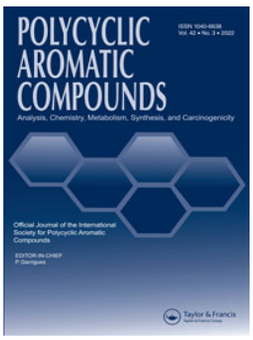

Polycyclic Aromatic Compounds

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Green and Efficient Synthesis of Novel Polysubstituted 2-Pyrrolidinones under Catalyst and Solvent-Free Conditions

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ABSTRACT

An efficient and green synthesis of novel 2-pyrrolidinone analogs by the reaction of various primary amines, alkyl acetoacetates, and maleic anhydride *via* grinding and neat conditions at room temperature has been described with good to high yields (68–94%). Various spectroscopic methods have characterized all the synthesized products (^{1}H NMR, ^{13}C NMR, MS, FT-IR, and CHN analysis). This protocol has several benefits: mild reaction condition, catalyst-free, economy, environmental-friendly, short reaction times ($\leq$ 25 min), good to high yields, and simple workup.

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KEYWORDS
2-Pyrrolidinones; primary amines; maleic anhydride; alkyl acetoacetate; multicomponent reactions

1. Introduction

Multicomponent reactions (MCRs) are considered important and successful in modern organic syntheses and medicinal chemistry. These reactions involve a one-pot process that allows the development of many chemical compounds with great structural diversity. Hence, MCRs have expanded rapidly over the past few decades. MCRs have several advantages, such as high atom economy, high efficiency, environmental compatibility, reduction of the number of steps, and reduction of reaction time compared to classical reactions.[1–7] Heterocyclic compounds have always played an important role in developing organic chemistry. Among heterocyclic compounds, compounds containing 2-pyrrolidinone nuclei are important classes of heterocyclic compounds containing nitrogen. They are important frameworks in many biologically active compounds and have found wide applications in the pharmaceutical industry, drug designing, and agricultural sectors.[8] Many natural materials and alkaloids have 2-pyrrolidinone scaffold, like Lactacystin,[9] (−)-Azaspirene,[10] Ypaoamide,[11] Pyrrocidine A, B,[12] Holomycin,[13] and Cotinine[14] (Figure 1). 2-pyrrolidones have many pharmacological properties, such as antitumor, anticonvulsant,[15] antibacterial, antifungal,[16] and anti-inflammatory effects. These compounds have attracted a lot of attention due to the mentioned properties, and the demand for them is high, so many efforts have been made to synthesize 2-pyrrolidinone.[17–19] A common method proposed for the synthesis of pyrrolidinones is the condensation reaction between aniline and aromatic aldehydes and dialkyl acetylene dicarboxylate in the presence of a PTSA catalyst.[20] In addition, the study on the articles showed that a variety of catalytic systems, such as TiO_2-np,[21] [BBSI][HSO_4],[22] and UiO-66-SO_3H[23] have been used to synthesize pyrrolidone derivatives. Despite advances in the synthesis protocol of pyrrolidinones, the proposed methods still have

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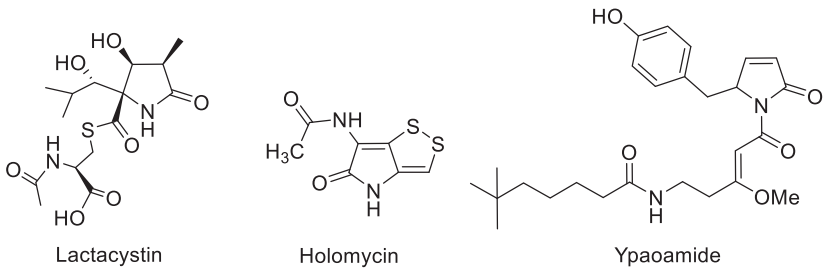


Figure 1. Selected natural products with 2-pyrrolidinone scaffold.

drawbacks, such as the need for thermal conditions, the difficult multi-step synthesis path, the need for catalysts, and long reaction times. These issues have aroused considerable interest in designing new synthetic pathways for pyrrolidone, such as the efficient MCR under solvent-free conditions. Since some solvents used in organic synthesis often might be wastes, solvent-free conditions are favorable from the viewpoint of ecological and environmental benign reasons in green chemistry. However, in the scope of green chemistry, the best solvent is regarded as no solvent at all. The grinding technique is one of the most widely used green methods for synthesizing organic compounds.[24] This technique is performed using abrasive wheels with high accuracy and regular surface polishing. Grinding is considered easy, solvent-free, highly efficient, and environmentally friendly.[25–27]

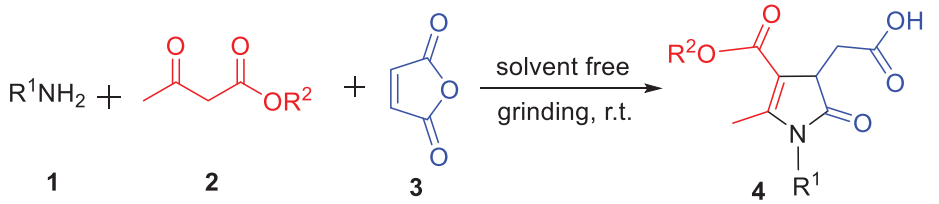
In line with our research into the development of new synthetic protocols in heterocyclic chemistry and the interest in MCRs, here is an efficient synthesis of novel 2-pyrrolidinone derivatives **4** using primary amine **1**, alkyl acetoacetate **2**, and maleic anhydride **3** in solvent-free conditions, at room temperature and without the need for catalysts by grinding, has been reported (Scheme 1).

