Tetrahedron 65 (2009) 328–335

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

N-(α-Amidoalkyl)benzotriazole-mediated synthesis of β′-amido β-diketones: a general synthetic protocol for *N*-[β-(3,5-di and 1,3,5-trisubstituted pyrazol-4-yl)alkyl] amides

İlhami Çelik *, Nevin Kanışkan, Şule Kökten

Department of Chemistry, Faculty of Science, Anadolu University, 26470 Eskişehir, Turkey

ARTICLE INFO

Article history:
Received 29 July 2008
Received in revised form 1 October 2008
Accepted 16 October 2008
Available online 1 November 2008

Keywords:
Benzotriazole
N-(α-Amidoalkyl)benzotriazole
Pyrazole
β′-Amido β-diketone

ABSTRACT

Various β′-amido-β-diketones were first synthesized with *N*-(α-amidoalkyl)benzotriazole-mediated amidoalkylation of 1,3-diketones in moderate yields. These intermediates undergo rapid condensation with hydrazines to give the corresponding *N*-[β-(3,5-di and 1,3,5-trisubstituted pyrazol-4-yl)alkyl]amides.

1. Introduction

Substituted pyrazoles represent an important class of heterocyclic compounds used in the pharmaceutical industry, since they form the core structures of many commercial drugs such as Zometapine,[1a] Sildenafil,[1b] Celebrex,[1c] and Rimonabant (Fig. 1).[1d] They are also known to show a wide range of biological properties such as selective Human C1s inhibition,[2a] antitumor cyclin-dependent kinase (CDK) inhibition,[2b] monoamine oxidase-B (MOA-B) inhibition, and anti-inflammation.[2c,11d] In addition to their biological activities, pyrazoles are also used for the preparation of pyrazole dyes,[3] couplers for photographic material,[4] herbicides,[5] and luminescent and fluorescent substances.[6] Recently, they have appeared as intermediates for fused pyrazoles,[7] chiral catalysts,[8] ligands,[9] and moieties to enhance regio- and stereoselectivity.

Many methods for the synthesis of pyrazoles have been developed.[10] The methods developed to synthesize pyrazoles are: (i) cyclocondensation of hydrazine with 2,3-dibromopropionitriles,[11a] propargyl aldehydes, 1,3-dicarbonyl compounds,[11b–f] or their functional derivatives such as enol ethers, acetales, enamine, α,β-ethynyl ketones, or esters,[11g–k] (ii) 1,3-dipolar cycloadditions of diazoalkanes or nitrile imines with alkynes or alkenes,[12] (iii) elimination of pyrazoline.[13] Among the methods reported, the most common method is the cyclocondensation of hydrazine with 1,3-dicarbonyl compounds or their functional derivatives, although it gives a mixture of isomers.

Benzotriazole-mediated amidoalkylation was introduced in 1988, and provides advantages over previously reported methods. It was already demonstrated for the amidoalkylation of (i) Grignards,[14a]

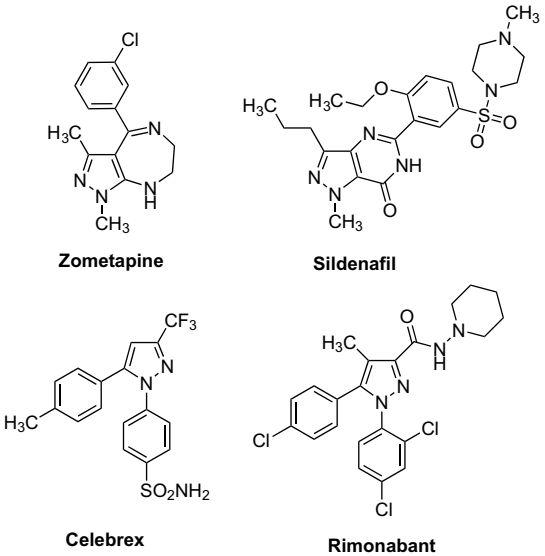
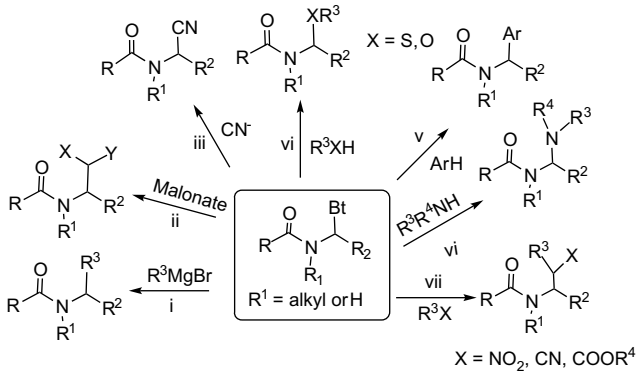


Figure 1. Some commercial drugs having pyrazole ring.

* Corresponding author. Tel.: +90 2223350580/4792; fax: +90 2223204910.
E-mail address: ilcelik@anadolu.edu.tr (İ. Çelik).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.10.047

(ii) malonates and acetoacetates,[14b] (iii) cyanide anion,[14c] (iv) mercaptans and alcohols,[14d,e] (v) electron-rich aromatics,[14f] (vi) amines,[14g] and (vii) nitroalkanes, nitriles, and esters[14h] (Scheme 1).



Scheme 1.

We now report that *N*-(α-amidoalkyl)benzotriazole-mediated amidoalkylation extends the amidoalkylation of 1,3-diketones to give the corresponding novel β′-amido β-diketones and the synthesis of *N*-[β-(3,5-di and 1,3,5-trisubstituted pyrazol-4-yl)alkyl]amides by condensation of hydrazines with the β′-amido β-diketones.

2. Result and discussion

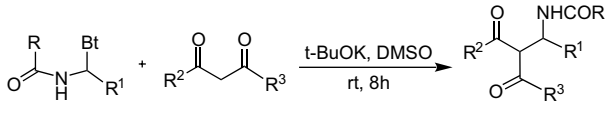
2.1. Preparation of *N*-(α-amidoalkyl)benzotriazoles

The amidoalkylating reagents employed, *N*-(α-amidoalkyl)-benzotriazoles **1a–j**, are easily available by the well-established condensation of benzotriazole, an aldehyde, and an amide in the presence of a catalytic amount of *p*-toluenesulfonic acid in toluene at reflux with azeotropic removal of water.[14] Aromatic and hetero-aromatic aldehydes gave stable products **1** in good yields, which were fully characterized on the basis of their ^{1}H and ^{13}C NMR spectra and elemental analyses. The ^{1}H and ^{13}C NMR spectra of these *N*-(α-amidoalkyl)benzotriazoles confirmed that the products **1a–j** are all benzotriazol-1-yl compounds with no isomerization to benzotriazol-2-yl isomers.

2.2. Synthesis of β′-amido β-diketones

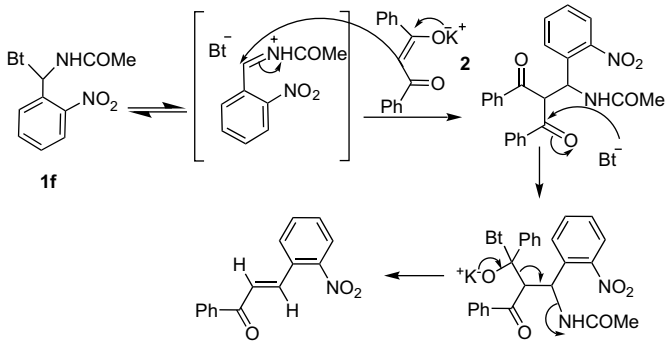
The synthesis of β-acetamido carbonyl compounds has attracted attention in organic synthesis, being used for the synthesis of various bioactive molecules such as antibiotic nikkomycins or neopolyoxines[15] and the preparation of 1,3-amino alcohols[16] or β-amino acids.[17] β′-Amido β-diketones were previously prepared by one-pot multi-component reactions (MCRs) using $CoCl_2$,[17] $FeCl_3$,[18a] and BiOCl[18b] as catalysts, and by the asymmetric Mannich reaction of dicarbonyl compounds with α-amido sulfones catalyzed by cinchona.[18c] Although multi-component reactions (MCRs) have been used for the preparation of β′-amido β-diketones, they also have some disadvantages. Acetoacetone was only used as a starting material in the methods mentioned above. Therefore, they obtained limited amounts of β′-amido β-diketones.

