Novel 1,5-Diphenylpyrazole Nonnucleoside HIV-1 Reverse Transcriptase Inhibitors with Enhanced Activity versus the Delavirdine-Resistant P236L Mutant: Lead Identification and SAR of 3- and 4-Substituted Derivatives

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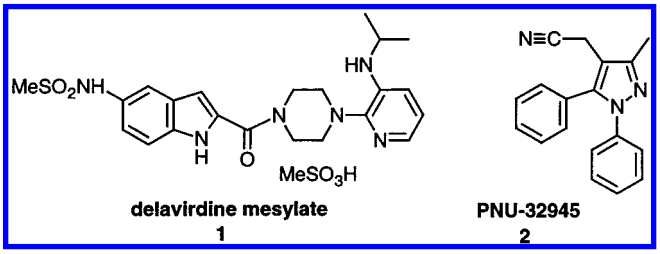
Through computationally directed broad screening, a novel 1,5-diphenylpyrazole (DPP) class of HIV-1 nonnucleoside reverse transcriptase inhibitors (NNRTIs) has been discovered. Compound **2** (PNU-32945) was found to have good activity versus wild-type (IC_{50} = 2.3 μM) and delavirdine-resistant P236L (IC_{50} = 1.1 μM) reverse transcriptase (RT). Also, PNU-32945 has an ED_{50} for inhibition of viral replication in cell cultures of 0.1 μM and was shown to be noncytotoxic with a CC_{50} > 10 μM. Structure−activity relationship studies on the 3- and 4-positions of PNU-32945 led to interesting selectivity and activity within the class. In particular, the 3-hydroxyethyl-4-ethyl congener **29** is a potent inhibitor of the P236L mutant (IC_{50} = 0.65 μM), whereas it is essentially inactive versus the wild-type enzyme (IC_{50} > 50 μM). Furthermore, this compound was significantly more active versus the P236L mutant than delavirdine. The synthesis and RT inhibitory activity of various 3- and 4-substituted analogues are discussed.

Introduction

The well-known ability of the human immunodeficiency virus (HIV) to efficiently generate resistance to both protease inhibitors and reverse transcriptase inhibitors (RTIs) has compelled researchers in these areas to develop novel analogues with enhanced activity against such mutants. The discovery of the bis(heteroaryl)piperazine (BHAP) class of nonnucleoside RTIs at Pharmacia & Upjohn led to the development of delavirdine mesylate (**1**) which is currently being marketed as Rescriptor (delavirdine mesylate tablets) for the treatment of patients suffering from HIV infection and AIDS.[1] The major reverse transcriptase (RT) mutant selected by serial HIV-1 passage in vitro in the presence of increasing concentrations of delavirdine contains a proline-to-leucine substitution at residue 236 of RT (P236L).[2] This single mutation confers strong resistance to delavirdine (P236L IC_{50} = 18 μM versus wild-type (WT) IC_{50} = 0.26 μM). Interestingly, the P236L mutant is sensitized to other nonnucleoside RTIs such as nevirapine and Merck's L-697,661.[3] Thus, we were interested in developing new analogues with enhanced activity versus the P236L mutant. Therefore, a search for a new class of nonnucleoside RTIs with the desired activity profile was initiated in order to discover a novel entity with activity against delavirdine-resistant virus.

Previously, a computationally directed broad screen of the Pharmacia & Upjohn chemical repository led to the discovery of several structurally diverse inhibitors of the WT RT enzyme.[4] Evaluation of these compounds against the P236L mutant revealed three structurally distinct classes as inhibitors. The alkylaminopiperidine BHAPs (AAP-BHAP)[3] and the pyrimidine thioethers[5] have been shown to have very good activity against both P236L RT in vitro and mutant viral replication in cell cultures.[3,5] The third class, exemplified by the diphenylpyrazole (DPP) PNU-32945, **2**, also has activity against the P236L mutant and thus served as a lead for structure−activity relationship (SAR) studies.



delavirdine mesylate **1** **PNU-32945** **2**

Chemistry

On first examination of PNU-32945 we decided to determine whether the nitrile moiety was critical for activity. Thus, 1,5-diphenyl-3-methylpyrazole analogues containing various substituents at the 4-position were synthesized as outlined in Scheme 1. Several analogues were prepared by derivatizing the readily available 1,5-diphenyl-3-methylpyrazole **(4)**, which was prepared as a single regioisomer in excellent yield by condensing 1-benzoylacetone **(3)** with phenylhydrazine (Scheme 1). Vilsmeier formylation[6] of **4** provided the aldehyde **5**, which was reduced to the alcohol and alkylated to give **6**. In addition, the aldehyde was subjected to a Jones oxidation[7] and Wittig olefination[8] to provide the acid and olefin derivatives **7** and **8**, respectively. Also, bromination of **4** gave high yields of the aryl bromide **9** which readily underwent metal−halogen exchange with