2. Results and discussion

To investigate the different reaction conditions and achieve optimal conditions for the synthesis of 2-pyrrolidinone derivatives, the reaction between primary amine, methyl acetoacetate, and maleic anhydride as the model reaction was studied. First, to optimize the reaction conditions, the effect of the solvent was evaluated, and for this purpose, various solvents were selected, and the results are collected in Table 1. According to the obtained results, it was observed that the reaction is performed in the absence of solvent in a shorter time and with higher efficiency. Therefore, a three-component response without solvent was selected for the synthesis of pyrrolidone derivatives.

The model reaction was evaluated at different temperatures to find the optimal reaction temperature. The results of Table 2 show that the reaction proceeds at a higher efficiency at room temperature. Also, to investigate the scope and limitations of the reaction, the behavior of a variety of primary amines in the synthesis of 2-pyrrolidinone derivatives was studied through this protocol under optimal conditions. As Table 3 shows, pyrrolidones **4a–p** with a wide range of substituents from electron-withdrawing and electron-donating groups were synthesized in good to excellent yield.

Then, the effect of using different alkyl acetoacetates, such as ethyl acetoacetate and ethyl benzoyl acetate in its reaction with primary amine **1** and maleic anhydride under optimal reaction conditions was investigated. It was found that the reaction was a quiet general in the presence of ethyl acetoacetate, and no reaction occurred with ethyl benzoyl acetate. Also, under these conditions, the reaction could be achieved on a multi-gram scale. The structures of all synthesized products **4a–p** were deduced by their Mass, FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectra. The Mass



Scheme 1. Synthesis of 2-pyrrolidinone derivatives under optimal conditions.

Table 1. Solvent effect on the synthesis of **4a**[a].

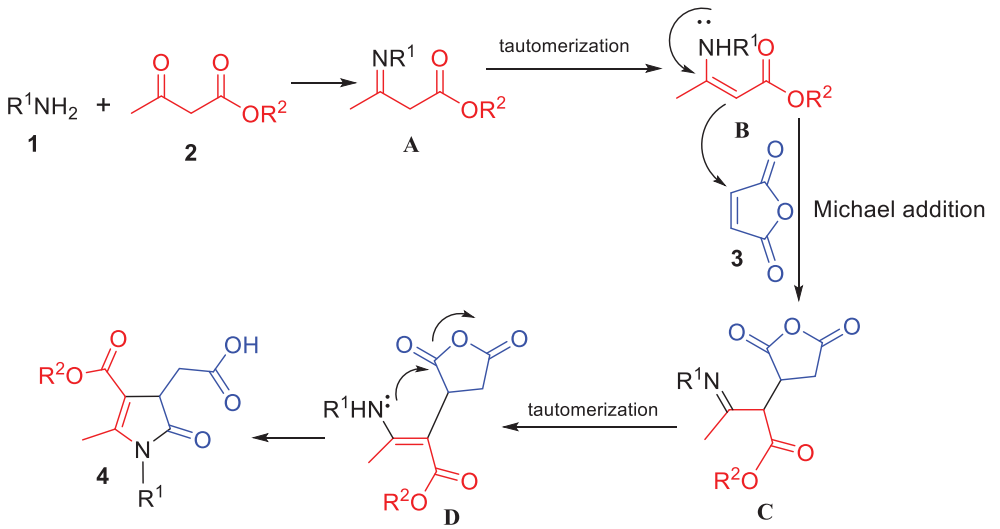
Entry	Solvent	Time (h)	Yeild (%)[b]
1	MeOH	12	34
2	EtOH	12	45
3	H_2O	12	24
4	CH_3CN	12	40
5	THF	9	63
6	CH_2Cl_2	9	60
7	Toluene	10	55
8	DMF	10	60
9	Solvent free	0.5	94

[a]Reaction conditions: benzylamine (1 mmol), methyl acetoacetate (1 mmol), and maleic anhydride (1.3 mmol) at room temperature. [b]Isolated yield.

Table 2. Temperature optimization for the synthesis of **4a**[a].

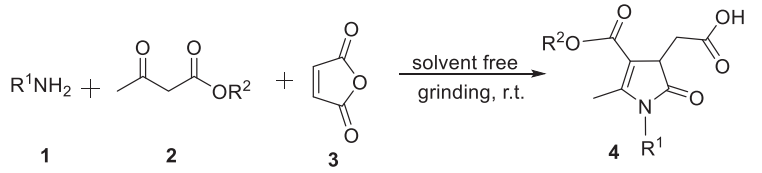
Entry	Temperature (°C)	Time (min)	Yield (%)[b]
1	0	50	trace
2	r.t	25	94
3	55	25	86
4	110	30	54

