (18.8 mg, 100%). HPLC: t_R = 3.72 min (95%, 254 nm). IR: ν_{MAX}/cm^{-1} 2970, 1631, 1608, 1113. ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.48 (m, 4H), 6.07 (s, 1H), 3.70 (brs, 8H), 2.67 (m, 4H), 1.25 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c 169.7, 155.6, 145.9, 141.3, 134.0, 128.0, 125.0, 104.0, 66.3, 48.2, 42.4, 21.5, 19.9, 13.8, 13.2. LC/MS (ESI): t_R = 3.72 min (*m*/*z* 341 $[MH]^+$). HRMS: $C_{18}H_{23}N_3O_2$ requires $(MH)^+$ 314.1869, found 341.1861.

4{***10,11***}**.** Orange gum (14.5 mg, 72%). HPLC: t_R = 3.11 min (99%, 254 nm). IR: ν_{MAX}/cm^{-1} 3280, 2978, 1643, 1606, 1507. ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.58 (d, *J* = 6 Hz, 2H), 7.88 (d, *J* = 8 Hz, 2H), 7.52 (d, *J* = 8 Hz, 2H), 7.26 (m, 2H), 6.70 (brs, 1H), 6.08 (s, 1H), 4.67 (d, *J* = 6 Hz, 2H), 2.67 (m, 4H), 1.25 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c 166.8, 155.8, 150.1, 147.3, 146.0, 142.9, 132.1, 127.9, 124.6, 122.4, 104.4, 42.9, 21.5, 20.1, 13.8, 13.1. LC/MS (ESI): t_R = 2.37 min (*m*/*z* 335 $[MH]^+$). HRMS: $C_{20}H_{22}N_4O$ requires $(MH)^+$ 335.1872, found 335.1865.

4{***11,1***}**.** Yellow gum (9.5 mg, 58%). HPLC: t_R = 3.00 min (98%, 254 nm). IR: ν_{MAX}/cm^{-1} 3312, 2926, 1639, 1609, 1507. ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.85 (d, *J* = 8 Hz, 2H), 7.51 (d, *J* = 8 Hz, 2H), 6.55 (brs, 1H), 6.01 (s, 1H), 3.65 (m, 2H), 3.56 (t, *J* = 5 Hz, 2H), 3.39 (s, 3H), 2.36 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c 166.6, 149.7, 142.4, 139.5, 132.7, 127.9, 124.0, 107.9, 71.1, 58.9, 39.8, 13.5, 12.7. LC/MS (ESI): t_R = 2.44 min (*m*/*z* 274 $[MH]^+$). HRMS: $C_{15}H_{21}N_3O_2$ requires $(MH)^+$ 274.1556, found 274.1553.

4{***11,4***}**.** Yellow gum (15.9 mg, 68%). HPLC: t_R = 3.01 min (99%, 254 nm). IR: ν_{MAX}/cm^{-1} 3288, 2942, 1634, 1507. ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.81 (d, *J* = 8 Hz, 2H), 7.50 (d, *J* = 8 Hz, 2H), 7.31 (m, 4H), 7.25 (m, 1H), 6.01 (brs 2H), 4.01 (m, 1H), 3.52 (s, 2H), 2.86 (brs, 2H), 2.32 (s, 3H), 2.29 (s, 3H), 2.19 (brm, 2H), 2.02 (brm, 2H), 1.58 (brm, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c 166.0, 149.7, 142.4, 139.5, 138.2, 133.0, 129.1, 128.2, 127.7, 127.1, 124.0, 107.9, 63.0, 52.3, 47.2, 32.3, 13.5, 12.7. LC/MS (ESI): t_R = 2.19 min (*m*/*z* 389 $[MH]^+$). HRMS $C_{24}H_{28}N_4O$ requires $(MH)^+$ 389.2341, found 389.2345.

4{***11,8***}**.** Orange gum (11.4 mg, 67%). HPLC: $t_R = 4.06$ min (99%, 254 nm). IR: ν_{MAX}/cm^{-1} 3298, 2959, 1632, 1507. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.81 (d, $J = 8$ Hz, 2H), 7.50 (d, $J = 8$ Hz, 2H), 6.08 (brs, 1H), 6.00 (s, 1H), 4.40 (m, 1H), 2.32 (s, 3H), 2.28 (s, 3H), 2.10 (m, 2H), 1.78−1.60 (m, 4H), 1.50 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_c 166.3, 149.7, 142.3, 139.5, 133.1, 127.7, 124.0, 107.9, 51.8, 33.2, 23.8, 13.5, 12.7. LC/MS (ESI): $t_R = 2.88$ min (*m*/*z* 284 $[MH]^+$). HRMS: $C_{17}H_{21}N_3O$ requires $(MH)^+$ 284.1763, found 284.1755.

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Supporting Information Available. Copies of ^{1}H NMR and ^{13}C NMR spectra for 20 representative library members and tabulated yield and purity data for the 192-member library. This information is available free of charge via the Internet at http://pubs.acs.org.

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(16) This study was performed using a Gilson ReactArray workstation connected to an analytical HPLC (www.reactarray.com).

(17) LC/MS analysis of the 192-member array **4**{*1*−*12*,*1*-*16*} subsequently showed that the 1,3-diketones **6**{*8*} and **6**{*12*} afforded separable (2:1) and (3:1) mixtures of regioisomeric pyrazoles, respectively. This may be attributable to a more similar steric environment at the R and R^1 carbonyl centres in these cases.

(18) In our experience, when compared to the corresponding manual process, automation of multistep PASP chemistries may lead to some slightly lower isolated yields. This is not a limiting issue, but is largely a consequence of minimizing resin wash volumes and restrictions imposed by the synthesis robot. More importantly, from a high-throughput perspective, compound purities are unaltered for both manual and automated processes.

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