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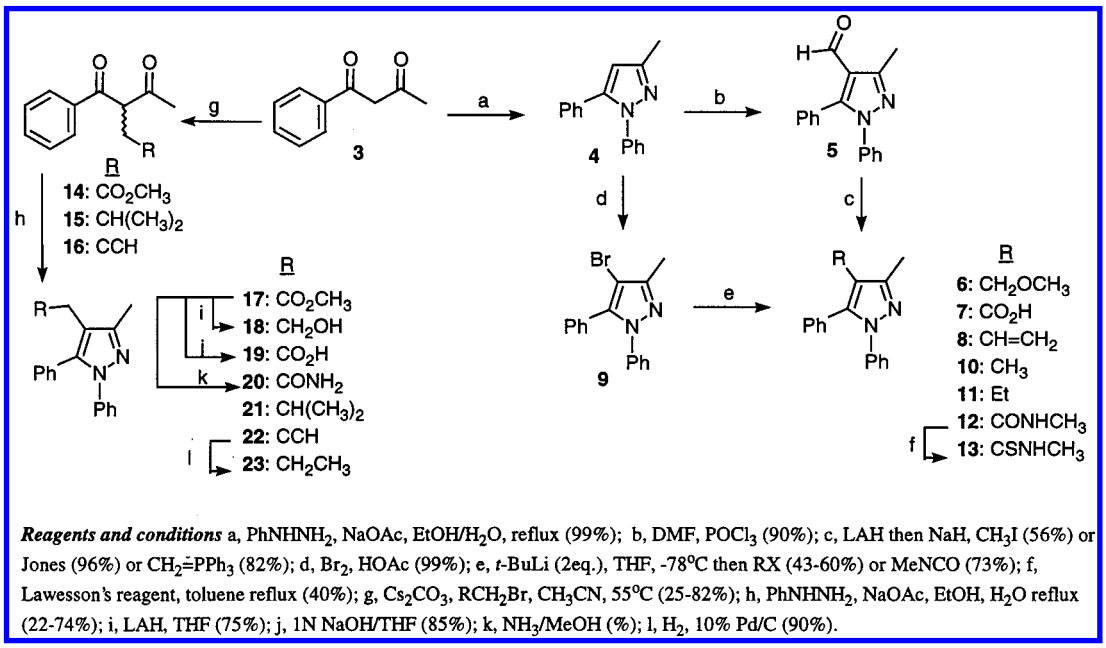
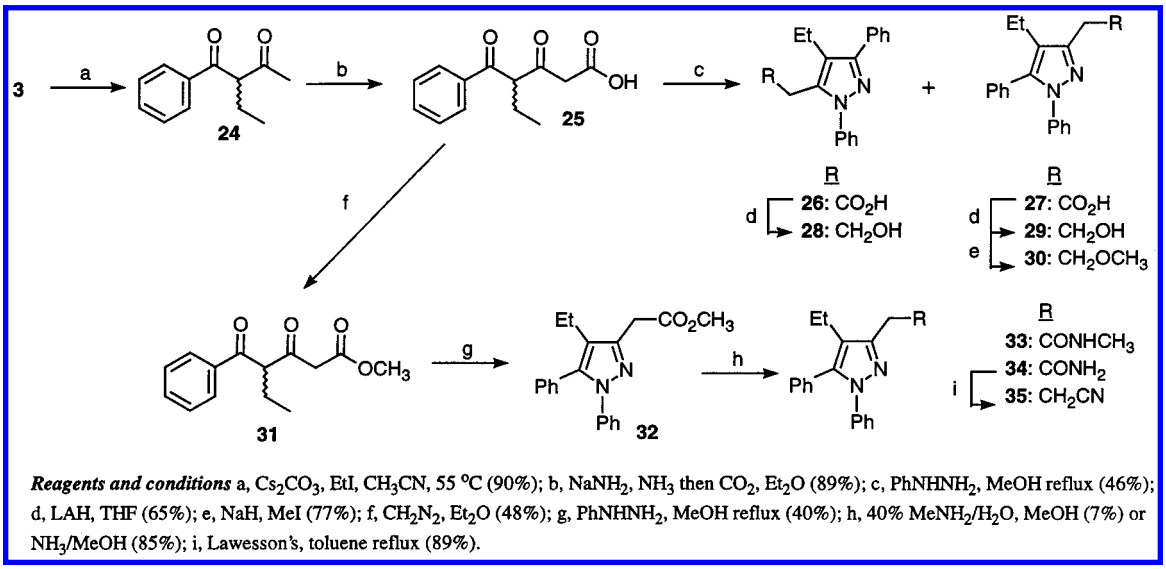
Scheme 1



Reagents and conditions a, $PhNHNH_2$, NaOAc, $EtOH/H_2O$, reflux (99%); b, DMF, $POCl_3$ (90%); c, LAH then NaH, CH_3I (56%) or Jones (96%) or $CH_2{=}PPh_3$ (82%); d, Br_2, HOAc (99%); e, *t*-BuLi (2eq.), THF, -78°C then RX (43-60%) or MeNCO (73%); f, Lawesson's reagent, toluene reflux (40%); g, Cs_2CO_3, RCH_2Br, CH_3CN, 55°C (25-82%); h, $PhNHNH_2$, NaOAc, EtOH, H_2O reflux (22-74%); i, LAH, THF (75%); j, 1N NaOH/THF (85%); k, NH_3/MeOH (%); l, H_2, 10% Pd/C (90%).

Scheme 2



Reagents and conditions a, Cs_2CO_3, EtI, CH_3CN, 55 °C (90%); b, $NaNH_2$, NH_3 then CO_2, Et_2O (89%); c, $PhNHNH_2$, MeOH reflux (46%); d, LAH, THF (65%); e, NaH, MeI (77%); f, CH_2N_2, Et_2O (48%); g, $PhNHNH_2$, MeOH reflux (40%); h, 40% $MeNH_2/H_2O$, MeOH (7%) or NH_3/MeOH (85%); i, Lawesson's, toluene reflux (89%).

t-BuLi followed by quench with alkyl halides and methyl isocyanate to afford the alkyl and amide analogues **10**–**12**. The amide derivative was further converted to the thioamide **13** with Lawesson's reagent.[9]

Another route to the desired 4-substituted pyrazole analogues involved functionalization of 1-benzoylacetone prior to pyrazole ring formation (Scheme 1). Thus, 1-benzoylacetone was deprotonated with cesium carbonate and reacted with various alkyl halides to afford diketo intermediates that were converted to the desired pyrazoles as shown. The ester **17** was further converted to the alcohol **18**, acid **19**, and primary carboxamide **20** congeners via standard chemistry. Finally, the acetylene analogue **22** was hydrogenated to afford the 4-propyl derivative **23**.

Since the 4-ethylpyrazole congener **11** retained significant activity and selectivity for P236L mutant versus WT RT (vide infra), this moiety was held constant while varying the 3-methyl substituent. The 1-ethyl-1-benzoylacetone intermediate **24** was prepared as shown in Scheme 2. Dianion generation by treatment of **24** with sodamide followed by carbon dioxide quench provided the labile β-keto acid **25** in good yield.[10] This acid could be quickly converted to the regioisomeric pyrazoles **26** and **27** by treatment with phenylhydrazine in refluxing methanol in low yields. This mixture was then treated with LAH to yield the alcohols **28** and **29** which were separated by chromatography.[11] The alcohol **29** was in turn methylated to provide the ether **30**.

