Microwave-Assisted Solution-Phase Synthesis of 1,4,5-Trisubstituted Pyrazoles

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A small parallel library of 1,4,5-trisubstituted pyrazoles was prepared in solution using a three-step procedure starting from Meldrum acid. The Meldrum acid was acylated with different acyl chlorides and the products opened with different alcohols and amines to give substituted β-keto esters and β-keto amines. Further reaction with *N*,*N*-dimethylformamide dimethylacetal and the final cyclisation were effectively carried out under microwave irradiation. Scavenger resins were employed exclusively in the first step, whereas use of microwaves allowed complete conversion of the starting materials in the other two steps.

The current development of new methods for the parallel synthesis of libraries of organic molecules has led to renewed interest in a technique in which individual organic molecules are prepared in solution. The advantages of this technique are the standard solution-phase reactivity of the organic molecules, and easy analysis of the reaction using conventional methods without any need for linker chemistry. A particularly important aspect is that the operational time for the preparation of a new library can be shorter than the time necessary to develop a reaction on solid phase. On the other hand, in order to automate the preparation of the library, all the steps must give pure compounds after simple workup, involving exclusively filtration or evaporation under vacuum. To reach this goal, polymer-supported reagents have been employed frequently, and recently the developments in the field have been reviewed extensively.[1−5] The main drawbacks of polymer-assisted solution-phase synthesis are related to the use of polymers that show low loading values and difficulty in swelling in several solvents. Moreover, the prices of several polymer-supported reagents or scavengers are sometimes very high.

In order to prepare a library of pharmacologically relevant heterocyclic scaffolds with a good level of potential molecular diversity in solution phase, we decided to optimize the synthesis of a trisubstituted pyrazole to obtain a protocol that could be easily automated. We wanted to improve the efficiency of each step to avoid purification and reduce the work-up procedures for a limited number of expensive supported regents. For these reasons, we considered the possibility to carry out as many steps as possible under microwave irradiation, as this technique has been generally accepted as a valuable aid in organic and combinatorial synthesis.[6−10] We chose the pyrazole ring for its intrinsic interest as the basic structure of several drugs,[11−16] and for the possibility to have a trisubstituted scaffold with potential large molecular diversity. Substituted pyrazoles have already been prepared in the solid phase[17−21] and in solution[22−25] following different synthetic strategies, where hydrazine derivatives cyclise with 1,3-dicarbonyl or α,β-unsaturated carbonyl compounds.

We decided to follow the retrosynthetic approach reported in Scheme 1, originally described by Schenone and co-workers,[26] and further employed by a group at Pfizer to prepare a selective NHE-1 inhibitor.[27] The reaction involved the cyclisation of a monosubstituted hydrazine with an enamino- β-keto ester **1** derived from a simple β-keto ester and *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA). The sites for molecular diversity in this approach are the substituents on hydrazine (R_3), the derivatives of the carboxylic function (ester OR_2 or amide NHR_2), and the substituents on the starting β-keto ester (R_1). Although several β-keto esters are commercially available, in order to obtain higher molecular diversity, we decided to prepare compounds **2** by reaction of Meldrum acid with an acyl chloride followed by ring-opening with different alcohols or amines.

The first problem was to carry out the preparation of the acyl Meldrum derivative **4** (Scheme 2) under conditions that could be easily automated. As a model reaction, we treated Meldrum acid with isobutanoyl chloride as described in the literature.[28] After hydrolytic workup, the desired product **4** could be obtained in good yield and pure enough to be used

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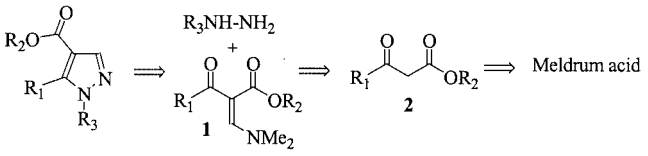
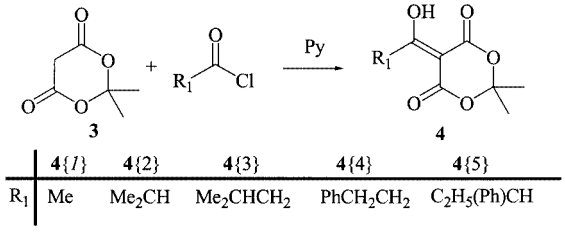


