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Tetrahedron
Tetrahedron 60 (2004) 4051–4069

Synthesis and iNOS/nNOS inhibitory activities of new benzoylpyrazoline derivatives

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Received 19 December 2003; revised 12 February 2004; accepted 2 March 2004

Abstract—A series of new Δ^2-pyrazoline derivatives has been synthesized by means of a 1,3-dipolar-cycloaddition reaction. Ethyl 3-(5-methoxy-2-nitrobenzoyl)-Δ^2-pyrazoline-5-carboxylate (**5a**) has been designed for the formation of the benzoylpyrazoline system present in these derivatives. Two synthetic routes have been utilized changing the starting products in the cycloaddition reaction. In both routes, the majority product obtained was only a Δ^2-pyrazoline. The intermediate ethyl 1-acyl-3-(2-nitrobenzoyl-5-substituted)-Δ^2-pyrazoline-5-carboxylate derivatives have been transformed into the final compounds by means of several chemical treatments. The compounds have been biologically evaluated as inhibitors of nitric oxide synthase (NOS), showing better affinity towards the inducible NOS isoform than versus neuronal NOS.

1. Introduction

Nitric oxide (NO) is a biologically active compound. The synthesis of NO is catalyzed by a family of enzymes called NO synthases (NOS). Three NOS isoforms have been well identified and named according to the cell type or conditions in which they were first described: endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS).[1] Each one of the isoforms converts L-arginine to L-citrulline and nitric oxide utilizing NADPH and O_2 as cofactors, as well as the flavin-adenine dinucleotide (FAD), the flavin mononucleotide (FMN), tetrahydrobiopterin, heme and calcium-calmoduline.[2] Nitric oxide has important physiological functions including neurotransmission, blood pressure homeostasis, platelet aggregation, and immunological defense mechanisms.[3] The magnitude and duration of NO synthesis make its action physiological or pathological. Thus, although NO participates in the synaptic transmission in a normal way, the excessive levels which are produced by nNOS can become neurotoxic, and can be involved in different neurological disorders such as Alzheimer's disease,[4] the amyotrophic lateral sclerosis[5] or Hungtinton's disease.[6] On the other hand, the high production of NO by the inducible isoform of the nitric oxide synthase is related to disorders like the septic shock,[7] inflammatory arthritis,[8] and inflammatory bowel disease.[9] Up to now, the current research is orientated (a) to establish the adequate inhibition level of NOS so that its beneficial effects are kept, and (b) to identify more selective inhibitor compounds of each NOS isoenzyme, since the control of certain pathological states could be achieved. Although many inhibitors of NOS are known, very few of them show selectivity for only one isoform.[10–12] The studies carried out until this moment indicate that the goal of attaining selectivity for iNOS over nNOS is more difficult than achieving selectivity for iNOS over eNOS.[13]

Melatonin (*N*-acetyl-5-methoxytryptamine) **1** is a hormone that is synthesized and secreted into the general circulation by the pineal gland.[14] Inhibitory actions of melatonin in the rat[15,16] and human[17] central nervous system (CNS) have been reported. These inhibitory actions may be the cause of the anticonvulsant, hypnotic, antitumoral, antioxidant and neuroprotective properties.[18] Diverse experiments, have suggested that melatonin attenuates glutamate-mediated responses in the rat striatum.[19] The inhibitory effects of melatonin in the striatum may be mediated through inhibition of NOS, as has been reported in rat cerebellum and hypothalamus.[20–22] This inhibition is dose-dependent and calmodulin-dependent.[23]

Recently, the Δ^2-pyrazoline compounds have raised a great interest because of their multiple pharmacological applications such as antibacterials, antifungicals, anticonvulsants,[24] hypotensives,[25] antidepressants,[26] analgesics, antiinflammatories[27] and neuroprotectives.[28] In this paper,

Keywords: Addition reactions; Pyrazolines; Benzisoxazoles; Anti-inflammatory compounds.
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doi:10.1016/j.tet.2004.03.013

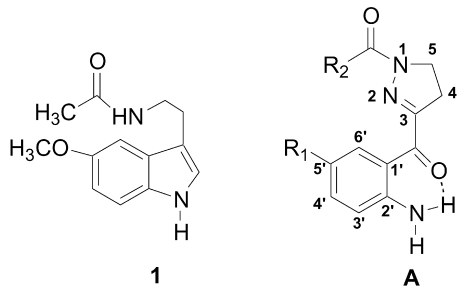
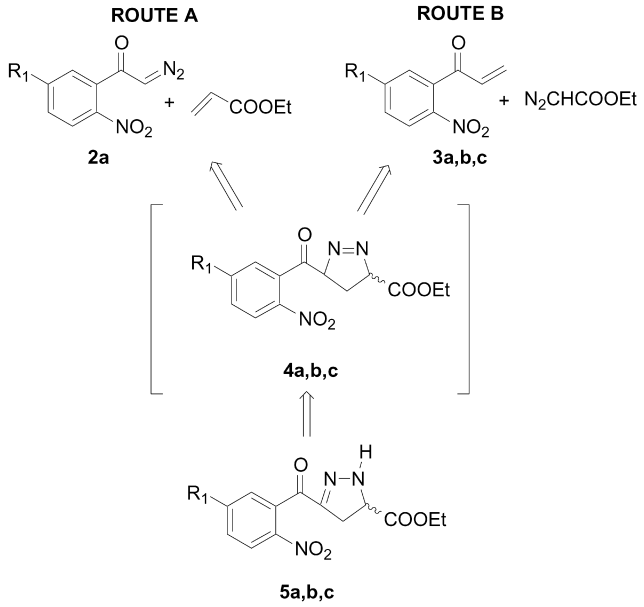


Figure 1.

taking as a prototype melatonin, we have carried out the synthesis of a new series of Δ^2-pyrazoline derivatives (represented by the general formula **A**) with the aim of searching for new selective inhibitors of NOS (Fig. 1).



Scheme 1.

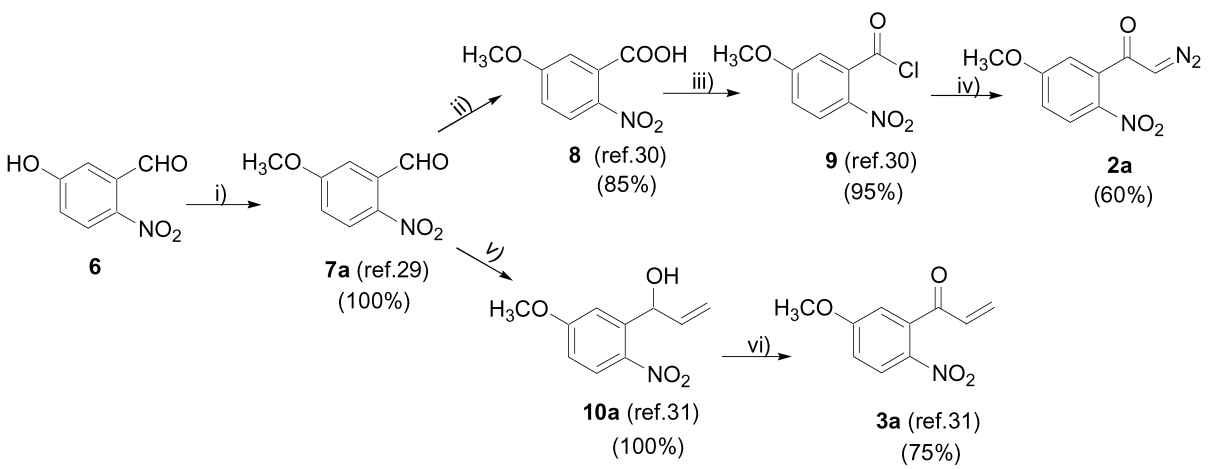
2. Results and discussion

2.1. Chemistry

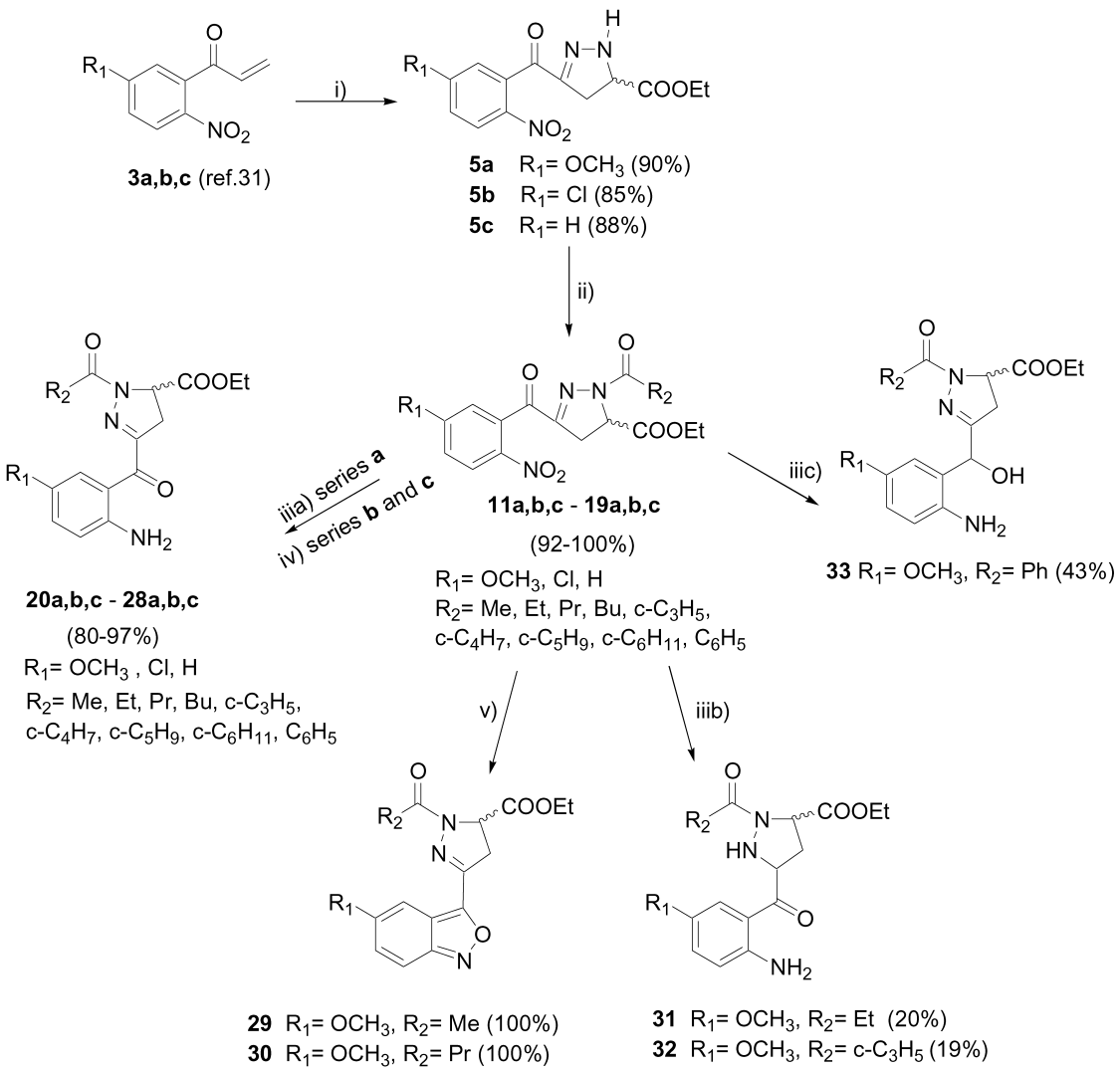
Scheme 1 shows the synthetic pathway used. The method employed for the formation of the ethyl 3-(2-nitro-5-substitutedbenzoyl)-Δ^2-pyrazoline-5-carboxylate derivatives is a 1,3-dipolar cycloaddition reaction. For the construction of the benzoylpyrazoline system by means of the procedure before mentioned, two options are possible, which seem to be of equal interest. The synthesis of pyrazoline **5a** has been taken as a model with the aim of analyzing which is the most suitable route to prepare these compounds. In the route A the 5-methoxy-2-nitrodiazoacetophenone **2a** acting as a 1,3-dipole, reacts with an active dipolarophile (ethyl acrylate) and in the route B, 5-methoxy-2-nitrophenyl vinyl ketone **3a**, acting as dipolarophile, reacts with ethyl diazoacetate. Both routes lead to the same intermediate ethyl 5-(5-methoxy-2-nitrobenzoyl)-Δ^1-pyrazoline-3-carboxylate **4a** which is not isolated, but it tautomerizes quickly to the racemate ethyl 3-(5-methoxy-2-nitrobenzoyl)-Δ^2-pyrazoline-5-carboxylate **5a**.

The two synthetic routes which lead to the intermediate **5a** are equally viable, and in both cases the yield of the 1,3-dipolar cycloaddition reaction was 80%. The choice of the route B as the method of synthesis for the construction of the benzoylpyrazolinic system was based on the easiness with which the starting compounds **2a** and **3a** were synthesized: for the preparation of the compound 5-methoxy-2-nitrodiazoacetophenone **2a**, 4 steps of synthesis with a global yield 48% were needed, whereas for the preparation of the compound 5-methoxy-2-nitrophenyl vinyl ketone **3a** only 3 steps of synthesis with a global yield 75% were necessary (Scheme 2).

Once the second strategy was chosen as the synthetic method, a modification of the conditions of reaction was carried out, using a base (pyridine) and a polar solvent (acetonitrile), so that the yield increased up to 90% in the case of Δ^2-pyrazoline **5a** and the time of reaction diminished (from 16 to 10 h). Accordingly, we took this



Scheme 2.



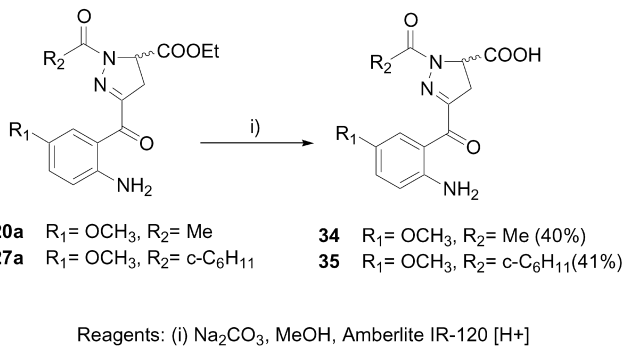
Reagents: (i) ethyl diazoacetate, Pyr, CH_3CN; (ii) Ac_2O o RCOCl, Et_3N, Cl_2CH_2; (iiia) H_2 Pd/C 10%, MeOH, 2,5 h (iv) Fe, $FeSO_4$, H_2O; (v) $SnCl_2$, EtOH; (iiib) H_2, Pd/C 10%, MeOH, 5 h.; (iiic) H_2, Pd/C 10%, MeOH, 7,5h.

Scheme 3.

procedure as the general method for the preparation of the benzoylpyrazolinic system in the different series a (R_1=OCH_3), b (R_1=Cl) and c (R_1=H). The use of pyridine could allow the change of 1-pyrazoline to 2-pyrazoline since its basic character facilitates the prototropy. Once the benzoylpyrazoline derivatives **5a**,**b**,**c** have been synthesized, they have been transformed into the corresponding acyl derivatives **11a**,**b**,**c**–**19a**,**b**,**c** by treating them with triethylamine and acetic anhydride or the corresponding acyl chloride. Twenty-seven intermediates are obtained, nine of each series, where the radical R_2 can be a lineal chain in the case of Me, Et, Pr and Bu, or a cyclic chain, in the case of *c*-C_3H_5, *c*-C_4H_7, *c*-C_5H_9, *c*-C_6H_{11} and Ph. The yields are similar in the three series and ranges between 92 and 100%. These acyl derivatives underwent diverse chemical treatments to perform the right modifications in the aromatic and pyrazolinic rings, with the aim of getting the different final compounds (Scheme 3).

The reduction of the nitro group belonging to the aromatic ring of the 27 acyl derivatives leads to compounds **20a**,**b**,**c**–**28a**,**b**,**c**. In series a, the reduction is accomplished by catalytic hydrogenation with Pd/C and the yield oscillates between 80 and 84%. In series b, the reduction was carried out with Fe and $FeSO_4$ in water, in order to avoid dechlorination, in this series the yield oscillates between 95 and 97%. In series c, the reduction was carried out whith $Fe/FeSO_4$ due to the better yield obtained with this method (95–96%).

The compounds **29** and **30** were obtained starting from the acyl derivatives **11a** and **13a** by treating them with $SnCl_2$ in ethanol with quantitative yield. The formation of these derivatives is justified by the attack of the hydroxyl group of the intermediate hydroxyamino reduction to the carbonyl group, the benzo[*c*]isoxazole ring being formed by posterior loss of a water molecule. Compounds **31**–**33** are formed by catalytic hydrogenation with Pd/C starting from the corresponding nitroarene (**12a**, **15a** and **19a**). Both, the quantity of catalyst and the time of reaction were higher



20a R_1= OCH_3, R_2= Me
27a R_1= OCH_3, R_2= c-C_6H_{11}

34 R_1= OCH_3, R_2= Me (40%)
35 R_1= OCH_3, R_2= c-C_6H_{11}(41%)

Reagents: (i) Na_2CO_3, MeOH, Amberlite IR-120 [H+]

Scheme 4.

than the ones used for the reduction of the aromatic nitro group, in this case the yield ranged between 19 and 43%. The derivatives **34** and **35** were obtained by hydrolysis starting from their esters **20a** and **27a** with Na_2CO_3, and posterior neutralization with Amberlite IR-120 $[H]^+$ resin, with 40–41% yield (Scheme 4).

2.2. Striatal nNOS and cerebral iNOS inhibitory activity

The effect of the final compounds on nNOS activity has been studied in striatum and rat brain (Table 1), with the object of evaluating its possible inhibition and selectivity versus the two isoforms of the nitric oxide synthase. The concentration of the compounds essayed has been 1 mM.

The nNOS activity was measured monitoring the conversion of L-[^{3}H]-arginine into L-[^{3}H]-citrulline, according to the method described by Bredt and coll.[32] For the measurement of the iNOS activity, the induction of the enzyme was achieved by means of the intravenous injection of lipopolysaccharide (LPS).

In general, the majority of compounds show better values of inhibition towards the iNOS isoform than towards the nNOS isoform. Next, a comparative analysis of the cerebral iNOS/striatal nNOS activities is carried out.

Among the benzoylpyrazoline derivatives **20a**,**b**,**c**–**28a**,**b**,**c**, compounds **28b** and **28c** with a phenyl group in R_2 showed higher affinity against iNOS than for nNOS. In **29** and **30** derivatives, there are not significant values of inhibition of both isoforms, and, accordingly, the elimination of the amino group in position 2 of the aromatic ring by formation of the benzo[*c*]isoxazole does not lead to positive results with regard to the NOS inhibition. This corroborates previous results obtained by our Group, which demonstrate the need of a hydrogen bond donor group in this position (an amino or amino monosubstituted group), for the formation of a hydrogen bond with the biologic target which is important for the NOS inhibitory activity.[12]

Compounds in which the rigidity has been diminished by reduction of the pyrazoline ring (compounds **31** and **32**) or

Table 1.

Compounds	Series	R_1	R_2	% nNOS inhibition	% iNOS inhibition
20	a	OCH_3	Me	21.74±4.20	7.07±1.67
	b	Cl		2.37±3.68	30.38±2.77
	c	H		—	—
21	a	OCH_3	Et	15.15±3.61	24.03±6.91
	b	Cl		3.90±5.29	25.39±1.61
	c	H		5.41±2.75	13.25±4.36
22	a	OCH_3	Pr	11.49±4.08	14.63±2.26
	b	Cl		3.71±3.53	20.34±3.78
	c	H		—	26.42±2.71
23	a	OCH_3	Bu	11.34±1.75	12.98±5.27
	b	Cl		4.57±3.21	8.86±7.39
	c	H		1.11±0.55	0.14±3.46
24	a	OCH_3	*c*-C_3H_5	4.94±2.38	8.25±5.25
	b	Cl		4.71±1.33	22.33±2.25
	c	H		5.49±0.34	14.50±6.48
25	a	OCH_3	*c*-C_4H_7	5.24±1.20	19.96±8.45
	b	Cl		—	4.43±9.62
	c	H		—	14.13±4.04
26	a	OCH_3	*c*-C_5H_9	11.59±0.57	3.53±5.92
	b	Cl		—	20.15±2.72
	c	H		—	23.28±3.14
27	a	OCH_3	*c*-C_6H_{11}	19.79±3.56	11.08±5.73
	b	Cl		—	4.94±1.37
	c	H		3.99±4.50	25.47±1.23
28	a	OCH_3	Ph	5.73±2.29	3.77±4.43
	b	Cl		—	35.62±3.23
	c	H		—	32.44±0.52
29	a	OCH_3	Me	—	—
30	a	OCH_3	Pr	—	—
31	a	OCH_3	Et	—	23.93±4.21
32	a	OCH_3	*c*-C_3H_5	—	22.05 ± 4.19
33	a	OCH_3	Ph	—	37.58±1.90
34	a	OCH_3	Me	—	22.66±6.07
35	a	OCH_3	*c*-C_6H_{11}	—	36.34±2.99

Values of inhibition striatal nNOS and cerebral iNOS. Each value is the mean of three experiments performed by triplicate in striatum (nNOS) and brain (iNOS) homogenates of rats.

by reduction of the carbonyl group (compound **33**), only present iNOS inhibition. Moreover, they present more significant inhibition values regarding the more similar rigid compounds **21a**, **24a** and **28a**. Again, the **33** derivative with a phenyl group in R_2 presents the highest value of iNOS inhibition.