Alternatively, treatment of diketo acid **25** with diazomethane[12] afforded the more stable ester **31** which was converted to the pyrazole **32**. This material was then transformed into the amide analogues **35** and **36**. The primary carboxamide was further converted to the nitrile **37** with Lawesson's reagent.[9]

Biology

The DPPs prepared above were tested in vitro for their ability to inhibit WT and P236L RT at three concentrations, and IC_{50}s were determined for active

Table 1. Activity[a] of Delavirdine Mesylate, **2** (PNU-32945), Nevirapine, and L-697,661 in Vitro versus WT and Mutant (P236L) HIV-1 RT

compound	IC_{50} (μM) WT	IC_{50} (μM) P236L	ED_{50} (μM) PBMC/D34	CC_{50} (μM) PBMC/D34
1 (delavirdine mesylate)	0.26	18.0	0.0001	>10
2 (PNU-32945)	2.31	1.14	0.1	>10
nevirapine	3.1	0.32	0.01−0.1	>10
L-697,661	0.8	0.11	<0.0001	>10

[a] Data shown were generated as described previously in ref 3.

analogues as described by us previously.[3] The inhibitory activities of 1,5-diphenyl-3-methylpyrazole analogues varied at the 4-position are summarized in Table 2. The majority of these analogues exhibited little or no inhibitory activity versus either RT enzyme. However, the 4-ethyl, 4-propyl, and 4-propargyl congeners **11**, **23**, and **22** possessed good activity. Furthermore, these analogues exhibit higher selectivity for P236L inhibition versus WT than the lead PNU-32945. In fact the ethyl analogue **11** was much more selective for the P236L mutant (IC_{50} = 0.52 μM) than the WT RT (IC_{50} = 14.5 μM). The 4-methyl and 4-isopropyl analogues **10** and **21**, however, were poorly active versus both enzymes indicating the importance of size and shape of the 4-substituent. Replacement of the purely aliphatic moieties with more polar substituents also led to losses in activity. For example, both amide and thioamide analogues **12** and **13** were poor RTIs. Likewise, the methoxymethyl, hydroxyethyl, and carboxylate compounds **6**, **18**, and **19** lost some or all RT inhibitory activity.

Since the 4-ethylpyrazole congener **11** retained significant activity, the 4-ethyl moiety was held constant while the substitution at the 3-position was varied (Table 3). As was seen above, most of these analogues lost activity against both enzymes with the noted exception of the hydroxyethyl analogue **29**. This compound had comparable activity to **11**, but it was much more selective for the P236L enzyme (P236L IC_{50} = 0.65 μM versus WT IC_{50} > 50 μM).

Conclusion

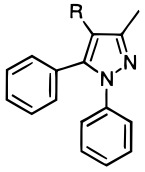
Through broad screening of the Pharmacia & Upjohn chemical library a novel 1,5-diphenylpyrazole class of NNRTIs has been discovered with enhanced activity against delavirdine-resistant P236L RT versus the WT enzyme. Structure−activity relationship studies on the 3- and 4-positions led to interesting selectivity and activity within the class. In particular, the 3-hydroxyethyl-4-ethyl congener **29** is a potent inhibitor of P236L RT, whereas it is essentially inactive versus the WT enzyme. Furthermore, this compound was significantly more active versus the P236L mutant than delavirdine.

Experimental Section

General. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer. Chemical shifts are reported in δ units (ppm) relative to TMS as internal standard. Mass spectra and combustion analyses were obtained by the Structural, Analytical and Medicinal Chemistry Department of Pharmacia & Upjohn, Inc. Unless otherwise indicated all reactions were conducted in commercially available anhydrous solvents under a nitrogen atmosphere in oven-dried glassware. Chromatography was carried out on EM Science 230−400 mesh ASTM silica gel. Elemental analyses were within ±0.4% of calculated values. Biological assays were performed as described previously in ref 3.

1,5-Diphenyl-3-methylpyrazole (4). Phenylhydrazine (13.3 g, 0.12 mol), 1-benzoylacetone (20 g, 0.12 mol), and NaOAc·$3H_2O$ (10.1 g, 0.074 mol) were mixed together in EtOH (150 mL) and H_2O (75 mL). The reaction was refluxed for 3 h, concentrated in vacuo, and partitioned between Et_2O and H_2O. The aqueous layer was extracted with Et_2O and the combined extracts were washed with 1 N NaOH, brine, and dried (Na_2SO_4). Removal of solvent in vacuo yielded 28.4 g (99%) of an orange oil that was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.55 (s, 3 H), 6.48 (s, 1 H), 7.36−7.49 (m, 10 H); HRMS (EI) calcd for $C_{16}H_{14}N_2$ 234.1157, found 234.1150.

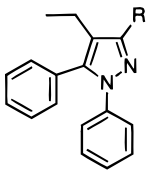
Table 2. Inhibitory Activities of 1,5-Diphenyl-3-methylpyrazole Analogues Varied at the 4-Position against WT and Mutant (P236L) HIV-1 RT[a]



compound		% inhibition 1 μM		10 μM		50 μM		IC_{50} (μM)	
no.	R	WT	P236L	WT	P236L	WT	P236L	WT	P236L
2	-CH_2CN	37	47	71	77	90	93	2.31 ± 0.25	1.14 ± 0.12
6	-CH_2OCH_3	0	0	0	18	14	50		
7	-COOH	4	0	0	1	1	4		
8	-CH=CH_2	3.6	21	10	26	18	59		
10	-CH_3	0	0	0	3	0	36		
11	-CH_2CH_3	1−2	50	42	81	67	94	14.5 ± 10.6	0.52 ± 0.06
12	-$CONHCH_3$	5	15	7	0	3	0		
13	-$CSNHCH_3$	0	0	0	0	0	0		
18	-CH_2CH_2OH	0	12	0	8	0	28		
19	-CH_2CO_2H	0	0	0	0	3	0		
20	-CH_2CONH_2	11	0	36	0	48	29		
21	-$CH(CH_3)_2$	0	0	18	8	6	13		
22	-propargyl	0	38	37	80	72	93	13.4 ± 6.2	1.54 ± 0.26
23	-$CH_2CH_2CH_3$	14	4	31	56	49	71		

[a] Data shown were generated as described previously in ref 3.

Table 3. Inhibitory Activities of 1,5-Diphenyl-4-ethylpyrazole Analogues Varied at the 3-Position against WT and Mutant (P236L) HIV-1 RT[a]



compound		% inhibition						IC_{50} (μM)	
		1 μM		10 μM		50 μM			
no.	R	WT	P236L	WT	P236L	WT	P236L	WT	P236L
11	$-CH_3$	2	50	42	81	67	94	14.5 ± 10.6	0.52 ± 0.06
27	$-CH_2CO_2H$	0	0	0	13	0	14		
29	$-CH_2CH_2OH$	0	58	18	84	42	95	>50	0.65 ± 0.10
30	$-CH_2CH_2OCH_3$	22	15	29	47	33	71		
32	$-CH_2CO_2CH_3$	5	21	20	41	34	55		
33	$-CH_2CONHMe$	1	6	3	8	7	12		
34	$-CH_2CONH_2$	12	16	18	29	39	52		
35	$-CH_2CN$	2	14	15	46	39	72		

[a] Data shown were generated as described previously in ref 3.