Scheme 1

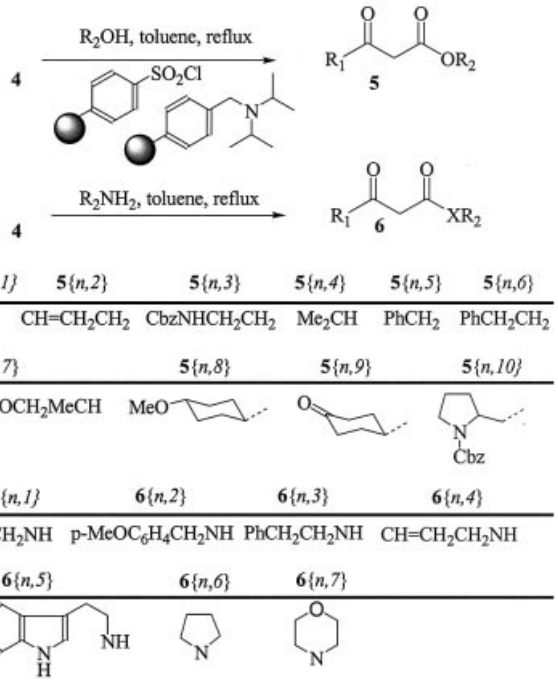
in the next step. To avoid the phase separation that follows the hydrolytic workup and that is difficult to automate, dichloromethane and pyridine contained in the reaction mixture were evaporated under high vacuum and the product **4** was extracted from the crude reaction mixture with ethyl acetate. Different amounts of pyridine included in the crude reaction mixture were extracted and removed by passing the ethyl acetate solution through a short path column of an acidic resin (such as Amberlite-IRC 86). Evaporation of ethyl acetate gave good yields of the expected acyl Meldrum derivative **4**. This protocol was repeated using various acyl chlorides and the results found to be reproducible. Unfortunately, we were not able to apply this procedure to interesting α-amino acid derivatives as they could introduce an additional site for molecular diversity. The use of mixed anhydrides, fluorides or other activating agents always gave unsatisfactory results.[29]



Scheme 2

The next step was the ring opening of **4** with different alcohols or amines to give β-keto esters **5** or β-keto amides **6** (Scheme 3). In the case of alcohols, the described procedure employs a large excess of a volatile alcohol with respect to the Meldrum derivative.[30]

With the aim of optimising the conditions, we looked for ways to minimise the amount of alcohol needed for a successful transformation. Different conditions were tried, such as changing the solvent, the temperature, the concentrations of the reagents, and adding also catalytic amounts of acid or base. Nevertheless, we found that with less than three equiv. of alcohol the reaction does not reach an acceptable level of conversion to avoid chromatographic separation from the starting material or other byproducts. The best reaction condition was to reflux the Meldrum derivative in the presence of three equiv. of the alcohol. The application of microwaves, in order to reduce the amount of alcohol needed, gave no obvious improvements. Volatile alcohols were preferentially employed in this step to simplify the final workup of removing the solvent under vacuum. When a less volatile alcohol, such as benzyl alcohol, was used, the excess of reagent could be removed by adding a



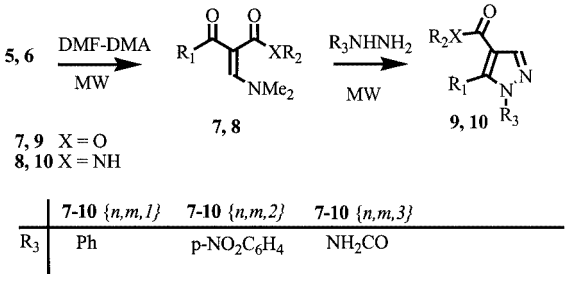
Scheme 3

PS-DVP-supported sulfonyl chloride to the solution, followed by a PS-DVB-supported tertiary amine. After filtration and evaporation of the solvent, the desired compounds were obtained sufficiently pure for the next step.

In the reaction of the acyl Meldrum acids **4** with amines, a stoichiometric amount of the nucleophile was needed.[31] Consequently, pure amides **6** were isolated after one hour in refluxing toluene after simple evaporation of the solvent.