The **34** and **35** acids obtained by hydrolysis of the ester function present affinity toward the iNOS isoform. The reduction of the size of the substituent leads to better inhibition values regarding their analogues **20a** and **27a**.

The comparative analysis between iNOS/nNOS activities shows that the compounds present better selectivity by the iNOS isoform versus nNOS. The inhibitory potency iNOS is improved with structures which present a decrease of the conformational rigidity or an acid group in position 5.

The results obtained with these compounds prompted us the attainment of selective inhibitors of an only NOS isoform, what could mean the control of certain pathologies. Besides, they would help us to know the structure and action mechanism of each isoform.

3. Conclusions

The synthesis and biologic evaluation of a new class of Δ^2-pyrazoline derivatives have been carried out. The benzoylpyrazoline moiety has been made by means of the 1,3-dipolar cycloaddition reaction using different starting compounds which lead to an only type of Δ^2-pyrazoline (**5a**). The compounds presented in this report show more affinity towards iNOS isoform, the values of inhibition produced by **28b**, **33** and **35** derivatives are remarkable. For the inhibition of the NOS activity, the presence of a free amino group in position 2 of the aromatic ring is important, since **29** and **30** compounds with a benzoisozaxole ring do not inhibit the nNOS and iNOS isoforms. This corroborates previous results obtained by our research group, where a hydrogen bond donor group in this position is needed.

4. Experimental

4.1. Chemistry

Reactions were performed under an inert atmosphere of argon. Solvents were dried according to standard methods. Melting points (mp) were taken in open capillaries on a Electrothermal melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a 400.1 MHz ^{1}H and 100.3 MHz ^{13}C NMR Bruker ARX-400 or 300.13 MHz ^{1}H and 75.58 MHz ^{13}C NMR Bruker AMX-300 spectrometers, and chemical shifts (ppm) are reported relative to the solvent peak ($CHCl_3$ in $CDCl_3$ at δ 7.24 and 77.1 ppm; CH_3OH in CD_3OD at 3.34 and 49.9 ppm). Signal are designated as follows: s, singlet; bs, broad singlet; d, doublet; dd, doublet of doublet; ddd, double doublet of doublet; t, triplet; pt, pseudotriplet; dt, double of triplet; tt, triplet of triplet; q, quadruplet; pc, pseudo-quadruplet; pq, pseudoquintuplet; m, multiplet. Coupling constants (J) are expressed in hertz. High-resolution mass spectroscopy (HRMS) was carried out on a VG AutoSpec Q high-resolution mass spectrometer (Fison Instrument). Elemental analyses were performed on a Perkin–Elmer 240 C and agreed with theoretical values within $\pm$0.4%. Flash-chromatography was carried out using silica gel 60, 230–240 mesh (Merck), and the solvent mixture reported within parentheses was used as eluent. Evaporations were carried out in vacuo with a rotary evaporator.

4.1.1. Starting materials

4.1.1.1. Synthesis of 5-methoxy-2-nitrodiazoacetophenone 2a. A 0.54 M solution of CH_2N_2 was added dropwise with stirring under argon at -10 °C to a solution of 5-methoxy-2-nitrobenzoyl chloride[30] (2 g, 9.27 mmol) in dry diethyl ether (10 mL). The reaction mixture was stirred for 3 h. Evaporation of the solvent rendered a residue that was purified by flash chromatography (ethyl acetate/hexane 1:2) to give **2**: 1.2 g (65% yield); thick oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, 1H, H-3′, $J_{3'-4'}$=9.0 Hz); 6.98 (dd, 1H, H-4′, $J_{4'-3'}$=9.0 Hz, $J_{4'-6'}$=2.8 Hz); 6.89 (d, 1H, H-6′, $J_{6'-4'}$=2.8 Hz); 5.4 (s, 1H, $-CH-N_2$); 3.9 (s, 3H, $-OCH_3$).^{13}C NMR (100 MHz, $CDCl_3$) δ 184.43 (C-1); 165.14 (C-5′); 140.45 (C-2′); 127.36 (C-3′, C-1′); 115.30 (C-4′); 113.44 (C-6′); 56.32 (C-2, $-OCH_3$). HR LSIMS calcd for $C_9H_7N_3O_4Na$ $(M+Na)^+$ 244.0334, found: 244.0333.

4.1.1.2. Synthesis of 2-nitrophenyl-5-substituted vinyl ketone 3a,b,c. 5-Methoxy-2-nitrobenzaldehyde **7a** (synthesized from 5-hydroxy-2-nitrobenzaldehide **6** with MeI and K_2CO_3 in THF),[29] commercial 5-chloro-2-nitrobenzaldehyde **7b** and commercial 2-nitrobenzaldehyde **7c**, were transformed into the corresponding allylic alcohols **10a**,**b**,**c** by quantitative addition of vinylmagnesium bromide.[31] Oxidation with CrO_3 leads to the 2-nitrophenyl-5-substituted vinylketone **3a**,**b**,**c**.[31]

4.1.1.3. General procedures for the preparation of compounds 5a,b,c. *Procedure 1*. Ethyl acrylate (0.04 mL, 0.39 mmol) was slowly added to stirred 5-methoxy-2-nitrodiazoacetophenone **2** (0.085 g, 0.39 mmol) at 65 °C. The reaction mixture was stirred for 16 h, CH_2Cl_2 was added, and washed with H_2O (2×20 mL). The organic phase was dried (Na_2SO_4), filtered, and evaporated. The residue was recrystallized from CH_2Cl_2/hexane.

Procedure 2. Ethyl diazoacetate (0.16 mL, 1.38 mmol) was slowly added to stirred 5-methoxy-2-nitrophenyl vinyl ketone **3a** (0.285 g, 1.38 mmol) at 65 °C. The reaction mixture was stirred for 16 h, CH_2Cl_2 was added, and washed with H_2O (2×20 mL). The organic phase was dried (Na_2SO_4), filtered and evaporated. The residue was recrystallized from CH_2Cl_2/hexane.

Procedure 3. Pyridine (0.013 mL, 0.172 mmol) was added to a solution of the corresponding 5-methoxy-2-nitrophenyl vinyl ketone **3a**,**b**,**c** (1.38 mmol) in 4 mL of dry acetonitrile. Ethyl diazoacetate was slowly added (0.16 mL, 1.38 mmol) to the stirred solution. The reaction mixture was stirred for 10 h and washed with 5% HCl (2×10 mL). The organic phase was dried (Na_2SO_4), filtered and evaporated to dryness. The residue was recrystallized from CH_2Cl_2/hexane.

*4.1.1.3.1. Ethyl 3-(5-methoxy-2-nitrobenzoyl)-Δ²-pyrazoline-5-carboxylate **5a***. Compound **5a** was obtained as a yellow solid (98.7 mg, 80% yield), as described in procedure 1. Compound **5a** was obtained as a yellow solid (98.7 mg, 80% yield), as described in the procedure 2. Compound **5a** was obtained as a yellow solid (111 mg, 90% yield) starting from **3a**,[31] as described in procedure 3; mp 144–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, 1H, H-3′, $J_{3'-4'}$=9.1 Hz); 7.00 (dd, 1H, H-4′, $J_{4'-3'}$=9.1 Hz, $J_{4'-6'}$=2.9 Hz); 6.87 (d, 1H, H-6′, $J_{6'-4'}$=2.9 Hz); 6.74 (bs, 1H, –NH); 4.49 (dd, 1H, H-5, $J_{5,4b}$=12.7 Hz, $J_{5,4a}$=5.6 Hz); 4.22 (c, 2H, –COOCH_2–CH_3, J=7.1 Hz); 3.89 (s, 3H, –OCH_3); 3.45 (H-4 a, J_{4a-4b}=17.5 Hz, J_{4a-5}=5.6 Hz); 3.29 (1H, H-4b, J_{4b-4a}=17.5 Hz, $J_{4b,5}$=12.7 Hz); 1.29 (t, 3H, –COO–CH_2–CH_3 J=7.1 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ187.41 (Ph–*C*O–); 171.27 (–*C*OO–CH_2–CH_3); 163.95 (C-5′); 150.07 (C-3); 140.29 (C-2′); 137.85 (C-1′); 126.59 (C-3′); 115.52 (C-4′); 113.58 (C-6′); 62.30 (–COO–*C*H_2–CH_3); 61.85 (C-5); 56.25 (–OCH_3); 33.44 (C-4); 14.17 (–COO–CH_2–*C*H_3). HR LSIMS calcd for $C_{14}H_{15}N_3O_6Na$ (M+Na)$^+$ 344.0858, found 344.0867.

*4.1.1.3.2. Ethyl 3-(5-chloro-2-nitrobenzoyl)-Δ²-pyrazoline-5-carboxylate **5b***. Compound **5b** was obtained as a yellow solid (382 mg, 85% yield) starting from **3b**,[31] as described in procedure 3; mp 143–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, 1H, H-3′, $J_{3'-4'}$=8.7 Hz); 7.55 (dd, 1H, H-4′, $J_{4'-3'}$=8.7 Hz, $J_{4'-6'}$=2.3 Hz); 7.44 (d, 1H, H-6′, $J_{6'-4'}$=2.3 Hz); 6.82 (bs, 1H, –NH); 4.52 (dd, 1H, H-5, J_{5-4b}=12.8 Hz, J_{5-4a}=5.7 Hz); 4.23 (c, 2H, –COO–CH_2–CH_3, J=7.1 Hz) 3.43 (dd, 1H, H-4a, J_{4a-4b}=17.6 Hz, J_{4a-5}=5.7 Hz); 3.28 (dd, 1H, H-4b, J_{4b-4a}=17.6 Hz, J_{4b-5}=12.8 Hz); 1.30 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.72 (Ph–*C*O–), 171.04 (–*C*OO–CH_2–CH_3); 149.49 (C-3); 145.81 (C-2′); 140.73 (C-5′); 136.68 (C-1′); 130.65 (C-4′); 129.27 (C-6′); 125.53 (C-3′); 62.39 (–COO–*C*H_2–CH_3); 61.97 (C-5); 35.17 (C-4); 14.17 (–COO–CH_2–*C*H_3). HR LSIMS calcd for $C_{13}H_{12}ClN_3O_5Na$ (M+Na)$^+$ 348.0363, found 348.0361.

*4.1.1.3.3. Ethyl 3-(2-nitrobenzoyl)-Δ²-pyrazoline-5-carboxylate **5c***. Compound **5c** was obtained as a yellow solid (353 mg, 88% yield) starting from **3c**,[31] as described in procedure 3; mp 107–109 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, 1H, H-3′, $J_{3'-4'}$=8.1 Hz); 7.71 (dt, 1H, H-5′, $J_{5'-4'}$=$J_{5'-6'}$=7.5 Hz, $J_{5'-3'}$=1.1 Hz); 7.60 (dt, 1H, H-4′, $J_{4'-3'}$=8.1 Hz, $J_{4'-5'}$=7.5 Hz, $J_{4'-6'}$=1.5 Hz); 7.49 (dd, 1H, H-6′, $J_{6'-5'}$=7.5 Hz, $J_{6'-4'}$=1.5 Hz); 6.75 (bs, 1H, –NH); 4.50 (dd, 1H, H-5, J_{5-4b}=12.6 Hz, J_{5-4a}=5.6 Hz); 4.22 (c, 2H, –COO–CH_2–CH_3, J=7.1 Hz); 3.45 (dd, 1H, H-4a, J_{4a-4b}=17.6 Hz, J_{4a-5}=5.6 Hz); 3.29 (dd, 1H, H-4b, J_{4b-4a}=17.6 Hz, J_{4b-5}=12.6 Hz); 1.29 (t, 3H, –COO–CH_2–CH_3 J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.38 (Ph–*C*O–); 171.20 (–*C*OO–CH_2–CH_3); 150.00 (C-3); 147.67 (C-2′); 135.15 (C-1′); 133.90 (C-5′); 130.78 (C-4′); 129.17 (C-6′); 124.03 (C-3′); 62.30 (–COO–*C*H_2–CH_3); 61.87 (C-5); 33.37 (C-4); 14.15 (–COO–CH_2–*C*H_3). HR LSIMS calcd for $C_{13}H_{13}N_3O_5Na$ (M+Na)$^+$ 314.0752, found 314.0753.

4.1.1.4. General procedure for the preparation of compounds 11a,b,c–19a,b,c. Triethylamine (a small excess molar) and acetic anhydride or the corresponding acyl chloride (a molar equivalent) was added to a solution of the corresponding pyrazoline **5a**, **5b** or **5c** (0.85 mmol) in dry CH_2Cl_2 (10 mL) at room temperature. The reaction mixture was stirred for 3 h, filtered and washed with H_2O, 10% HCl, 2 M NaOH, H_2O and brine. The organic phase was dried (Na_2SO_4), and filtered. Evaporation of the solvent rendered a residue that was purified by flash chromatography (ethyl acetate–hexane 1:4).

*4.1.1.4.1. Ethyl 1-acetyl-3-(5-methoxy-2-nitrobenzoyl)-Δ²-pyrazoline-5-carboxylate **11a***. White solid; yield 100%; mp 102–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, 1H, H-3′, $J_{3'-4'}$=9.1 Hz); 7.06 (dd, 1H, H-4′, $J_{4'-3'}$=9.1 Hz, $J_{4'-6'}$=2.7 Hz); 6.92 (d, 1H, H-6′, $J_{6'-4'}$=2.7 Hz); 4.94 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.2 Hz); 4.21 (c, 2H, –COO–CH_2–CH_3, J=7.1 Hz); 3.93 (s, 3H, –OCH_3); 3.52 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.9 Hz); 3.28 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.2 Hz); 2.11 (s, 3H, –CO–CH_3); 1.27 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.06 (Ph–*C*O–); 169.84, 168.97 (–*C*OOCH_2CH_3, –N–*C*O–); 164.05 (C-5′); 152.51 (C-3); 140.75 (C-2′); 136.33 (C-1′); 126.57 (C-3′); 116.06 (C-4′); 114. 09 (C-6′); 62.33 (–COO*C*H_2CH_3); 59.89 (C-5); 56.36 (–OCH_3); 35.65 (C-4); 21.07 (–CO–*C*H_3); 14.04 (–COOCH_2*C*H_3). HR LSIMS calcd for $C_{16}H_{18}N_3O_7$ (M^++1) 364.1144, found 364.1144.

*4.1.1.4.2. Ethyl 3-(5-methoxy-2-nitrobenzoyl)-1-propionyl-Δ²-pyrazoline-5-carboxylate **12a***. White solid; yield 98%; mp 116–118 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, 1H, H-3′, $J_{3'-4'}$=9.1 Hz); 7.07 (dd, 1H, H-4′, $J_{4'-3'}$=9.1 Hz, $J_{4'-6'}$=2.8 Hz); 6.93 (d, 1H, H-6′, $J_{6'-4'}$=2.8 Hz); 4.94 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.2 Hz); 4.21 (c, 2H, –COO–CH_2–CH_3, J=7.1 Hz); 3.93 (s, 3H, –OCH_3); 3.51 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.9 Hz); 3.27 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.2 Hz); 2.42 (m, 2H, –CO–CH_2–CH_3); 1.28 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz); 1.04 (t, 3H, –CO–CH_2–CH_3 J=7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.12 (Ph–*C*O–); 173.31 (–N–CO–); 169.10 (–*C*OO–CH_2–CH_3); 164.07 (C-5′); 152.34 (C-3); 140.77 (C-2′); 136.47 (C-1′); 126.59 (C-3′); 116.08 (C-4′); 114. 06 (C-6′); 62.18 (–COO–*C*H_2–CH_3); 59.04 (C-5); 56.36 (–OCH_3); 35.39 (C-4); 26.85 (–CO–*C*H_2–CH_3); 14.06 (–COO–CH_2–*C*H_3); 8.37 (–CO–CH_2–*C*H_3). HR LSIMS calcd for $C_{17}H_{19}N_3O_7Na$ (M+Na)$^+$ 400.1120, found 400.1120.

*4.1.1.4.3. Ethyl 1-butyryl-3-(5-methoxy-2-nitrobenzoyl)-Δ²-pyrazoline-5-carboxylate **13a***. White solid; yield 98%; mp 106–108 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, 1H, H-3′, $J_{3'-4'}$=9.1 Hz); 7.07 (dd, 1H, H-4′, $J_{4'-3'}$=9.1 Hz, $J_{4'-6'}$=2.8 Hz); 6.93 (d, 1H, H-6′, $J_{6'-4'}$=2.8 Hz); 4.95 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.2 Hz); 4.21 (C, 2H, –COOCH_2CH_3, J=7.1 Hz); 3.94 (s, 3H, –OCH_3); 3.51 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.9 Hz); 3.27 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.2 Hz); 2.39 (m, 2H, –CO–CH_2–CH_2–CH_3); 1.55 (m, 2H, –CO–CH_2–CH_2–CH_3); 1.28 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz); 0.84 (t, 3H, –CO–CH_2–CH_2–CH_3, J=7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.16 (Ph–*C*O–); 172.61 (–N–CO–); 169.09 (–*C*OO–CH_2–CH_3); 164.08 (C-5′); 152.34 (C-3); 140.77 (C-2′); 136.50 (C-1′); 126.58 (C-3′); 116.11 (C-4′); 114. 06

(C-6′); 62.21 (–COO–CH_2–CH_3); 59.01 (C-5); 56.36 (–OCH_3); 35.42, 35.26 (–CO–CH_2–CH_2–CH_3, C-4); 18.03 (–CO–CH_2–CH_2–CH_3); 14.07 (–COO–CH_2–CH_3); 13.68 (–CO–CH_2–CH_2–CH_3). HR LSIMS calcd for $C_{18}H_{21}N_3O_7Na$ $(M+Na)^+$ 414.1277, found 414.1272.

4.1.1.4.4. Ethyl 3-(5-methoxy-2-nitrobenzoyl)-1-pentanoyl-Δ²-pyrazoline-5-carboxylate ***14a***. White solid; yield 96%; mp 73–75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, 1H, H-3′, $J_{3'-4'}$=9.1 Hz); 7.07 (dd, 1H, H-4′, $J_{4'-3'}$=9.1 Hz, $J_{4'-6'}$=2.8 Hz); 6.93 (d, 1H, H-6′, $J_{6'-4'}$=2.8 Hz); 4.94 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.2 Hz); 4.21 (C, 2H, –COOCH_2CH$_3$, J=7.1 Hz); 3.93 (s, 3H, –OCH_3); 3.51 (dd, 1H, H-4a, J_{4a-4b}=18.6 Hz, J_{4a-5}=12.9 Hz); 3.26 (dd, 1H, H-4b, J_{4b-4a}=18.6 Hz, J_{4b-5}=6.2 Hz); 2.40 (m, 2H, –CO–CH_2–CH_2–CH_2–CH_3); 1.48 (m, 2H, –CO–CH_2–CH_2–CH_2–CH_3); 1.27 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz); 1.23 (m, 2H, –CO–CH_2–CH_2–CH_2–CH_3); 0.80 (t, 3H, –CO–CH_2–CH_2–CH_2–CH_3, J=7.3 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ 187.13 (Ph–*C*O–); 172.79 (–N–CO–); 169.05 (–*C*OO–CH_2–CH_3); 164.08 (C-5′); 152.33 (C-3); 140.77 (C-2′); 136.54 (C-1′); 126.55 (C-3′); 116.06 (C-4′); 114. 03 (C-6′); 62.19 (–COO–CH_2–CH_3); 59.03 (C-5); 56.37 (–OCH_3); 35.42 (C-4); 33.19 (–CO–CH_2–CH_2–CH_2–CH_3); 26.66 (–CO–CH_2–CH_2–CH_2–CH_3); 22.40 (–CO–CH_2–CH_2–CH_2–CH_3); 14.06 (–COO–CH_2–CH_3); 13.64 (–CO–CH_2–CH_2–CH_2–CH_3). HR LSIMS calcd for $C_{19}H_{23}N_3O_7Na$ $(M+Na)^+$ 428.1433, found 428.1434.

4.1.1.4.5. Ethyl 1-cyclopropanecarbonyl-3-(5-methoxy-2-nitrobenzoyl)-Δ²-pyrazoline-5-carboxylate ***15a***. White solid; yield 99%; mp 137–139 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, 1H, H-3′, $J_{3'-4'}$=9.1 Hz); 7.06 (dd, 1H, H-4′, $J_{4'-3'}$=9.1 Hz, $J_{4'-6'}$=2.8 Hz); 6.94 (d, 1H, H-6′, $J_{6'-4'}$=2.8 Hz); 4.94 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.4 Hz); 4.21 (c, 2H, –COO–CH_2–CH$_3$, J=7.1 Hz); 3.93 (s, 3H, –OCH_3); 3.53 (dd, 1H, H-4a, J_{4a-4b}=18.6 Hz, J_{4a-5}=12.9 Hz); 3.29 (dd, 1H, H-4b, J_{4b-4a}=18.6 Hz, J_{4b-5}=6.4 Hz); 2.12 (m, 1H, H-1$_{cycloprop.}$); 1.26 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz); 1.06–0.98, 0.85–0.78 (2m, 4H, H-2, H-3$_{cycloprop.}$).^{13}C NMR (75 MHz, $CDCl_3$) δ 187.29 (Ph–*C*O–); 173.12 (–N–CO–); 169.11 (–*C*OO–CH_2–CH_3); 164.09 (C-5′); 152.57 (C-3); 140.61 (C-2′); 136.63 (C-1′); 126.65 (C-3′); 116.09 (C-4′); 114. 01 (C-6′); 62.14 (–COO–CH_2–CH_3); 59.34 (C-5); 56.38 (–OCH_3); 35.37 (C-4); 14.08 (–COO–CH_2–CH_3); 11.45 (C-1$_{cycloprop.}$); 9.44, 9.39 (C-2, C-3$_{cycloprop.}$). HR LSIMS calcd $C_{18}H_{19}N_3O_7Na$ $(M+Na)^+$ 412.1120, found: 412.1122.