Anal. Calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.52; H, 6.05; N, 11.72.

1,5-Diphenyl-3-methyl-4-formylpyrazole (5). Compound **4** (12.2 g, 52.2 mmol) was dissolved in 26 mL of DMF and heated to 90 °C. Then 10.0 mL of phosphorus oxychloride (65.2 mmol) was added dropwise and stirring was continued for 7 h. The reaction was not complete by TLC, so an additional 26 mL of DMF and 10 mL of phosphorus oxychloride were added at room temperature. After addition, the reaction was heated to 90 °C for 2 h and then cooled to 0 °C and quenched by the cautious addition of ice chips and water. Then 130 mL of 2 N NaOH was added (to pH 5.5−6.0) and the mixture was extracted with EtOAc (4×). The organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated in vacuo. Recrystallization from CH_3OH afforded 10.15 g (74%) of the title aldehyde: mp 135−137 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (s, 1 H), 7.38−7.28 (m, 3 H), 7.26−7.12 (m, 7 H), 2.56 (s, 3 H). Anal. Calcd for $C_{17}H_{14}N_2O_1$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.53; H, 5.53; N, 10.77.

1,5-Diphenyl-3-methyl-4-methoxymethylpyrazole (6). Compound **5** (1.0 g, 3.81 mmol) was dissolved in 2 mL of THF and cooled to 0 °C. Then 1.91 mL of LAH (1.0 M in THF, 1.91 mmol) was added and the reaction was stirred 30 min. Then the reaction was quenched by the dropwise addition of 0.072 mL of water, 0.072 mL of 10% NaOH, and 0.22 mL of water. The reaction was filtered through Celite, and concentrated in vacuo. Purification by flash chromatography (50% EtOAc/hexane) provided 0.87 g (86%) of the intermediate alcohol. This material (0.40 g, 1.52 mmol) was dissolved in 7.5 mL of THF and cooled to 0 °C. Then 0.12 g of NaH (30% dispersion in mineral oil, 1.54 mmol) was added and the reaction was stirred 15 min. Then iodomethane (0.96 mL, 1.54 mmol) was added and the reaction was warmed to room temperature for 3 h. Then it was cooled to 0 °C, quenched by the dropwise addition of water, and extracted with $CHCl_3$. The organic layers were dried over Na_2SO_4, concentrated in vacuo and purified by flash column chromatography (15% EtOAc/hexane) to afford 0.236 g (56%) of the title pyrazole as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (m, 3 H), 7.36 (m, 7 H), 4.38 (s, 2 H), 3.50 (s, 3 H), 2.56 (s, 3 H). Anal. Calcd for $C_{18}H_{18}N_2O{\cdot}0.1H_2O$: C, 77.17; H, 6.55; N, 10.00. Found: C, 77.17; H, 6.43; N, 9.93.

1,5-Diphenyl-3-methylpyrazole-4-carboxylic Acid (7). Compound **5** (0.53 g, 2.0 mmol) was dissolved in 16 mL of acetone and 5 mL of Jones' reagent was added. The reaction was stirred 30 min at room temperature, poured into water, and extracted with hexane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford 0.53 g (96%) of the title acid: mp 195−200 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 3 H), 7.20 (m, 5 H), 7.08 (m, 2 H), 2.54 (s, 3 H); HRMS calcd for $C_{17}H_{14}N_2O_2$ 278.1055, found 278.1071. Anal. Calcd for $C_{17}H_{14}N_2O_2{\cdot}H_2O$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.75; H, 4.87; N, 8.94.

1,5-Diphenyl-3-methyl-4-vinylpyrazole (8). Methyltriphenylphosphonium bromide (0.55 g, 1.52 mmol) was dissolved in 3 mL of THF and cooled to −20 °C. Then 0.95 mL of *n*-butyllithium (1.6 M in hexane, 1.52 mmol) was added and the reaction was stirred 30 min and then warmed to 0 °C. Then compound **5** (0.20 g, 0.76 mmol) dissolved in 2 mL of THF was added and the reaction was stirred 1 h at 0 °C. It was poured into water, extracted with EtOAc, dried over Na_2SO_4, filtered through a plug of silica gel and concentrated in vacuo. Purification by flash column chromatography (5% EtOAc/hexane) provided 0.16 g (82%) of the title pyrazole: mp 111−112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (m, 3 H), 7.32 (m, 7 H), 6.59 (dd, J = 11.6, 18.0 Hz, 1 H), 5.48 (dd, J = 1.5, 18.0 Hz, 1 H), 5.23 (dd, J = 1.5, 11.6 Hz, 1 H), 2.60 (s, 3 H); MS m/z 260 (M + H). Anal. Calcd for $C_{18}H_{16}N_2{\cdot}0.1H_2O$: C, 82.48; H, 6.23; N, 10.69. Found: C, 82.53; H, 6.21; N, 10.61.

1,5-Diphenyl-3-methyl-4-bromopyrazole (9). Compound **4** (5 g, 21.3 mmol) was dissolved in acetic acid (55 mL) and cooled in an ice bath. Bromine (4.1 g, 25.6 mmol) was added dropwise while stirring under N_2. After 30 min the reaction was diluted with 1 N NaOH (100 mL) and extracted with $CHCl_3$. The extracts were washed with brine and dried (Na_2SO_4). Removal of solvent in vacuo gave a light brown oil which was homogeneous by TLC and NMR. This material was used without further purification 6.6 g (99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3 H), 7.08−7.42 (m, 10 H).