The β-keto esters **5** and the β-keto amides **6** were further reacted by refluxing in neat DMF-DMA as reported previously.[27] Employing **5** as a model compound and following these conditions, the expected enamino keto ester was obtained in acceptable yields, although not acceptably pure for the next step. We looked again for reaction conditions compatible with automation. The desired product was isolated in good yields and with higher purity when the reaction was carried out at room temperature for longer time than when performed in refluxing solvent. Nevertheless, a certain amount of the starting material was still present preventing the use of the crude in the cyclisation. Moreover, due to the similar properties of the starting material and the products, it was impossible to find a scavenger that selectively removes one in the presence of the other. In this case, the use of microwaves was crucial for the success of the reaction. In fact, submitting a solution of **5** in DMF-DMA to microwave irradiation (using a domestic oven under MORE conditions)[32–34] at 60 W for five minutes (five cycles of 1 min followed by 1 min of rest) a complete conversion of the starting material was obtained and pure product **7** could be isolated after simple evaporation of DMF-DMA. The procedure was repeated with β-keto esters **5** and β-keto amides **6**, which gave high yields of the desired products with a high level of purity.[35]

Products **7** and **8** were finally cyclised with a monosubstituted hydrazine hydrochloride in refluxing ethanol in the presence of Et_3N under nitrogen. After filtration of the insoluble components, the solvent was evaporated under vacuum and pyrazoles **9** or **10** were extracted from the crude product with ethyl acetate or diethyl ether (Scheme 4). The solution was passed through a short column of silica gel and the solvents evaporated to give the expected product in excellent yields and acceptable purity. To reduce the time required for the final step (8 h under conventional heating) the reaction was carried out under microwave irradiation, allowing the formation of the desired pyrazole after heating for eight minutes at 60 W (eight cycles of 1 min of heating followed by 1 min of rest). The identity and the purity of the products was determined by ^1H and ^{13}C NMR spectroscopy, and ES-MS analysis. The formation of the 1,4,5-trisubstituted pyrazole was based on the resonance of the pyrazole proton at $\delta = 7.9-8.1$ ppm in the ^1H NMR spectrum.



Scheme 4

Following this protocol, a small parallel library was prepared by choosing from a variety of distinctive groups to create three varying sites of diversity (Table 1). As substituent R_1, we added different aliphatic and aromatic groups and as R_2 we used different aliphatic, aromatic and heterocyclic groups containing additional functionalities that could be exploited for a further increase of diversity. The chemoselectivity and the versatility of the process were demonstrated by the preparation of pyrazoles having a protected amine at R_2 (**9**{*1,3,1*}, **9**{*1,10,1*}), or even a free carbonyl group (**9**{*1,9,1*}), susceptible to further functionalisation. As substituent R_3, we were limited to aromatic rings due to the scarcity of commercially available monosubstituted hydrazines, although several hydrazines could be prepared starting from aniline derivatives.[36] The steps that required the microwave assistance were carried out in sealed tubes collected in a beaker and placed inside a modified household apparatus that allowed an acceptable efficacy of the process. Of course, the use of a parallel automated apparatus that controls the microwave irradiation of any single reactor will improve the protocol.

In conclusion, we have demonstrated that parallel libraries of pharmacologically important compounds, such as trisubstituted pyrazoles, can be prepared in the solution phase. The correct choice of synthetic approach and the use of microwaves limit as much as possible the use of expensive supported reagents or scavengers which, in any case, were successfully used in the first step. Moreover, the variety of substrates employed here suggests the extension of the protocol to many other compounds to largely increase the molecular diversity.