4.1.1.4.6. Ethyl 1-cyclobutanecarbonyl-3-(5-methoxy-2-nitrobenzoyl)-Δ²-pyrazoline-5-carboxylate ***16a***. White solid; yield 99%; mp 137–139 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, 1H, H-3′, $J_{3'-4'}$=9.1 Hz); 7.08 (dd, 1H, H-4′, $J_{4'-3'}$=9.1 Hz, $J_{4'-6'}$=2.8 Hz); 6.91 (d, 1H, H-6′, $J_{6'-4'}$=2.8 Hz); 4.93 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.1 Hz); 4.22 (c, 2H, –COO–CH_2–CH$_3$, J=7.1 Hz); 3.94 (s, 3H, –OCH_3); 3.48 (dd, 1H, H-4a, J_{4a-4b}=18.6 Hz, J_{4a-5}=12.9 Hz); 3.39 (m, 1-H, H-1$_{cyclobut.}$); 3.24 (dd, 1H, H-4b, J_{4b-4a}=18.6 Hz, J_{4b-5}=6.1 Hz); 2.25–2.15, 1.98–1.72 (2m, 6H, H-2, H-3, H-4$_{cyclobut.}$); 1.28 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.18 (Ph–*C*O–); 174.11 (–N–CO–); 169.09 (–*C*OO–CH_2–CH_3); 164.09 (C-5′); 152.36 (C-3); 140.67 (C-2′); 136.67 (C-1′); 126.56 (C-3′); 116.11 (C-4′); 113.94 (C-6′); 62.19 (–COO–CH_2–CH_3); 59.11 (C-5); 56.38 (–OCH_3); 37.36 (C-1$_{cyclobut.}$); 35.19 (C-4); 24.58, 24.30 (C-2, C-4$_{cyclobut.}$); 18.15 (C-3$_{cyclobut.}$); 14.08 (–COO–CH_2–CH_3). HR LSIMS calcd for $C_{19}H_{21}N_3O_7Na$ $(M+Na)^+$ 426.1277, found: 426.1281.

4.1.1.4.7. Ethyl 1-cyclopentanecarbonyl-3-(5-methoxy-2-nitrobenzoyl)-Δ²-pyrazoline-5-carboxylate ***17a***. White solid; yield 98%; mp 129–131 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, 1H, H-3′, $J_{3'-4'}$=9.1 Hz); 7.07 (dd, 1H, H-4′, $J_{4'-3'}$=9.1 Hz, $J_{4'-6'}$=2.8 Hz); 6.93 (d, 1H, H-6′, $J_{6'-4'}$=2.8 Hz); 4.94 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.2 Hz); 4.21 (m, 2H, –COOCH_2CH$_3$); 3.93 (s, 3H, –OCH_3); 3.50 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.9 Hz); 3.26 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.2 Hz); 3.06 (m, 1H, H-1$_{cyclopent.}$); 1.65–1.40 (m, 8H, H-2, H-3, H-4, H-5$_{cyclopent.}$); (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ 187.26 (Ph–*C*O–); 175.69 (–N–CO–); 169.14 (–*C*OO–CH_2–CH_3); 164.09 (C-5′); 152.18 (C-3); 140.71 (C-2′); 136.67 (C-1′); 126.58 (C-3′); 116.12 (C-4′); 113.96 (C-6′); 62.14 (–COO–CH_2–CH_3); 59.18 (C-5); 56.37 (–OCH_3); 41.89 (C-1$_{cyclopent.}$); 35.24 (C-4); 29.59, 29.20 (C-2, C-5$_{cyclopent.}$); 26.24, 26.12 (C-3, C-4$_{cyclopent.}$); 14.06 (–COO–CH_2–CH_3). HR LSIMS calcd for $C_{20}H_{23}N_3O_7Na$ $(M+Na)^+$ 440.1433, found: 440.1437.

4.1.1.4.8. Ethyl 1-cyclohexanecarbonyl-3-(5-methoxy-2-nitrobenzoyl)-Δ²-pyrazoline-5-carboxylate ***18a***. White solid; yield 98%; mp 116–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, 1H, H-3′, $J_{3'-4'}$=9.1 Hz); 7.07 (dd, 1H, H-4′, $J_{4'-3'}$=9.1 Hz, $J_{4'-6'}$=2.8 Hz); 6.93 (d, 1H, H-6′, $J_{6'-4'}$=2.8 Hz); 4.92 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.0 Hz); 4.19 (m, 2H, –COOCH_2CH$_3$); 3.93 (s, 3H, –OCH_3); 3.49 (dd, 1H, H-4a, J_{4a-4b}=18.6 Hz, J_{4a-5}=12.9 Hz); 3.24 (dd, 1H, H-4b, J_{4b-4a}=18.6 Hz, J_{4b-5}=6.0 Hz); 2.65 (tt, 1H, H-1$_{cyclohex.}$, $J_{transdiaxial}$=11.5 Hz, J_{cis}=3.2 Hz); 1.75–1.56 (m, 5H, H$_{ec.\ cyclohex.}$); 1.26 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz); 1.40–1.05 (m, 5H, H$_{ax.\ cyclohex.}$).^{13}C NMR (75 MHz, $CDCl_3$) δ 187.11 (Ph–*C*O–); 175.41 (–N–CO–); 169.05 (–*C*OO–CH_2–CH_3); 164.08 (C-5′); 152.06 (C-3); 140.88 (C-2′); 136.58 (C-1′); 126.43 (C-3′); 116.09 (C-4′); 114.06 (C-6′); 62.13 (–COO–CH_2–CH_3); 59.10 (C-5); 56.36 (–OCH_3); 41.55 (C-1$_{cyclohex.}$); 35.18 (C-4); 28.49, 28.45 (C-2, C-6$_{cyclohex.}$); 25.80, 25.54, 25.50 (C-3, C-4, C-5$_{cyclohex.}$); 14.06 (–COO–CH_2–CH_3). HR LSIMS calcd for $C_{21}H_{25}N_3O_7Na$ $(M+Na)^+$ 454.1590, found 454.1583.

4.1.1.4.9. Ethyl 1-benzoyl-3-(5-methoxy-2-nitrobenzoyl)-Δ²-pyrazoline-5-carboxylate ***19a***. White solid; yield 94%; mp 134–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, 1H, H-3′, $J_{3'-4'}$=9.1 Hz); 7.60 (dd, 2H, H-2, H-6$_{benz.}$, $J_{2\text{-}3benz.}$=7.1 Hz, $J_{2\text{-}4benz.}$=1.3 Hz); 7.40 (tt, 1H, H-4$_{benz.}$, $J_{4\text{-}3benz.}$=7.4 Hz, $J_{4\text{-}2benz.}$=1.3 Hz); 7.26 (pt, 2H, H-3, H-5$_{benz.}$, $J_{3\text{-}4benz.}$=7.4 Hz, $J_{3\text{-}2benz.}$=7.1 Hz); 7.01 (dd, 1H, H-4′, $J_{4'-3'}$=9.1 Hz, $J_{4'-6'}$=2.8 Hz); 6.87 (d, 1H, H-6′, $J_{6'-4'}$=2.8 Hz); 5.17 (dd, 1H, H-5, J_{5-4a}=12.7 Hz, J_{5-4b}=6.1 Hz); 4.26 (c, 2H, –COOCH_2CH$_3$, J=7.1 Hz); 3.89 (s, 3H, –OCH_3); 3.57 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.7 Hz); 3.31 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz,

J_{4b-5}=6.1 Hz); 1.30 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ 187.18 (Ph–*C*O–); 168.96, 167.32 (–*C*OO–CH_2–CH_3, –N–CO–); 164.20 (C-5′); 153.30 (C-3); 140.49 (C-2′); 136.64 (C-1′); 132.04 (C-$1_{benz.}$); 131.89 (C-$4_{benz.}$); 129.97 (C-2, C-$6_{benz.}$); 127.72 (C-3, C-$5_{benz.}$); 126.52 (C-3′); 116.12 (C-4′); 113.95 (C-6′); 62.92 (–COO–*C*H_2–CH_3); 60.36 (C-5); 56.34 (–OCH_3); 34.90 (C-4); 14.13 (–COO–CH_2–*C*H_3). HR LSIMS calcd for $C_{21}H_{19}N_3O_7Na$ $(M+Na)^+$ 448.1120, found: 448.1118.

4.1.1.4.10. Ethyl 1-acetyl-3-(5-chloro-2-nitrobenzoyl)-Δ^2-pyrazoline-5-carboxylate ***11b***. White solid; yield 94%; mp 134–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, 1H, H-3′, $J_{3'-4'}$=8.7 Hz); 7.63 (dd, 1H, H-4′, $J_{4'-3'}$=8.7 Hz, $J_{4'-6'}$=2.3 Hz); 7.51 (d, 1H, H-6′, $J_{6'-4'}$=2.3 Hz); 4.96 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.1 Hz); 4.22 (c, 2H, –COO–CH_2–CH_3, J=7.1 Hz); 3.51 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.9 Hz); 3.26 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.1 Hz); 2.12 (s, 3H, –CO–CH_3); 1.28 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.52 (Ph–*C*O–); 169.82, 168.79 (–*C*OO–CH_2–CH_3, –N–CO–); 152.10 (C-3); 146.33 (C-2′); 141.04 (C-5′); 135.11 (C-1′); 131.52 (C-4′); 129.61 (C-6′); 125.45 (C-3′); 62.33 (–COO–*C*H_2–CH_3); 59.11 (C-5); 35.48 (C-4); 21.08 (–CO–*C*H_3); 14.06 (–COO–CH_2–*C*H_3). HR LSIMS calcd for $C_{15}H_{14}ClN_3O_6Na$ $(M+Na)^+$ 390.0468, found 390.0462.

4.1.1.4.11. Ethyl 3-(5-chloro-2-nitrobenzoyl)-1-propionyl-Δ^2-pyrazoline-5-carboxylate ***12b***. White solid; yield 98%; mp 87–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, 1H, H-3′, $J_{3'-4'}$=8.7 Hz); 7.63 (dd, 1H, H-4′, $J_{4'-3'}$= 8.7 Hz, $J_{4'-6'}$=2.3 Hz); 7.51 (d, 1H, H-6′, $J_{6'-4'}$=2.3 Hz); 4.95 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.2 Hz); 4.21 (c, 2H, –COO–CH_2–CH_3, J=7.1 Hz); 3.49 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.9 Hz); 3.25 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.2 Hz); 2.44 (m, 2H, –CO–CH_2–CH_3); 1.27 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz), 1.05 (t, 3H, –CO–CH_2–*C*H_3, J=7.5 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ 185.58 (Ph–*C*O–); 173.28 (–N–CO–); 168.91 (–*C*OO–CH_2–CH_3); 151.92 (C-3); 146.27 (C-2′); 141.03 (C-5′); 135.21 (C-1′); 131.51 (C-4′); 129.58 (C-6′); 125.45 (C-3′); 62.28 (–COO–CH_2–CH_3); 59.20 (C-5); 35.19 (C-4); 26.83 (–CO–*C*H_2–CH_3); 14.06 (–COO–CH_2–*C*H_3); 8.34 (–CO–CH_2–*C*H_3). HR LSIMS calcd for $C_{16}H_{16}ClN_3O_6Na$ $(M+Na)^+$ 404.0625, found 404.0630.

4.1.1.4.12. Ethyl 1-butyryl-3-(5-chloro-2-nitrobenzoyl)-Δ^2-pyrazoline-5-carboxylate ***13b***. White solid; yield 98%; mp 82–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, 1H, H-3′, $J_{3'-4'}$=8.7 Hz); 7.64 (dd, 1H, H-4′, $J_{4'-3'}$=8.7 Hz, $J_{4'-6'}$= 2.1 Hz); 7.52 (d, 1H, H-6′, $J_{6'-4'}$=2.1 Hz); 4.97 (dd, 1H, H-5, J_{5-4a}=13.0 Hz, J_{5-4b}=6.1 Hz); 4.22 (c, 2H, –COO–CH_2–CH_3, J=7.1 Hz); 3.50 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=13.0 Hz); 3.26 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.1 Hz); 2.46 (1 pq, –CO–CH_2–CH_2–CH_3, Ha, J_{gem}=15.3 Hz, J_{Ha-CH2}=7.4 Hz); 2.37 (1 pq, –CO–CH_2–CH_2–CH_3, Hb, J_{gem}=15.3 Hz, J_{Hb-CH_2}= 7.4 Hz); 1.57 (m, 2H, –CO–CH_2–CH_2–CH_3); 1.29 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz); 0.87 (t, 3H, –CO–CH_2–CH_2–CH_3, J=7.4 Hz).^{13}C NMR (100 MHz, $CDCl_3$) δ 185.60 (Ph–*C*O–); 172.56 (–N–CO–); 168.89 (–*C*OO–CH_2–CH_3); 151.92 (C-3); 146.28 (C-2′); 141.04 (C-5′); 135.24 (C-1′); 131.48 (C-4′); 129.60 (C-6′); 125.44 (C-3′); 62.28 (–COO–*C*H_2–CH_3); 59.18 (C-5); 35.21 (–CO–*C*H_2–CH_2–CH_3, C-4); 17.98 (–CO–CH_2–*C*H_2–CH_3); 14.07 (–COO–CH_2–*C*H_3); 13.68 (–CO–CH_2–CH_2–*C*H_3). HR LSIMS: calcd for $C_{17}H_{18}ClN_3O_6Na$ $(M+Na)^+$ 418.0781, found 418.0783.

4.1.1.4.13. Ethyl 3-(5-chloro-2-nitrobenzoyl)-1-pentanoyl-Δ^2-pyrazoline-5-carboxylate ***14b***. White solid; yield 95%; mp 97–99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, 1H, H-3′, $J_{3'-4'}$=8.7 Hz); 7.63 (dd, 1H, H-4′, $J_{4'-3'}$= 8.7 Hz, $J_{4'-6'}$=2.3 Hz); 7.51 (d, 1H, H-6′, $J_{6'-4'}$=2.3 Hz); 4.96 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.1 Hz); 4.21 (c, 2H, –COO–CH_2–CH_3, J=7.1 Hz); 3.49 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.9 Hz); 3.25 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.1 Hz); 2.42 (m, 2H, –CO–CH_2–CH_2–CH_2–CH_3); 1.51 (m, 2H, –CO–CH_2–CH_2–CH_2–CH_3); 1.27 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz); 1.25 (m, 2H, –CO–CH_2–CH_2–CH_2–CH_3) 0.82 (t, 3H, –CO–CH_2–CH_2–CH_2–CH_3, J=7.3 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ 185.60 (Ph–*C*O–); 172.76 (–N–CO–); 168.88 (–*C*OO–CH_2–CH_3); 151.94 (C-3); 146.26 (C-2′); 141.05 (C-5′); 135.30 (C-1′); 131.44 (C-4′); 129.58 (C-6′); 125.44 (C-3′); 62.28 (–COO–CH_2–CH_3); 59.19 (C-5); 35.23 (C-4); 33.14 (–CO–*C*H_2–CH_2–CH_2–CH_3); 26.60 (–CO–CH_2–*C*H_2–CH_2–CH_3); 22.25 (–CO–CH_2–CH_2–*C*H_2–CH_3); 14.06 (–COO–CH_2–*C*H_3); 13.65 (–CO–CH_2–CH_2–CH_2–*C*H_3).HR LSIMS calcd for $C_{18}H_{21}ClN_3O_6$ (M^++1) 410.1118, found 410.1118.

4.1.1.4.14. Ethyl 3-(5-chloro-2-nitrobenzoyl)-1-cyclopropanecarbonyl-Δ^2-pyrazoline-5-carboxylate ***15b***. White solid; yield 98%; mp 129–131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, 1H, H-3′, $J_{3'-4'}$=8.7 Hz); 7.61 (dd, 1H, H-4′, $J_{4'-3'}$=8.7 Hz, $J_{4'-6'}$=2.3 Hz); 7.52 (d, 1H, H-6′, $J_{6'-4'}$=2.3 Hz); 4.95 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.1 Hz); 4.20 (m, 2H, –COO–CH_2–CH_3); 3.51 (dd, 1H, H-4a, J_{4a-4b}=18.6 Hz, J_{4a-5}=12.9 Hz); 3.27 (dd, 1H, H-4b, J_{4b-4a}=18.6 Hz, J_{4b-5}=6.3 Hz); 2.10 (m, 1H, H-$1_{cycloprop.}$); 1.26 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz); 1.02, 0.83 (2m, 4H, H-2, H-$3_{cycloprop.}$) ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.73 (Ph–*C*O–); 173.11 (–N–CO–); 168.90 (–*C*OO–CH_2–CH_3); 152.13 (C-3); 146.12 (C-2′); 141.04 (C-5′); 135.35 (C-1′); 131.40 (C-4′); 129.59 (C-6′); 125.56 (C-3′); 62.21 (–COO–*C*H_2–CH_3); 59.51 (C-5); 35.16 (C-4); 14.10 (–COO–CH_2–*C*H_3); 11.50 (C-$1_{cycloprop.}$); 9.54, 9.47 (C-2, C-$3_{cycloprop.}$). HR LSIMS calcd for $C_{17}H_{16}ClN_3O_6Na$ $(M+Na)^+$ 416.0625, found: 416.0621.

4.1.1.4.15. Ethyl 3-(5-chloro-2-nitrobenzoyl)-1-cyclobutanecarbonyl-Δ^2-pyrazoline-5-carboxylate ***16b***. White solid; yield 98%; mp 97–99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, 1H, H-3′, $J_{3'-4'}$=8.7 Hz); 7.64 (dd, 1H, H-4′, $J_{4'-3'}$=8.7 Hz, $J_{4'-6'}$=2.3 Hz); 7.50 (d, 1H, H-6′, $J_{6'-4'}$=2.3 Hz); 4.95 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}= 6.1 Hz); 4.22 (c, 2H, –COO–CH_2–CH_3, J=7.1 Hz); 3.47 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.9 Hz); 3.41 (m, 1H, H-$1_{cyclobut.}$); 3.23 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.1 Hz); 2.25–2.15, 1.98–1.72 (2m, 6H, H-2, H-3, H-$4_{cyclobut.}$); 1.28 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.64 (Ph–*C*O–); 174.10

(–N–CO–); 168.90 (–*C*OO–CH_2–CH_3); 152.00 (C-3); 146.12 (C-2′); 141.07 (C-5′); 135.44 (C-1′); 131.42 (C-4′); 129.55 (C-6′); 125.45 (C-3′); 62.27 (–COO–*C*H_2–CH_3); 59.28 (C-5); 37.32 (C-$1_{cyclobut.}$); 35.01 (C-4); 24.71, 24.22 (C-2, C-$4_{cyclobut.}$); 18.18 (C-$3_{cyclobut.}$); 14.08 (–COO–CH_2–*C*H_3). HR LSIMS calcd for $C_{18}H_{18}ClN_3O_6Na$ $(M+Na)^+$ 430.0783, found: 430.0781.

4.1.1.4.16. Ethyl 3-(5-chloro-2-nitrobenzoyl)-1-cyclopentanecarbonyl-Δ²-pyrazoline-5-carboxylate ***17b***. White solid; yield 97%; mp 74–76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, 1H, H-3′, $J_{3'-4'}$=8.7 Hz); 7.63 (dd, 1H, H-4′, $J_{4'-3'}$=8.7 Hz, $J_{4'-6'}$=2.3 Hz); 7.51 (d, 1H, H-6′, $J_{6'-4'}$=2.3 Hz); 4.96 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.1 Hz); 4.21 (m, 2H, –COO–C*H*$_2$–CH_3); 3.49 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.9 Hz); 3.24 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.1 Hz); 3.06 (m, 1H, H-$1_{cyclopent.}$); 1.81–1.42 (m, 8H, H-2, H-3, H-4, H-$5_{cyclopent.}$); 1.27 (t, 3H, –COO–CH_2–C*H*$_3$, *J*=7.1 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ 185.69 (Ph–*C*O–); 175.68 (–N–CO–); 168.93 (–*C*OO–CH_2–CH_3); 151.80 (C-3); 146.15 (C-2′); 141.04 (C-5′); 135.41 (C-1′); 131.42 (C-4′); 129.57 (C-6′); 125.46 (C-3′); 62.21 (–COO–*C*H_2–CH_3); 59.33 (C-5); 41.85 (C-$1_{cyclopent.}$); 35.05 (C-4); 29.71, 29.20 (C-2, C-$5_{cyclopent.}$); 26.24, 26.11 (C-3, C-$4_{cyclopent.}$); 14.06 (–COO–CH_2–*C*H_3). HR LSIMS calcd for $C_{19}H_{20}ClN_3O_6$-Na $(M+Na)^+$ 444.0938, found 444.0940.