1,5-Diphenyl-3,4-dimethylpyrazole (10). Compound **9** (0.5 g, 1.6 mmol) was dissolved in dry THF (5 mL) and cooled to −78 °C under N_2. Then *t*-BuLi (1.7 M, 1.9 mL, 3.2 mmol) was added slowly. The reaction was stirred for 10 min after which time MeI (0.5 mL, 8.0 mmol) was added dropwise. Stirring was continued at −78 °C for 45 min before the reaction was allowed to warm to room temperature and quenched with H_2O. The reaction was partitioned between 1 N $NaHCO_3$ and $CHCl_3$. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to a residue which was chromatographed on a 2 × 40 cm column with hexane/Et_2O (9:1). The product was isolated as a colorless oil in a yield of 0.17 g (43%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.04 (s, 3 H), 2.35 (s, 3 H), 7.13−7.36 (m, 10 H); HRMS calcd for $C_{17}H_{16}N_2$ 248.1313, found 248.1320. Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.23; H, 6.50; N, 11.28. Found: C, 82.32; H, 6.60; N, 11.31.

1,5-Diphenyl-3-methyl-4-ethylpyrazole (11). Compound **9** (0.5 g, 1.6 mmol) was dissolved in dry THF (5 mL) and cooled to −78 °C under N_2. Then *t*-BuLi (1.7 M, 1.9 mL, 3.2 mmol) was added slowly. The reaction was stirred for 10 min after which time EtI (0.26 mL, 3.2 mmol) was added dropwise. Stirring was continued at −78 °C for 45 min and the reaction

was allowed to warm to room temperature and quenched with H_2O. The reaction was partitioned between 1 N $NaHCO_3$ and $CHCl_3$. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to an oil which was chromatographed on a 2 × 45 cm column with hexane/Et_2O (9:1). The product was isolated as a colorless oil in a yield of 0.25 g (60%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, J = 7.6 Hz, 3 H), 2.56 (s, 3 H), 2.66 (q, J = 7.55 Hz, 2 H), 7.32−7.54 (m, 10 H); HRMS calcd for $C_{18}H_{18}N_2$ 262.1470, found 262.1477. Anal. Calcd for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.01; H, 6.84; N, 10.50.

1,5-Diphenyl-3-methyl-4-*(N*-methylformido*)*pyrazole (12). Compound **9** (0.5 g, 1.6 mmol) was dissolved in dry THF (5 mL) and cooled to −78 °C under N_2. Then *t*-BuLi (1.7 M, 1.9 mL, 3.2 mmol) was added slowly. The reaction was stirred for 10 min after which time methylisocyanate (0.1 mL, 1.6 mmol) was added dropwise. Stirring was continued at −78 °C for 45 min and the reaction was allowed to room temperature before being quenched with H_2O. The reaction was partitioned between 1 N $NaHCO_3$ and $CHCl_3$. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to a residue which was crystallized from $CHCl_3$ in a yield of 0.34 g (73%): mp 133−135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 3 H), 2.70 (d, J = 4.8 Hz, 3 H), 5.10 (br, 1 H), 7.10−7.14 (m, 2 H), 7.21−7.26 (m, 5 H), 7.36−7.38 (m, 3 H); HRMS calcd for $C_{18}H_{17}N_3O$ 291.1372, found 291.1379. Anal. Calcd for $C_{18}H_{17}N_3O\cdot 0.1H_2O$: C, 73.75; H, 5.91; N, 14.33. Found: C, 73.69; H, 5.92; N, 14.25.

1,5-Diphenyl-3-methyl-4-(*N*-methylthioformamido)-pyrazole (13). Compound **12** (0.24 g, 0.82 mmol) and Lawesson's reagent (0.17 g, 0.41 mmol) were refluxed in dry toluene under N_2 for 2 h. The solvent was removed in vacuo and the residue was chromatographed on a 2 × 40 cm column with EtOAc/hexane (1:2). The product was isolated and crystallized from EtOAc/hexane to yield 0.1 g (40%): mp 174−175 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.67 (s, 3 H), 3.15 (d, J = 4.94 Hz, 3 H), 7.08 (br s, 1 H), 7.25−7.48 (m, 10 H); HRMS calcd for $C_{18}H_{17}N_3S$ 307.1143, found 307.1139. Anal. Calcd for $C_{18}H_{17}N_3S$: C, 70.33; H, 5.57; N, 13.67. Found: C, 70.32; H, 5.64; N, 13.65.

Methyl 3-Acetyl-4-oxo-4-phenylbutanoate (14). 1-Benzoylacetone (2.5 g, 15.4 mmol) was dissolved in acetone (30 mL) and cooled to 0 °C. Cesium carbonate (15.4 mmol) was added and the enolate was allowed to warm to room temperature. Methyl bromoacetate (1.5 mL, 15.4 mmol) was added and the reaction was refluxed for 5 h. Water (50 mL) was added and the reaction was concentrated in vacuo and extracted with $CHCl_3$. The extracts were washed with brine and dried (Na_2SO_4). Removal of solvent gave a yellow oil which was chromatographed on a 4 × 30 cm column to yield pure product as a colorless oil 2.9 g (82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.11 (s, 3 H), 2.85−3.02 (m, 2 H), 3.59 (s, 3 H), 4.97 (t, J = 7.03 Hz, 1 H), 7.36−7.47 (m, 2 H), 7.52−7.58 (m, 1 H), 7.94−7.98 (m, 2 H).

2-Isobutyl-1-phenyl-1,3-butanedione (15). Following the procedure for the preparation of **14**, but starting with benzoylacetone (10.0 g, 61.7 mmol), 2-iodopropane (9.2 mL, 92.5 mmol) and cesium carbonate (20.1 g, 61.7 mmol) stirring at 55 °C for 18 h and workup as above. The crude product was purified by chromatography (2% EtOAc/hexane) to provided 3.17 g (15%) of the title diketone as an oil.

2-Acetyl-1-phenyl-4-pentyn-1-one (16). Following the procedure for the preparation of **14**, but starting with benzoylacetone (5.0 g, 30.83 mmol), propargyl bromide (5.15 mL, 46.2 mmol) and cesium carbonate (30.83 mmol), stirring 72 h at room temperature, and purifying by chromatography (5% EtOAc/hexane) provided 3.78 g (61%) of the title diketone as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (m, 2 H), 7.62 (m, 1 H), 7.48 (m, 2 H), 4.71 (t, J = 7.9 Hz, 1 H), 2.93 (ddd, J = 2.6, 7.9, 17.2 Hz, 1 H), 2.78 (ddd, J = 2.6, 7.9, 17.2 Hz, 1 H), 2.19 (s, 3 H), 2.00 (t, J = 2.6 Hz, 1 H).