Table 1. Library of 1,4,5-trisubstituted pyrazoles **9** and **10**

Compound	Empirical formula	MS $[M + H]^+$ Found	Compound	Empirical formula	MS $[M + H]^+$ Found
9{*1-1-1*}	$C_{13}H_{14}N_2O_2$	231.6	**9**{*3−10−1*}	$C_{27}H_{31}N_3O_4$	462.6
9{*1-2-1*}	$C_{14}H_{24}NO_2$	243.7	**9**{*4-1-1*}	$C_{20}H_{20}N_2O_2$	321.4
9{*1-2-2*}	$C_{14}H_{23}N_3O_4$	287.6	**9**{*4-2-1*}	$C_{21}H_{20}N_2O_2$	333.5
9{*1-3-2*}	$C_{21}H_{20}N_4O_6$	425.4	**9**{*4-4-1*}	$C_{21}H_{22}N_2O_2$	335.7
9{*1-4-1*}	$C_{14}H_{16}N_2O_2$	245.3	**9**{*4-9-1*}	$C_{24}H_{24}N_2O_3$	389.2
9{*1-5-1*}	$C_{18}H_{16}N_2O_2$	293.6	**9**{*5-1-1*}	$C_{21}H_{22}N_2O_2$	335.4
9{*1-5-3*}	$C_{13}H_{13}N_3O_3$	260.6	**9**{*5-2-1*}	$C_{22}H_{22}N_2O_2$	347.6
9{*2-1-1*}	$C_{15}H_{18}N_2O_2$	259.7	**9**{*5-7-1*}	$C_{26}H_{32}N_2O_3$	421.7
9{*2-2-1*}	$C_{16}H_{18}N_2O_2$	271.6	**9**{*5-9-1*}	$C_{26}H_{30}N_2O_3$	419.5
9{*2-3-1*}	$C_{23}H_{25}N_3O_4$	408.5	**10**{*1-1-1*}	$C_{18}H_{17}N_3O$	292.4
9{*2-5-1*}	$C_{20}H_{20}N_2O_3$	321.6	**10**{*1-2-1*}	$C_{19}H_{19}N_3O_2$	322.7
9{*2-5-2*}	$C_{20}H_{19}N_3O_4$	366.5	**10**{*1-3-1*}	$C_{19}H_{19}N_3O$	306.3
9{*2-5-3*}	$C_{15}H_{17}N_3O_3$	287.5	**10**{*2-2-1*}	$C_{21}H_{23}N_3O_2$	350.4
9{*2-6-1*}	$C_{21}H_{22}N_2O_2$	335.5	**10**{*2-4-1*}	$C_{17}H_{21}N_3O$	284.6
9{*2-7-1*}	$C_{20}H_{28}N_2O_3$	345.4	**10**{*2-5-1*}	$C_{23}H_{24}N_4O$	373.4
9{*2-8-1*}	$C_{20}H_{26}N_2O_3$	343.5	**10**{*2-6-1*}	$C_{17}H_{21}N_3O$	284.7
9{*2-9-1*}	$C_{19}H_{22}N_2O_3$	327.4	**10**{*2-7-1*}	$C_{17}H_{21}N_3O_2$	300.3
9{*2−10−1*}	$C_{26}H_{29}N_3O_4$	448.7	**10**{*3-2-1*}	$C_{22}H_{25}N_3O_2$	364.7
9{*3-1-1*}	$C_{16}H_{20}N_2O_2$	273.5	**10**{*4-1-1*}	$C_{25}H_{23}N_3O$	382.6
9{*3-3-1*}	$C_{24}H_{27}N_3O_4$	421.5	**10**{*5-1-1*}	$C_{26}H_{25}N_3O$	396.5
9{*3-5-1*}	$C_{21}H_{22}N_2O_2$	334.4	**10**{*5-2-1*}	$C_{27}H_{27}N_3O_2$	426.7

Experimental Section

Starting materials and reagents including PS-DVB supported reagents were purchased from Acros Organics (Geel, Belgium). The reactions under microwave irradiation were carried out in a pressure tube (Sigma−Aldrich) placed inside a domestic oven, containing a beaker with water (200 mL), to modulate the microwave energy input into the reaction mixture. Exposure to microwaves of the sample was performed in cycles of one minute of irradiation followed by at least one minute of rest. During the rest period the hot water contained in the beaker was replaced.

Except the model compounds described below, the components of the library were characterized by HPLC-MS (ESI) through their M + 1 values (see Table 1).