The second step in our synthetic sequence was the preparation of the β′-amido β-diketones by the reaction of potassium enolates, prepared in situ by treating the corresponding 1,3-diketones with *t*-BuOK in DMSO at room temperature, with **1a–j**. *N*-(α-Amidoalkyl)-benzotriazoles **1a–j** reacted efficiently with the appropriate 1,3-diketones **2** in the presence of 1.2 equiv *t*-BuOK in DMSO at room temperature to afford the amidoalkylated product **3** in good yields (**12–90**%) (Scheme 2 and Table 1). The formation of the β′-amido β-diketones of type **3** is indicated by the loss of benzotriazole signals in the ^{1}H and ^{13}C NMR spectra. The doublets at 7.93–6.20 ppm and at 6.45–6.23 ppm in the ^{1}H NMR spectra of **3a–j** were assigned to the NH proton and double activated methine protons, respectively. The doublets in the ^{1}H NMR spectra of **3a–j** were assigned to the methine proton next to NH. In the ^{13}C NMR spectra of compounds **3a–j**, resonances arising from the diketone and amide carbonyls are found in the regions 205.6–195.9 ppm, 202.8–193.7 ppm, and 178.4–169.5 ppm. The ^{1}H and ^{13}C NMR spectra of **3a–j** showed that while **3b** was a diastereoisomeric mixture, **3a**,**c–j** were single diastereomers. The ratio of *syn*/*anti* diastereomers was determined by the ^{1}H NMR spectra. The structures of compounds **3a–j** were also supported by their elemental analyses and spectral data.



Scheme 2.

During the course of our work, we noticed that when the aldehyde contains a nitro group, it gives both byproduct **3f′**, which is the major product, and the expected product **3f**. This byproduct **3f′** was fully characterized by ^{1}H and ^{13}C NMR spectroscopy and elemental analyses. Scheme 3 gives a possible explanation for the formation of the byproduct.



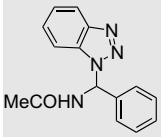
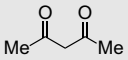
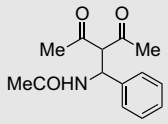
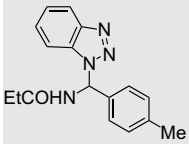
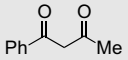
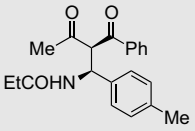
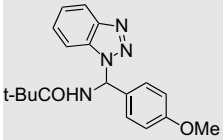
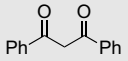
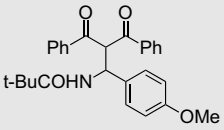
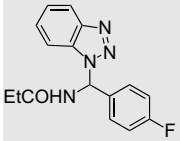
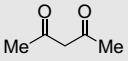
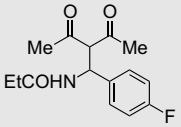
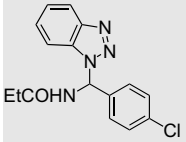
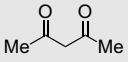
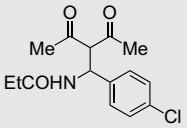
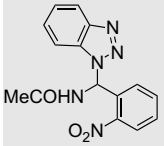
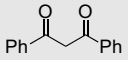
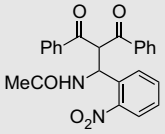
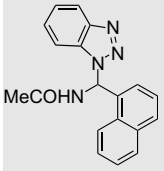
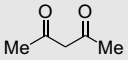
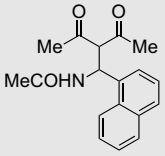
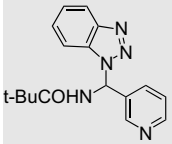
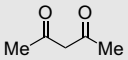
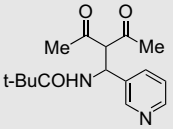
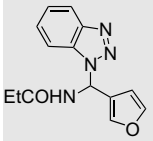
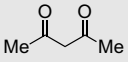
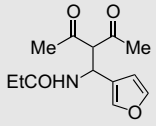
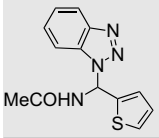
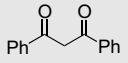
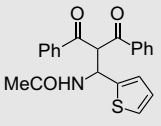
Scheme 3.

We assumed that it provides the alkene owing to electronic effects or electron withdrawing nature of the nitro group.

2.3. Synthesis of *N*-[β-(3,5-di and 1,3,5-trisubstituted pyrazol-4-yl)alkyl]amides

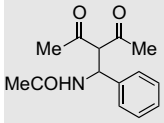
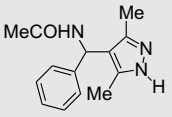
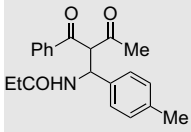
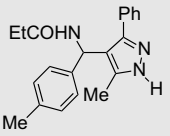
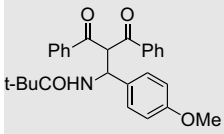
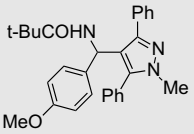
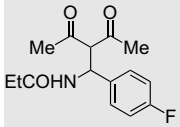
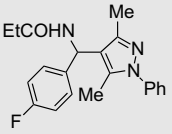
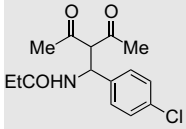
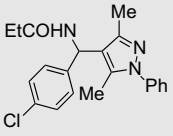
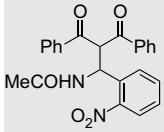
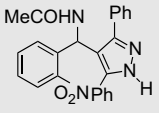
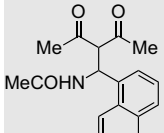
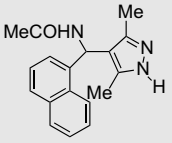
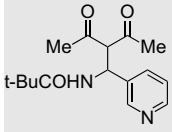
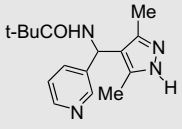
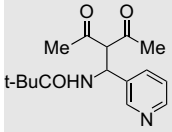
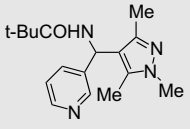
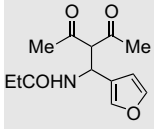
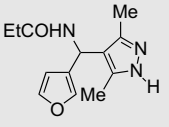
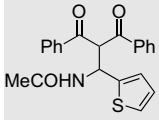
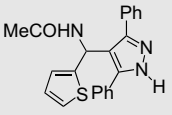
As mentioned above, many methods for the preparation of pyrazoles have been developed. In spite of the fact that among these methods, cyclocondensation of hydrazine with 1,3-dicarbonyl compounds or their functional derivatives give a mixture of isomers, it is the most common method for the preparation of pyrazoles. In this manner, the next step in our synthetic sequence was to obtain *N*-[β-(3,5-di and 1,3,5-trisubstituted pyrazol-4-yl)alkyl]-amides by the cyclocondensation of hydrazine or substituted hydrazine with β′-amido β-diketones. A solution of hydrazine was slowly added to the corresponding β′-amido β-diketone in absolute EtOH and then the mixture was stirred at reflux for 1 h. The solvent was evaporated and the residue was placed on a silica gel column and eluted with hexanes/EtOAc (1:1) to give the corresponding

Table 1
Preparation of β′-amido β-diketones **3a–j**

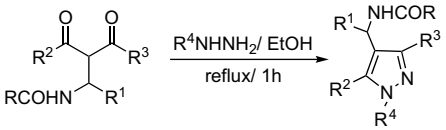
N-(α-Amidoalkyl)benzotriazole		Diketone	Product		Yield (%)
	**1a**			**3a**	89[a]
	**1b**			**3b**	69[b]
	**1c**			**3c**	53
	**1d**			**3d**	79
	**1e**			**3e**	68
	**1f**			**3f**	12
	**1g**			**3g**	85
	**1h**			**3h**	90
	**1i**			**3i**	88
	**1j**			**3j**	44

[a] Lit.[18b] yield.
[b] Diastereomeric ratio was evaluated by ^{1}H NMR analysis.