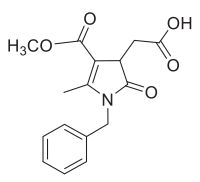
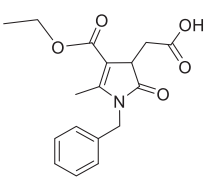
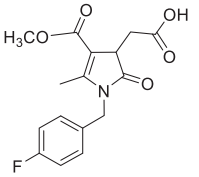
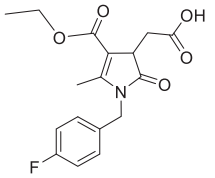
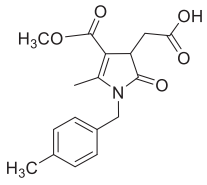
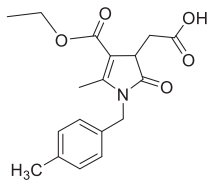
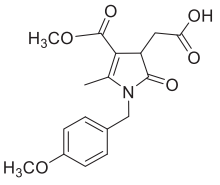
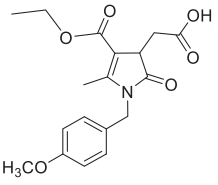
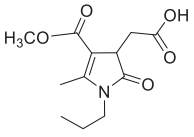
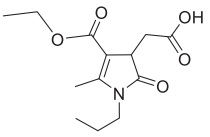
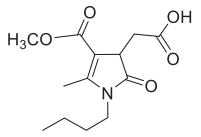
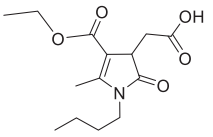
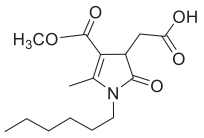
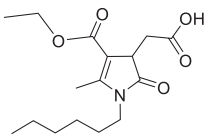
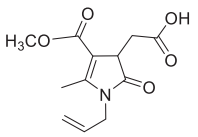
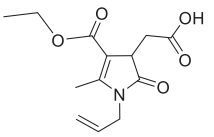
[a]Reaction conditions: primary amine (1 mmol), alkyl acetoacetate (1 mmol), and maleic anhydride (1.3 mmol). [b]Isolated yield



Scheme 2. Plausible reaction mechanism for the synthesis of pyrrolidinone derivatives.

Table 3. Synthesis of various 2-pyrrolidinones under optimized reaction conditions[a].



 **4a**, 20 min, 94%	 **4b**, 20 min, 90%	 **4c**, 20 min, 85%	 **4d**, 20 min, 75%
 **4e**, 20 min, 73%	 **4f**, 20 min, 70%	 **4g**, 20 min, 93%	 **4h**, 20 min, 85%
 **4i**, 15 min, 82%	 **4j**, 15 min, 80%	 **4k**, 15 min, 75%	 **4l**, 15 min, 84%
 **4m**, 20 min, 87%	 **4n**, 20 min, 90%	 **4o**, 25 min, 72%	 **4p**, 25 min, 68%

[a]Reaction conditions: primary amine (1 mmol), alkyl acetoacetate (1 mmol), and maleic anhydride (1.3 mmol) at room temperature.

spectra of these compounds displayed molecular ion peaks at the appropriate m/z values. For example, the ^{1}HNMR spectrum of **4a** exhibited a doublet signal at 2.32 ppm ($J = 2.2$ Hz), two multiple signals at 3.05–3.21 ppm correspond to the CH_2CO_2H and $\delta = 3.54$–3.58 the CH group of ring lactam. Also, a sharp singlet signal at 3.7 corresponding to the protons of the methoxy group and a multiplet $\delta = 7.2$ ppm for the aromatic region are easily detectable. The signal of the OH appears as the relatively broad signal at $\delta = 10.08$ ppm. In the IR spectrum of **4a**, one broad absorption band at 2400–3400, three bands at 1722, 1700, and 1662 cm^{-1}, were observed, which correspond to OH, C = O of ester, C = O acid, and amid frequencies, respectively.

According to work done in the past,[8,28,29] the proposed mechanism for forming 2-pyrrolidinones is illustrated in Scheme 2. The amine reacts with β-ketoester to form imine A. Then imin A, tautomerize to enamine B. Also, enamine B undergoes Michael addition with maleic anhydride to generate intermediate C, which converts to more stable tautomeric form D. The intramolecular cyclization in intermediate D forms the desired 2-pyrrolidinones derivatives.

3. Conclusion

In summary, we have reported a novel and facile one-pot, three-component synthesis of pyrrolidinone derivatives from primary amines under solvent-free condition *via* grinding at room temperature. The structure of all products was confirmed by Mass, ^{1}HNMR, ^{13}CNMR, and FTIR analysis. The advantages of this work include high product yields, no need for solvent and catalyst, short reaction time, and usefulness of the obtained products. The simplicity of this procedure can make it an attractive method for the synthesis of pyrrolidinones compared to other methods presented.

4. Experimental

4.1. Chemicals and experimental methods

All chemicals were purchased from Merck (Germany) and Fluka (Buchs, Switzerland), and all materials were analytical grade and used without further purification. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. Melting points were measured with an Electrothermal 9100 apparatus. IR spectra were obtained by a Perkin–Elmer 783 infrared spectrophotometer. In all cases, ^{1}H and ^{13}C NMR spectra were recorded using a Bruker DRX-250 Avance spectrometer at 300.13 and 75.47 MHz, respectively.

4.2. General procedure for the preparation of 2-pyrrolidinone derivatives

A mixture of the primary amine (1.0 mmol) and alkyl acetoacetate (1.0 mmol) was thoroughly mixed in a mortar, then grinding at room temperature without solvent. After 20 min, finely powdered maleic anhydride (1.3 mmol) was added to the mixture. TLC monitored the reaction. After completion of the reaction, the product obtained was purified by silica gel chromatography (n-hexane/EtOAc 8:6).