Methyl (4-(1,5-Diphenyl-3-methyl)pyrazolyl)acetate (17). Phenylhydrazine (0.84 mL, 8.5 mmol) and methyl 3-acetyl-4-oxo-4-phenylbutanoate **(14)** (1.0 g, 4.27 mmol) were dissolved in MeOH (50 mL) and refluxed under N_2 for 4 h. The solvent was removed and the residue partitioned between Et_2O and H_2O. The organic layer was dried (Na_2SO_4) and concentrated to an oil which was chromatographed on a 4 × 30 cm column with EtOAc/hexane (1:3). The product was isolated as a colorless oil: 0.80 g (61%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3 H), 3.39 (s, 2 H), 3.65 (s, 3 H), 7.10−7.22 (m, 7 H), 7.26−7.32 (m, 3 H); HRMS calcd for $C_{19}H_{18}N_2O_2$ 306.1368, found 306.1369.

1,5-Diphenyl-3-methyl-4-(2-hydroxyethyl)pyrazole (18). Compound **17** (0.64 g, 2.1 mmol) was dissolved in dry THF (15 mL) and cooled to −78 °C. While stirring under N_2 a solution of LAH (1 M, 2.1 mL) was added and the reaction was allowed to warm to room temperature and quenched with H_2O (0.12 mL), 15% NaOH (0.12 mL), and H_2O (0.36 mL). The solid was filtered off and the filtrate was partitioned between $CHCl_3$ and H_2O. The organic layer was washed with brine and dried (Na_2SO_4). Removal of solvent gave a yellow oil which was chromatographed on a 2 × 40 cm column with EtOAc/hexane (1:2). The product was isolated as a white foam in a yield of 0.44 g (75%): mp 108−109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75 (br s, 1 H), 2.34 (s, 3 H), 2.68 (t, J = 7.0 Hz, 2 H), 3.64 (t, J = 7.0 Hz, 2 H), 7.11−7.24 (m, 7 H), 7.28−7.32 (m, 3 H); HRMS calcd for $C_{18}H_{18}N_2O$ 278.1419, found 278.1420. Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.53; H, 6.63; N, 9.93.

4-(1,5-Diphenyl-3-methylpyrazolyl)acetic Acid (19). Compound **17** (0.10 g, 0.33 mmol) was dissolved in THF (10 mL) and 1 N NaOH (5 mL) was added. The reaction was stirred overnight and partitioned between 1 N HCl and $CHCl_3$. The aqueous layer was extracted with $CHCl_3$ and the combined extracts were washed with brine and dried (Na_2SO_4). Removal of solvent gave an oil which was chromatographed on a 2 × 40 cm column with EtOAc/hexane/HOAc (30:60:1). The acid was isolated as a white foam in a yield of 80 mg (85%): mp 161−162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3 H), 3.37 (s, 2 H), 7.09−7.19 (m, 7 H), 7.25−7.27 (m, 3 H), 10.3 (br, 1 H); HRMS calcd for $C_{18}H_{16}N_2O_2$ 292.1212, found 292.1207. Anal. Calcd for $C_{18}H_{16}N_2O_2\cdot 1.2H_2O$: C, 68.86; H, 5.91; N, 8.92. Found: C, 69.18; H, 5.66; N, 8.53.

2-(3-Methyl-1,5-diphenyl-1*H*-pyrazol-4-yl)acetamide (20). Compound **2** (200 mg, 0.73 mmol) was placed in 37% HCl (0.5 mL) and heated to 40 °C for 2 h. The mixture was poured into water and extracted with EtOAc. The extracts were washed with 1 N NaOH and dried (Na_2SO_4). Removal of solvent gave a residue that was crystallized from EtOAc/hexane to give 160 mg (75%): mp 129−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3 H), 3.40 (s, 2 H), 5.45 (br s, 1 H), 5.62 (br s, 1 H), 7.18−7.27 (m, 7 H), 7.35−7.37 (m, 3 H); MS m/z 292 (M + H). Anal. Calcd for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.03; H, 5.89; N, 14.32.

1,5-Diphenyl-3-methyl-4-isopropylpyrazole (21). Compound **15** (1.0 g, 4.90 mmol), phenylhydrazine (0.48 mL, 4.90 mmol) and sodium acetate (0.66 g, 4.90 mmol) were placed in 6 mL of ethanol and 3 mL of water and heated to reflux for 2.5 h. Then the reaction was cooled to room temperature, poured into water, extracted with $CHCl_3$, dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (5% methyl *tert*-butyl ether/hexane) afforded 0.30 g (22%) of the title pyrazole: mp 79−80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 3 H), 7.13 (m, 7 H), 2.85 (m, 1 H), 2.42 (s, 3 H), 1.21 (d, J = 7.1 Hz, 6 H); HRMS calcd for $C_{19}H_{20}N_2$ 276.1626, found 276.1617. Anal. Calcd for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.35; H, 7.29; N, 10.03.

1,5-Diphenyl-3-methyl-4-propargylpyrazole (22). Compound **16** (0.51 mg, 2.54 mmol), phenylhydrazine (0.25 mL, 2.54 mmol) and sodium acetate (0.35 g, 2.54 mmol) were placed in 3.3 mL of ethanol and 1.7 mL of water and heated to reflux for 4 h. Then an additional 0.05 mL of phenylhydrazine was added and the reaction was refluxed a further 3 h. Then the reaction was cooled to room temperature, and poured into water, and adjusted to pH 2 with 1 N HCl. The mixture was extracted with $CHCl_3$, dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (2% CH_3-

OH/toluene) afforded 0.51 g (74%) of the title pyrazole as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 3 H), 7.25 (m, 5 H), 3.37 (d, J = 2.8 Hz, 2 H), 2.49 (s, 3 H), 2.11 (t, J = 2.8 Hz, 1 H); HRMS calcd for $C_{19}H_{16}N_2$ 272.1313, found 272.1311. Anal. Calcd for $C_{19}H_{16}N_2 \cdot 0.15CHCl_3$: C, 79.25; H, 5.61; N, 9.65. Found: C, 79.28; H, 5.63; N, 9.74.