Table 2
Sythesis of *N*-[β-(3,5-di and 1,3,5-trisubstituted pyrazol-4-yl)alkyl]amides **4a–k**

β′-Amido β-diketone		Hydrazine	Product		Yield (%)[a]
	**3a**	NH_2NH_2		**4a**	66
	**3b**	NH_2NH_2		**4b**	78
	**3c**	$MeNHNH_2$		**4c**	84
	**3d**	$PhNHNH_2$		**4d**	80
	**3e**	$PhNHNH_2$		**4e**	82
	**3f**	NH_2NH_2		**4f**	89
	**3g**	NH_2NH_2		**4g**	95
	**3h**	NH_2NH_2		**4h**	63
	**3h**	$MeNHNH_2$		**4i**	78
	**3i**	NH_2NH_2		**4j**	77
	**3j**	NH_2NH_2		**4k**	59

[a] Isolated yields.



Scheme 4.

N-[β-(3,5-di and 1,3,5-trisubstituted pyrazol-4-yl) alkyl] amide **4** in good yields (**59**–**95**%) (Scheme 4 and Table 2).

The formation of the substituted pyrazole of **4** is indicated by the loss of the carbonyl signals in ^{13}C NMR spectra. The doublets at 6.97–6.19 ppm and at 6.23–5.96 ppm in the ^{1}H NMR spectra of **4a**–**k** were assigned to the methine proton next to the NH and NH protons, respectively. The structure of compounds **4a**–**k** was also supported by their elemental analyses and spectral data.

3. Conclusion

In summary, we have developed a novel and convenient route for the synthesis of a wide range of β′-amido β-diketones **3a**–**j**. The method developed is simple and applicable to the preparation of β′-amido β-diketones **3a**–**j**. In many cases, β′-amido β-diketones were obtained in high yields. β′-Amido β-diketones were treated with hydrazine and substituted hydrazines to form *N*-[β-(3,5-di and 1,3,5-trisubstituted pyrazol-4-yl)alkyl]amides **4a**–**k** in good to excellent yields. Our method proved that it is useful for the preparation of chiral pyrazole amides and allowed us to reach novel pyrazole amides.

4. Experimental section

4.1. General

All melting points are uncorrected. The glassware was routinely oven-dried at 110 °C for a minimum of 4 h. DMSO was dried over molecular sieves prior to use. Column chromatography was performed on silica gel 70–230 mesh. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance 500 DPX spectrometer (^{1}H at 500 MHz and ^{13}C at 125 MHz) in $CDCl_3$ with TMS as the internal standard. Elemental analyses were carried out on a VarioEL III instrument. FTIR spectra were determined on a PerkinElmer 100 FT-IR spectrometer.

4.2. General procedure for the preparation of *N*-(α-amidoalkyl)benzotriazoles (1a–j)

N-(α-Amidoalkyl)benzotriazoles **1** were prepared according to the literature procedure.[14a]

4.2.1. N-(Benzotriazol-1-yl-phenylmethyl)acetamide ***1a***

White crystals, mp 175–177 °C (lit.[14h] mp 174–177 °C); IR ν_{max} (KBr): 3298 (NH), 1654 (CO) cm^{-1}; ^{1}H NMR δ 8.24 (d, *J*=9.0 Hz, 1H), 8.03 (d, *J*=8.3 Hz, 1H), 7.93 (d, *J*=9.1 Hz, 1H), 7.66 (d, *J*=8.33 Hz, 1H), 7.44 (t, *J*=7.6 Hz, 1H), 7.36 (t, *J*=7.6 Hz, 1H), 7.31–7.29 (m, 5H), 2.06 (s, 3H); ^{13}C NMR δ 170.5, 145.6, 136.1, 132.8, 129.2, 129.0, 128.0, 126.5, 124.5, 119.8, 110.0, 64.7, 22.9. Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.52; H, 5.25; N, 21.20.

4.2.2. N-(Benzotriazol-1-yl-p-tolylmethyl)propionamide ***1b***

White crystals, yield 68%, mp 112–113 °C; IR ν_{max} (KBr): 3314 (NH), 1667 (CO) cm^{-1}; ^{1}H NMR δ 8.07 (d, *J*=8.4 Hz, 1H), 7.88 (d, *J*=9.1 Hz, 1H), 7.67 (d, *J*=8.4 Hz, 1H), 7.49 (t, *J*=7.3 Hz, 2H), 7.39 (t, *J*=7.3 Hz, 1H), 7.19–7.13 (m, 4H), 2.39–2.34 (m, 1H), 2.33 (s, 3H), 2.32–2.27 (m, 1H), 1.15 (t, *J*=7.6 Hz, 3H); ^{13}C NMR δ 173.6, 145.7, 139.2, 133.5, 132.8, 129.7, 127.9, 126.3, 124.3, 119.9, 109.9, 64.4, 29.2, 21.0, 9.2. Anal. Calcd for $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16; N, 19.03. Found: C, 69.20; H, 6.31; N, 18.95.

4.2.3. N-[Benzotriazol-1-yl-(4-methoxyphenyl)methyl]-2,2-dimethyl propionamide ***1c***

White crystals, yield 82%, mp 134–140 °C; IR ν_{max} (KBr): 3401 (NH), 1667 (CO) cm^{-1}; ^{1}H NMR δ 8.08 (d, *J*=8.4 Hz, 1H), 7.81 (d, *J*=8.8 Hz, 1H), 7.64 (d, *J*=8.4 Hz, 1H), 7.49 (t, *J*=7.5 Hz, 1H), 7.39 (t, *J*=7.6 Hz, 1H), 7.26 (d, *J*=8.6 Hz, 1H), 7.19 (d, *J*=8.8 Hz, 2H), 6.88 (d, *J*=8.8 Hz, 2H), 3.79 (s, 3H), 1.25(s, 9H); ^{13}C NMR δ 178.2, 160.2, 145.7, 132.7, 128.8, 127.9, 127.7, 124.3, 119.9, 114.5, 109.7, 64.4, 55.4, 38.9, 27.4. Anal. Calcd for $C_{19}H_{22}N_4O_2$: C, 67.44; H, 6.55; N, 16.56. Found: C, 67.20; H, 6.87; N, 16.41.

4.2.4. N-[Benzotriazol-1-yl-(4-fluorophenyl)methyl]-propionamide ***1d***

White crystals, yield 63%, mp 123–125 °C; IR ν_{max} (KBr): 3284 (NH), 1652 (CO) cm^{-1}; ^{1}H NMR δ 8.09 (d, *J*=8.4 Hz, 1H), 7.91 (d, *J*=9.3 Hz, 1H), 7.67 (d, *J*=8.3 Hz, 1H), 7.53 (t, *J*=7.6 Hz, 1H), 7.42 (t, *J*=7.7 Hz, 2H), 7.29 (t, *J*=6.8 Hz, 2H), 7.04 (t, *J*=8.5 Hz, 2H), 2.39–2.29 (m, 2H), 1.17 (t, *J*=7.5 Hz, 3H); ^{13}C NMR δ 173.5, 145.7, 132.7, 128.5, 128.4, 128.2, 124.6, 120.0, 116.2, 116.0, 109.7, 63.7, 29.3, 9.2. Anal. Calcd for $C_{16}H_{15}FN_4O$: C, 64.42; H, 5.07; N, 18.78. Found: C, 64.37; H, 5.01; N, 18.52.