4.2.1. [1-Benzyl-4-(methoxycarbonyl)-5-methyl-2-oxo-2,3-dihydro-1H-pyrrol-3-yl]acetic acid (4a)

White powder; yield: 92%; mp: 86–89 °C. R_f (75% EtOAc/*n*-hexane): 0.48. IR (KBr) (ν_{max}, cm^{-1}): 2400–3400 (OH), 1722 (CO_2Me), 1700 (CO_2H), 1662 (C = O, Amide); MS: *m/z* (%): 303 (4) [M$^+$], 257 (21), 243 (10), 91 (100), 42 (28); Anal. Calcd (%) for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.48; H, 5.78; N, 5.61; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.32 (3 H, d, J = 2.2 Hz, Me), 3.05–3.21 (2 H, m, CH_2CO_2H), 3.56 (1 H, m, CH), 3.71 (3 H, s, OMe), 4.67–4.89 (2 H, AB system, ^{2}J = 16.0 Hz, CH_2Ph), 7.20–7.33 (5 H, m, CH_{arom}), 10.08 (1 H, br, CO_2H) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 12.8 (Me), 33.4 (CH_2CO_2H), 42.8 (CH_2Ph), 43.7 (CH), 51.0 (OMe), 105.9 (C_{ipso}-CO_2Me), 126.7, 127.6, 128.8, 136.2 (C_{arom}), 155.5 (C_{ipso}-Me), 164.4 (C = O Amide), 176.4 (CO_2Me), 178.1 (CO_2H) ppm.

4.2.2. [1-Benzyl-4-(ethoxycarbonyl)-5-methyl-2-oxo-2,3-dihydro-1H-pyrrol-3-yl]acetic acid (4b)

White powder; yield: 90%; mp: 89–92 °C. R_f (75% EtOAc/*n*-hexane): 0.57. IR (KBr) (ν_{max}, cm^{-1}): 2520–3590 (OH), 1728 (CO_2Et), 1710 (CO_2H), 1675 (C = O, Amide); MS: *m/z* (%): 317 (7) [M$^+$],

271 (35), 243 (16), 226 (5), 91 (100). Anal.calcd (%) for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.69; H, 5.82; N, 4.35; ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 1.25$ (3 H, t, $^3J = 7.1$ Hz, OCH_2Me), 2.31 (3 H, d, $J = 2.1$ Hz, C = C*Me*), 3.04-3.21 (2 H, m, CH_2CO_2H), 3.56 (1 H, m, CH), 4.03–4.27 (2 H, m, OCH_2CH_3), 4.66–4.86 (2 H, AB system, $^2J = 16.0$ Hz, CH_2Ph), 7.19–7.31 (5 H, m, CH_{arom}), 9.34 (1 H, br, CO_2H) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 12.8$ (OCH_2Me), 14.2 (C = C*Me*), 33.5 (CH_2CO_2H), 42.9 (CH_2Ph), 43.6 (CH), 59.9 (OCH_2Me), 106.2 (C_{ipso}-CO_2Et), 126.7, 127.6, 128.8, 136.2 (C_{arom}), 155.3 (C_{ipso}-Me), 164.1 (C = O Amide), 176.1 (CO_2Et), 178.3 (CO_2H) ppm.

4.2.3. [1-(4-fluorobenzyl)-4-(methoxycarbonyl)-5-methyl-2-oxo-2,3-dihydro-1H-pyrrol-3-yl]acetic acid (4c)

White powder; yield: 85%; mp: 109–111 °C. R_f (75% EtOAc/*n*-hexane): 0.35. IR (KBr) (ν_{max}, cm^{-1}): 2500–3590 (OH), 1725 (CO_2Me), 1715 (CO_2H), 1673 (C = O, Amide); MS: *m/z* (%): 321 (1) [M^+], 275 (6), 109 (73), 57 (37), 43 (100). Anal. calcd (%) for $C_{16}H_{16}NO_5F$: C, 59.81; H, 5.02; N, 4.36. Found: C, 59.71; H, 5.12; N, 4.32; ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 2.32$ (3 H, d, $J = 1.6$ Hz, Me), 3.07–3.23 (2 H, m, CH_2CO_2H), 3.52 (1 H, m, CH), 3.71 (3 H, s, OMe), 4.57–4.91 (2 H, AB system, $^2J = 16.0$ Hz, CH_2Ph), 6.96–7.26 (4 H, m, CH_{arom}), 10.31 (1 H, br, CO_2H) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 12.8$ (Me), 33.3(CH_2CO_2H), 42.7 (CH_2Ph), 43.0 (CH), 51.0 (OMe), 105.9 (C_{ipso}-CO_2Me), 115.7 ($^2J_{C\text{-}F} = 21$ Hz), 128.5($^3J_{C\text{-}F} = 8.2$ Hz), 132.01($^4J_{C\text{-}F} = 8.2$ Hz), 155.5 (C_{ipso}-Me),162.03($^1J_{C\text{-}F} = 217$ Hz, C-F) (C_{arom}), 163.8 (C = O Amide), 176.6 (CO_2Me), 178.1 (CO_2H) ppm.

4.2.4. [4-(ethoxycarbonyl)-1-(4-fluorobenzyl)-5-methyl-2-oxo-2,3-dihydro-1H-pyrrol-3-yl]acetic acid (4d)

White powder; yield: 75%; mp: 102–104 °C. R_f (75% EtOAc/*n*-hexane): 0.58. IR (KBr) (ν_{max}, cm^{-1}): 2780–3760 (OH), 1720 (CO_2Et), 1715 (CO_2H), 1678 (C = O, Amide); MS: *m/z* (%): 335 (2) [M^+], 289 (10), 261 (5), 109 (100), 57 (52). Anal. calcd (%) for $C_{17}H_{18}NO_5F$: C, 60.89; H, 5.41; N, 4.18. Found: C, 60.92; H, 5.35; N, 4.23; ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 1.27$ (3 H, t, $^3J = 7.2$ Hz, OCH_2Me), 2.32 (3 H, d, C = C*Me*), 3.08–3.25 (2 H, m, CH_2CO_2H), 3.52 (1 H, m, CH), 4.12-4.25 (2 H, m, OCH_2CH_3), 4.57-4.91 (2 H, AB system, $^2J = 15.9$ Hz, CH_2Ph), 6.96–7.26 (4 H, m, CH_{arom}), 10.5 (1 H, br, CO_2H) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 12.7$ (OCH_2Me), 14.2 (C = C*Me*), 33.3 (CH_2CO_2H), 42.7 (CH_2Ph), 43.0 (CH), 59.9 (OCH_2Me), 106.2 (C_{ipso}-CO_2Et), 115.7 ($^2J_{C\text{-}F} = 21.4$ Hz),128.6($^3J_{C\text{-}F} = 8.1$ Hz),132.0($^4J_{C\text{-}F} = 2.1$ Hz),155.0 (C_{ipso}-Me), 162.1($^1J_{C\text{-}F} = 244$ Hz, C-F)(C_{arom}), 163.9 (C = O Amide), 176.6 (CO_2Et), 178.1 (CO_2H) ppm.