1,5-Diphenyl-3-methyl-4-propylpyrazole (23). Compound **22** (0.19 g, 0.71 mmol) was dissolved in 25 mL of ethanol and 90 mg of 10% palladium on carbon was added. The reaction was hydrogenated on a Parr shaker for 2 h at 40 psi. Filtration and concentration afforded 0.18 g (90%) of the title pyrazole: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 3 H), 7.16 (m, 7 H), 2.38 (t, J = 7.6 Hz, 2 H), 2.34 (s, 3 H), 1.46 (sextet, J = 7.6 Hz, 2 H), 0.85 (t, J = 7.6 Hz, 3 H); HRMS calcd for $C_{19}H_{20}N_2$ 276.1626, found 272.1617.

2-Acetylbenzophenone (24). 1-Benzoylacetone (20 g, 0.123 mol) was dissolved in acetonitrile (300 mL) and cesium carbonate (40.2 g, 0.123 mol) was added followed by EtI (14.8 mL, 0.184 mol). The reaction was heated at 55 °C for 5 h before being diluted with H_2O. The reaction was concentrated in vacuo and extraxted with $CHCl_3$ (3×). The extracts were dried (Na_2SO_4) and concentrated to an oil. Purification on a 5 × 45 cm column with EtOAc/Hex (1:9) yielded 21 g (90%) of product as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (m, 2 H), 7.45 (m, 1 H), 7.33 (m, 2 H), 4.20 (t, J = 7.1 Hz, 1 H), 1.98 (s, 3 H), 1.88 (m, 2 H), 0.80 (t, J = 7.1 Hz, 3 H).

3,5-Diketo-4-ethyl-5-phenylpentanoic Acid (25). Compound **24** (4.3 g, 22.6 mmol) was added dropwise to a mixture of $NaNH_2$ (3.1 g, 79.6 mmol) in liquid NH_3 (150 mL). The yellow solution was stirred for 1 h at room temperature under N_2 with a dry ice acetone gas condenser on top of the flask to recondense the evaporating NH_3. Et_2O (50 mL) was added and the NH_3 was evaporated on a steam bath under a stream of N_2. This was replaced with anhydrous Et_2O. The ether solution was heated on the steam bath for 5 min after the NH_3 had evaporated to ensure its complete removal. While stirring at room temperature CO_2 gas was bubbled into the ether solution of the dianion for 30 min. The reaction was poured into an ice solution of 6 N HCl and extracted with Et_2O. The organic extracts were dried (Na_2SO_4) and the solvent was removed to yield 4.7 g (89%) of the acid as a light orange solid. This material due to its extreme instability was refrigerated and used without further purification.

2-(1,5-Diphenyl-4-ethylpyrazole)acetic Acid (27) and 5-(3-Diphenyl-4-ethylpyrazole)acetic Acid (26). Compound **25** (2.0 g, 8.54 mmol) was placed in a flask. Methanol (20 mL) was added quickly followed by phenylhydrazine (3.4 mL, 17.1 mmol). The reaction was refluxed under N_2 for 3 h and concentrated in vacuo. The residue was partitioned between 1 N HCl and $CHCl_3$. The aqueous layer was extracted with $CHCl_3$ and the combined extracts were back extracted with 1 M $NaHCO_3$. The $NaHCO_3$ was acidified with 6 N HCl and extracted with $CHCl_3$. The extracts were dried (Na_2SO_4) and the solvent was removed in vacuo to give the product as a mixture of isomers. These were separated on a 2 × 40 cm column with EtOAc/hexane/HOAc (30:60:1). The desired product **27** (low R_f) was isolated as a solid in a yield of 0.8 g (31%): mp 208−209 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (t, J = 7.6 Hz, 3 H), 2.37 (q, 7.6 Hz, 2 H), 3.79 (s, 2 H), 7.07−7.28 (m, 10 H); HRMS calcd for $C_{19}H_{18}N_2O_2$ 306.1368, found 306.1367. Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.28; H, 5.94; N, 9.14.

The other regioisomer **26** (high R_f) was isolated in a yield of 0.4 g (15%): mp 153−154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.40 (br, 1 H), 7.52 (m, 2 H), 7.32−7.05 (m, 8 H), 3.46 (s, 2 H), 2.43 (q, J = 7.6 Hz, 2 H), 0.94 (t, J = 7.6 Hz, 3 H); HRMS calcd for $C_{19}H_{18}N_2O_2$ 306.1368, found 306.1368. Anal. Calcd for $C_{19}H_{18}N_2O_2 \cdot 0.2H_2O$: C, 73.62; H, 5.98; N, 9.04. Found: C, 73.59; H, 5.82; N, 9.02.

1,5-Diphenyl-3-(2-hydroxyethyl)-4-ethylpyrazole (29) and 1,3-Diphenyl-4-ethyl-5-(2-hydroxyethyl)pyrazole (28). A mixture of **27** and **26** (0.20 g, 0.65 mmol) was dissolved in dry THF (10 mL) and cooled to −78 °C. A solution of 1 M LAH (0.65 mL) was added and the reaction was warmed to room temperature and quenched. The precipitate was filtered off and the filtrate was partitioned between $CHCl_3$ and 1 N $NaHCO_3$. The organic layer was dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was purified on a 2 × 30 cm column with EtOAc/hexane (1:2). The low R_f material **29** was isolated (75 mg, 39%) as was the high R_f isomer **28** (50 mg, 26%). **29:** mp 100−101 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (t, J = 7.6 Hz, 3 H), 2.37 (q, 7.5 Hz, 2 H), 2.87 (t, J = 5.7 Hz, 2 H), 3.41 (br, 1 H), 3.98 (br, 2 H) 7.08−7.19 (m, 7 H), 7.25−7.29 (m, 3 H); HRMS calcd for $C_{19}H_{20}N_2O$ 292.1576, found 292.1582. Anal. Calcd for $C_{19}H_{20}N_2O \cdot 0.25H_2O$: C, 76.88; H, 6.96; N, 9.44. Found: C, 77.02; H, 6.85; N, 9.31.

28: mp 123−124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, J = 7.53 Hz, 3 H), 1.66 (br, 1 H), 2.54 (q, 7.54 Hz, 2 H), 2.82 (t, J = 7.13 Hz, 2 H), 3.49 (t, J = 7.09 Hz, 2 H), 7.17−7.36 (m, 8 H), 7.54−7.58 (m, 2 H); HRMS calcd for $C_{19}H_{20}N_2O$ 292.1576, found 292.1576. Anal. Calcd for $C_{19}H_{20}N_2O \cdot 0.2H_2O$: C, 77.10; H, 6.95; N, 9.46. Found: C, 77.28; H, 6.85; N, 9.44.