4.1.1.4.17. Ethyl 3-(5-chloro-2-nitrobenzoyl)-1-cyclohexanecarbonyl-Δ²-pyrazoline-5-carboxylate ***18b***. White syrup; yield 98%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, 1H, H-3′, $J_{3'-4'}$=8.7 Hz); 7.63 (dd, 1H, H-4′, $J_{4'-3'}$=8.7 Hz, $J_{4'-6'}$= 2.3 Hz); 7.51 (d, 1H, H-6′, $J_{6'-4'}$=2.3 Hz); 4.94 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.0 Hz); 4.20 (m, 2H, –COO–C*H*$_2$–CH_3); 3.47 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}= 12.9 Hz); 3.23 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.0 Hz); 2.66 (tt, H-$1_{cyclohex.}$, $J_{transdiaxial}$=11.5 Hz, J_{cis}=3.3 Hz); 1.72–1.04 (m, 10H, H-2, H-3, H-4, H-5, H-$6_{cyclohex.}$); 1.26 (t, 3H, –COO–CH_2–C*H*$_3$, *J*=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.54 (Ph–*C*O–); 175.39 (–N–CO–); 168.84 (–*C*OO–CH_2–CH_3); 151.67 (C-3); 146.27 (C-2′); 140.97 (C-5′); 135.28 (C-1′); 131.39 (C-4′); 129.64 (C-6′); 125.31 (C-3′); 62.19 (–COO–*C*H_2–CH_3); 59.21 (C-5); 41.51 (C-$1_{cyclohex.}$); 34.97 (C-4); 28.56, 28.40 (C-2, C-$6_{cyclohex.}$); 25.53, 25.45, 25.38 (C-3, C-4, C-$5_{cyclohex.}$); 14.03 (–COO–CH_2–*C*H_3). HR LSIMS calcd for $C_{20}H_{22}ClN_3O_6Na$ $(M+Na)^+$ 458.1094, found 458.1097.

4.1.1.4.18. Ethyl 1-benzoyl-3-(5-chloro-2-nitrobenzoyl)-Δ²-pyrazoline-5-carboxylate ***19b***. White syrup; yield 98%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, 1H, H-3′, $J_{3'-4'}$= 8.7 Hz); 7.56 (m, 3H, H-4′, H-2, H-$6_{benz.}$); 7.45 (d, 1H, H-6′, $J_{6'-4'}$=2.2 Hz); 7.41 (tt, 1H, H-$4_{benz.}$, J_{4-3}=6.8 Hz, J_{4-2}=1.2 Hz); 7.27 (pt, 2H, H-3, H-$5_{benz.}$, $J_{3\text{-}2benz.}$=7.4 Hz, $J_{3\text{-}4benz.}$=6.8 Hz); 5.18 (dd, 1H, H-5, J_{5-4a}=12.8 Hz, J_{5-4b}=6.2 Hz); 4.25 (c, 2H, –COO–C*H*$_2$–CH_3, *J*= 7.1 Hz); 3.56 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}= 12.8 Hz); 3.31 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}= 6.2 Hz); 1.29 (t, 3H, –COO–CH_2–C*H*$_3$, *J*=7.1 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ185.62 (Ph–*C*O–); 168.75, 167.39 (–*C*OO–CH_2–CH_3, –N–CO–); 152.87 (C-3); 146.15 (C-2′); 141.06 (C-5′); 135.35 (C-1′); 133.20 (C-$1_{benz.}$); 131.94 (C-$4_{benz.}$); 131.26 (C-4′); 129.76 (C-2, C-$6_{benz.}$); 129.42 (C-6′); 127.72 (C-3, C-$5_{benz.}$); 125.37 (C-3′); 62.30 (–COO–*C*H_2–CH_3); 60.40 (C-5); 34.69 (C-4); 14.05 (–COO–CH_2–*C*H_3). HR LSIMS calcd for $C_{20}H_{16}ClN_3O_6Na$ $(M+Na)^+$ 452.0625, found 452.0623.

4.1.1.4.19. Ethyl 1-acetyl-3-(2-nitrobenzoyl)-Δ²-pyrazoline-5-carboxylate ***11c***. White solid; yield 99%; mp 112–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, 1H, H-3′, $J_{3'-4'}$=8.1 Hz); 7.78 (t, 1H, H-5′, $J_{5'-6'}$=$J_{5'-4'}$=7.5 Hz); 7.69 (dt, 1H, H-4′, $J_{4'-3'}$=8.1 Hz, $J_{4'-5'}$=7.5 Hz, $J_{4'-6'}$= 1.1 Hz); 7.57 (dd, 1H, H-6′, $J_{6'-5'}$=7.5 Hz, $J_{6'-4'}$=1.1 Hz); 4.96 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.1 Hz); 4.23 (c, 2H, –COO–C*H*$_2$–CH_3, *J*=7.1 Hz); 3.53 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.9 Hz); 3.29 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.1 Hz); 2.12 (s, 3H, –CO–CH_3); 1.29 (t, 3H, –COO–CH_2–C*H*$_3$, *J*=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.06 (Ph–*C*O–); 169.88, 168.92 (–*C*OO–CH_2–CH_3, –N–CO–); 152.44 (C-3); 148.26 (C-2′); 134.15 (C-5′); 133.67 (C-1′); 131.66 (C-4′); 129.59 (C-6′); 123.95 (C-3′); 62.27 (–COO–*C*H_2–CH_3); 58.99 (C-5); 35.62 (C-4); 21.05 (–CO–CH_3); 14.06 (–COO–CH_2–*C*H_3). HR LSIMS calcd for $C_{15}H_{15}N_3O_6Na$ $(M+Na)^+$ 356.0858, found 356.0858.

4.1.1.4.20. Ethyl 3-(2-nitrobenzoyl)-1-propionyl-Δ²-pyrazoline-5-carboxylate ***12c***. White solid; yield 98%; mp 106–108 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, 1H, H-3′, $J_{3'-4'}$=8.1 Hz); 7.77 (dt, 1H, H-5′, $J_{5'-6'}$=$J_{5'-4'}$=7.5 Hz, $J_{5'-3'}$=1.2 Hz); 7.68 (dt, 1H, H-4′, $J_{4'-3'}$=8.1 Hz, $J_{4'-5'}$=7.5 Hz, $J_{4'-6'}$=1.6 Hz); 7.55 (dd, 1H, H-6′, $J_{6'-5'}$= 7.5 Hz, $J_{6'-4'}$=1.6 Hz); 4.95 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.2 Hz); 4.21 (c, 2H, –COO–C*H*$_2$–CH_3, *J*=7.1 Hz); 3.50 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.9 Hz); 3.26 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.2 Hz); 2.43 (m, 2H, –CO–C*H*$_2$–CH_3); 1.27 (t, 3H, –COO–CH_2–C*H*$_3$, *J*=7.1 Hz); 1.04 (t, 3H, –CO–CH_2–C*H*$_3$, *J*=7.5 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ 187.13 (Ph–*C*O–); 173.33 (–N–CO–); 169.04 (–*C*OO–CH_2–CH_3); 152.27 (C-3); 148.19 (C-2′); 134.15 (C-5′); 133.79 (C-1′); 131.60 (C-4′); 129.56 (C-6′); 123.97 (C-3′); 62.20 (–COO–*C*H_2–CH_3); 59.11 (C-5); 35.34 (C-4); 26.81 (–CO–*C*H_2–CH_3); 14.06 (–COO–CH_2–*C*H_3); 8.35 (–CO–CH_2–*C*H_3). HR LSIMS calcd for $C_{16}H_{17}N_3O_6Na$ $(M+Na)^+$ 370.1015, found 370.1014.

4.1.1.4.21. Ethyl 1-butyryl-3-(2-nitrobenzoyl)-Δ²-pyrazoline-5-carboxylate ***13c***. White syrup; yield 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, 1H, H-3′, $J_{3'-4'}$= 8.1 Hz); 7.76 (t, 1H, H-5′, $J_{5'-6'}$=$J_{5'-4'}$=7.5 Hz); 7.67 (dt, 1H, H-4′, $J_{4'-3'}$=8.1 Hz, $J_{4'-5'}$=7.5 Hz, $J_{4'-6'}$=1.2 Hz); 7.54 (dd, 1H, H-6′, $J_{6'-5'}$=7.5 Hz, $J_{6'-4'}$=1.2 Hz); 4.95 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.1 Hz); 4.20 (c, 2H, –COO–C*H*$_2$–CH_3, *J*=7.1 Hz); 3.49 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.9 Hz); 3.25 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.1 Hz); 2.42 (pq, 1H, –CO–C*H*$_2$–CH_2–CH_3, Ha, J_{gem}=15.0 Hz, J_{Ha-CH2}=7.4 Hz); 2.34 (pq, 1H, –CO–C*H*$_2$–CH_2–CH_3, Hb, J_{gem}=15.0 Hz, J_{Hb-CH2}=7.4 Hz); 1.54 (m, 2H, –CO–CH_2–C*H*$_2$–CH_3); 1.26 (t, 3H, –COO–CH_2–C*H*$_3$, *J*=7.1 Hz); 0.83 (t, 3H, –CO–CH_2–CH_2–C*H*$_3$, *J*=7.4 Hz).^{13}C NMR (100 MHz, $CDCl_3$) δ 187.10 (Ph–*C*O–); 172.53 (–N–CO–); 168.94 (–*C*OO–CH_2–CH_3); 152.23 (C-3); 148.07 (C-2′); 134.12 (C-5′); 133.73 (C-1′); 131.56 (C-4′); 129.47 (C-6′); 123.89 (C-3′);

62.12 (–COO–CH_2–CH_3); 59.01 (C-5); 35.29, 35.13 (–CO–CH_2–CH_2–CH_3, C-4); 17.91 (–CO–CH_2–CH_2–CH_3); 13.99, 13.58 (–COO–CH_2–CH_3, –CO–CH_2–CH_2–CH_3). HR LSIMS calcd for $C_{18}H_{21}N_3O_6Na$ $(M+Na)^+$ 398.1328, found 398.1325.

4.1.1.4.22. Ethyl 3-(2-nitrobenzoyl)-1-pentanoyl-Δ^2-pyrazoline-5-carboxylate ***14c***. White syrup; yield 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, 1H, H-3′, $J_{3'-4'}$= 8.1 Hz); 7.74 (dt, 1H, H-5′, $J_{5'-6'}=J_{5'-4'}$=7.5 Hz, $J_{5'-3'}$= 0.7 Hz); 7.65 (dt, 1H, H-4′, $J_{4'-3'}$=8.1 Hz, $J_{4'-5'}$=7.5 Hz, $J_{4'-6'}$=1.3 Hz); 7.52 (dd, 1H, H-6′, $J_{6'-5'}$=7.5 Hz, $J_{6'-4'}$= 1.1 Hz); 4.92 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.1 Hz); 4.17 (c, 2H, –COO–CH_2–CH_3, J=7.1 Hz); 3.48 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.9 Hz); 3.23 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.1 Hz); 2.42 (pq, 1H, –CO–CH_2–CH_2–CH_2–CH_3, Ha, J_{gem}=15.1 Hz, J_{Ha-CH2}= 7.6 Hz); 2.33 (pq, 1H, –CO–CH_2–CH_2–CH_2–CH_3, Hb, J_{gem}=15.1 Hz, J_{Hb-CH2}=7.6 Hz); 1.45 (m, 2H, –CO–CH_2–CH_2–CH_2–CH_3); 1.23 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz); 1.17 (m, 2H, –CO–CH_2–CH_2–CH_2–CH_3) 0.75 (t, 3H, –CO–CH_2–CH_2–CH_2–CH_3, J=7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ187.03 (Ph–CO–); 172.66 (–N–CO–); 168.86(–COO–CH_2–CH_3); 152.21 (C-3); 147.98 (C-2′); 134.08 (C-5′); 133.68 (C-1′); 131.49 (C-4′); 129.38 (C-6′); 123.82 (C-3′); 62.03 (–COO–CH_2–CH_3); 58.97 (C-5); 35.23 (C-4); 32.98 (–CO–CH_2–CH_2–CH_2–CH_3); 26.46 (–CO–CH_2–CH_2–CH_2–CH_3); 22.07 (–CO–CH_2–CH_2–CH_2–CH_3); 13.90, 13.48 (–COO–CH_2–CH_3, –CO–CH_2–CH_2–CH_2–CH_3). HR LSIMS calcd for $C_{18}H_{21}N_3O_6Na$ $(M+Na)^+$ 398.1328, found 398.13253.

4.1.1.4.23. Ethyl 1-cyclopropanecarbonyl-3-(2-nitrobenzoyl)-Δ^2-pyrazoline-5-carboxylate ***15c***. White solid; yield 98%; mp 116–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (dd, 1H, H-3′, $J_{3'-4'}$=8.1 Hz, $J_{3'-5'}$=1.2 Hz); 7.77 (dt, 1H, H-5′, $J_{5'-6'}=J_{5'-4'}$=7.5 Hz, $J_{5'-3'}$=1.2 Hz); 7.67 (dt, 1H, H-4′, $J_{4'-3'}$=8.1 Hz, $J_{4'-5'}$=7.5 Hz, $J_{4'-6'}$=1.6 Hz); 7.57 (dd, 1H, H-6′, $J_{6'-5'}$=7.5 Hz, $J_{6'-4'}$=1.6 Hz); 4.95 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.3 Hz); 4.21 (m, 2H, –COO–CH_2–CH_3); 3.52 (dd, 1H, H-4a, J_{4a-4b}=18.6 Hz, J_{4a-5}=12.9 Hz); 3.28 (dd, 1H, H-4b, J_{4b-4a}=18.6 Hz, J_{4b-5}=6.3 Hz); 2.11 (m, 1H, H-$1_{cycloprop.}$); 1.26 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz); 1.01–0.98, 0.84–0.79 (2m, 4H, H-2, H-$3_{cycloprop.}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.27 (Ph–CO–); 173.14 (–N–CO–); 169.03 (–COO–CH_2–CH_3); 152.47 (C-3); 148.09 (C-2′); 134.14 (C-5′); 133.91 (C-1′); 131.52 (C-4′); 129.61 (C-6′); 124.03 (C-3′); 62.15 (–COO–CH_2–CH_3); 59.41 (C-5); 35.32 (C-4); 14.07 (–COO–CH_2–CH_3); 11.44 (C-$1_{cycloprop.}$); 9.39, 9.35 (C-2, C-$3_{cycloprop.}$). HR LSIMS calcd for $C_{17}H_{17}N_3O_6Na$ $(M+Na)^+$ 382.1015, found 382.1014.

4.1.1.4.24. Ethyl 1-cyclobutanecarbonyl-3-(2-nitrobenzoyl)-Δ^2-pyrazoline-5-carboxylate ***16c***. White syrup; yield 99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (dd, 1H, H-3′, $J_{3'-4'}$=8.0 Hz, $J_{3'-5'}$=1.1 Hz); 7.77 (dt, 1H, H-5′, $J_{5'-6'}=J_{5'-4'}$=7.5 Hz, $J_{5'-3'}$=1.1 Hz); 7.68 (dt, 1H, H-4′, $J_{4'-3'}$= 8.0 Hz, $J_{4'-5'}$=7.5 Hz, $J_{4'-6'}$=1.6 Hz); 7.52 (dd, 1H, H-6′, $J_{6'-5'}$=7.5 Hz, $J_{6'-4'}$=1.6 Hz); 4.93 (dd, 1H, H-5, J_{5-4a}=12.8 Hz, J_{5-4b}=6.1 Hz); 4.21 (c, 2H, –COO–CH_2–CH_3, J=7.1 Hz); 3.47 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}= 12.9 Hz); 3.38 (m, 1H, H-$1_{cyclobut.}$); 3.24 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.1 Hz); 2.27–2.13, 1.98–1.73 (2m, 6H, H-2, H-3, H-$4_{cyclobut.}$); 1.27 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ 187.23 (Ph–CO–); 174.11 (–N–CO–); 169.01 (–COO–CH_2–CH_3); 152.35 (C-3); 147.94 (C-2′); 134.20 (C-5′); 134.00 (C-1′); 131.53 (C-4′); 129.43 (C-6′); 123.95 (C-3′); 62.18 (–COO–CH_2–CH_3); 59.16 (C-5); 37.31 (C-$1_{cyclobut.}$); 35.13 (C-4); 24.68, 24.18 (C-2, C-$4_{cyclobut.}$); 18.13 (C-$3_{cyclobut.}$); 14.05 (–COO–CH_2–CH_3). HR LSIMS calcd for $C_{18}H_{19}N_3O_6Na$ $(M+Na)^+$ 396.1171, found 396.1169.

4.1.1.4.25. Ethyl 1-cyclopentanecarbonyl-3-(2-nitrobenzoyl)-Δ^2-pyrazoline-5-carboxylate ***17c***. White syrup; yield 97%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (dd, 1H, H-3′, $J_{3'-4'}$=8.1 Hz, $J_{3'-5'}$=1.1 Hz); 7.77 (dt, 1H, H-5′, $J_{5'-6'}=J_{5'-4'}$=7.5 Hz, $J_{5'-3'}$=1.1 Hz); 7.67 (dt, 1H, H-4′, $J_{4'-3'}$=8.1 Hz, $J_{4'-5'}$=7.5 Hz, $J_{4'-6'}$=1.6 Hz); 7.54 (dd, 1H, H-6′, $J_{6'-5'}$=7.5 Hz, $J_{6'-4'}$=1.6 Hz); 4.94 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.1 Hz); 4.20 (m, 2H, –COO–CH_2–CH_3); 3.49 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}= 12.9 Hz); 3.25 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}= 6.1 Hz); 3.06 (m, 1H, H-$1_{cyclopent.}$); 1.91–1.06 (m, 8H, H-2, H-3, H-4, H-$5_{cyclopent}$); 1.26 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.29 (Ph–CO–); 175.70 (–N–CO–); 169.05 (–COO–CH_2–CH_3); 152.17 (C-3); 147.96 (C-2′); 134.18 (C-5′); 133.99 (C-1′); 131.53 (C-4′); 129.45 (C-6′); 123.97 (C-3′); 62.12 (–COO–CH_2–CH_3); 59.22 (C-5); 41.84 (C-$1_{cyclopent.}$); 35.18 (C-4); 29.66, 29.14 (C-2, C-$5_{cyclopent.}$); 26.20, 26.07 (C-3, C-$4_{cyclopent.}$), 14.03 (–COO–CH_2–CH_3). HR LSIMS calcd for $C_{19}H_{21}N_3O_6Na$ $(M+Na)^+$ 410.1328, found 410.1326.

4.1.1.4.26. Ethyl 1-cyclohexanecarbonyl-3-(2-nitrobenzoyl)-Δ^2-pyrazoline-5-carboxylate ***18c***. White syrup; yield 98%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (dd, 1H, H-3′, $J_{3'-4'}$=8.1 Hz, $J_{3'-5'}$=1.1 Hz); 7.77 (dt, 1H, H-5′, $J_{5'-4'}$=7.6 Hz, $J_{5'-6'}$=7.5 Hz, $J_{5'-3'}$=1.1 Hz); 7.68 (dt, 1H, H-4′, $J_{4'-3'}$=8.1 Hz, $J_{4'-5'}$=7.6 Hz, $J_{4'-6'}$=1.6 Hz); 7.54 (dd, 1H, H-6′, $J_{6'-5'}$=7.5 Hz, $J_{6'-4'}$=1.6 Hz); 4.92 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.0 Hz); 4.19 (m, 2H, –COO–CH_2–CH_3); 3.48 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}= 12.9 Hz); 3.24 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}= 6.0 Hz); 2.65 (tt, H-$1_{cyclohex.}$, $J_{transdiaxial}$=11.5 Hz, J_{cis}=3.2 Hz); 1.72–1.04 (m, 10H, H-2, H-3, H-4, H-5, H-$6_{cyclohex.}$); 1.25 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.17 (Ph–CO–); 175.43 (–N–CO–); 168.97 (–COO–CH_2–CH_3); 152.07 (C-3); 148.10 (C-2′); 134.17 (C-5′); 133.91 (C-1′); 131.53 (C-4′); 129.52 (C-6′); 123.83 (C-3′); 62.13 (–COO–CH_2–CH_3); 59.12 (C-5); 41.50 (C-$1_{cyclohex.}$); 35.12 (C-4); 28.54, 28.38 (C-2, C-$6_{cyclohex.}$); 25.77, 25.53, 25.46 (C-3, C-4, C-$5_{cyclohex.}$), 14.03 (–COO–CH_2–CH_3). HR LSIMS calcd for $C_{20}H_{23}N_3O_6Na$ $(M+Na)^+$ 424.1484, found 424.1485.