4.2.5. N-[Benzotriazol-1-yl-(4-chlorophenyl)methyl]-propionamide ***1e***

White crystals, yield 74%, mp 133–134 °C; IR ν_{max} (KBr): 3298 (NH), 1650 (CO) cm^{-1}; ^{1}H NMR δ 8.07 (d, *J*=8.3 Hz, 1H), 7.91 (d, *J*=9.0 Hz, 1H), 7.72 (d, *J*=9.0 Hz, 1H), 7.68 (d, *J*=8.3 Hz, 1H), 7.52 (t, *J*=7.5 Hz, 1H), 7.42 (t, *J*=7.5 Hz, 1H), 7.30 (d, *J*=8.3 Hz, 2H), 7.22 (d, *J*=8.1 Hz, 2H), 2.43–2.28 (m, 2H), 1.15 (t, *J*=7.4 Hz, 3H); ^{13}C NMR δ 173.8, 145.6, 135.3, 134.9, 132.8, 129.2, 128.2, 128.0, 124.6, 119.9, 109.8, 63.7, 29.2, 9.2. Anal. Calcd for $C_{16}H_{15}ClN_4O$: C, 61.05; H, 4.80; N, 17.80. Found: C, 61.16; H, 5.01; N, 17.62.

4.2.6. N-[Benzotriazol-1-yl-(2-nitrophenyl)methyl]acetamide ***1f***

Yellow powder, yield 70%, mp 157–158 °C; IR ν_{max} (KBr): 3245 (NH), 1691 (CO) cm^{-1}; ^{1}H NMR δ 8.64 (d, *J*=9.3 Hz, 1H), 8.07–8.04 (m, 2H), 7.98 (d, *J*=8.4 Hz, 1H), 7.88 (d, *J*=8.4 Hz, 1H), 7.77 (d, *J*=8.1 Hz, 1H), 7.62–7.56 (m, 3H), 7.42 (t, *J*=7.7 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR δ 169.9, 147.9, 145.4, 133.8, 132.8, 130.7, 130.4, 129.3, 128.5, 125.6, 124.9, 119.5, 110.6, 60.8, 22.9. Anal. Calcd for $C_{15}H_{13}N_5O_3$: C, 57.87; H, 4.21; N, 22.20. Found: C, 57.67; H, 4.35; N, 22.10.

4.2.7. N-(Benzotriazol-1-yl-naphthalen-1-yl-methyl)acetamide ***1g***

White crystals, yield 82%, mp 154–156 °C; IR ν_{max} (KBr): 3311 (NH), 1663 (CO) cm^{-1}; ^{1}H NMR δ 8.59 (d, *J*=9.3 Hz, 1H), 8.09 (dd, *J*=11.6, 8.3 Hz, 2H), 7.94 (d, *J*=7.7 Hz, 1H), 7.87 (d, *J*=7.7 Hz, 1H), 7.64–7.57 (m, 2H), 7.54–7.51 (m, 2H), 7.45–7.35 (m, 3H), 7.31 (t, *J*=7.8 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR δ 169.8, 133.9, 132.6, 131.7, 130.3, 130.2, 129.1, 127.9, 127.6, 126.5, 125.1, 124.5, 124.4, 122.4, 120.0, 118.4, 109.9, 62.4, 23.0. Anal. Calcd for $C_{19}H_{16}N_4O$: C, 72.13; H, 5.10; N, 17.71. Found: C, 72.01; H, 5.23; N, 17.81.

4.2.8. N-(Benzotriazole-1-yl-pyridin-3-yl-methyl)propionamide ***1h***

White crystals, yield 85%, mp 73–75 °C; IR ν_{max} (KBr): 3336 (NH), 1674 (CO) cm^{-1}; ^{1}H NMR δ 8.62 (d, *J*=2.1 Hz, 1H), 8.58 (d, *J*=3.9 Hz, 1H), 8.06 (d, *J*=8.4 Hz, 1H), 8.00 (d, *J*=9.0 Hz, 1H), 7.83 (d, *J*=8.2 Hz, 1H), 7.71 (d, *J*=8.4 Hz, 1H), 7.52 (t, *J*=7.3 Hz, 2H), 7.41 (t, *J*=7.3 Hz, 1H), 7.25 (dd, *J*=8.0, 4.9 Hz, 1H), 1.24 (s, 9H); ^{13}C NMR δ 178.7, 150.2, 147.9, 145.6, 134.4, 132.8, 132.6, 128.4, 124.7, 123.7, 120.0, 109.6, 62.7, 39.0, 27.2. Anal. Calcd for $C_{17}H_{19}N_5O$: C, 66.00; H, 6.16; N, 22.64. Found: C, 65.71; H, 6.52; N, 22.79.

4.2.9. N-(Benzotriazol-1-yl-furan-3-yl-methyl)propionamide ***1i***

Yellow powder, yield 56%, mp 175–177 °C; IR ν_{max} (KBr): 3255 (NH), 1685 (CO) cm^{-1}; ^1H NMR δ 8.07 (d, J=8.4 Hz, 1H), 7.88 (d, J=9.1 Hz, 1H), 7.80 (d, J=8.3 Hz, 1H), 7.52 (t, J=7.8 Hz, 1H), 7.48 (s, 1H), 7.45 (d, J=9.1 Hz, 1H), 7.43–7.39 (m, 3H), 2.38–2.21 (m, 2H), 1.13 (t, J=7.5 Hz, 3H); ^{13}C NMR δ 173.6, 145.5, 144.2, 140.9, 132.5, 128.1, 124.5, 122.5, 119.8, 110.0, 109.2, 58.2, 29.1, 9.2. Anal. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 61.83; H, 5.30; N, 20.63.

4.2.10. N-(Benzotriazol-1-yl-thiophen-2-yl-methyl)acetamide ***1j***

Brown crystals, yield 67%, mp 141–142 °C; IR ν_{max} (KBr): 3240 (NH), 1684 (CO) cm^{-1}; ^1H NMR δ 8.56 (d, J=8.9 Hz, 1H), 8.17 (d, J=8.9 Hz, 1H), 8.05 (d, J=8.2 Hz, 1H), 7.76 (d, J=8.2 Hz, 1H), 7.50 (t, J=7.6 Hz, 1H), 7.40 (t, J=7.6 Hz, 1H), 7.28 (d, J=4.8 Hz, 1H), 7.03 (d, J=3.4 Hz, 1H), 6.92 (AB, J_{AB}=4.8, 3.8 Hz, 1H), 2.06 (s, 3H); ^{13}C NMR δ 170.2, 145.4, 138.8, 132.3, 127.9, 126.9, 126.8, 126.7, 124.4, 119.7, 110.0, 61.0, 22.6. Anal. Calcd for $C_{13}H_{12}N_4OS$: C, 57.34; H, 4.44; N, 20.57. Found: C, 57.16; H, 4.50; N, 20.21.

4.3. General procedure for the preparation of β′-amido β-diketones (3a–j)

A mixture of 1,3-diketone (2 mmol) and potassium *tert*-butoxide (0.25 g, 2.4 mmol) in DMSO (10 mL) was stirred at room temperature for 40 min. To the resulting solution, *N*-(α-amidoalkyl)benzotriazoles **1** (2 mmol) in DMSO (10 mL) was added dropwise and the mixture was stirred at room temperature for 8 h. The mixture was poured into water (40 mL) and then extracted with ethyl acetate (4×25 mL). The extracts were washed with water, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was placed in a silica gel column and eluted with hexanes/EtOAc (1:1) to give the pure product **3**.

4.3.1. N-(2-Acetyl-3-oxo-1-phenylbutyl)acetamide ***3a***

White crystals, yield 89% mp 133–134 °C (lit.[18b] mp 132–133 °C); IR ν_{max} (KBr): 3359 (NH), 1700 (CO, diketone), 1670 (CO, diketone), 1649 (CO, amide), 1586, 1529, 1456, 1366, 1298, 1274, 1201, 1162, 1104, 953, 891, 758, 706, 617 cm^{-1}; ^1H NMR δ 7.35–7.25 (m, 5H), 7.13 (d, J=9.5 Hz, 1H), 5.88 (dd, J=9.4, 5.9 Hz, 1H), 4.32 (d, J=5.9 Hz, 1H), 2.27 (s, 3H), 2.11 (s, 3H), 2.01 (s, 3H); ^{13}C NMR δ 205.3, 202.6, 169.8, 139.3, 128.9, 127.7, 126.4, 70.5, 51.9, 31.1, 30.0, 23.3. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.85; H, 6.82; N, 5.60.