4.2.5. [4-(methoxycarbonyl)-5-methyl-1-(4-methylbenzyl)-2-oxo-2,3-dihydro-1H-pyrrol-3-yl]acetic acid (4e)

White powder; yield: 73%; mp: 86–89 °C. R_f (75% EtOAc/*n*-hexane): 0.43. IR (KBr) (ν_{max}, cm^{-1}): 2512–3260 (OH), 1722 (CO_2Me), 1710 (CO_2H), 1660 (C = O, Amide); MS: *m/z* (%): 317 (1) [M^+], 149 (60), 104 (50), 57 (66), 43 (99). Anal. calcd (%) for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 63.09; H, 5.84; N, 4.23; ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 2.31$ (6 H, m, CH_3Ar, C = C*Me*), 3.08–3.12 (2 H, m, CH_2CO_2H), 3.56 (1 H, m, CH), 3.70 (3 H, s, OMe), 4.63–4.83 (2 H, AB system, $^2J = 15.9$. Hz, CH_2Ph), 7.09 (4 H, m, CH_{arom}), 9.23 (1 H, br, CO_2H) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 12.8$ (C = C*Me*), 21.1 (CH_3Ar) 33.5 (CH_2CO_2H), 42.8 (CH_2Ph), 43.5 (CH), 50.9 (OMe), 105.9 (C_{ipso}-CO_2Me), 126.8, 129.5, 133.2, 137.3 (C_{arom}), 155.7 (C_{ipso}-Me), 164.4 (C = O Amide), 176.2 (CO_2Me), 178.2 (CO_2H) ppm.

4.2.6. [4-(ethoxycarbonyl)-5-methyl-1-(4- methylbenzyl)-2-oxo-2,3-dihydro-1H-pyrrol-3-yl]acetic acid (4f)

White powder; yield: 70%; mp: 145–147 °C. R_f (75% EtOAc/*n*-hexane): 0.61. IR (KBr) (ν_{max}, cm^{-1}): 2400–3560 (OH), 1720 (CO_2Et), 1712 (CO_2H), 1678 (C = O, Amide); MS: *m/z* (%): 331 (4) [M^+], 285 (14), 257 (5), 105 (100), 42 (14). Anal.calcd (%) for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.08; H, 6.45; N, 4.32; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.27 (3 H, t, ^3J = 7.1 Hz, OCH_2*Me*), 2.33 (6 H, m, CH_3Ar, C = C*Me*), 3.05–3.20 (2 H, m, *CH_2*CO_2H), 3.57 (1 H, m, CH), 4.17 (2 H, m, O*CH_2*CH_3), 4.63–4.85 (2 H, AB system, ^2J = 15.9 Hz, *CH_2*Ph), 7.1 (4 H, m, CH_{arom}), 10.12 (1 H, br, CO_2*H*) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 12.8 (OCH_2*Me*), 14.2 (C = C*Me*), 21 (CH_3Ar) 33.6 (*CH_2*CO_2H), 42.8 (*CH_2*Ph), 43.5 (CH), 59.9 (O*CH_2*Me), 106.1 (C_{ipso}-CO_2Et), 126.8, 129.5, 133.2, 137.3(C_{arom}), 155.4 (C_{ipso}-Me), 164 (C = O Amide), 176.5 (*CO_2*Et), 178.2 (CO_2H) ppm.

4.2.7. [1-(4-methoxybenzyl)-4-(methoxycarbonyl)-5-methyl-2-oxo-2,3-dihydro-1H-pyrrol-3-yl]acetic acid (4g)

White powder; yield: 93%; mp: 116–118 °C. R_f (75% EtOAc/*n*-hexane): 0.28. IR (KBr) (ν_{max}, cm^{-1}): 2510–3625 (OH), 1720 (CO_2Me), 1715 (CO_2H), 1670 (C = O, Amide); MS: *m/z* (%): 333 (9) [M^+], 315 (5), 287(7), 121 (100), 42 (5). Anal.calcd (%) for $C_{17}H_{19}NO_6$: C, 61.25; H, 5.75; N, 4.20. Found: C, 61.04; H, 5.73; N, 4.15. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.34 (3 H, d, *J* = 2.2 Hz, Me), 3.03–3.18 (2 H, m, *CH_2*CO_2H), 3.53 (1 H, m, CH), 3.70 (3 H, s, OMe), 3.77 (3 H, s, ArO*Me*), 4.56–4.8 (2 H, AB system, ^2J = 15.7 Hz, *CH_2*Ph), 6.82-7.16 (4 H, m, CH_{arom}), 10.34 (1 H, br, CO_2*H*) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 12.8 (Me), 14.6 (*CH_2*CO_2H), 33.5 (*CH_2*Ph), 42.8 (CH), 51.0 (ArO*Me*), 55.2 (OMe), 105.9 (C_{ipso}-CO_2Me), 114, 114.2, 128.2(C_{arom}), 155.6 (C_{ipso}-Me), 159 (C_{arom}), 164.5 (C = O Amide), 175.8 (*CO_2*Me), 178.3 (CO_2H) ppm.