4.1.1.4.27. Ethyl 1-benzoyl-3-(2-nitrobenzoyl)-Δ^2-pyrazoline-5-carboxylate ***19c***. White solid; yield 92%; mp 135–137 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, 1H, H-3′, $J_{3'-4'}$=8.1 Hz, $J_{3'-5'}$=1.1 Hz); 7.70 (dt, 1H, H-5′, $J_{5'-4'}$= 7.7 Hz, $J_{5'-6'}$=7.4 Hz, $J_{5'-3'}$=1.1 Hz); 7.61 (m, 3H, H-4′, H-2, H-$6_{benz.}$); 7.49 (dd, 1H, H-6′, $J_{6'-5'}$=7.4 Hz, $J_{6'-4'}$= 1.5 Hz); 7.39 (tt, 1H, H-$4_{benz.}$, $J_{4\text{-}3benz.}$=6.7 Hz, $J_{4\text{-}2benz.}$= 1.2 Hz); 7.25 (pt, 2H, H-3, H-$5_{benz.}$, $J_{3\text{-}2benz.}$=7.1 Hz,

$J_{3\text{-}4benz.}$=6.7 Hz); 5.17 (dd, 1H, H-5, J_{5-4a}=12.7 Hz, J_{5-4b}=6.2 Hz); 4.26 (c, 2H, –COO–C*H*$_2$–CH$_3$, *J*=7.1 Hz); 3.57 (dd, 1H, H-4a, J_{4a-4b}=18.6 Hz, J_{4a-5}=12.7 Hz); 3.33 (dd, 1H, H-4b, J_{4b-4a}=18.6 Hz, J_{4b-5}=6.2 Hz); 0.97 (t, 3H, –COO–CH$_2$–C*H*$_3$, *J*=7.1 Hz). ^{13}C NMR (75 MHz, CDCl$_3$) δ 187.29 (Ph–*C*O–); 168.89, 167.33 (–*C*OO–CH$_2$–CH$_3$, –N–CO–); 153.34 (C-3); 148.26 (C-2′); 134.30 (C-5′); 134.02 (C-1′); 131.97 (C-1$_{benz.}$); 131.84, 131.42 (C-4$_{benz.}$, C-4′); 129.86 (C-2, C-6$_{benz.}$); 129.36 (C-6′); 127.67 (C-3, C-5$_{benz.}$); 123.90 (C-3′); 62.26 (–COO–*C*H$_2$–CH$_3$); 60.36 (C-5); 34.83 (C-4); 14.09 (–COO–CH$_2$–*C*H$_3$). HR LSIMS calcd for $C_{20}H_{17}N_3O_6Na$ (M+Na)$^+$ 418.1015, found: 418.1014.

4.1.2. Final products

4.1.2.1. General procedure for the preparation of compounds 20a–28a. A mixture of nitroarenes **11a–19a** (0.512 mmol) and 10% Pd/C (20 mg) was dissolved in methanol (30 mL) and stirred under a hydrogen atmosphere (70 psi) for 1.5 h. The mixture was filtered through celite and evaporated. The resultant residue was dissolved in CH_2Cl_2, and this solution was washed with water, dried (Na_2SO_4), and concentrated. The resultant solid was dissolved and purified by flash chromatography (ether–hexane 1:2).

4.1.2.1.1. Ethyl 1-acetyl-3-(2-amino-5-methoxybenzoyl)-Δ^2-pyrazoline-5-carboxylate ***20a***. Orange solid; yield 80%; mp 210–212 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.04 (d, 1H, H-6′, $J_{6'-4'}$=2.9 Hz); 7.02 (dd, 1H, H-4′, $J_{4'-3'}$=9.0 Hz, $J_{4'-6'}$=2.9 Hz); 6.65 (d, 1H, H-3′, $J_{3'-4'}$=9.0 Hz); 6.04 (bs, 2H, –NH$_2$); 4.90 (dd, 1H, H-5, J_{5-4a}=12.8 Hz, J_{5-4b}=6.2 Hz); 4.23 (c, 2H, –COO–C*H*$_2$–CH$_3$, *J*=7.1 Hz); 3.76 (s, 3H, –OCH$_3$); 3.61 (dd, 1H, H-4a, J_{4a-4b}=18.8 Hz, J_{4a-5}=12.8 Hz); 3.31 (dd, 1H, H-4b, J_{4b-4a}=18.8 Hz, $J_{4b,5}$=6.2 Hz); 2.41 (s, 3H, –CO–CH$_3$); 1.29 (t, 3H, –COO–CH$_2$–C*H*$_3$, *J*=7.1 Hz). ^{13}C NMR (75 MHz, CDCl$_3$) δ 186.37 (Ph–*C*O–); 169.93, 169.51 (–N–CO–, –*C*OO–CH$_2$–CH$_3$); 153.89 (C-3); 150.13 (C-5′); 146.90 (C-2′); 125.47 (C-4′); 118.62 (C-3′); 116.10 (C-1′); 114.31 (C-6′); 62.13 (–COO–*C*H$_2$–CH$_3$); 57.44 (C-5); 55.74 (–OCH$_3$); 38.05 (C-4); 21.52 (–CO–CH$_3$); 14.14 (–COO–CH$_2$–*C*H$_3$). HR LSIMS calcd for $C_{16}H_{19}N_3O_5Na$ (M+Na)$^+$ 356.1222, found 356.1223. Anal. for $C_{16}H_{19}N_3O_5$: calcd: C, 57.65; H, 5.75; N, 12.61. Found: C, 57.46; H, 5.70; N, 12.21.

4.1.2.1.2. Ethyl 3-(2-amino-5-methoxybenzoyl)- 1-propionyl-Δ^2-pyrazoline-5-carboxylate ***21a***. Orange solid; yield 80%; mp 140–141 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.03 (d, 1H, H-6′, $J_{6'-4'}$=3.0 Hz); 7.02 (dd, 1H, H-4′, $J_{4'-3'}$=9.0 Hz, $J_{4'-6'}$=3.0 Hz); 6.64 (d, 1H, H-3′, $J_{3'-4'}$=9.0 Hz); 6.06 (bs, 2H, –NH$_2$); 4.90 (dd, 1H, H-5, J_{5-4a}=12.8 Hz, J_{5-4b}=6.3 Hz); 4.23 (c, 2H, –COO–C*H*$_2$–CH$_3$, *J*=7.1 Hz); 3.76 (s, 3H, –OCH$_3$); 3.59 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.8 Hz); 3.28 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, $J_{4b,5}$=6.3 Hz); 2.78 (m, 2H, –CO–C*H*$_2$–CH$_3$); 1.28 (t, 3H, –COO–CH$_2$–C*H*$_3$, *J*=7.1 Hz); 1.21 (t, 3H, –CO–CH$_2$–C*H*$_3$, *J*=7.5 Hz). ^{13}C NMR (75 MHz, CDCl$_3$) δ 186.45 (Ph–*C*O–); 173.42 (–N–CO–); 169.62 (–*C*OO–CH$_2$–CH$_3$); 153.70 (C-3); 150.12 (C-5′); 146.88 (C-2′); 125.42 (C-4′); 118.61 (C-3′); 116.48 (C-1′); 114.30 (C-6′); 62.06 (–COO–*C*H$_2$–CH$_3$); 57.52 (C-5); 55.71 (–OCH$_3$); 37.76 (C-4); 27.33 (–CO–*C*H$_2$–CH$_3$); 14.13 (–COO–CH$_2$–*C*H$_3$); 8.91 (–CO–CH$_2$–*C*H$_3$). HR LSIMS calcd for $C_{17}H_{21}N_3O_5Na$ (M+Na)$^+$ 370.1378, found 370.1377. Anal. for $C_{17}H_{21}N_3O_5$: calcd: C, 58.78; H, 6.09; N, 12.10. Found: C, 59.15; H, 6.27; N, 11.81.

4.1.2.1.3. Ethyl 3-(2-amino-5-methoxybenzoyl)-1-butyryl-Δ^2-pyrazoline-5-carboxylate ***22a***. Orange solid; yield 80%; mp 153–155 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.04 (d, 1H, H-6′, $J_{6'-4'}$=2.9 Hz); 7.02 (dd, 1H, H-4′, $J_{4'-3'}$=9.0 Hz, $J_{4'-6'}$=2.9 Hz); 6.65 (d, 1H, H-3′, $J_{3'-4'}$=9.0 Hz); 6.07 (bs, 2H, –NH$_2$); 4.90 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.3 Hz); 4.20 (c, 2H, –COO–C*H*$_2$–CH$_3$, *J*=7.1 Hz); 3.77 (s, 3H, –OCH$_3$); 3.59 (dd, 1H, H-4a, J_{4a-4b}=18.8 Hz, J_{4a-5}=12.9 Hz); 3.29 (dd, 1H, H-4b, J_{4b-4a}=18.8 Hz, $J_{4b,5}$=6.3 Hz); 2.80 (pq, 1H, –CO–C*H*$_2$–CH$_2$–CH$_3$, Ha, J_{gem}=15.1 Hz, J_{Ha-CH2}=7.5 Hz); 2.68 (pq, 1H, –CO–C*H*$_2$–CH$_2$–CH$_3$, Hb, J_{gem}=15.1 Hz, J_{Hb-CH2}=7.5 Hz); 1.74 (m, 2H, –CO–CH$_2$–C*H*$_2$–CH$_3$); 1.28 (t, 3H, –COO–CH$_2$–C*H*$_3$, *J*=7.1 Hz); 0.97 (t, 3H, –CO–CH$_2$–CH$_2$–C*H*$_3$, *J*=7.4 Hz).^{13}C NMR (75 MHz, CDCl$_3$) δ 186.43 (Ph–*C*O–); 172.64 (–N–CO–); 169.61 (–*C*OO–CH$_2$–CH$_3$); 153.70 (C-3); 150.14 (C-5′); 146.93 (C-2′); 125.52 (C-4′); 118.63 (C-3′); 116.12 (C-1′); 114.23 (C-6′); 62.06 (–COO–*C*H$_2$–CH$_3$); 57.47 (C-5); 55.71 (–OCH$_3$); 37.79 (C-4); 35.83 (–CO–*C*H$_2$–CH$_2$–CH$_3$); 18.30, (–CO–CH$_2$–*C*H$_2$–CH$_3$); 14.14, 13.85 (–COO–CH$_2$–*C*H$_3$, –CO–CH$_2$–CH$_2$–*C*H$_3$). HR LSIMS calcd for $C_{18}H_{23}N_3O_5Na$ (M+Na)$^+$ 384.1535, found: 384.1537. Anal. for $C_{18}H_{23}N_3O_5$: calcd: C, 59.82; H, 6.41; N, 11.63. Found: C, 59.45; H, 6.46; N, 11.53.

4.1.2.1.4. Ethyl 3-(2-amino-5-methoxybenzoyl)-1-pentanoyl-Δ^2-pyrazoline-5-carboxylate ***23a***. Orange solid; yield 80%; mp 108–110 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.03 (d, 1H, H-6′, $J_{6'-4'}$=2.9 Hz); 7.01 (dd, 1H, H-4′, $J_{4'-3'}$=9.0 Hz, $J_{4'-6'}$=2.9 Hz); 6.64 (d, 1H, H-3′, $J_{3'-4'}$=9.0 Hz); 6.07 (bs, 2H, –NH$_2$); 4.89 (dd, 1H, H-5, J_{5-4a}=12.8 Hz, J_{5-4b}=6.3 Hz); 4.22 (c, 2H, –COO–C*H*$_2$–CH$_3$, *J*=7.1 Hz); 3.76 (s, 3H, –OCH$_3$); 3.58 (dd, 1H, H-4a, J_{4a-4b}=18.8 Hz, J_{4a-5}=12.8 Hz); 3.28 (dd, 1H, H-4b, J_{4b-4a}=18.8 Hz, $J_{4b,5}$=6.3 Hz); 2.81 (pq, 1H, –CO–C*H*$_2$–CH$_2$–CH$_2$–CH$_3$, Ha, J_{gem}=15.3 Hz, J_{Ha-CH2}=7.6 Hz); 2.70 (pq, 1H, –CO–C*H*$_2$–CH$_2$–CH$_2$–CH$_3$, Hb, J_{gem}=15.3 Hz, J_{Hb-CH2}=7.6 Hz); 1.69 (m, 2H, –CO–CH$_2$–C*H*$_2$–CH$_2$–CH$_3$); 1.40 (m, 2H, –CO–CH$_2$–CH$_2$–C*H*$_2$–CH$_3$) 1.27 (t, 3H, –COO–CH$_2$–C*H*$_3$, *J*=7.1 Hz); 0.91 (t, 3H, –CO–CH$_2$–CH$_2$–CH$_2$–C*H*$_3$, *J*=7.3 Hz).^{13}C NMR (75 MHz, CDCl$_3$) δ 186.44 (Ph–*C*O–); 172.77 (–N–CO–); 169.60 (–*C*OO–CH$_2$–CH$_3$); 153.67 (C-3); 150.13 (C-5′); 146.92 (C-2′); 125.45 (C-4′); 118.61 (C-3′); 116.14 (C-1′); 114.33 (C-6′); 62.04 (–COO–*C*H$_2$–CH$_3$); 57.49 (C-5); 55.71 (–OCH$_3$); 37.78 (C-4); 33.67 (–CO–*C*H$_2$–CH$_2$–CH$_2$–CH$_3$); 26.84 (–CO–CH$_2$–*C*H$_2$–CH$_2$–CH$_3$); 22.46 (–CO–CH$_2$–CH$_2$–*C*H$_2$–CH$_3$); 14.12, 13.85 (–COO–CH$_2$–*C*H$_3$, –CO–CH$_2$–CH$_2$–CH$_2$–*C*H$_3$). HR LSIMS calcd for $C_{19}H_{25}N_3O_5Na$ (M+Na)$^+$ 398.1691, found 398.1692. Anal. for $C_{19}H_{25}N_3O_5$: calcd: C, 60.79; H, 6.71; N, 11.90. Found: C, 60.47; H, 6.86; N, 11.55.

4.1.2.1.5. Ethyl 3-(2-amino-5-methoxybenzoyl)-1-cyclopropanecarbonyl-Δ^2-pyrazoline-5-carboxylate ***24a***. Orange solid; yield 84%; mp 118–120 °C. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 8.02 (d, 1H, H-6′, $J_{6'-4'}$=2.9 Hz); 7.01 (dd, 1H, H-4′, $J_{4'-3'}$=9.0 Hz, $J_{4'-6'}$=2.9 Hz); 6.65 (d, 1H, H-3′, $J_{3'-4'}$=9.0 Hz); 6.03 (bs, 2H, $-NH_2$); 4.90 (dd, 1H, H-5, J_{5-4a}=12.8 Hz, J_{5-4b}=6.5 Hz); 4.22 (m, 2H, $-COO-CH_2-CH_3$); 3.73 (s, 3H, $-OCH_3$); 3.60 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.8 Hz); 3.30 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, $J_{4b,5}$=6.5 Hz); 2.57 (m, 1H, H-$1_{cycloprop.}$); 1.28 (t, 3H, $-COO-CH_2-CH_3$, J=7.1 Hz); 1.16–1.06, 0.92–0.87 (2m, 4H, H-2, H-$3_{cycloprop.}$).^{13}C NMR (75 MHz, $CDCl_3$) δ186.77 (Ph–CO–); 173.20 (–N–CO–); 169.60 ($-COO-CH_2-CH_3$); 153.62 (C-3); 150.07 (C-5′); 146.73 (C-2′); 125.25 (C-4′); 118.56 (C-3′); 116.26 (C-1′); 114.61 (C-6′); 62.01 ($-COO-CH_2-CH_3$); 57.93 (C-5); 55.66 ($-OCH_3$); 37.63 (C-4); 14.13 ($-COO-CH_2-CH_3$); 11.84 (C-$1_{cycloprop.}$); 9.10, 9.01 (C-2, C-$3_{cycloprop.}$). HR LSIMS calcd for $C_{18}H_{21}N_3O_5Na$ $(M+Na)^+$ 382.1378, found 382.1376. Anal. for $C_{18}H_{21}N_3O_5$: calcd: C, 60.16; H, 5.89; N, 11.69. Found: C, 60.51; H, 5.66; N, 12.02.

4.1.2.1.6. Ethyl 3-(2-amino-5-methoxybenzoyl)-1-cyclobutanecarbonyl-Δ²-pyrazoline-5-carboxylate ***25a***. Orange solid; yield 82%; mp 112–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, 1H, H-6′, $J_{6'-4'}$=2.9 Hz); 7.02 (dd, 1H, H-4′, $J_{4'-3'}$=9.0 Hz, $J_{4'-6'}$=2.9 Hz); 6.65 (d, 1H, H-3′, $J_{3'-4'}$=9.0 Hz); 6.03 (bs, 2H, $-NH_2$); 4.89 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.2 Hz); 4.23 (c, 2H, $-COO-CH_2-CH_3$, J=7.1 Hz); 3.82 (m, 1H, H-$1_{cyclobut.}$); 3.80 (s, 3H, $-OCH_3$); 3.56 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}= 12.9 Hz); 3.26 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, $J_{4b,5}$= 6.2 Hz); 2.44–2.13, 2.05–1.88 (2m, 6H, H-2, H-3, H-$4_{cyclobut.}$); 1.29 (t, 3H, $-COO-CH_2-CH_3$, J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.72 (Ph–CO–); 174.17 (–N–CO–); 169.62 ($-COO-CH_2-CH_3$); 153.55 (C-3); 150.17 (C-5′); 146.93 (C-2′); 125.52 (C-4′); 118.54 (C-3′); 116.34 (C-1′); 114.89 (C-6′); 62.06 ($-COO-CH_2-CH_3$); 57.57 (C-5); 55.85 ($-OCH_3$); 37.64 (C-$1_{cyclobut.}$); 37.56 (C-4); 25.22, 24.61 (C-2, C-$4_{cyclobut.}$); 18.49 (C-$3_{cyclobut.}$); 14.14 ($-COO-CH_2-CH_3$). HR LSIMS calcd for $C_{19}H_{23}N_3O_5Na$ $(M+Na)^+$ 396.1535, found 396.1533. Anal. for $C_{19}H_{23}N_3O_5$: calcd: C, 61.11; H, 6.21; N, 11.25. Found: C, 60.79; H, 6.43; N, 11.30.

4.1.2.1.7. Ethyl 3-(2-amino-5-methoxybenzoyl)-1-cyclopentanecarbonyl-Δ²-pyrazoline-5-carboxylate ***26a***. Orange solid; yield 84%; mp 125–127 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, 1H, H-6′, $J_{6'-4'}$=2.9 Hz); 7.02 (dd, 1H, H-4′, $J_{4'-3'}$=9.0 Hz, $J_{4'-6'}$=2.9 Hz); 6.64 (d, 1H, H-3′, $J_{3'-4'}$=9.0 Hz); 6.03 (sa, 2H, $-NH_2$); 4.90 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.2 Hz); 4.21 (m, 2H, $-COO-CH_2-CH_3$); 3.76 (s, 3H, $-OCH_3$); 3.58 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.9 Hz); 3.51 (m, 1H, H-$1_{cyclopent.}$); 3.27 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, $J_{4b,5}$=6.2 Hz); 1.91–1.54 (m, 8H, H-2, H-3, H-4, H-$5_{cyclopent.}$); 1.27 (t, 3H, $-COO-CH_2-CH_3$, J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.63 (Ph–CO–); 175.69 (–N–CO–); 169.65 ($-COO-CH_2-CH_3$); 153.51 (C-3); 150.14 (C-5′); 146.88 (C-2′); 125.45 (C-4′); 118.62 (C-3′); 116.23 (C-1′); 114.38 (C-6′); 61.99 ($-COO-CH_2-CH_3$); 57.60 (C-5); 55.69 ($-OCH_3$); 42.37 (C-$1_{cyclopent.}$); 37.60 (C-4); 30.26, 29.47 (C-2, C-$5_{cyclopent.}$); 26.17, 26.06 (C-3, C-$4_{cyclopent.}$); 14.13 ($-COO-CH_2-CH_3$). HR LSIMS calcd for: $C_{20}H_{25}N_3O_5Na$ $(M+Na)^+$ 410.1691, found 410.1695. Anal. for $C_{20}H_{25}N_3O_5$: calcd: C, 62.00; H, 6.50; N, 10.85. Found: C, 61.71; H, 6.70; N, 10.86.

4.1.2.1.8. Ethyl 3-(2-amino-5-methoxybenzoyl)-1-cyclohexanecarbonyl-Δ²-pyrazoline-5-carboxylate ***27a***. Orange solid; yield 82%; mp 127–129 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, 1H, H-6′, $J_{6'-4'}$=2.9 Hz); 7.02 (dd, 1H, H-4′, $J_{4'-3'}$=9.0 Hz, $J_{4'-6'}$=2.9 Hz); 6.65 (d, 1H, H-3′, $J_{3'-4'}$=9.0 Hz); 6.07 (bs, 2H, $-NH_2$); 4.89 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.2 Hz); 4.21 (m, 2H, $-COO-CH_2-CH_3$); 3.78 (s, 3H, $-OCH_3$); 3.57 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.9 Hz); 3.26 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, $J_{4b,5}$=6.2 Hz); 3.15 (tt, 1H, H-$1_{cyclohex.}$, $J_{transdiaxial}$=11.6 Hz, J_{cis}=3.5 Hz); 2.02–1.46 (m, 10H, H-2, H-3, H-4, H-5, H-$6_{cyclohex.}$); 1.26 (t, 3H, $-COO-CH_2-CH_3$, J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.62 (Ph–CO–); 175.61 (–N–CO–); 169.62 ($-COO-CH_2-CH_3$); 153.63 (C-3); 150.18 (C-5′); 146.91 (C-2′); 125.50 (C-4′); 118.60 (C-3′); 116.18 (C-1′); 114.47 (C-6′); 61.97 ($-COO-CH_2-CH_3$); 57.48 (C-5); 55.89 ($-OCH_3$); 41.54 (C-$1_{cyclohex.}$); 37.53 (C-4); 28.98, 28.50 (C-2, C-$6_{cyclohex.}$); 25.83, 25.76, 25.59 (C-3, C-4, C-$5_{cyclohex.}$); 14.13 ($-COO-CH_2-CH_3$). HR LSIMS calcd for $C_{21}H_{27}N_3O_5Na$ $(M+Na)^+$ 424.1848, found 424.1845. Anal. for $C_{21}H_{27}N_3O_5$: calcd: C, 62.83; H, 6.78; N, 10.47. Found: C, 62.46; H, 6.85; N, 10.41.