4.3.2. N-(2-Benzoyl-3-oxo-1-p-tolylbutyl)propionamide ***3b***

White crystals, yield 69%, mp 59–60 °C; diastereoisomeric mixture (*syn*/*anti*: 50:50); IR ν_{max} (KBr): 3285 (NH), 1723 (CO, diketone), 1676 (CO, diketone), 1647 (CO, amide) cm^{-1}; ^1H NMR δ 7.95 (d, J=8.2 Hz, 1H), 7.80 (d, J=8.2 Hz, 1H), 7.63–7.57 (m, 1H), 7.50 (t, J=7.7 Hz, 1H), 7.45 (t, J=7.8 Hz, 1.5H), 7.24 (d, J=8.0 Hz, 1H), 7.20 (d, J=8.1 Hz, 1H), 7.11 (d, J=8.0 Hz, 1H), 7.08 (d, J=8.0 Hz, 1H), 6.57 (d, J=9.3 Hz, 0.5H), 6.01 (dd, J=9.2, 4.2 Hz, 0.5H), 5.95 (t, J=8.5 Hz, 0.5H), 5.19 (d, J=4.3 Hz, 0.5H), 5.14 (d, J=7.6 Hz, 0.5H), 2.41 (s, 1.5H), 2.32–2.29 (m, 1H), 2.31 (s, 1.5H), 2.28 (s, 1.5H), 2.23–2.21 (m, 1H), 2.19 (s, 1.5H), 1.18 (t, J=7.6 Hz, 1.5H), 1.13 (t, J=7.6 Hz, 1.5H); ^{13}C NMR δ 204.2, 202.5, 197.4, 193.9, 173.5, 173.1, 137.5, 137.2, 136.9, 136.4, 136.0, 134.0, 133.9, 129.5, 129.4, 129.0, 128.9, 128.6, 128.3, 126.7, 126.3, 67.0, 64.3, 52.2, 51.8, 29.8, 29.4, 29.0, 21.0, 9.7. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 75.64; H, 7.20; N, 4.11.

4.3.3. N-[2-Benzoyl-1-(4-methoxyphenyl)-3-oxo-3-phenylpropyl]-2,2-dimethyl propionamide ***3c***

White crystals, yield 53%, mp 180–181 °C; IR ν_{max} (KBr): 3386 (NH), 1690 (CO, diketone), 1655 (CO, amide) cm^{-1}; ^1H NMR δ 8.07 (d, J=8.1 Hz, 2H), 7.93 (d, J=8.6 Hz, 1H), 7.82 (d, J=8.2 Hz, 2H), 7.67 (t, J=7.4 Hz, 1H), 7.58–7.52 (m, 3H), 7.40 (t, J=7.8 Hz, 2H), 7.33 (d, J=8.6 Hz, 2H), 6.84 (d, J=8.6 Hz, 2H), 6.04 (d, J=3.5 Hz, 1H), 5.86 (dd, J=8.6, 3.3 Hz, 1H), 3.77 (s, 3H), 1.23 (s, 9H); ^{13}C NMR δ 196.7, 193.8, 178.0, 158.8, 136.5, 135.2, 134.1, 133.8, 132.3, 129.3, 128.9, 128.6, 128.3, 127.7, 114.1, 59.0, 55.3, 52.2, 38.8, 27.5. Anal. Calcd for $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16. Found: C, 75.61; H, 6.81; N, 3.02.

4.3.4. N-[2-Acetyl-1-(4-fluorophenyl)-3-oxobutyl]propionamide ***3d***

White crystals, yield 79%, mp 138–139 °C; IR ν_{max} (KBr): 3291 (NH), 1723 (CO, diketone), 1701 (CO, diketone), 1647 (CO, amide) cm^{-1}; ^1H NMR δ 7.28–7.25 (m, 2H), 7.09 (d, J=9.2 Hz, 1H), 7.02 (d, J=8.6 Hz, 2H), 5.84 (dd, J=9.3, 6.0 Hz, 1H), 4.29 (d, J=5.9 Hz, 1H), 2.26 (s, 3H), 2.22 (q, J=7.6 Hz, 2H), 2.11 (s, 3H), 1.13 (t, J=7.6 Hz, 3H); ^{13}C NMR δ 205.1, 202.4, 173.5, 128.2, 128.1, 115.8, 115.6, 70.6, 51.1, 31.0, 30.0, 29.7, 9.7. Anal. Calcd for $C_{15}H_{18}FNO_3$: C, 64.50; H, 6.50; N, 5.01. Found: C, 64.42; H, 6.67; N, 4.88.

4.3.5. N-[2-Acetyl-1-(4-chlorophenyl)-3-oxobutyl]propionamide ***3e***

White crystals, yield 68%, mp 146–147 °C; IR ν_{max} (KBr): 3288 (NH), 1703 (CO, diketone), 1701 (CO, diketone), 1646 (CO, amide) cm^{-1}; ^1H NMR δ 7.32–7.29 (m, 2H), 7.23 (d, J=8.5 Hz, 2H), 7.06 (d, J=9.2 Hz, 1H), 5.84 (dd, J=9.3, 5.6 Hz, 1H), 4.28 (d, J=5.6 Hz, 1H), 2.29 (s, 3H), 2.25 (q, J=7.6 Hz, 2H), 2.11 (s, 3H), 1.15 (t, J=7.6 Hz, 3H); ^{13}C NMR δ 205.1, 202.3, 173.5, 138.0, 133.6, 129.0, 127.8, 70.2, 51.1, 31.2, 29.9, 29.7, 9.7. Anal. Calcd for $C_{15}H_{18}ClNO_3$: C, 60.91; H, 6.13; N, 4.74. Found: C, 60.73; H, 6.34; N, 4.54.

4.3.6. N-[2-Benzoyl-(2-nitrophenyl)-3-oxo-3-phenylpropyl]acetamide ***3f***

Yellow crystals, yield 12%, mp 106–107 °C; IR ν_{max} (KBr): 3284 (NH), 1695 (CO, diketone), 1669 (CO, amide) cm^{-1}; ^1H NMR δ 8.15 (d, J=7.6 Hz, 2H), 7.97 (d, J=7.2 Hz, 1H), 7.80 (d, J=7.5 Hz, 2H), 7.77 (d, J=7.9 Hz, 1H), 7.65 (t, J=7.4 Hz, 1H), 7.57–7.52 (m, 5H), 7.39 (t, J=7.9 Hz, 3H), 6.45 (d, J=4.7 Hz, 1H), 6.28 (dd, J=7.9, 4.4 Hz, 1H), 2.00 (s, 3H); ^{13}C NMR δ 195.9, 193.7, 169.6, 148.2, 136.5, 135.3, 134.9, 134.3, 134.1, 133.5, 131.0, 129.2, 129.0, 128.9, 128.7, 128.3, 125.1, 56.6, 50.3, 23.2. Anal. Calcd for $C_{24}H_{20}N_2O_5$: C, 69.22; H, 4.84; N, 6.73. Found: C, 68.84; H, 5.05; N, 6.96.

4.3.7. N-(2-Acetyl-1-naphthalen-1-yl-3-oxobutyl)acetamide ***3g***

White crystals, yield 85%, mp 181–182 °C; IR ν_{max} (KBr): 3258 (NH), 1722 (CO, diketone), 1703 (CO, diketone), 1648 (CO, amide) cm^{-1}; ^1H NMR δ 8.22 (d, J=8.5 Hz, 1H), 7.89 (d, J=8.1 Hz, 1H), 7.79 (t, J=4.7 Hz, 1H), 7.63 (t, J=7.7 Hz, 1H), 7.54 (t, J=7.5 Hz, 1H), 7.40 (d, J=4.0 Hz, 2H), 7.34 (br s, 1H), 6.67 (dd, J=9.2, 5.8 Hz, 1H), 4.49 (d, J=5.7 Hz, 1H), 2.34 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H); ^{13}C NMR δ 205.6, 202.3, 169.5, 134.7, 134.0, 130.2, 129.3, 128.7, 127.1, 126.0, 125.2, 124.1, 122.4, 69.5, 48.2, 31.5, 29.8, 23.2. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.36; H, 6.41; N, 4.81.