4.2.8. [4-(ethoxycarbonyl)-1-(4-methoxybenzyl)-5-methyl-2-oxo-2,3-dihydro-1H-pyrrol-3-yl]acetic acid (4h)

White powder; yield: 85%; mp: 110–113 °C. R_f (75% EtOAc/*n*-hexane): 0.50. IR (KBr) (ν_{max}, cm^{-1}): 2450–3560 (OH), 1720 (CO_2Et), 1698 (CO_2H), 1680 (C = O, Amide); MS: *m/z* (%): 347 (4) [M^+], 301 (5), 209 (83), 195 (36), 121 (100). Anal.calcd (%) for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09; N, 4.03. Found: C, 62.05; H, 6.15; N, 4.29; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.26 (3 H, t, ^3J = 7.1 Hz, OCH_2*Me*), 2.33 (3 H, d, *J* = 2.2 Hz, C = C*Me*), 3.05-3.18 (2 H, m, *CH_2*CO_2H), 3.54 (1 H, m, CH), 3.7 (3 H, s, OMe), 4.17 (2 H, m, O*CH_2*CH_3), 4.57–4.84 (2 H, AB system, ^2J = 15.7 Hz, *CH_2*Ph), 6.81–7.16 (4 H, m, CH_{arom}), 9.51 (1 H, br, CO_2*H*) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 12.8 (OCH_2*Me*), 14.2 (C = C*Me*), 33.5 (*CH_2*CO_2H), 42.8 (*CH_2*Ph), 43.1 (CH), 55.2 (ArO*Me*) 59.9 (O*CH_2*Me), 106.1 (C_{ipso}-CO_2Et), 114.2, 128.2, 128.3(C_{arom}), 155.4 (C_{ipso}-Me), 159 (C_{arom}), 164 (C = O Amide), 176.4 (*CO_2*Et), 178.2 (CO_2H) ppm.

4.2.9. [4-(methoxycarbonyl)-5-methyl-2-oxo-1-propyl-2,3-dihydro-1H-pyrrol-3-yl]acetic acid (4i)

Yellow oil; yield: 82%; R_f (75% EtOAc/*n*-hexane): 0.50. IR (KBr) (ν_{max}, cm^{-1}): 2380–3510 (OH), 1720 (CO_2Me), 1690 (CO_2H), 1660 (C = O, Amide); MS: *m/z* (%): 255 (17) [M^+], 224 (15), 195 (52), 209 (100), 42 (68). Anal. calcd (%) for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.67; H, 6.70; N, 5.39; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.87 (3 H, t, ^3J = 2.2 Hz, NCH_2CH_2*Me*), 1.15 (2 H, m, NCH_2*CH_2*Me), 2.41 (3 H, d, *J* = 2.1 Hz, C = C*Me*), 2.95–2.99 (2 H, m, *CH_2*CO_2H), 3.3–3.50 (3 H, m, CH, N*CH_2*CH_2Me), 3.68 (3 H, s, OMe), 9.22 (1 H, br, CO_2*H*) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 11.1 (NCH_2CH_2*Me*), 12.4 (C = C*Me*), 22.1 (NCH_2*CH_2*Me), 33.6 (*CH_2*CO_2H), 41.8 (N*CH_2*CH_2Me), 42.7 (CH), 50.4 (OMe), 105.7(C_{ipso}-CO_2Me), 155.6 (C_{ipso}-Me), 164.5 (C = O Amide), 175.6 (*CO_2*Me), 178.3 (CO_2H) ppm.

4.2.10. [4-(ethoxycarbonyl)-5-methyl-2-oxo-1-propyl-2,3-dihydro-1H-pyrrol-3-yl]acetic acid (4j)

Yellow oil; yield: 80%; R_f (75% EtOAc/*n*-hexane):0.51. IR (KBr) (ν_{max}, cm^{-1}):2500–3560 (OH), 1730 (CO_2Et), 1702 (CO_2H), 1668 (C = O, Amide); MS: *m/z* (%):269 (44) [M^+], 224 (35), 223(100), 195 (79), 166 (33). Anal.calcd (%) for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.83; H, 7.31; N, 4.93; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.89 (3 H, t, ^3J = 7.3 Hz, $NCH_2CH_2\mathit{Me}$), 1.26 (3 H, t, ^3J = 7.1 Hz, $OCH_2\mathit{Me}$), 1.60 (2 H, m, $NCH_2\mathit{CH_2}Me$), 2.42 (3 H, d, J = 2.1 Hz, C = C*Me*), 2.99-3.03 (2 H, m, $\mathit{CH_2}CO_2H$), 3.40 (2 H, m, $N\mathit{CH_2}CH_2Me$), 3.52 (1 H, m, CH), 4.14–4.20 (2 H, m, $O\mathit{CH_2}Me$), 9.04 (1 H, br, $CO_2\mathit{H}$) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 11.2 ($NCH_2CH_2\mathit{Me}$), 12.4($OCH_2\mathit{Me}$), 14.3 (C = C*Me*), 22.1 ($NCH_2\mathit{CH_2}Me$), 33.6 ($\mathit{CH_2}CO_2H$), 41.8 ($N\mathit{CH_2}CH_2Me$), 42.6 (CH), 59.8 ($O\mathit{CH_2}Me$), 105.7(C_{ipso}-CO_2Et), 155.4 (C_{ipso}-Me), 164.1 (C = O Amide), 176.1 ($\mathit{CO_2}Et$), 178.4 (CO_2H) ppm.