*4.1.2.1.9. Ethyl 3-(2-amino-5-methoxybenzoyl)-1-benzoyl-Δ²-pyrazoline-5-carboxylate (****28a****).* Orange solid; yield 82%; mp 118–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (m, 3H, H-6′, H-$2_{benz.}$, H-$6_{benz.}$); 7.42 (m, 3H, H-$3_{benz.}$, H-$4_{benz.}$, H-$5_{benz.}$); 6.94 (dd, 1H, H-4′, $J_{4'-3'}$= 9.0 Hz, $J_{4'-6'}$=2.9 Hz); 6.61 (d, 1H, H-3′, $J_{3'-4'}$=9.0 Hz); 5.12 (dd, 1H, H-5, J_{5-4a}=12.7 Hz, J_{5-4b}=6.5 Hz); 4.28 (m, 2H, $-COO-CH_2-CH_3$); 3.64 (dd, 1H, H-4a, J_{4a-4b}= 18.7 Hz, J_{4b-5}=12.7 Hz); 3.36 (dd, 1H, H-4b, J_{4b-4a}= 18.7 Hz, J_{4b-5}=6.5 Hz); 3.26 (s, 3H, $-OCH_3$); 1.31 (t, 3H, $-COO-CH_2-CH_3$, J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.17 (Ph–CO–); 169.54, 168.19 ($-COO-CH_2-CH_3$, –N–CO–); 154.66 (C-3); 150.17 (C-5′); 146.86 (C-2′); 133.20 (C-$1_{benz.}$); 131.55 (C-$4_{benz.}$); 129.72 (C-$2_{benz.}$, C-$6_{benz.}$); 128.01 (C-$3_{benz.}$, C-$5_{benz.}$); 125.73 (C-4′); 118.56 (C-3′); 116.02 (C-1′); 114.04 (C-6′); 62.15 ($-COO-CH_2-CH_3$); 58.53 (C-5); 55.44 ($-OCH_3$); 37.38 (C-4); 14.17 ($-COO-CH_2-CH_3$). HR LSIMS calcd for $C_{21}H_{21}N_3O_5Na$ $(M+Na)^+$ 418.1378, found 418.1377. Anal. for $C_{21}H_{21}N_3O_5$: calcd: C, 63.79; H, 5.35; N, 10.63. Found: C, 63.51; H, 5.49; N, 10.70.

4.1.2.2. General procedure for the preparation of compounds 20b,c–28b,c. To a suspension of the corresponding nitroarene **11b**,**c**–**19b**,**c** (0.524 mmol) in refluxing water was added Fe (0.29 g, 5.24 mmol) and $FeSO_4$ (0.15 g, 0.524 mmol). The reaction mixture was refluxed for 3 h, filtered through Celite, and washed thoroughly with CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (3×15 mL) and EtOAc (3×15 mL). The organic phase was washed with brine, dried (Na_2SO_4), and evaporated. The residue was recrystallized from CH_2Cl_2/hexane.

4.1.2.2.1. Ethyl 1-acetyl-3-(2-amino-5-chlorobenzoyl)-Δ²-pyrazoline-5-carboxylate ***20b***. Orange solid; yield 95%; mp 193–195 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, 1H, H-6′, $J_{6'-4'}$=2.4 Hz); 7.25 (dd, 1H, H-4′,

$J_{4'-3'}$=8.8 Hz, $J_{4'-6'}$=2.4 Hz); 6.64 (d, 1H, H-3′, $J_{3'-4'}$=8.8 Hz); 6.28 (bs, 2H, $-NH_2$); 4.91 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}= 6.3 Hz); 4.24 (c, 2H, $-COO-CH_2-CH_3$, J=7.1 Hz); 3.61 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.9 Hz); 3.29 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.3 Hz); 2.40 (s, 3H, $-CO-CH_3$); 1.29 (t, 3H, $-COO-CH_2-CH_3$, J= 7.1 Hz).^{13}C NMR (100 MHz, $CDCl_3$) δ 186.15 (Ph–*C*O–); 170.21, 169.41 (–N–CO–, –*C*OO–CH_2-CH_3); 153.06 (C-3); 150.07 (C-2′); 135.13 (C-4′); 132.64 (C-6′); 120.48 (C-5′); 118.52 (C-3′); 116.91 (C-1′); 62.18 ($-COO-CH_2-CH_3$); 57.59 (C-5); 37.69 (C-4); 21.46 ($-CO-CH_3$); 14.11 ($-COO-CH_2-CH_3$). HR LSIMS calcd for $C_{15}H_{17}ClN_3O_4$ (M^++1) 338.0907, found 338.0906. Anal. for $C_{15}H_{16}ClN_3O_4$: calcd: C, 53.34; H, 4.77; N, 12.44. Found: C, 52.99; H, 4.59; N, 12.15.

4.1.2.2.2. Ethyl 3-(2-amino-5-chlorobenzoyl)-1-propionyl-Δ²-pyrazoline-5-carboxylate ***21b***. Orange solid; yield 95%; mp 148–150 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, 1H, H-6′, $J_{6'-4'}$=2.5 Hz); 7.24 (dd, 1H, H-4′, $J_{4'-3'}$=8.9 Hz, $J_{4'-6'}$=2.5 Hz); 6.63 (d, 1H, H-3′, $J_{3'-4'}$= 8.9 Hz); 6.28 (bs, 2H, $-NH_2$); 4.90 (dd, 1H, H-5, J_{5-4a}=12.8 Hz, J_{5-4b}= 6.3 Hz); 4.23 (c, 2H, $-COO-CH_2-CH_3$, J=7.1 Hz); 3.55 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}= 12.8 Hz); 3.25 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}= 6.3 Hz); 2.79 (m, 2H, $-CO-CH_2-CH_3$); 1.28 (t, 3H, $-COO-CH_2-CH_3$, J=7.1 Hz); 1.24 (t, 3H, $-CO-CH_2-CH_3$, J=7.5 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ 186.27 (Ph–*C*O–); 173.73 (–N–CO–); 169.52 (–*C*OO–CH_2-CH_3); 152.84 (C-3); 150.05 (C-2′); 135.08 (C-4′); 132.69 (C-6′); 120.47 (C-5′); 118.52 (C-3′); 116.98 (C-1′); 62.12 ($-COO-CH_2-CH_3$); 57.72 (C-5); 37.42 (C-4); 27.41 ($-CO-CH_2-CH_3$); 14.12 ($-COO-CH_2-CH_3$); 8.88 ($-CO-CH_2-CH_3$). HR LSIMS calcd for $C_{16}H_{18}ClN_3O_4Na$ $(M+Na)^+$ 374.0883, found 374.0882. Anal. for $C_{16}H_{18}ClN_3O_4$: calcd: C, 54.63; H, 5.16; N, 11.94 Found: C, 54.26; H, 4.76; N, 11.66.

4.1.2.2.3. Ethyl 3-(2-amino-5-chlorobenzoyl)-1-butyryl-Δ²-pyrazoline-5-carboxylate ***22b***. Orange solid; yield 95%; mp 144–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, 1H, H-6′, $J_{6'-4'}$=2.4 Hz); 7.26 (dd, 1H, H-4′, $J_{4'-3'}$=8.8 Hz, $J_{4'-6'}$=2.4 Hz); 6.65 (d, 1H, H-3′, $J_{3'-4'}$=8.8 Hz); 6.27 (bs, 2H, $-NH_2$); 4.92 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}= 6.2 Hz); 4.24 (c, 2H, $-COO-CH_2-CH_3$, J=7.1 Hz); 3.57 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.9 Hz); 3.27 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.2 Hz); 2.82 (pq, 1H, $-CO-CH_2-CH_2-CH_3$, Ha, J_{gem}=14.9 Hz, J_{Ha-CH2}= 7.3 Hz); 2.69 (pq, 1H, $-CO-CH_2-CH_2-CH_3$, Hb, J_{gem}=14.9 Hz, J_{Hb-CH2}=7.3 Hz); 1.79 (m, 2H, $-CO-CH_2-CH_2-CH_3$); 1.29 (t, 3H, $-COO-CH_2-CH_3$, J= 7.1 Hz); 1.04 (t, 3H, $-CO-CH_2-CH_2-CH_3$, J=7.4 Hz). ^{13}C NMR (75.57 MHz, $CDCl_3$) δ 186.26 (Ph–*C*O–); 173.03 (–N–CO–); 169.48 (–*C*OO–CH_2-CH_3); 152.82 (C-3); 150.04 (C-2′); 135.08 (C-4′); 132.72 (C-6′); 120.50 (C-5′); 118.51 (C-3′); 116.98 (C-1′); 62.11 ($-COO-CH_2-CH_3$); 57.66 (C-5); 37.42 (C-4); 36.02 ($-CO-CH_2-CH_2-CH_3$); 18.66 ($-CO-CH_2-CH_2-CH_3$); 14.11, 13.94 ($-COO-CH_2-CH_3$, $-CO-CH_2-CH_2-CH_3$). HR LSIMS calcd for $C_{17}H_{20}ClN_3O_4Na$ $(M+Na)^+$ 388.1040, found 388.1041. Anal. for $C_{17}H_{20}ClN_3O_4$: calcd: C, 55.82; H, 5.51; N, 11.49 Found: C, 55.47; H, 5.44; N, 11.27.

4.1.2.2.4. Ethyl 3-(2-amino-5-chlorobenzoyl)-1-pentanoyl-Δ²-pyrazoline-5-carboxylate ***23b***. Orange solid; yield 95%; mp 108–110 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, 1H, H-6′, $J_{6'-4'}$=2.4 Hz); 7.24 (dd, 1H, H-4′, $J_{4'-3'}$=8.8 Hz, $J_{4'-6'}$=2.4 Hz); 6.64 (d, 1H, H-3′, $J_{3'-4'}$= 8.8 Hz); 6.28 (bs, 2H, $-NH_2$); 4.90 (dd, 1H, H-5, J_{5-4a}= 12.9 Hz, J_{5-4b}=6.3 Hz); 4.23 (c, 2H, $-COO-CH_2-CH_3$, J=7.1 Hz); 3.56 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}= 12.9 Hz); 3.26 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}= 6.3 Hz); 2.83 (pq, 1H, $-CO-CH_2-CH_2-CH_2-CH_3$, Ha, J_{gem}=14.9 Hz, J_{Ha-CH2}=7.7 Hz); 2.70 (pq, 1H, $-CO-CH_2-CH_2-CH_2-CH_3$, Hb, J_{gem}=14.9 Hz, J_{Hb-CH2}= 7.7 Hz); 1.71 (m, 2H, $-CO-CH_2-CH_2-CH_2-CH_3$); 1.45 (m, 2H, $-CO-CH_2-CH_2-CH_2-CH_3$); 1.28 (t, 3H, $-COO-CH_2-CH_3$, J=7.1 Hz); 0.94 (t, 3H, $-CO-CH_2-CH_2-CH_2-CH_3$, J=7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.25 (Ph–*C*O–); 173.18 (–N–CO–); 169.48 (–*C*OO–CH_2-CH_3); 152.83 (C-3); 150.05 (C-2′); 135.08 (C-4′); 132.70 (C-6′); 120.50 (C-5′); 118.52 (C-3′); 116.99 (C-1′); 62.11 ($-COO-CH_2-CH_3$); 57.67 (C-5); 37.44 (C-4); 33.86 ($-CO-CH_2-CH_2-CH_2-CH_3$); 27.17 ($-CO-CH_2-CH_2-CH_2-CH_3$); 22.54 ($-CO-CH_2-CH_2-CH_2-CH_3$); 14.12, 13.84 ($-COO-CH_2-CH_3$, $-CO-CH_2-CH_2-CH_2-CH_3$). HR LSIMS calcd for $C_{18}H_{22}ClN_3O_4Na$ $(M+Na)^+$ 402.1196, found 402.1199. Anal. for $C_{18}H_{22}ClN_3O_4$: calcd: C, 56.92; H, 5.84; N, 11.06. Found: C, 56.52; H, 5.95; N, 10.92.

4.1.2.2.5. Ethyl 3-(2-amino-5-chlorobenzoyl)-1-cyclopropanecarbonyl-Δ²-pyrazoline-5-carboxylate ***24b***. Orange solid; yield 97%; mp 155–157 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, 1H, H-6′, $J_{6'-4'}$=2.4 Hz); 7.24 (dd, 1H, H-4′, $J_{4'-3'}$=8.8 Hz, $J_{4'-6'}$=2.3 Hz); 6.63 (d, 1H, H-3′, $J_{3'-4'}$=8.8 Hz); 6.28 (bs, 2H, $-NH_2$); 4.91 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.6 Hz); 4.22 (m, 2H, $-COO-CH_2-CH_3$); 3.57 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}= 12.9 Hz); 3.28 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}= 6.6 Hz); 2.57 (m, 1H, H-$1_{cycloprop.}$); 1.28 (t, 3H, $-COO-CH_2-CH_3$, J=7.1 Hz); 1.08, 0.98 (2m, H-2, H-$3_{cycloprop.}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.41 (Ph–*C*O–); 173.43 (–N–CO–); 169.52 (–*C*OO–CH_2-CH_3); 152.96 (C-3); 150.01 (C-2′); 135.03 (C-4′); 132.75 (C-6′); 120.46 (C-5′); 118.50 (C-3′); 117.07 (C-1′); 62.06 ($-COO-CH_2-CH_3$); 58.08 (C-5); 37.32 (C-4); 14.13 ($-COO-CH_2-CH_3$); 11.92 (C-$1_{cycloprop.}$); 9.32, 9.24 (C-2, C-$3_{cycloprop.}$). HR LSIMS: calcd for $C_{17}H_{18}ClN_3O_4Na$ $(M+Na)^+$ 386.0883; found: 386.0885. Anal. for $C_{17}H_{18}ClN_3O_4$: calcd: C, 56.13; H, 4.99; N, 11.55. Found: C, 55.96; H, 4.85; N, 11.44.

4.1.2.2.6. Ethyl 3-(2-amino-5-chlorobenzoyl)-1-cyclobutanecarbonyl-Δ²-pyrazoline-5-carboxylate ***25b***. Orange solid; yield 96%; mp 134–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, 1H, H-6′, $J_{6'-4'}$=2.5 Hz); 7.26 (dd, 1H, H-4′, $J_{4'-3'}$=8.8 Hz, $J_{4'-6'}$=2.5 Hz); 6.64 (d, 1H, H-3′, $J_{3'-4'}$=8.8 Hz); 6.25 (bs, 2H, $-NH_2$); 4.90 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.2 Hz); 4.24 (m, 2H, $-COO-CH_2-CH_3$); 3.79 (m, 1H, H-$1_{cyclobut.}$); 3.54 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.9 Hz); 3.24 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.2 Hz); 2.47–1.89 (m, 6H, H-2, H-3, H-$4_{cyclobut.}$); 1.30 (t, 3H, $-COO-CH_2-CH_3$, J= 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.30 (Ph–*C*O–); 174.43 (–N–CO–); 169.51 (–*C*OO–CH_2-CH_3); 152.69 (C-3); 149.98 (C-2′); 135.01 (C-4′); 132.77 (C-6′); 120.46 (C-5′); 118.48 (C-3′); 117.00 (C-1′); 62.10 ($-COO-CH_2-CH_3$);

57.75 (C-5); 37.87 (C-$1_{cyclobut.}$); 37.16 (C-4); 25.17, 24.41 (C-2, C-$4_{cyclobut.}$); 18.37 (C-$3_{cyclobut.}$); 14.13 (–COO–CH_2–CH_3). HR LSIMS calcd for $C_{18}H_{20}ClN_3O_4Na$ $(M+Na)^+$ 400.1040, found 400.1040. Anal. for $C_{18}H_{20}ClN_3O_4$: calcd: C, 55.52; H, 5.34; N, 11.12. Found: C, 57.11; H, 5.62; N, 10.87.

4.1.2.2.7. Ethyl 3-(2-amino-5-chlorobenzoyl)-1-cyclopentanecarbonyl-Δ^2-pyrazoline-5-carboxylate ***26b***. Orange solid; yield 96%; mp 135–137 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, 1H, H-6′, $J_{6'-4'}$=2.5 Hz); 7.24 (dd, 1H, H-4′, $J_{4'-3'}$=8.9 Hz, $J_{4'-6'}$=2.5 Hz); 6.63 (d, 1H, H-3′, $J_{3'-4'}$=8.9 Hz); 4.90 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.2 Hz); 4.22 (m, 2H, –COO–CH_2–CH_3); 3.55 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.9 Hz); 3.47 (m, 1H, H-$1_{cyclopent.}$); 3.24 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.2 Hz); 2.11–1.58 (m, 8H, H-2, H-3, H-4, H-$5_{cyclopent.}$); 1.28 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.46 (Ph–*C*O–); 175.86 (–N–CO–); 169.54 (–*C*OO–CH_2–CH_3); 152.44 (C-3); 150.00 (C-2′); 135.00 (C-4′); 132.87 (C-6′); 120.57 (C-5′); 118.50 (C-3′); 117.16 (C-1′); 62.05 (–COO–*C*H_2–CH_3); 57.89 (C-5); 42.62 (C-$1_{cyclopent.}$); 37.21 (C-4); 30.11, 29.30 (C-2, C-$5_{cyclopent.}$); 26.26, 26.14 (C-3, C-$4_{cyclopent.}$); 14.13 (–COO–CH_2–*C*H_3). HR LSIMS calcd for $C_{19}H_{22}ClN_3O_4Na$ $(M+Na)^+$ 414.1196, found 414.1194. Anal. for $C_{19}H_{22}ClN_3O_4$: calcd: C, 58.24; H, 5.66; N, 10.72. Found: C, 58.08; H, 5.92; N, 10.70.

4.1.2.2.8. Ethyl 3-(2-amino-5-chlorobenzoyl)-1-cyclohexanecarbonyl-Δ^2-pyrazoline-5-carboxylate ***27b***. Orange solid; yield 95%; mp 135–137 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, 1H, H-6′, $J_{6'-4'}$=2.4 Hz); 7.25 (dd, 1H, H-4′, $J_{4'-3'}$=8.8 Hz, $J_{4'-6'}$=2.4 Hz); 6.64 (d, 1H, H-3′, $J_{3'-4'}$=8.8 Hz); 6.26 (bs, 2H, $-NH_2$); 4.88 (dd, 1H, H-5, J_{5-4a}=12.8 Hz, J_{5-4b}=6.1 Hz); 4.21 (m, 2H, –COO–CH_2–CH_3); 3.53 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.8 Hz); 3.24 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.1 Hz); 3.11 (tt, 1H, H-$1_{cyclohex.}$, $J_{transdiaxial}$=11.5 Hz, J_{cis}=3.4 Hz); 2.05–1.19 (m, 10H, H-2, H-3, H-4, H-5, H-$6_{cyclohex.}$); 1.27 (t, 3H, –COO–CH_2–*C*H_3, J=7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.20 (Ph–*C*O–); 175.79 (–N–CO–); 169.49 (–*C*OO–CH_2–CH_3); 152.67 (C-3); 150.07 (C-2′); 135.01 (C-4′); 132.79 (C-6′); 120.58 (C-5′); 118.50 (C-3′); 117.14 (C-1′); 62.02 (–COO–*C*H_2–CH_3); 57.75 (C-5); 42.11 (C-$1_{cyclohex.}$); 37.19 (C-4); 28.60, 28.58 (C-2, C-$6_{cyclohex.}$); 25.95, 25.89, 25.68 (C-3, C-4, C-$5_{cyclohex.}$); 14.12 (–COO–CH_2–*C*H_3). HR LSIMS calcd for $C_{20}H_{24}ClN_3O_4Na$ $(M+Na)^+$ 428.1355, found 428.1353. Anal. for $C_{20}H_{24}ClN_3O_4$: calcd: C, 59.18; H, 5.96; N, 10.35. Found: C, 58.80; H, 5.62; N, 10.05.