4.3.8. N-(2-Acetyl-3-oxo-1-pyridin-3-yl-butyl)-2,2-dimethyl propionamide ***3h***

White crystals, yield 90%, mp 164–165 °C; IR ν_{max} (KBr): 3329 (NH), 1726 (CO, diketone), 1704 (CO, diketone), 1635 (CO, amide) cm^{-1}; ^1H NMR δ 8.57 (d, J=2.2 Hz, 1H), 8.53 (dd, J=4.8, 3.4 Hz, 1H), 7.59 (d, J=8.1 Hz, 1H), 7.45 (d, J=9.1 Hz, 1H), 7.29–7.28 (m, 1H), 5.89 (dd, J=9.1, 4.7 Hz, 1H), 4.35 (d, J=4.7 Hz, 1H), 2.36 (s, 3H), 2.11 (s, 3H), 1.22 (s, 9H); ^{13}C NMR 205.3, 202.2, 178.4, 149.0, 147.9, 135.3, 134.2, 123.5, 69.4, 49.4, 38.9, 31.5, 29.7, 27.3. Anal. Calcd. for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 65.97; H, 7.61; N, 9.93.

*4.3.9. N-(2-Acetyl-1-furan-3-yl-3-oxobutyl)propionamide **3i***

White crystals, yield 88%, mp 128–130 °C; IR ν_{max} (KBr): 3304 (NH), 1721 (CO, diketone), 1699 (CO, diketone), 1647 (CO, amide) cm^{-1}; ^1H NMR δ 7.33 (d, J=13.1 Hz, 2H), 6.96 (d, J=9.3 Hz, 1H), 6.31 (s, 1H), 5.81 (dd, J=9.4, 5.4 Hz, 1H), 4.23 (d, J=5.6 Hz, 1H), 2.28 (s, 3H), 2.19 (q, J=7.6 Hz, 2H), 2.17 (s, 3H), 1.11 (t, J=7.6 Hz, 3H); ^{13}C NMR δ 205.1, 202.8, 173.5, 143.5, 139.7, 124.5, 109.1, 69.8, 44.5, 31.0, 30.0, 29.6, 9.7. Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.34; H, 6.83; N, 5.75.

*4.3.10. N-(2-Benzoyl-3-oxo-3-phenyl-1-thiophen-2-yl-propyl)acetamide **3j***

White crystals, yield 44%, mp 148–149 °C; IR ν_{max} (KBr): 3346 (NH), 1690 (CO, diketone), 1658 (CO, amide) cm^{-1}; ^1H NMR δ 8.05 (d, J=8.5 Hz, 2H), 7.90 (d, J=8.4 Hz, 2H), 7.65 (t, J=7.4 Hz, 1H), 7.60–7.55 (m, 4H), 7.44 (t, J=7.8 Hz, 2H), 7.18 (dd, J=5.1, 1.1 Hz, 1H), 6.98 (d, J=3.5 Hz, 1H), 6.90 (dd, J=5.1, 3.6 Hz, 1H), 6.20 (dd, J=9.1, 3.9 Hz, 1H), 6.13 (d, J=3.9 Hz, 1H), 2.00 (s, 3H); ^{13}C NMR δ 196.1, 193.7, 169.7, 143.2, 136.1, 134.2, 134.0, 129.3, 129.0, 128.6, 128.4, 126.8, 125.3, 125.1, 120.0, 59.1, 49.4, 23.2. Anal. Calcd for $C_{22}H_{19}NO_3S$: C, 70.00; H, 5.07; N, 3.71. Found: C, 69.91; H, 5.17; N, 3.57.

4.4. General procedure for the preparation of *N*-[β-(3,5-di and 1,3,5-trisubstituted pyrazol-4-yl)alkyl] amides (4a–j)

A solution of hydrazine (3 mmol) was slowly added to the corresponding β′-amido β-diketone (2 mmol) in absolute EtOH (10 mL) and the mixture was stirred at reflux for 1 h. The residue was placed on a silica gel column and eluted with hexanes/EtOAc (1:1) to give the pure product **4**.

*4.4.1. N-[(3,5-Dimethyl-1H-pyrazol-4-yl)phenylmethyl]-acetamide **4a***

White crystals. Yield 66%, mp 208–209 °C; IR ν_{max} (KBr): 3405–3150 (NH, br) 1646 (CO) cm^{-1}; ^1H NMR δ 7.33 (t, J=7.5 Hz, 2H), 7.28 (t, J=7.2 Hz, 1H), 7.22 (d, J=7.6 Hz, 2H), 6.28 (d, J=8.0 Hz, 1H), 6.10 (d, J=7.8 Hz, 1H), 2.10 (s, 3H), 2.08 (s, 6H); ^{13}C NMR δ 169.4, 142.8, 140.5, 128.5, 127.1, 126.4, 115.7, 48.0, 23.2, 11.5. Anal. Calcd for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found: C, 69.02; H, 6.93; N, 17.04.

*4.4.2. N-[(3-Methyl-5-phenyl-1H-pyrazol-4-yl)-(p-tolyl)-methyl]propionamide **4b***

White crystals, yield 78%, mp 143–144 °C; IR ν_{max} (KBr): 3428–3124 (NH, br), 1647 (CO) cm^{-1}; ^1H NMR δ 7.43–7.40 (m, 2H), 7.36 (dd, J=5.0, 1.6 Hz, 3H), 7.13 (d, J=8.2 Hz, 2H), 7.09 (d, J=8.0 Hz, 2H), 6.39 (d, J=8.4 Hz, 1H), 5.96 (d, J=8.4 Hz, 1H), 2.35 (s, 3H), 2.16–2.09 (m, 2H), 2.08 (s, 3H), 1.04 (t, J=7.6 Hz, 3H); ^{13}C NMR δ 172.6, 138.4, 136.9, 129.3, 128.8, 128.4, 126.7, 115.6, 47.7, 29.6, 25.1, 21.0, 9.5. Anal. Calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60. Found: C, 75.47; H, 7.16; N, 12.56.

*4.4.3. N-[(4-Methoxyphenyl)-(1-methyl-3,5-diphenyl-1H-pyrazol-4-yl)methyl]-2,2-dimethyl propionamide **4c***

White crystals, yield 84%, mp 111–112 °C; IR ν_{max} (KBr): 3448 (NH), 1660 (CO) cm^{-1}; ^1H NMR δ 7.43–7.38 (m, 5H), 7.35–7.32 (m, 5H), 7.13 (d, J=8.2 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H), 6.34 (d, J=9.1 Hz, 1H), 6.09 (d, J=9.0 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 0.87 (s, 9H); ^{13}C NMR δ 176.9, 158.6, 149.2, 142.4, 135.3, 129.9, 129.0, 128.7, 128.5, 128.0, 113.9, 55.3, 47.3, 38.4, 37.3, 27.1. Anal. Calcd for $C_{29}H_{31}N_3O_2$: C, 76.79; H, 6.89; N, 9.26. Found: C, 76.55; H, 7.05; N, 9.04.

*4.4.4. N-[(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)-(4-fluoro-phenyl)methyl]propionamide **4d***

Yellow crystals, yield 80%, mp 178–179 °C; IR ν_{max} (KBr): 3255 (NH), 1669 (CO) cm^{-1}; ^1H NMR δ 7.49 (t, J=7.7 Hz, 2H), 7.44–7.39 (m, 3H), 7.24 (dd, J=8.4, 5.4 Hz, 2H), 7.04 (t, J=8.6 Hz, 2H), 6.33 (d, J=7.7 Hz, 1H), 6.03(d, J=7.6 Hz, 1H), 2.39–2.34 (m, 2H), 2.21 (s, 3H), 2.10 (s, 3H), 1.25 (t, J=7.6 Hz, 3H); ^{13}C NMR δ 173.0, 147.2, 137.8, 129.1, 128.1, 128.0, 127.8, 125.1, 117.8, 115.5, 115.3, 47.6, 29.7, 13.0, 11.1, 9.9. Anal. Calcd for $C_{21}H_{22}FN_3O$: C, 71.77; H, 6.31; N, 11.96. Found: C, 71.68; H, 6.51; N, 11.86.