4.2.11. Spectra and physical data of [1-butyl-4-(methoxycarbonyl)-5-methyl-2-oxo-2,3-dihydro-1H-pyrrol-3-yl]acetic acid (4k)

White powder; yield: 75%; mp: 91–94 °C. R_f (75% EtOAc/*n*-hexane): 0.43. IR (KBr) (ν_{max}, cm^{-1}):2450–3420 (OH), 1723 (CO_2Me), 1690 (CO_2H), 1660 (C = O, Amide); MS: *m/z* (%): 269 (20) [M^+], 238 (27), 223(100), 209 (54), 41 (51). Anal. calcd (%) for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.71; H, 6.94; N, 5.28; ^{1}H NMR (300.13 MHz, $CDCl_3$):δ = 0.91 (3 H, t, ^3J = 7.2 Hz, $NCH_2CH_2\mathit{CH_2}Me$), 1.30 (2 H, m, $NCH_2\mathit{CH_2}CH_2Me$), 1.51 (2 H, m, $NCH_2\mathit{CH_2}CH_2Me$), 2.42 (3 H, d, J = 2.0 Hz, C = C*Me*), 2.98 (2 H, m, $\mathit{CH_2}CO_2H$), 3.40–3.66 (3 H, m, CH, $N\mathit{CH_2}CH_2CH_2Me$), 3.70 (3 H, s, OMe), 9.15 (1 H, br, $CO_2\mathit{H}$) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 12.4 ($NCH_2CH_2\mathit{CH_2}Me$), 13.6 (C = C*Me*), 19.9 ($NCH_2CH_2\mathit{CH_2}Me$), 30.9 ($NCH_2\mathit{CH_2}CH_2Me$), 33.6 ($\mathit{CH_2}CO_2H$), 40.1 ($N\mathit{CH_2}CH_2CH_2Me$), 42.7 (CH), 50.9 (OMe), 105.7 (C_{ipso}-CO_2Me), 155.6 (C_{ipso}-Me), 164.5 (C = O Amide), 176.0 ($\mathit{CO_2}Me$), 178.3 (CO_2H) ppm.

4.2.12. [1-butyl-4-(ethoxycarbonyl)-5-methyl-2-oxo-2,3-dihydro-1H-pyrrol-3-yl]acetic acid (4l)

White powder; yield: 84%; mp: 93–95 °C. R_f (75% EtOAc/*n*-hexane): 0.57. IR (KBr) (ν_{max}, cm^{-1}): 2425–3450 (OH), 1728 (CO_2Et), 1680 (CO_2H), 1652 (C = O, Amide); MS: *m/z* (%):283 (36) [M^+], 237 (100), 209 (37), 166 (42), 41 (28). Anal.calcd (%) for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.54; H, 7.54; N, 4.90; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.88 (3 H, t, ^3J = 7.2 Hz, $NCH_2CH_2\mathit{CH_2}Me$), 1.25 (5 H, m, $NCH_2CH_2\mathit{CH_2}Me$, $OCH_2\mathit{Me}$), 1.43 (2 H, m, $NCH_2\mathit{CH_2}CH_2Me$), 2.40 (3 H, d, J = 2.2 Hz, C = C*Me*), 2.96-3.00 (2 H, m, $\mathit{CH_2}CO_2H$), 3.38–3.43 (3 H, m, $N\mathit{CH_2}CH_2CH_2Me$, CH), 4.11–4.17 (2 H, m, $O\mathit{CH_2}Me$), 9.22 (1 H, br, $CO_2\mathit{H}$) ppm.^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 12.3 ($NCH_2CH_2\mathit{CH_2}Me$), 13.6 ($OCH_2\mathit{Me}$), 14.2 (C = C*Me*), 19.9 ($NCH_2CH_2\mathit{CH_2}Me$), 30.9 ($NCH_2\mathit{CH_2}CH_2Me$), 33.6 ($\mathit{CH_2}CO_2H$), 40.1 ($N\mathit{CH_2}CH_2CH_2Me$), 42.6 (CH), 59.8 ($O\mathit{CH_2}Me$), 105.9(C_{ipso}-CO_2Et), 155.4 (C_{ipso}-Me), 164.1 (C = O Amide), 176.1 ($\mathit{CO_2}Et$), 178.3 (CO_2H) ppm.

4.2.13. [1-hexyl-4-(methoxycarbonyl)-5-methyl-2-oxo-2,3-dihydro-1H-pyrrol-3-yl]acetic acid(4m)

Yellow oil; yield: 87%; R_f (75% EtOAc/*n*-hexane): 0.64. IR (KBr) (ν_{max}, cm^{-1}):2420–3580 (OH), 1726 (CO_2Me), 1700 (CO_2H), 1670 (C = O, Amide); MS: *m/z* (%): 297 (42) [M^+], 266 (21), 251 (100), 237 (44), 167 (45). Anal. calcd (%) for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.36; H, 7.85; N, 4.60; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.84 (3 H, t, ^3J = 6.6 Hz, $N(CH_2)_4\mathit{CH_2}Me$), 1.19–1.27 (6 H, m, $NCH_2CH_2(\mathit{CH_2})_3Me$), 1.45 (2 H, m, $NCH_2\mathit{CH_2}(CH_2)_3Me$), 2.44 (3 H, d, J = 2.1 Hz, C = C*Me*), 2.96-2.99 (2 H, m, $\mathit{CH_2}CO_2H$), 3.40–3.56 (3 H, m, CH, $N\mathit{CH_2}(CH_2)_4Me$), 3.70 (3 H, s, OMe), 8.56 (1 H, br, $CO_2\mathit{H}$) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 12.4 (NCH_2 $(CH_2)_4\mathit{Me}$), 13.9 (C = C*Me*), 22.4, 26.4, 28.8, 31.3 (NCH_2 $(CH_2)_4Me$), 33.6

(CH_2CO_2H), 40.3 ($NCH_2(CH_2)_4Me$), 42.7 (CH), 50.9 (OMe), 105.7 (C_{ipso}-CO_2Me), 155.6 (C_{ipso}-Me), 164.5 (C = O Amide), 176 (CO_2Me), 178.3 (CO_2H) ppm.