4.1.2.2.9. Ethyl 3-(2-amino-5-chlorobenzoyl)-1-benzoyl-Δ^2-pyrazoline-5-carboxylate ***28b***. Orange solid; yield 95%; mp 181–183 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, 1H, H-6′, $J_{6'-4'}$=2.4 Hz); 7.96 (dd, 2H, H-$2_{benz.}$, H-$6_{benz.}$, $J_{2\text{-}3benz.}$=7.4 Hz, $J_{2\text{-}4benz.}$=1.6 Hz); 7.50 (m, 3H, H-3, H-$4_{benz.}$, H-$5_{benz.}$); 7.20 (dd, 1H, H-4′, $J_{4'-3'}$=8.9 Hz, $J_{4'-6'}$=2.4 Hz); 6.59 (d, 1H, H-3′, $J_{3'-4'}$=8.9 Hz); 6.25 (bs, 2H, $-NH_2$); 5.14 (dd, 1H, H-5, J_{5-4a}=12.8 Hz, J_{5-4b}=6.4 Hz); 4.28 (m, 2H, –COO–CH_2–CH_3); 3.61 (dd, 1H, H-4a, J_{4a-4b}=18.8 Hz, J_{4a-5}=12.8 Hz); 3.32 (dd, 1H, H-4b, J_{4b-4a}=18.8 Hz, J_{4b-5}=6.4 Hz); 1.31 (t, 3H, –COO–CH_2–*C*H_3, J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.90 (Ph–*C*O–); 169.48 (–*C*OO–CH_2–CH_3); 167.87 (–N–CO–); 153.95 (C-3); 150.09 (C-2′); 135.11 (C-4′); 133.48 (C-$1_{benz.}$); 132.53 (C-6′); 131.93 (C-$4_{benz.}$); 129.89 (C-2, C-$6_{benz.}$); 128.26 (C-3, C-$5_{benz.}$); 120.54 (C-5′); 118.52 (C-3′); 116.88 (C-1′); 62.22 (–COO–*C*H_2–CH_3); 58.83 (C-5); 36.84 (C-4); 14.18 (–COO–CH_2–*C*H_3). HR LSIMS calcd for $C_{20}H_{18}ClN_3O_4Na$ $(M+Na)^+$ 422.0883, found 422.0881. Anal. for $C_{20}H_{18}ClN_3O_4$: calcd: C, 60.08; H, 4.54; N, 10.51. Found: C, 59.80; H, 4.17; N, 10.46.

4.1.2.2.10. Ethyl 1-acetyl-3-(2-aminobenzoyl)-Δ^2-pyrazoline-5-carboxylate ***20c***. Yellow solid; yield 95%; mp100–102 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (dd, 1H, H-6′, $J_{6'-5'}$=8.2 Hz, $J_{6'-4'}$=1.5 Hz); 7.28 (ddd, 1H, H-4′, $J_{4'-3'}$=8.4 Hz, $J_{4'-5'}$=7.0 Hz, $J_{4'-6'}$=1.5 Hz); 6.71 (d, 1H, H-3′, $J_{3'-4'}$=8.4 Hz); 6.69 (dd, 1H, H-5′, $J_{5'-6'}$=8.2 Hz, $J_{5'-4'}$=7.0 Hz); 4.90 (dd, 1H, H-5, J_{5-4a}=12.8 Hz, J_{5-4b}=6.1 Hz); 4.23 (c, 2H, –COO–*C*H_2–CH_3, J=7.1 Hz); 3.60 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.8 Hz); 3.27 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.1 Hz); 2.40 (s, 3H, –CO–CH_3); 1.28 (t, 3H, –COO–CH_2–*C*H_3, J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.53 (Ph–*C*O–); 170.12, 169.51 (–N–CO–, –*C*OO–CH_2–CH_3); 153.38 (C-3); 151.20 (C-2′); 135.25 (C-4′); 133.62 (C-6′); 117.31 (C-3′); 116.92 (C-1′); 116.31 (C-5′); 62.08 (–COO–*C*H_2–CH_3); 57.52 (C-5); 37.90 (C-4); 21.46 (–CO–*C*H_3); 14.12 (–COO–CH_2–*C*H_3). HR LSIMS calcd for $C_{15}H_{17}N_3O_4Na$ $(M+Na)^+$ 326.1116, found 326.1116). Anal. for $C_{15}H_{17}N_3O_4$: calcd: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.77; H, 5.60; N, 14.25.

4.1.2.2.11. Ethyl 3-(2-aminobenzoyl)-1-propionyl-Δ^2-pyrazoline-5-carboxylate ***21c***. Yellow solid; yield 95%; mp132–133 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (dd, 1H, H-6′, $J_{6'-5'}$=8.2 Hz, $J_{6'-4'}$=1.5 Hz); 7.32 (ddd, 1H, H-4′, $J_{4'-3'}$=8.5 Hz, $J_{4'-5'}$=7.0 Hz, $J_{4'-6'}$=1.5 Hz); 6.72 (d, 1H, H-3′, $J_{3'-4'}$=8.5 Hz); 6.70 (ddd, 1H, H-5′, $J_{5'-6'}$=8.2 Hz, $J_{5'-4'}$=7.0 Hz, $J_{5'-3'}$=1.1 Hz); 4.90 (dd, 1H, H-5, J_{5-4a}=12.8 Hz, J_{5-4b}=6.2 Hz); 4.23 (c, 2H, –COO–*C*H_2–CH_3, J=7.1 Hz); 3.58 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.8 Hz); 3.25 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.2 Hz); 2.77 (m, 2H, –CO–*C*H_2–CH_3); 1.28 (t, 3H, –COO–CH_2–*C*H_3, J=7.1 Hz); 1.20 (t, 3H, –CO–CH_2–*C*H_3, J=7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.62 (Ph–*C*O–); 173.60 (–N–CO–), 169.61 (–*C*OO–CH_2–CH_3); 153.14 (C-3); 150.92 (C-2′); 135.19 (C-4′); 133.62 (C-6′); 117.41 (C-3′); 117.13 (C-1′); 116.45 (C-5′); 62.02 (–COO–*C*H_2–CH_3); 57.64 (C-5); 37.59 (C-4); 27.27 (–CO–*C*H_2–CH_3); 14.11 (–COO–CH_2–*C*H_3); 8.75 (–CO–CH_2–*C*H_3). HR LSIMS calcd for $C_{16}H_{19}N_3O_4Na$ $(M+Na)^+$ 340.1273, found 340.1273. Anal. for $C_{16}H_{19}N_3O_4$: calcd: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.26; H, 6.32; N, 13.13.

4.1.2.2.12. Ethyl 3-(2-aminobenzoyl)-1-butyryl-Δ^2-pyrazoline-5-carboxylate ***22c***. Yellow solid; yield 95%; mp 90–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, 1H, H-6′, $J_{6'-5'}$=8.2 Hz); 7.28 (m, H-4′); 6.67 (d, 1H, H-3′, $J_{3'-4'}$=8.6 Hz); 6.66 (m, H-5′); 6.26 (bs, 2H, $-NH_2$); 4.90 (dd, 1H, H-5, J_{5-4a}=12.8 Hz, J_{5-4b}=6.1 Hz); 4.22 (c, 2H, –COO–*C*H_2–CH_3, J=7.1 Hz); 3.57 (dd, 1H, H-4a, J_{4a-4b}=18.6 Hz, J_{4a-5}=12.8 Hz); 3.25 (dd, 1H, H-4b,

J_{4b-4a}=18.6 Hz, J_{4b-5}=6.1 Hz); 2.78 (pq, 1H, Ha, –CO–CH_2–CH_2–CH_3, J_{gem}=15.0 Hz, J_{Ha-CH2}=7.4 Hz); 2.66 (pq, 1H, Hb, –CO–CH_2–CH_2–CH_3, J_{gem}=15.0 Hz, J_{Hb-CH2}=7.4 Hz); 1.74 (m, 2H, –CO–CH_2–CH_2–CH_3); 1.27 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz); 0.99 (t, 3H, –CO–CH_2–CH_2–CH_3, J=7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.59 (Ph–*C*O–); 172.85 (–N–CO–), 169.60 (–*C*OO–CH_2–CH_3); 153.15 (C-3); 151.64 (C-2′); 135.20 (C-4′); 133.62 (C-6′); 117.31 (C-3′); 116.65 (C-1′); 115.95 (C-5′); 61.99 (–COO–*C*H_2–CH_3); 57.54 (C-5); 37.63 (C-4); 35.68 (–CO–*C*H_2–CH_2–CH_3); 18.36 (–CO–CH_2–*C*H_2–CH_3) 14.09, 13.83 (–COO–CH_2–*C*H_3, –CO–CH_2–CH_2–*C*H_3). HR LSIMS calcd for $C_{17}H_{21}N_3O_4Na$ $(M+Na)^+$ 354.1429, found 354.1433. Anal. for $C_{17}H_{21}N_3O_4$: calcd: C, 61.62; H, 6.39; N, 12.68. Found: C, 61.24; H, 6.45; N, 12.63.

4.1.2.2.13. Ethyl 3-(2-aminobenzoyl)-1-pentanoyl-Δ²-pyrazoline-5-carboxylate ***23c***. Yellow solid; yield 95%; mp 88–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, 1H, H-6′, $J_{6'-5'}$=8.2 Hz); 7.30 (m, H-4′); 6.68 (d, 1H, H-3′, $J_{3'-4'}$=8.4 Hz); 6.66 (pt, 1H, H-5′, $J_{5'-6'}$=8.2 Hz, $J_{5'-4'}$=7.1 Hz); 6.24 (bs, 2H, $-NH_2$); 4.90 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.1 Hz); 4.22 (c, 2H, –COO–CH_2–CH_3, J=7.1 Hz); 3.58 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.9 Hz); 3.25 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.1 Hz); 2.80 (pq, 1H, Ha, –CO–CH_2–CH_2–CH_2–CH_3, J_{gem}=15.0 Hz, J_{Ha-CH2}=7.6 Hz); 2.68 (pq, 1H, Hb, –CO–CH_2–CH_2–CH_2–CH_3, J_{gem}=15.0 Hz, J_{Hb-CH2}=7.6 Hz); 1.70 (m, 2H, –CO–CH_2–CH_2–CH_2–CH_3); 1.40 (m, 2H, –CO–CH_2–CH_2–CH_2–CH_3); 1.28 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz); 0.92 (t, 3H, –CO–CH_2–CH_2–CH_2–*C*H_3, J=7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.61 (Ph–*C*O–); 173.05 (–N–CO–), 169.60 (–*C*OO–CH_2–CH_3); 153.15 (C-3); 151.63 (C-2′); 135.22 (C-4′); 133.66 (C-6′); 117.11 (C-3′); 116.70 (C-1′); 115.97 (C-5′); 62.01 (–COO–*C*H_2–CH_3); 57.56 (C-5); 37.65 (C-4); 33.62 (–CO–*C*H_2–CH_2–CH_2–CH_3); 27.03 (–CO–CH_2–*C*H_2–CH_2–CH_3) 22.44 (–CO–CH_2–CH_2–*C*H_2–CH_3); 14.11, 13.87 (–COO–CH_2–*C*H_3, –CO–CH_2–CH_2–CH_2–*C*H_3). HR LSIMS calcd for $C_{18}H_{23}N_3O_4Na$ $(M+Na)^+$ 368.1586, found 368.1589. Anal. for $C_{18}H_{23}N_3O_4$: calcd: C, 62.59; H, 6.71; N, 12.17. Found: C, 62.24; H, 6.90; N, 12.13.

4.1.2.2.14. Ethyl 3-(2-aminobenzoyl)-1-cyclopropane-carbonyl-Δ²-pyrazoline-5-carboxylate ***24c***. Yellow solid; yield 95%; mp 88–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (dd, 1H, H-6′, $J_{6'-5'}$=8.8 Hz, $J_{6'-4'}$=1.6 Hz); 7.30 (ddd, 1H, H-4′, $J_{4'-3'}$=8.3 Hz, $J_{4'-5'}$=7.0 Hz, $J_{4'-6'}$=1.6 Hz); 6.67 (m, H-5′); 6.24 (bs, 2H, $-NH_2$); 4.90 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.4 Hz); 4.22 (m, 2H, –COO–CH_2–CH_3); 3.60 (dd, 1H, H-4a, J_{4a-4b}=18.6 Hz, J_{4a-5}=12.8 Hz); 3.27 (dd, 1H, H-4b, J_{4b-4a}=18.6 Hz, J_{4b-5}=6.4 Hz); 2.55 (m, 1H, H-$1_{cycloprop.}$); 1.27 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz); 1.15–1.05, 0.96–0.89 (2m, 4H, H-2, H-$3_{cycloprop.}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.74 (Ph–*C*O–); 173.34 (–N–CO–), 169.63 (–*C*OO–CH_2–CH_3); 153.36 (C-3); 151.58 (C-2′); 135.17 (C-4′); 133.73 (C-6′); 117.08 (C-3′); 116.78 (C-1′); 116.02 (C-5′); 61.97 (–COO–*C*H_2–CH_3); 57.94 (C-5); 37.55 (C-4); 14.12 (–COO–CH_2–*C*H_3); 11.80 (C-$1_{cycloprop.}$); 9.27, 9.21 (C-2, C-$3_{cycloprop.}$). HR LSIMS calcd for $C_{17}H_{19}N_3O_4Na$ $(M+Na)^+$ 352.1269, found 352.1273. Anal. for $C_{17}H_{19}N_3O_4$: calcd: C, 62.00; H, 5.81; N, 12.76. Found: C, 61.81; H, 6.20; N, 12.62.

4.1.2.2.15. Ethyl 3-(2-aminobenzoyl)-1-cyclobutane-carbonyl-Δ²-pyrazoline-5-carboxylate ***25c***. Yellow solid; yield 96%; mp 104–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, 1H, H-6′, $J_{6'-5'}$=7.6 Hz); 7.31 (m, 1H, H-4′); 6.68 (d, 1H, H-3′, $J_{3'-4'}$=7.9 Hz); 6.67 (m, 1H, H-5′); 6.22 (bs, 2H, $-NH_2$); 4.89 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.1 Hz); 4.23 (c, 2H, –COO–CH_2–CH_3, J=7.1 Hz); 3.77 (m, 1H, H-$1_{cyclobut.}$); 3.55 (dd, 1H, H-4a, J_{4a-4b}=18.6 Hz, J_{4a-5}=12.9 Hz); 3.23 (dd, 1H, H-4b, J_{4b-4a}=18.6 Hz, J_{4b-5}=6.1 Hz); 2.46–2.16, 2.04–1.85 (m, 6H, H-2, H-3, H-$4_{cyclobut.}$); 1.29 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.72 (Ph–*C*O–); 174.17 (–N–CO–), 169.62 (–*C*OO–CH_2–CH_3); 153.03 (C-3); 151.57 (C-2′); 135.19 (C-4′); 133.75 (C-6′); 117.08 (C-3′); 116.78 (C-1′); 115.93 (C-5′); 62.01 (–COO–*C*H_2–CH_3); 57.66 (C-5); 37.69 (C-$1_{cyclobut.}$); 37.40 (C-4); 25.15, 24.48 (C-2, C-$4_{cyclobut.}$); 18.33 (C-$3_{cyclobut.}$); 14.13 (–COO–CH_2–*C*H_3). HR LSIMS calcd for $C_{18}H_{21}N_3O_4Na$ $(M+Na)^+$ 366.1429, found 366.1430. Anal. for $C_{18}H_{21}N_3O_4$: calcd: C, 62.96; H, 6.16; N, 12.24. Found: C, 62.59; H, 6.19; N, 12.14.

4.1.2.2.16. Ethyl 3-(2-aminobenzoyl)-1-cyclopentane-carbonyl-Δ²-pyrazoline-5-carboxylate ***26c***. Yellow solid; yield 96%; mp 118–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, 1H, H-6′, $J_{6'-5'}$=8.1 Hz); 7.30 (m, 1H, H-4′); 6.68 (d, 1H, H-3′, $J_{3'4'}$=8.3 Hz); 6.66 (m, 1H, H-5′); 6.22 (bs, 2H, $-NH_2$); 4.90 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.1 Hz); 4.21 (m, 2H, –COO–CH_2–CH_3); 3.57 (dd, 1H, H-4a, J_{4a-4b}=18.6 Hz, J_{4a-5}=12.9 Hz); 3.47 (m, 1H, H-$1_{cyclopent.}$); 3.24 (dd, 1H, H-4b, J_{4b-4a}=18.6 Hz, J_{4b-5}=6.1 Hz); 2.04–1.55 (m, 8H, H-2, H-3, H-4, H-$5_{cyclopent.}$); 1.27 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.72 (Ph–*C*O–); 175.69 (–N–CO–), 169.65 (–*C*OO–CH_2–CH_3); 152.85 (C-3); 151.58 (C-2′); 135.15 (C-4′); 133.69 (C-6′); 117.09 (C-3′); 116.78 (C-1′); 115.93 (C-5′); 61.93 (–COO–*C*H_2–CH_3); 57.71 (C-5); 42.23 (C-$1_{cyclopent.}$); 37.42 (C-4); 30.06, 29.35 (C-2, C-$5_{cyclopent.}$); 26.33, 26.20 (C-3, C-$4_{cyclopent.}$); 14.10 (–COO–CH_2–*C*H_3). HR LSIMS calcd for $C_{19}H_{23}N_3O_4Na$ $(M+Na)^+$ 380.1586, found 380.1585. Anal. for $C_{19}H_{23}N_3O_4$: calcd: C, 63.85; H, 6.49; N, 11.76. Found: C, 63.63; H, 6.58; N, 11.76.

4.1.2.2.17. Ethyl 3-(2-aminobenzoyl)-1-cyclohexane-carbonyl-Δ²-pyrazoline-5-carboxylate ***27c***. Yellow solid; yield 96%; mp 117–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (dd, 1H, H-6′, $J_{6'-5'}$=8.2 Hz, $J_{6'-4'}$=1.2 Hz); 7.31 (m, 1H, H-4′); 6.68 (d, 1H, H-3′, $J_{3'4'}$=8.3 Hz); 6.66 (m, 1H, H-5′); 6.24 (bs, 2H, $-NH_2$); 4.89 (dd, 1H, H-5, J_{5-4a}=12.9 Hz, J_{5-4b}=6.1 Hz); 4.21 (m, 2H, –COO–CH_2–CH_3); 3.56 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}=12.9 Hz); 3.24 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}=6.1 Hz); 3.08 (tt, H-$1_{cyclohex.}$, $J_{transdiaxial}$=11.5 Hz, J_{cis}=3.2 Hz); 2.02–1.19 (m, 10H, H-2, H-3, H-4, H-5, H-$6_{cyclohex.}$); 1.26 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.62 (Ph–*C*O–); 175.61 (–N–CO–), 169.72 (–*C*OO–CH_2–CH_3); 152.94 (C-3); 151.60 (C-2′); 135.16 (C-4′); 133.65 (C-6′); 117.12 (C-3′); 116.78 (C-1′); 115.89 (C-5′); 61.94

(–COO–CH_2–CH_3); 57.58 (C-5); 41.86 (C-$1_{cyclohex.}$); 37.40 (C-4); 28.99, 28.52 (C-2, C-$6_{cyclohex.}$); 25.91, 25.76, 25.60 (C-3, C-4, C-$5_{cyclohex.}$); 14.10 (–COO–CH_2–CH_3). HR LSIMS calcd for $C_{20}H_{25}N_3O_4Na$ $(M+Na)^+$ 394.1742, found 394.1739. Anal. for $C_{20}H_{25}N_3O_4$: calcd: C, 64.67; H, 6.78; N, 11.31. Found: C, 64.44; H, 7.06; N, 11.26.

4.1.2.2.18. Ethyl 3-(2-aminobenzoyl)-1-benzoyl-Δ^2-pyrazoline-5-carboxylate ***28c***. Yellow solid; yield 95%; mp 125–127 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (dd, 1H, H-6′, $J_{6'-5'}$=8.3 Hz, $J_{6'-4'}$=1.2 Hz); 7.95 (dd, 2H, H-2, H-$6_{benz.}$, $J_{2\text{-}3benz.}$=7.1 Hz, $J_{2\text{-}4benz.}$=1.5 Hz); 7.46 (m, 3H, H-4′, H-3, H-$5_{benz.}$); 7.27 (m, 1H, H-$4_{benz.}$); 6.65 (d, 1H, H-3′, $J_{3'4'}$=8.3 Hz); 6.56 (pt, 1H, H-5′, $J_{5'-6'}$=8.3 Hz, $J_{5'-4'}$= 7.0 Hz); 6.24 (sa, 2H, $-NH_2$); 5.13 (dd, 1H, H-5, J_{5-4a}= 12.8 Hz, J_{5-4b}=6.4 Hz); 4.27 (c, 2H, –COO–CH_2–CH_3, J=7.1 Hz); 3.64 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}= 12.8 Hz); 3.32 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}= 6.4 Hz); 1.31 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.34 (Ph–*C*O–); 169.56 (–*C*OO–CH_2–CH_3); 167.67 (–N–CO–); 154.18 (C-3); 151.68 (C-2′); 135.23 (C-4′); 133.70 (C-6′); 132.83 (C-$1_{benz.}$); 131.84 (C-$4_{benz.}$); 130.13 (C-2, C-$6_{benz.}$); 127.89 (C-3, C-$5_{benz.}$); 117.08 (C-3′);116.70 (C-1′); 115.99 (C-5′); 62.11 (–COO–*C*H_2–CH_3); 58.52 (C-5); 37.12 (C-4); 14.17 (–COO–CH_2–*C*H_3). HR LSIMS calcd for $C_{20}H_{19}N_3O_4Na$ $(M+Na)^+$ 388.1273, found 388.1273. Anal. for $C_{20}H_{25}N_3O_4$: calcd: C, 65.74; H, 5.24; N, 11.50. Found: C, 65.41; H, 4.97; N, 11.42.

4.1.2.3. General procedure for the preparation of compounds 29 and 30. A mixture of nitroarene **20a** or **22a** (0.511 mmol) and $SnCl_2$ (2.55 mmol) was dissolved in ethanol and was stirred under reflux for 1 h. The solution was neutralized to pH=7 with $NaHCO_3$, extracted with ethyl acetate (2×15 mL), and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was recrystallized from CH_2Cl_2–hexane.