*4.4.5. N-[(4-Chlorophenyl)-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)methyl]propionamide **4e***

White crystals, yield 82%, mp 179–180 °C; IR ν_{max} (KBr): 3247 (NH), 1670 (CO) cm^{-1}; ^1H NMR δ 7.49 (t, J=7.6 Hz, 2H), 7.43–7.38 (m, 3H), 7.32 (d, J=8.4 Hz, 2H), 7.20 (d, J=8.4 Hz, 2H), 6.31 (d, J=7.7 Hz, 1H), 6.09 (d, J=7.5 Hz, 1H), 2.40–2.32 (m, 2H), 2.20 (s, 3H), 2.08 (s, 3H), 1.24 (t, J=7.6 Hz, 3H); ^{13}C NMR δ 173.0, 147.2, 139.3, 139.2, 137.8, 133.0, 129.2, 128.7, 127.8, 125.1, 117.6, 47.6, 29.6, 13.0, 11.1, 9.9. Anal. Calcd for $C_{21}H_{22}ClN_3O$: C, 68.56; H, 6.03; N, 11.42. Found: C, 68.37; H, 6.24; N, 11.23.

*4.4.6. N-[(3,5-Diphenyl-1H-pyrazol-4-yl)-(2-nitrophenyl)-methyl]acetamide **4f***

White crystals, yield 89%, mp 255–256 °C; ν_{max} (KBr): 3412 (NH), 3340–3122 (NH, br), 1655 (CO) cm^{-1}; ^1H NMR δ 7.59 (dd, J=7.9, 1.3 Hz, 1H), 7.30 (d, J=4.5 Hz, 2H), 7.26 (d, J=4.4 Hz, 8H), 7.22 (dt, J=6.9, 1.4 Hz, 2H), 7.16 (dt, J=7.0, 1.3 Hz, 1H), 6.97 (d, J=7.8 Hz, 1H), 6.23 (d, J=7.8 Hz, 1H), 1.78 (s, 3H); ^{13}C NMR δ 169.0, 148.5, 135.0, 132.2, 129.7, 128.7, 128.5, 128.4, 128.1, 124.8, 113.9, 47.1, 22.7. Anal. Calcd for $C_{24}H_{20}N_4O_3$: C, 69.89; H, 4.89; N, 13.58. Found: C, 69.66; H, 5.01; N, 13.37.

*4.4.7. N-[(3,5-Dimethyl-1H-pyrazol-4-yl)naphthalen-1-yl-methyl]acetamide **4g***

White crystals, yield 95%, mp 245–246 °C; IR ν_{max} (KBr): 3410–3155 (NH, br), 1649 (CO) cm^{-1}; ^1H NMR δ 7.89 (t, J=8.3 Hz, 2H), 7.83 (d, J=7.8 Hz, 1H), 7.50–7.46 (m, 2H), 7.44 (d, J=7.7 Hz, 1H), 7.41 (d, J=6.7 Hz, 1H), 6.87 (d, J=7.7 Hz, 1H), 5.96 (d, J=7.7 Hz, 1H), 2.11 (s, 3H), 2.04 (s, 6H); ^{13}C NMR δ 168.6, 135.6, 134.1, 130.9, 128.8, 128.5, 126.4, 125.9, 125.0, 123.9, 123.5, 115.1, 65.9, 46.4, 23.2, 11.6. Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.79; H, 6.69; N, 14.28.

*4.4.8. N-[(3,5-Dimethyl-1H-pyrazol-4-yl)-(pyridin-3-yl)methyl]-2,2-dimethyl propionamide **4h***

White crystals, yield 63%, mp 127–128 °C; IR ν_{max} (KBr): 3461–3158 (NH, br), 1645 (CO) cm^{-1}; ^1H NMR δ 8.54 (d, J=15.0 Hz, 2H), 7.57 (br s, 1H), 7.49 (d, J=8.3 Hz, 1H), 7.31 (s, 1H), 6.26 (d, J=7.2 Hz, 1H), 6.18 (d, J=7.2 Hz, 1H), 2.12 (s, 6H), 1.29 (s, 9H); ^{13}C NMR 177.9, 148.1, 147.7, 142.8, 136.7, 134.4, 123.6, 115.0, 46.2, 38.9, 31.6, 27.6, 11.5. Anal. Calcd for $C_{16}H_{22}N_4O$: C, 67.11; H, 7.74; N, 19.56. Found: C, 67.28; H, 7.93; N, 19.38.

*4.4.9. 2,2-Dimethyl-N-[pyridin-3-yl-(1,3,5-trimethyl-1H-pyrazol-4-yl)methyl]propionamide **4i***

White crystals, yield 78%, mp 142–143 °C; IR ν_{max} (KBr): 3309 (NH), 1629 (CO) cm^{-1}; ^1H NMR δ 8.51–8.46 (m, 2H), 7.47 (d, J=7.9 Hz, 1H), 7.27–7.24 (m, 1H), 6.19 (d, J=7.3 Hz, 1H), 6.08 (d, J=7.2 Hz, 1H), 3.70 (s, 3H), 2.12 (s, 3H), 2.02 (s, 3H), 1.26 (s, 9H); ^{13}C NMR δ 177.7, 148.3, 148.1, 145.1, 136.6, 134.1, 123.3, 115.4, 46.5, 36.0, 27.6, 27.3, 12.9, 9.9. Anal. Calcd for $C_{17}H_{24}N_4O$: C, 67.97; H, 8.05; N, 18.65. Found: C, 67.74; H, 8.14; N, 18.46.

*4.4.10. N-[(3,5-Dimethyl-1H-pyrazol-4-yl)-furan-3-yl-methyl]propionamide **4j***

Yellow crystals, yield 77%, mp 177–178 °C; IR ν_{max} (KBr): 3464–3125 (NH, br), 1651(CO) cm^{-1}; ^1H NMR δ 9.35 (br s, 1H), 7.37 (s, 1H), 7.13 (s, 1H), 6.26 (d, J=7.9 Hz, 1H), 6.22 (s, 1H), 6.10 (d, J=7.3 Hz, 1H), 2.30–2.22 (m, 2H), 2.17 (s, 6H), 1.16 (t, J=7.6 Hz, 3H); ^{13}C NMR

δ 173.0, 143.6, 142.4, 139.9, 126.5, 115.0, 109.8, 41.5, 29.6, 11.4, 9.9. Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.07; H, 7.08; N, 16.72.

4.4.11. *N*-[(3,5-Diphenyl-1*H*-pyrazol-4-yl)-thiophen-2-yl-methyl]acetamide **4k**

White crystals, yield 59%, mp 167–169 °C; IR ν_{max} (KBr): 3426 (NH), 3352–3131 (NH, br) cm^{-1}; ^1H NMR δ 7.52–7.48 (m, 4H), 7.40–7.39 (m, 6H), 7.29 (d, *J*=4.3 Hz, 1H), 6.95 (t, *J*=4.3 Hz, 1H), 6.87 (dd, *J*=3.4, 1.1 Hz, 1H), 6.66 (d, *J*=8.9 Hz, 1H), 5.98 (d, *J*=8.9 Hz, 1H), 1.68 (s, 3H); ^{13}C NMR δ 168.7, 147.7, 129.0, 128.8, 128.5, 127.2, 125.4, 115.9, 45.1, 22.9. Anal. Calcd for $C_{22}H_{19}N_3OS$: C, 70.75; H, 5.13; N, 11.25. Found: C, 70.55; H, 5.37; N, 10.98.