1,5-Diphenyl-3-(2-methoxyethyl)-4-ethylpyrazole (30). Compound **29** (210 mg, 0.70 mmol) was dissolved in dry THF at 0 °C. Sodium hydride (60%, 30 mg, 0.77 mmol) was added and the reaction was stirred 15 min. MeI (0.048 mL, 0.77 mmol) was added and stirring was continued at 0 °C for 30 min and allowed to warm to room temperature. The reaction was quenched with water and worked up to give an oil which was chromatographed on a 2 × 40 cm column with EtOAc/hexane (1:9). The product was isolated as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, J = 7.53 Hz, 3 H), 2.47 (q, J = 7.55 Hz, 2 H), 3.02 (t, J = 7.57 Hz, 2 H), 3.42 (s, 3 H), 3.81 (t, J = 7.68 Hz, 2 H), 7.16−7.25 (m, 7 H), 7.30−7.33 (m, 3 H); HRMS calcd for $C_{20}H_{22}N_2O$ 306.1732, found 306.1741. Anal. Calcd for $C_{20}H_{22}N_2O \cdot 0.5H_2O$: C, 76.16; H, 7.35; N, 8.88. Found: C, 76.02; H, 7.32; N, 8.41.

Methyl 3,5-Diketo-4-ethyl-5-phenylpentanoate (31). Excess trimethylsilyldiazomethane (2 M) was added to **25** (2.0 g, 8.54 mmol) followed by benzene (10 mL) and methanol (20 mL). The reaction was stirred at room temperature for 1 h and the solvent was removed in vacuo. The residue was chromatographed on a 2 × 45 cm column with EtOAc/hexane (1:9). The product was isolated as an oil in a yield of 0.9 g (48%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.41 Hz, 3 H), 1.91−2.02 (m, 2 H), 3.46 (s, 2 H), 3.57 (s, 3 H), 4.52 (t, J = 6.86 Hz, 1 H), 7.37−7.48 (m, 2 H), 7.52−7.57 (m, 1 H), 7.89−7.94 (m, 2 H).

Methyl 2-(1,5-Diphenyl-4-ethyl-3-pyrazolyl)acetate (32). Compound **31**(0.90 g, 3.62 mmol), phenylhydrazine (0.53 mL, 5.43 mmol), and $NaOAc \cdot 3H_2O$ (0.49 g, 3.6 mmol) were refluxed in methanol for 3 h. The solvent was evaporated and the residue was partitioned between EtOAc and H_2O. The organic layer was washed with brine and dried (Na_2SO_4). Removal of solvent gave an oil which was purified on a 2 × 40 cm column with EtOAc/hexane (1:9) to yield 0.46 g (40%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, J = 7.49 Hz, 3 H), 2.39 (q, J = 7.53 Hz, 2 H), 3.67 (s, 3 H), 3.73 (s, 2 H), 7.06−7.17 (m, 7 H), 7.23−7.27 (m, 3 H); HRMS calcd for $C_{20}H_{20}N_2O_2$ 320.1525, found 320.1516. Anal. Calcd for $C_{20}H_{20}N_2O_2 \cdot H_2O$: C, 73.33; H, 6.40; N, 8.55. Found: C, 73.70; H, 5.91; N, 8.16.

1,5-Diphenyl-3-(*N*-methylmethylcarboxamido)-4-ethylpyrazole (33). Compound **32** (77.0 mg, 2.4 mmol) was dissolved in methanol (5 mL) and methylamine (40%/H_2O) (5 mL) was added and the reaction was capped tightly and stirred overnight. The solvent was removed in vacuo and the residue was chromatographed with EtOAc/hexane to give 50 mg (7%) of pure product as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, J = 7.53 Hz, 3 H), 2.37 (q, J = 7.57 Hz, 2 H), 2.72 (d, J = 4.81 Hz, 3 H), 3.62 (s, 2 H), 6.80 (br s, 1 H), 7.07−7.26 (m, 10 H); HRMS calcd for $C_{20}H_{21}N_3O$ 319.1685, found 319.1680. Anal. Calcd for $C_{20}H_{21}N_3O \cdot 1.0H_2O$: C, 71.19; H, 6.87; N, 12.45. Found: C, 70.81; H, 6.54; N, 12.41.

2-(1,5-Diphenyl-4-ethyl-3-pyrazolyl)acetamide (34). Compound **32** (40 mg, 0.12 mmol) was dissolved in a saturated solution of NH_3/MeOH. The reaction was capped tightly and stirred overnight. Reaction was not complete therefore NH_3 gas was bubbled in for 1 h and the reaction was stirred an

additional 2 days while capped tightly. The solvent and excess NH_3 were removed in vacuo and the residue was crystallized from MeOH/Et_2O to yield 30 mg (85%): mp 215−216 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, J = 7.61 Hz, 3 H), 2.46 (q, J = 7.54 Hz, 2 H), 3.72 (s, 3 H), 5.45 (br s, 1 H), 6.95 (br s, 1 H), 7.15−7.26 (m, 7 H), 7.30−7.36 (m, 3 H); HRMS calcd for $C_{19}H_{19}N_3O$ 305.1528, found 305.1532. Anal. Calcd for $C_{19}H_{19}N_3O \cdot 0.5H_2O$: C, 72.59; H, 6.41; N, 13.37. Found: C, 72.53; H, 6.03; N, 13.34.

1,5-Diphenyl-3-cyanomethyl-4-ethylpyrazole (35). Compound **34** (0.10 g, 0.33 mmol) and Lawesson's reagent (0.13 g, 0.33 mmol) were dissolved in dry toluene and heated to ruflux under N_2 for 2 h. The solvent was evaporated in vacuo and the residue was chromatographed on a 2 × 30 cm column with EtOAc/hexane (1:9). The product was isolated as a white solid which crystallized from Et_2O in a yield of 84 mg (89%): mp 99−100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, J = 7.62 Hz, 3 H), 2.72 (q, J = 7.55 Hz, 2 H), 4.02 (s, 2 H), 7.34−7.48 (m, 7 H), 7.52−7.55 (m, 3 H); HRMS calcd for $C_{19}H_{17}N_3$ 287.1422, found 287.1422. Anal. Calcd for $C_{19}H_{17}N_3$: C, 79.42; H, 5.96; N, 14.62. Found: C, 79.29; H, 6.14; N, 14.45.

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