β-Keto Esters 5. General Procedure. 4-Methyl-3-oxopentanoic Acid Benzyl Ester: Dry pyridine (0.098 g, 1.2 mmol) was slowly added, followed by isobutanoyl chloride (0. 053 g, 0.5 mmol), to a solution of Meldrum acid (0.072 g, 0.5 mmol) in dry CH_2Cl_2 (3 mL) in a flask equipped with a magnetic stirrer at 0 °C. The mixture was stirred at 0 °C for 1 h and at room temp. for an additional hour. The solvent was evaporated under vacuum (1.5 Torr) and the crude product was extracted with ethyl acetate (3 × 3 mL). The fractions were collected and passed through a short column filled with Amberlite-IRC-86 (1.0 g, previously swelled with MeOH). The Amberlite was washed with ethyl acetate (5 mL) and the collected washings were dried over dry $MgSO_4$ and evaporated under vacuum to give pure **4**{*2*}. This product was dissolved in dry toluene (8 mL); benzyl alcohol (0.162 g, 1.5 mmol) was added, and the mixture was refluxed for 2 h. After cooling to room temperature, sulfonyl chloride polystyrene resin (0.7 g of 1.3 mmol/g loaded beads) was added, followed by diisopropylaminomethyl polystyrene resin (0.58 g of 2.4 mmol/g loaded beads). After stirring for 2 h, TLC analysis showed the disappearance of benzyl alcohol. The solution was filtered and the solvent evaporated to give pure **5**{*2*−*5*} (81 mg, 74% overall yield). The identity of the product was confirmed by comparison of the ^{1}H NMR and mass spectra with the literature data.[37]

β-Keto Amides 6. General Procedure: Compound **4**, obtained as described previously, was dissolved in dry toluene (5 mL) containing allylamine (0.028 g, 0.5 mmol) and the mixture was refluxed under nitrogen for 1 h. The solvent was evaporated to give pure **6**{*2*−*5*} (80 mg, 70% overall yield). The identity of the product was confirmed by comparison of the ^{1}H NMR and mass spectra with the literature data.[31]

Pyrazoles 9 and 10: Compound **5**{*2*−*5*} (81 mg, 0.36 mmol) was dissolved in DMF-DMA (0.8 mL) in a pressure tube that was closed and placed inside a domestic microwave oven containing a beaker filled with water. The tube was submitted to 3 cycles of 1 min of irradiation at 60 W followed by 1 min of rest. The tube was cooled and the DMF-DMA was removed under vacuum. Absolute ethanol (1 mL) was added to the crude product, followed by phenylhydrazine hydrochloride (53 mg, 0.36 mmol) and Et_3N (50 μL, 0.5 mmol). The tube was closed and submitted to 5 cyles of 1 min of irradiation at 60 W followed by 1 min of rest. The tube was cooled and the solvent was evaporated. Ethyl acetate (5 mL) was added and the solution was passed through a short column of silica gel (1 g of silica gel for flash chromatography, eluent: ethyl acetate). The solvent was removed to give the product **9**{*2-5-1*}, HPLC purity 92% (84 mg, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$) 1.39 (d, *J* = 7 Hz, 6 H), 3.32 (m, 1 H), 5.36 (s, 2 H), 7.37 (m, 10 H), 8.10 (s, 1 H) ppm. MS (ESI +ve ion): 321.6 [M + H]$^+$

The same experimental procedure was followed using the products reported in Schemes 2−4. All the pyrazoles were purified by passing through a short column of silica gel. The purity of all the products prepared was higher than 90% (HPLC-ESIMS analysis). The following analytical data are representative of the library components.

Benzyl 5-Methyl-1-phenyl-1*H*-pyrazole-4-carboxylate [9{*1-5-1*}]: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.54 (s, 3 H), 5.32 (s, 2 H), 7.31−7.53 (m, 10 H), 7.96 (s, 1 H) ppm. MS (ESI +ve ion): *m*/*z* = 293.6 [M + H]$^+$

Benzyl 1-Carbamoyl-5-methyl--1*H*-pyrazole-4-carboxylate [9{*1-5-3*}]: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 5.20 (s, 2 H), 7.30 (m, 5 H), 7.98 (s, 1 H), 8.56 (br. s, 2 H) ppm. MS (ESI +ve ion): *m*/*z* = 260.6 [M + H]$^+$

(2-Benzyloxycarbonylaminoethyl) 5-Isopropyl-1-phenyl-1*H*-pyrazole-4-carboxylate [9{*2-3-1*}]: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 7 Hz, 6 H), 2.54 (m, 1 H), 3.38 (m, 2 H), 4.12 (m, 2 H), 5.10 (s, 2 H), 5.26 (br. s, 1 H), 7.35 (m, 10 H), 8.05 (s, 1 H) ppm. MS (ESI +ve ion): *m*/*z* = 408.5 [M + H]$^+$