References and notes

1. (a) De Wald, H. A.; Lobbestael, S.; Poschel, B. P. H. *J. Med. Chem.* **1981**, *24*, 982–987; (b) Terret, N. K.; Bell, A. S.; Brown, D.; Ellips, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1819–1824; (c) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Cater, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Vennhuizen, A. W.; Zhang, Y. Y.; Isakson, P. *J. Med. Chem.* **1997**, *40*, 1347–1365; (d) Rinaldi-Carmona, M.; Barth, F.; Heaulme, M.; Shire, D.; Calandra, B.; Congy, C.; Martinez, S.; Maruani, J.; Neliat, G.; Caput, D.; Ferrara, P.; Soubrie, P.; Breliere, J. C.; Le Fur, G. *FEBs Lett.* **1994**, *350*, 240–244.
2. (a) Pitt, G. R.; Batt, A. R.; Haigh, R. M.; Penson, A. M.; Robson, P. A.; Rooker, D. P.; Tartar, A. L.; Trim, J. E.; Yea, C. R.; Roe, M. B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3043–3047; (b) Lin, R.; Chiu, G.; Yu, Y.; Connolly, P. J.; Li, S.; Lu, Y.; Adams, M.; Fuentes-Pesquera, A. R.; Emanuel, S. L.; Greenberger, L. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4557–4561; (c) Gokhan-Kelekci, N.; Yabanoglu, S.; Kupeli, E.; Salgin, U.; Ozgen, O.; Ucar, G.; Yesilada, E.; Kendi, E.; Yesilada, A.; Bilgin, A. A. *Bioorg. Med.Chem. Lett.* **2007**, *15*, 5775–5786.
3. Loewe, I.; Balzer, W. R.; Gerstung, S. Ger. Offen. 19619112, 1997; *Chem. Abstr.* **1997**, *128*, 16281.
4. Csunderlik, C.; Bercean, V.; Peter, F.; Bedea, V. *ARKIVOC* **2002**, *ii*, 133–141.
5. Siddal, T. L.; Ouse, D. G.; Benko, Z. L.; Garvin, G. M.; Jackson, J. L.; McQuiston, J. M.; Ricks, M. J.; Thibault, T. D.; Turner, J. A.; VanHeertum, J. C.; Weimer, M. R. *Pest Manag. Sci.* **2002**, *58*, 1175–1186.
6. Funaki, J.; Imai, K.; Araki, K.; Danel, A.; Tomasik, P. *Pol. J. Chem.* **2004**, *78*, 843–850.
7. Baroni, E. E.; Kovyrzina, K. A. *Zh. Obshch. Khim.* **1961**, *31*, 1641–1645.
8. (a) Kashima, C.; Miwa, Y.; Shibata, S.; Nakozono, H. *J. Heterocycl. Chem.* **2003**, *40*, 681–687; (b) Kashima, C.; Higashide, K.; Miwa, Y.; Tsukamoto, Y. *J. Heterocycl. Chem.* **2002**, *39*, 917–925.
9. (a) Mukherjee, A.; Sarkar, A. *ARKIVOC* **2003**, *ix*, 87–95; (b) Sanz, D.; Jimenez, J. A.; Claramunt, R. M.; Elguero, J. *ARKIVOC* **2004**, *iv*, 100–108.
10. (a) Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 3, pp 1–75; (b) Kost, A. N.; Grandberg, I. I. *Adv. Heterocycl. Chem.* **1966**, *6*, 347–429.
11. (a) Ege, G.; Franz, H. *J. Heterocycl. Chem.* **1982**, *19*, 1267–1273; (b) Sing, S. K.; Reddy, M. S.; Shivaramakrishna, S.; Kavitha, D.; Vasudev, R.; Babu, J. M.; Sivalakshmidevi, A.; Rao, Y. K. *Tetrahedron Lett.* **2004**, *45*, 7679–7682; (c) Katritzky, A. R.; Galuszka, B.; Rachwal, S.; Black, M. *J. Heterocycl. Chem.* **1994**, *31*, 917–923; (d) Polshettiwar, V.; Varma, R. S. *Tetrahedron Lett.* **2008**, *49*, 397–400; (e) Heller, S. T.; Natarajan, S. R. *Org. Lett.* **2006**, *8*, 2675–2678; (f) Fustero, S.; Román, R.; Sanz-Cervera, J. F.; Simón-Fuentes, A.; Cuñat, A. C.; Villanova, S.; Murguía, M. *J. Org. Chem.* **2008**, *73*, 3523–3529; (g) Nishiwaki, N.; Matsushima, K.; Chatani, M.; Tamura, M.; Arida, M. *Synlett* **2004**, 703–707; (h) Vicente, V.; Fruchier, A.; Elguero, J. *ARKIVOC* **2004**, *iii*, 5–10; (i) Norris, T.; Colon-Cruz, R.; Ripin, D. H. B. *Org. Biomol. Chem.* **2005**, *3*, 1844–1849; (j) Bishop, B. C.; Brands, K. M. J.; Gibb, A. D.; Kennedy, D. J. *Synthesis* **2004**, 43–52; (k) Miller, R. D.; Reiser, O. *J. Heterocycl. Chem.* **1993**, *30*, 755–763.
12. (a) Conti, P.; Pinto, A.; Tamborini, L.; Rizzo, V.; Micheli, C. De. *Tetrahedron* **2007**, *63*, 5554–5560; (b) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; John Wiley & Sons: New York, NY, 1984; Vol I; (c) Aggarwal, V. K.; Vicente, J.; Bonnert, R. V. *J. Org. Chem.* **2003**, *68*, 5381–5383; (d) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565–632; (e) Jung, M. E.; Trifunovich, I. D. *Tetrahedron Lett.* **1992**, *33*, 2921–2924; (f) Nakano, Y.; Hamaguchi, M.; Nagai, T. *J. Org. Chem.* **1989**, *54*, 5912–5919; (g) Foti, F.; Grassi, G.; Risitano, F. *Tetrahedron Lett.* **1999**, *40*, 2605–2606; (h) Deng, X.; Mani, N. S. *J. Org. Chem.* **2008**, *73*, 2412–2415.
13. (a) Yoshimatsu, M.; Kawahigashi, M.; Honda, E.; Kataoka, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 695–700; (b) Kamitori, Y.; Hojo, M.; Masuda, M. R.; Fujishiro, M.; Wada, M. *Heterocycles* **1994**, *38*, 21–25; (c) Katritzky, A. R.; Musgrave, R. P.; Breytenbach, J. C. *J. Heterocycl. Chem.* **1996**, *33*, 1637–1646.
14. (a) Katritzky, A. R.; Drewniak, M.; Lue, P. *J. Org. Chem.* **1988**, *53*, 5854–5856; (b) Katritzky, A. R.; Pernak, J.; Fan, W. Q. *J. Org. Chem.* **1991**, *56*, 4439–4443; (c) Katritzky, A. R.; Shobana, N.; Harris, P. A. *Org. Prep. Proceed. Int.* **1992**, 121–126; (d) Katritzky, A. R.; Takahashi, I.; Fan, W. Q.; Pernak, J. *Synthesis* **1991**, 1147–1150; (e) Katritzky, A. R.; Fan, W. Q.; Black, M.; Pernak, J. *J. Org. Chem.* **1992**, *57*, 547–549; (f) Katritzky, A. R.; Pernak, J.; Fan, W. Q. *Synthesis* **1991**, 868–870; (g) Katritzky, A. R.; Urogdi, L.; Mayence, A. *J. Org. Chem.* **1990**, *55*, 2206–2214; (h) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Celik, I. *ARKIVOC* **2007**, *xi*, 96–113.
15. (a) Kobinata, K.; Uramoto, M.; Nishii, M.; Kusakabe, H.; Nakamura, G.; Isono, K. *Agric. Biol. Chem.* **1980**, *44*, 1709–1711; (b) Daehn, U.; Hagenmaier, H.; Hoehne, H.; Koenig, W. A.; Wolf, G.; Zaehner, H. *Arch. Microdiol* **1976**, *107*, 249.
16. (a) Barluenga, J.; Viado, A. L.; Aguilar, E.; Fustero, S.; Olano, B. *J. Org. Chem.* **1993**, *58*, 5972–5975; (b) Enders, D.; Moser, M.; Geibel, G.; Laufer, M. C. *Synthesis* **2004**, 2040–2046.
17. Mukhopadhyay, M.; Bhatia, B.; Iqbal, J. *Tetrahedron Lett.* **1997**, *38*, 1083–1086.
18. (a) Khan, A. B.; Parvin, P.; Choudhury, L. H. *Tetrahedron* **2007**, *63*, 5593–5601; (b) Ghosh, R.; Maiti, S.; Ghosh, S.; Mukherjeeb, A. K. *Synthesis* **2007**, 190–196; (c) Lou, S.; Dai, P.; Schaus, S. E. *J. Org. Chem.* **2007**, *72*, 9998–10008.