4.2.14. [4-(ethoxycarbonyl)-1-hexyl-5-methyl-2-oxo-2,3-dihydro-1H-pyrrol-3-yl]acetic acid (4n)

Yellow oil; yield: 90%; R_f (75% EtOAc/*n*-hexane): 0.64. IR (KBr) (ν_{max}, cm^{-1}):2380–3490 (OH), 1725 (CO_2Et), 1710 (CO_2H), 1670 (C = O, Amide); MS: *m/z* (%): 311 (62) [M^+], 266 (32), 265 (100), 237 (56), 43 (45). Anal. calcd (%) for $C_{16}H_{25}NO_5$: C, 61.72; H, 8.09; N, 4.50. Found: C, 61.62; H, 8.34; N, 4.69; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.84 (3 H, t, ^3J = 6.6 Hz, $N(CH_2)_4CH_2Me$), 1.24 (9 H, m, $NCH_2CH_2(CH_2)_3Me$, OCH_2Me), 1.49 (2 H, m, $NCH_2CH_2(CH_2)_3Me$), 2.41 (3H, d, J = 2.1 Hz, C = C*Me*), 2.96-2.99 (2 H, m, CH_2CO_2H), 3.39-3.51 (3 H, m, CH, $NCH_2(CH_2)_4Me$), 4.14 (2 H, m, OCH_2Me), 8.52 (1 H, br, CO_2H) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 12.4 (NCH_2 $(CH_2)_4Me$), 13.9 (OCH_2Me), 14.2 (C = C*Me*), 22.4, 26.4, 28.8, 31.3 (NCH_2 $(CH_2)_4Me$), 33.6 (CH_2CO_2H), 40.3 ($NCH_2(CH_2)_4Me$), 42.6 (CH), 59.8 (OCH_2Me), 105.9 (C_{ipso}-CO_2Et), 155.4 (C_{ipso}-Me), 164.1 (C = O Amide), 176.0 (CO_2Et), 178.3 (CO_2H) ppm.

4.2.15. [1-allyl-4-(methoxycarbonyl)-5-methyl-2-oxo-2,3-dihydro-1H-pyrrol-3-yl]acetic acid (4o)

Yellow oil; yield: 72%; R_f (75% EtOAc/*n*-hexane): 0.35. IR (KBr) (ν_{max}, cm^{-1}): 2425–3560 (OH), 1733 (CO_2Me), 1709 (CO_2H), 1668 (C = O, Amide); MS: *m/z* (%): 253 (22) [M^+], 222 (13), 207 (85), 193 (49), 42 (34). Anal. calcd (%) for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.77; H, 5.83; N, 5.39; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.41 (3 H, d, J = 2.3 Hz, Me), 2.96–3.11 (2 H, m, CH_2CO_2H), 3.48 (1 H, m, CH), 3.71 (3 H, s, OMe), 4.07–4.22 (2 H, m, NCH_2), 5.15 (2 H, m, CH=CH_2), 5.76 (1 H, m, CH=CH_2), 9.24 (1 H, br, CO_2H) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 12.4 (Me), 33.5 (CH_2CO_2H), 42.2 (CH), 42.7 (NCH_2), 51.0 (OMe), 105.9 (C_{ipso}-CO_2Me), 117.1 (CH=CH_2), 132.0 (CH = CH_2), 155.6 (C_{ipso}-Me), 164.5 (C = O Amide), 175.6 (CO_2Me), 178.0 (CO_2H) ppm.

4.2.16. [1-allyl-4-(ethoxycarbonyl)-5-methyl-2-oxo-2,3-dihydro-1H-pyrrol-3-yl]acetic acid (4p)

Yellow oil; yield: 68%; R_f (75% EtOAc/*n*-hexane): 0.51. IR (KBr) (ν_{max}, cm^{-1}): 2580–3610 (OH), 1728 (CO_2Et), 1712 (CO_2H), 1728 (C = O, Amide); MS: *m/z* (%): 267 (9) [M^+], 221 (100), 193 (80), 176 (38), 148 (50). Anal. calcd (%) for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.64; H, 6.70; N, 5.39; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.24 (3 H, t, J = 3.3 Hz, OCH_2Me) 2.41 (3 H, d, J = 2.3 Hz, C = C*Me*), 2.90–3.01 (2 H, m, CH_2CO_2H), 3.47 (1 H, m, CH), 3.87–4.25 (4 H, m, NCH_2, OCH_2Me), 5.13 (2 H, m, CH=CH_2), 5.76 (1 H, m, CH=CH_2), 9.10 (1 H, br, CO_2H) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 12.4 (OCH_2Me), 14.2 (C = C*Me*), 33.5 (CH_2CO_2H), 42.2 (CH), 42.7 (NCH_2), 59.9 (OCH_2Me), 106.1 (C_{ipso}-CO_2Et), 117.0 (CH=CH_2), 132.0 (CH = CH_2), 155.3 (C_{ipso}-Me), 164.1 (C = O Amide), 175.8 (CO_2Et), 178.0 (CO_2H) ppm.

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Disclosure statement

The authors declare no conflict of interest.

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