Ethyl 5-Isopropyl-1-phenyl-1*H*-pyrazole-4-carboxylate [9{*2-1-1*}]: ^{1}H NMR (300 MHz, $CDCl_3$) : δ = 1.30 (t, *J* = 7 Hz, 3 H), 1.36 (d, *J* = 7 Hz, 6 H), 3.25 (m, 1 H), 4.32 (q, *J* = 7 Hz, 2 H), 7.48 (m, 5 H), 8.04 (s, 1 H) ppm. MS (ESI +ve ion): *m*/*z* = 259.7 [M + H]$^+$

(2-Phenylethyl) 5-Isopropyl-1-phenyl-1*H*-pyrazole-4-carboxylate [9{*2-6-1*}]: ^{1}H NMR (300 MHz, $CDCl_3$) : δ = 1.21 (d, *J* = 7 Hz, 6 H), 2.79 (m, 2 H), 3.28 (m, 1 H), 4.27 (m, 2 H), 7.35 (m, 10 H), 8.00 (s, 1 H) ppm. MS (ESI +ve ion): *m*/*z* = 335.5 [M + H]$^+$

(2-*tert*-Butoxy-1-methylethyl) 5-Isopropyl-1-phenyl-1*H*-pyrazole-4-carboxylate [9{*2-7-1*}]: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (s, 9 H), 1.26 (d, *J* = 7 Hz, 6 H), 1.32 (d, *J* = 7 Hz, 3 H), 2.99 (m, 1 H), 3.78 (m, 2 H), 4.17 (m, 1 H), 7.35 (m, 5 H), 8.09 (s, 1 H) ppm. MS (ESI +ve ion): *m*/*z* = 345.4 [M + H]$^+$

(4-Oxocyclohexyl)-1-Phenyl-5-phenylethyl-1*H*-pyrazole-4-carboxylate [9{*4-9-1*}]: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.18 (m, 4 H), 2.78 (m, 4 H), 2.90 (m, 4 H), 4.14 (m, 1 H), 7.23−7.70 (m, 10 H), 7.89 (s, 1 H) ppm. MS (ESI +ve ion): *m*/*z* = 389.2 [M + H]$^+$

***N*-(4-Methoxybenzyl)-5-isopropyl-1-phenyl-1*H*-pyrazole-4-carboxyamide [10{*2-2-1*}]:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 7 Hz, 6 H), 2.78 (m, 1 H), 3.78 (s, 3 H), 4.39 (m, 2 H), 6.87, 7.02, 7.25, 7.50 (m, 11 H), 7.85 (s, 1 H) ppm. MS (ESI +ve ion): *m*/*z* = 350.4 [M + H]$^+$

***N*-Allyl-5-isopropyl-1-phenyl-1*H*-pyrazole-4-carboxyamide [10{*2-4-1*}]:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (d, *J* = 7 Hz, 6 H), 2.98 (m, 1 H), 4.23 (m, 2 H), 5.16, 5.26 (two s, 2 H),6.08 (m, 1 H) 6.66 (br. s, 1 H) 7.25 (m, 5 H), 7.95 (s, 1 H) ppm. MS (ESI +ve ion): *m*/*z* = 270.1 [M + H]$^+$

***N*-[2-(3-Indolyl)ethyl]-5-isopropyl-1-phenyl-1*H*-pyrazole-4-carboxyamide [10{*2-5-1*}]:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 7 Hz, 6 H), 2.88 (m, 1 H), 3.08 (m, 2 H), 3.97 (m, 2 H), 6.87, 7.02, 7.25, 7.85 (m, 11 H), 8.06 (s, 1 H), 10.6 (br. s, 1 H) ppm. MS (ESI +ve ion): *m*/*z* = 373.4 [M + H]$^+$

4-[(5-Isopropyl-1-phenyl-1*H*-pyrazole-4-yl)carbonyl]morpholine [10{*2-7-1*}]: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 7 Hz, 6 H), 2.78 (m, 1 H), 3.48 (m, 4 H), 4.29 (m, 4 H), 7.25 (m, 5 H), 7.95 (s, 1 H) ppm. MS (ESI +ve ion): *m*/*z* = 300.3 [M + H]$^+$

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