4.1.2.3.1. Ethyl 1-acetyl-3-(5-methoxybenzo[c]isoxazol-3-yl)-Δ^2-pyrazoline-5-carboxylate ***29***. Orange solid; yield 100%; mp 156–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, 1H, H-7′, $J_{7'-6'}$=9.5 Hz); 7.09 (dd, 1H, H-6′, $J_{6'-7'}$= 9.5 Hz, $J_{6'-4'}$=2.2 Hz); 6.98 (d, 1H, H-4′, $J_{4'-6'}$=2.2 Hz); 5.03 (dd, 1H, H-5, J_{5-4a}=12.6 Hz, J_{5-4b}=6.0 Hz); 4.25 (c, 2H, –COO–CH_2–CH_3, J=7.1 Hz); 3.87 (s, 3H, $-OCH_3$); 3.79 (dd, 1H, H-4a, J_{4a-4b}=18.2 Hz, J_{4a-5}=12.6 Hz); 3.51 (dd, 1H, H-4b, J_{4b-4a}=18.2 Hz, J_{4b-5}=6.0 Hz); 2.47 (s, 3H, –CO–CH_3); 1.30 (t, 3H, –COO–CH_2–CH_3, J= 7.1 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ 169.43, 169.36 (–*C*OO–CH_2–CH_3, –N–CO–); 158.15 (C-5′); 155.57, 154.97 (C-3, C-7′a); 144.35 (C-3′); 128.63 (C-6′); 117.46 (C-3′a); 117.09 (C-7′); 94.81 (C-4′); 62.25 (–COO–*C*H_2–CH_3); 57.35 (C-5); 55.52 ($-OCH_3$); 37.28 (C-4); 21.41 (–CO–*C*H_3); 14.15 (–COO–CH_2–*C*H_3). HR LSIMS calcd for $C_{16}H_{17}N_3O_5Na$ $(M+Na)^+$ 354.1069, found 354.1065. Anal. for $C_{16}H_{17}N_3O_5$: calcd: C, 58.00; H, 5.17; N, 12.68. Found: C, 57.68; H, 5.13; N, 12.49.

4.1.2.3.2. Ethyl 1-butyryl-3-(5-methoxybenzo[c]isoxazol-3-yl)-Δ^2-pyrazoline-5-carboxylate ***30***. Orange solid; yield 100%; mp 144–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, 1H, H-7′, $J_{7'-6'}$=9.6 Hz); 7.09 (dd, 1H, H-6′, $J_{6'-7'}$= 9.6 Hz, $J_{6'-4'}$=2.3 Hz); 6.99 (d, 1H, H-4′, $J_{4'-6'}$=2.3 Hz); 5.03 (dd, 1H, H-5, J_{5-4a}=12.6 Hz, J_{5-4b}= 6.0 Hz); 4.24 (c, 2H, –COO–CH_2–CH_3, J= 7.1 Hz); 3.87 (s, 3H, $-OCH_3$); 3.78 (dd, 1H, H-4a, J_{4a-4b}=18.2 Hz, J_{4a-5}=12.6 Hz); 3.50 (dd, 1H, H-4b, J_{4b-4a}=18.2 Hz, J_{4b-5}=6.0 Hz); 2.86 (pq, 1H, –CO–CH_2–CH_2–CH_3, H-a, J_{gem}=14.7 Hz, J_{Ha-CH2}= 7.5 Hz); 2.74 (pq, 1H, –CO–CH_2–CH_2–CH_3, H-b, J_{gem}= 14.7 Hz, J_{Hb-CH2}= 7.5 Hz); 1.79 (m, 2H, –CO–CH_2–CH_2–CH_3); 1.29 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz); 1.03 (t, 3H, –CO–CH_2–CH_2–CH_3, J=7.4 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ 172.09 (–N–CO–); 169.50 (–*C*OO–CH_2–CH_3); 158.12 (C-5′); 155.55, 154.14 (C-3, C-7′a); 144.11 (C-3′); 128.59 (C-6′); 117.43 (C-3′a); 117.10 (C-7′); 94.85 (C-4′); 62.18 (–COO–*C*H_2–CH_3); 57.44 (C-5); 55.46 ($-OCH_3$); 37.01 (–CO–*C*H_2–CH_2–CH_3); 36.03 (C-4); 18.49 (–CO–CH_2–*C*H_2–CH_3); 14.14, 14.11 (–COO–CH_2–*C*H_3, –CO–CH_2–CH_2–*C*H_3). HR LSIMS calcd for $C_{18}H_{21}N_3O_5Na$ $(M+Na)^+$ 382.1378, found 382.1379. Anal. for $C_{18}H_{21}N_3O_5$: calcd: C, 60.16; H, 5.89; N, 11.69. Found: C, 60.38; H, 6.19; N, 11.35.

4.1.2.4. General procedure for the preparation of compounds 31 and 32. A mixture of nitroarene **21a** or **24a** (0.512 mmol) and 10% Pd/C (60 mg) was dissolved in methanol (30 mL) and stirred under a hydrogen atmosphere (70 psi) for 5 h. The mixture was filtered through celite and evaporated. The resultant residue was dissolved in CH_2Cl_2, and this solution was washed with water, dried (Na_2SO_4), and concentrated. The resultant solid was dissolved and purified by flash chromatography (ethyl acetate–hexane 1:3).

4.1.2.4.1. Ethyl 5-(2-amino-5-methoxybenzoyl)-2-propionylpyrazolidine-3-carboxylate4 ***31***. Orange solid; yield 20%; mp 81–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 1H, H-6′); 7.02 (dd, 1H, H-4′, $J_{4'-3'}$=8.9 Hz, $J_{4'-6'}$= 2.8 Hz); 6.66 (d, 1H, H-3′, $J_{3'-4'}$=8.9 Hz); 6.06 (bs, 2H, $-NH_2$); 5.33 (d, 1H, H-1, J_{1-5}=11.7 Hz); 4.96 (dd, 1H, H-3, J_{3-4a}=9.2 Hz, J_{3-4b}=6.5 Hz); 4.59 (m, 1H, H-5); 4.17 (m, 2H, –COO–CH_2–CH_3); 3.76 (s, 3H, $-OCH_3$); 2.93 (ddd, 1H, H-4a, J_{4a-4b}=13.0 Hz, J_{4a-3}=9.2 Hz, J_{4a-5}= 8.0 Hz); 2.61 (m, 2H, –CO–CH_2–CH_3); 2.12 (ddd, 1H, H-4b, J_{4b-4a}=13.0 Hz, J_{4b-5}=9.4 Hz, J_{4b-3}=6.5 Hz); 1.24 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz); 1.14 (t, 3H, –CO–CH_2–CH_3, J=7.5 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ 196.09 (Ph–*C*O–); 175.13 (–N–CO–); 171.33 (–*C*OO–CH_2–CH_3); 150.29 (C-5′); 146.50 (C-2′); 124.91 (C-4′); 119.14 (C-3′); 114.99 (C-1′); 112.45 (C-6′); 62.69 (C-5); 61.69 (–COO–*C*H_2–CH_3); 58.06 (C-3); 56.15 ($-OCH_3$); 37.97 (C-4); 26.95 (–CO–*C*H_2–CH_3); 14.17 (–COO–CH_2–*C*H_3); 9.15 (–CO–CH_2–*C*H_3). HR LSIMS calcd for $C_{17}H_{23}N_3O_5Na$ $(M+Na)^+$ 372.1535, found 372.1534. Anal. for $C_{17}H_{23}N_3O_5$: calcd: C, 58.44; H, 6.64; N, 12.03. Found: C, 58.06; H, 6.35; N, 12.27.

4.1.2.4.2. Ethyl 5-(2-amino-5-methoxybenzoyl)-2-cyclopropanecarbonylpyrazolidine-3-carboxylate ***32***. Orange solid; yield 19%; mp 78–80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, 1H, H-6′, $J_{6'-4'}$=2.8 Hz); 7.02 (dd, 1H, H-4′, $J_{4'-3'}$=9.0 Hz, $J_{4'-6'}$=2.8 Hz); 6.68 (d, 1H, H-3′, $J_{3'-4'}$=9.0 Hz); 6.03 (bs, 2H, $-NH_2$); 5.13 (d, 1H, H-1, J_{1-5}=8.7 Hz); 4.98 (m, 1H, H-5); 4.74 (dd, 1H, H-3, J_{3-4a}= 9.4 Hz, J_{3-4b}=3.6 Hz); 4.23 (c, 2H, –COO–CH_2–CH_3,

J=7.1 Hz); 3.77 (s, 3H, –OCH_3); 2.64 (m, 1H, H-4a); 2.40 (m, 2H, H-4b, H-$1_{cycloprop.}$); 1.29 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz); 1.00–0.66 (m, 4H, H-2, H-$3_{cycloprop.}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.50 (Ph–*C*O–); 174.44 (–N–CO–); 171.96 (–*C*OO–CH_2–CH_3); 150.08 (C-5′); 146.40 (C-2′); 124.36 (C-4′); 118.95 (C-3′); 115.44 (C-1′); 113.40 (C-6′); 61.79 (C-5); 61.53 (–COO–*C*H_2–CH_3); 59.00 (C-3); 56.16 (–OCH_3); 36.89 (C-4); 14.20 (–COO–CH_2–*C*H_3); 11.54 (C-$1_{cycloprop.}$); 8.19, 8.06 (C-2, C-$3_{cycloprop.}$). HR LSIMS: calcd for $C_{18}H_{23}N_3O_5Na$ $(M+Na)^+$ 384.1535, found 384.1539. Anal. for $C_{18}H_{23}N_3O_5$: calcd: C, 59.82; H, 6.41; N, 11.63. Found: C, 59.43; H, 6.05; N, 11.29.

4.1.2.5. Synthesis of ethyl 3-(2-amino-5-methoxy-α-hydroxybencyl)-1-benzoyl-Δ^2-pyrazoline-5-carboxylate 33. A mixture of nitroarene **28a** (0.512 mmol) and 10% Pd/C (80 mg) was dissolved in methanol (30 mL) and stirred under a hydrogen atmosphere (70 psi) for 7.5 h. The mixture was filtered through celite and evaporated. The resultant residue was dissolved in CH_2Cl_2, and this solution was washed with water, dried (Na_2SO_4), and concentrated. The resultant solid was dissolved and purified by flash chromatography (ethyl acetate–hexane 1:2) to give **33**: 87 mg (43% yield); white solid; mp 74–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, 2H, H-2, H-$6_{benz.}$, $J_{2\text{-}3benz.}$= 7.1 Hz, $J_{2\text{-}4benz.}$=1.4 Hz); 7.47 (tt, 1H, H-$4_{benz.}$, $J_{4\text{-}3benz.}$= 7.4, $J_{4\text{-}2benz.}$=1.4 Hz); 7.43 (pt, 2H, H-3, H-$5_{benz.}$, $J_{3\text{-}4benz.}$=7.4 Hz, $J_{3\text{-}2benz.}$=7.1 Hz); 6.78 (d, 1H, H-6′, $J_{6'-4'}$=2.9 Hz); 6.73 (dd, 1H, H-4′, $J_{4'-3'}$=8.6 Hz, $J_{4'-6'}$=2.9 Hz); 6.62 (d, 1H, H-3′, $J_{3'-4'}$=8.6 Hz); 5.46 (s, 1H, –C*H*–OH); 5.02 (dd, 1H, H-5, J_{5-4a}=12.2 Hz, J_{5-4b}=6.0 Hz); 4.18 (m, 1H, –COO–CH_2–CH_3); 3.74 (s, 3H, –OCH_3); 3.19 (dd, 1H, H-4a, J_{4a-4b}=18.4 Hz, J_{4a-5}= 12.2 Hz); 2.81 (dd, 1H, H-4b, J_{4b-4a}=18.4 Hz, J_{4b-5}= 6.0 Hz); 1.22 (t, 3H, –COO–CH_2–CH_3, J=7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.84 (–*C*OO–CH_2–CH_3); 166.99 (–N–CO–); 159.59 (C-3); 153.11 (C-5′); 138.09 (C-2′); 133.48 (C-$1_{benz.}$); 131.33 (C-$4_{benz.}$); 129.76 (C-2, C-$6_{benz.}$); 127.84 (C-3, C-$5_{benz.}$); 124.65 (C-1′); 118.83 (C-3′); 115.02 (C-4′); 113.43 (C-6′); 70.49 (–CH–OH); 61.88 (–COO–*C*H_2–CH_3); 59.10 (C-5); 55.84 (–OCH_3); 36.11 (C-4); 14.05 (–COO–CH_2–*C*H_3). HR LSIMS: calcd for $C_{21}H_{23}N_3O_5Na$ $(M+Na)^+$ 420.1535, found 420.1529. Anal. for $C_{21}H_{23}N_3O_5$: calcd: C, 63.46; H, 5.83; N, 10.57. Found: C, 63.42; H, 6.17; N, 10.35.

4.1.2.6. General procedure for the preparation of compounds 34 and 35. An aqueous solution of Na_2CO_3 (2 M, 1.5 mL) was added with stirring to a suspension of the corresponding ester **20a** or **27a** (0.548 mmol) at 65 °C for 6 h. The reaction mixture was then cooled at room temperature and neutralized with resin Amberlite IR-120 [H^+], stirred carefully for 20 min, next a solution of NH_4OH (18%, 10 mL) was added and stirred for 20 min, the mixture was filtered and the filtrate was concentrated to dryness. The resulting residue was purified by flash chromatography (acetone–methanol 10:1).

*4.1.2.6.1. 1-Acetyl-3-(2-amino-5-methoxybenzoyl)-Δ^2-pyrazoline-5-carboxylic acid **34**.* Orange solid; yield 40%; mp 260–262 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 8.06 (d, 1H, H-6′, $J_{6'-4'}$=3.0 Hz); 6.98 (dd, 1H, H-4′, $J_{4'-3'}$=9.1 Hz, $J_{4'-6'}$=3.0 Hz); 6.74 (d, 1H, H-3′, $J_{3'-4'}$=9.1 Hz); 4.73 (dd, 1H, H-5, J_{5-4a}=12.6 Hz, J_{5-4b}=5.8 Hz); 3.75 (s, 3H, –OCH_3); 3.58 (dd, 1H, H-4a, J_{4a-4b}=18.7 Hz, J_{4a-5}= 12.6 Hz); 3.23 (dd, 1H, H-4b, J_{4b-4a}=18.7 Hz, J_{4b-5}= 5.8 Hz); 2.38 (s, 3H, –CO–CH_3). ^{13}C NMR (75 MHz, CD_3OD) δ 188.39 (Ph–*C*O–); 176.99 (–COOH); 172.11 (–N–CO–); 156.57 (C-3); 150.98 (C-5′); 148.90 (C-2′); 126.16 (C-4′); 119.48 (C-3′); 117.05 (C-1′); 115.46 (C-6′); 61.40 (C-5); 56.23 (–OCH_3); 39.86 (C-4); 21.78 (–CO–*C*H_3). HR LSIMS calcd for $C_{14}H_{14}DN_3O_5Na$ $(M+Na)^+$ 329.0970, found 329.0972. Anal. for $C_{14}H_{15}N_3O_5$: calcd: C, 55.08; H, 4.95; N, 13.76. Found: C, 54.72; H, 4.55; N, 13.36.

*4.1.2.6.2. 3-(2-Amino-5-methoxybenzoyl)-1-cyclohexanecarbonyl-Δ^2-pyrazoline-5-carboxylic acid **35**.* Orange solid; yield 41%; mp 276–278 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 8.03 (d, 1H, H-6′, $J_{6'-4'}$=2.9 Hz); 7.00 Hz (dd, 1H, H-4′, $J_{4'-3'}$=9.0 Hz, $J_{4'-6'}$=2.9 Hz); 6.74 (d, 1H, H-3′, $J_{3'-4'}$=9.0 Hz); 4.71 (dd, 1H, H-5, J_{5-4a}= 12.6 Hz, J_{5-4b}= 5.9 Hz); 3.78 (s, 3H, –OCH_3); 3.57 (dd, 1H, H-4a, J_{4a-4b}= 18.6 Hz, J_{4a-5}=12.6 Hz); 3.30 (m, 1H, H-$1_{cyclohex.}$); 3.21 (dd, 1H, H-4b, J_{4b-4a}=18.6 Hz, J_{4b-5}= 5.9 Hz); 2.05–1.73 (m, 5H, $H_{ec.\ cyclohex.}$); 1.54–1.27 (m, 5H, $H_{ax.\ cyclohex.}$). ^{13}C NMR (75 MHz, CD_3OD) δ 188.72 (Ph–*C*O–); 177.36 (–N–CO–); 176.99 (–COOH); 156.24 (C-3); 151.04 (C-5′); 148.78 (C-2′); 126.01 (C-4′); 119.45 (C-3′); 117.28 (C-1′); 115.46 (C-6′); 61.56 (C-5); 56.49 (–OCH_3); 42.98 (C-$1_{cyclohex.}$); 39.33 (C-4); 30.22, 29.63 (C-2, C-$6_{cyclohex.}$); 27.06, 26.92, 26.82 (C-3, C-4, C-$5_{cyclohex.}$). HR LSIMS: calcd for $C_{19}H_{23}N_3O_5Na$ $(M+Na)^+$ 396.1529, found 396.1535. Anal. for $C_{19}H_{23}N_3O_5$: calcd: C, 61.11; H, 6.21; N, 11.25. Found: C, 60.81; H, 5.95; N, 10.87.

4.2. Biological activity

4.2.1. Striatal nNOS activity determination. L-Arginine, L-citrulline, *N*-(2-hydroxymethyl)piperazine-*N*-(2-hydroxypropanesulfonic acid) (HEPES), DL-dithiothreitol (DTT), leupeptin, aprotinin, pepstatin, phenylmethylsulfonylfluoride (PMSF), hypoxantine-9-β-D-ribofuranosid (inosine), ethylene-glycol-bis-(β-aminoethyl ether)-*N*,*N*,*N*,*N*,-tetraacetic acid (EGTA), bovine serum albumin (BSA), Dowex-50 W (50x8-200), FAD, NADPH and 5,6,7,8-tetrahydro-L-biopterin dihydrocloride (H_4-biopterin) were obtained from Sigma Química (Spain). L-[^{3}H]-arginine (58 Ci/mmol) was obtained from Amersham (Amersham, Bucks, UK). Tris (hydroxymethyl)-aminomethane (Tris–HCl) and calcium chloride were obtained from Merck (Spain).

The rats were killed by cervical dislocation, and the striata were quickly collected and immediately used to measure NOS activity. Upon removal, the tissues were cooled in ice-cold homogenizing buffer (25 mM Tris, 0.5 mM DTT, 10 μg/mL leupeptin, 10 μg/mL pepstatine, 10 μg/mL aprotinine, 1 mM PMSF, pH 7.6). Two striata were placed in 1.25 mL of the same buffer and homogenized in a Polytron (10 s×6). The crude homogenate was centrifuged for 5 min at 1000*g*, and aliquots of the supernatant were either stored at −20 °C for total protein determination[33] or used immediately to measure NOS activity. The nNOS activity was measured by the Bredt and Snyder[32] method, monitoring the conversion of L-[^{3}H]-arginine to

L-[^{3}H]-citrulline. The final incubation volume was 100 μL and consisted of 10 μL crude homogenate added to a buffer to give a final concentration of 25 mM Tris, 1 mM DTT, 30 μM H_4-biopterin, 10 μM FAD, 0.5 mM inosine, 0.5 mg/mL BSA, 0.1 mM $CaCl_2$, 10 μM L-arginine, and 50 nM L-[^{3}H]-arginine, at pH 7.6. The reaction was started by the addition of 10 μL of NADPH (0.75 mM final) and continued for 30 min at 37 °C. Control incubations were performed by the omision of NADPH. The reaction was halted by the addition of 400 μL of cold 0.1 M Hepes, 10 mM EGTA, and 0.175 mg/mL L-citrulline, pH 5.5. The reaction mixture was decanted into a 2 mL column packet with Dowex-50 W ion-exchange resin (Na^+ form) and eluted with 1.2 mL of water. L-[^{3}H]-Citrulline was quantified by liquid scintillation spectroscopy. The retention of L-[^{3}H]-arginine in this process was greater than 98%. Specific enzyme activity was determined by subtracting the control value, which usually amounted to less than 1% of the radioactivity added. The nNOS activity was expressed as picomoles of L-[^{3}H]-citruline produced (mg of protein)$^{-1}$ min^{-1}.

4.2.2. Cerebral iNOS activity determination. The induction of the enzyme was achieved by intravenous inyection of lipopolysacharide (LPS) 10 mg/kg. Six hours after the injection, the rat brains were removed and homogenized in homogenizing buffer (25 mM Tris–HCl, 0.5 mM DTT, 10 μg/mL leupeptin, 10 μg/mL pepstatin, 10 μg/mL aprotinin, 1 mM PMSF, pH 7.6) cold (4 °C) for 0.05 mg tissue/mL buffer.

Once the homogenizing of the tissue has been obtained, it was incubated in the presence of EGTA 10 mM to eliminate the existing nNOS activity. The rest of the process followed to measure the iNOS activity is the same as the one described to measure the striatal nNOS activity.

Acknowledgements

We thank the Spanish Comisión Interministerial de Ciencia y Tecnología (SAF2002-01688) and from the Fondo de Investigación Sanitaria (PI021181) for financial support of this work. The award of a grant from the Junta de Andalucía to M.D.C.P. is gratefully acknowledged.

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