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Non-steroidal Anti-inflammatory Agents. Part 23 [1]

Synthesis and Pharmacological Activity of Enaminones which Inhibit both Bovine Cyclooxygenase and 5-Lipoxygenase

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Abstract. The synthesis and stereochemical characteristics of pyrrolidino-, isoquinolino- and indolo-enaminones **2**–**11** are reported. The inhibition of cyclooxygenase was determined in a bovine thrombocyte intact cell assay and that of 5-lipoxygenase using intact bovine polymorphonuclear leucocytes. Except compound **2c'** which is a well-balanced dual inhibitor of both enzymes, all other enaminone derivatives are weak inhibitors of both cyclooxygenase and 5-lipoxygenase. Structure-activity relationships of the enaminones in relation to known anti-inflammatory drugs are discussed.

Enaminones are widely used synthons in organic synthesis [2, 3], and the enaminone structure is part of anticonvulsive systems [4]. Isoxazoles with cardiovascular activity are formed by ANSARO (addition of the nucleophile, spiro annulation, ring opening) ring transformation of pyrrolidino enaminones [5]. Inhibition of cyclooxygenase is the main mechanism of action of non-steroidal anti-inflammatory drugs (NSAIDs), which are therapeutic agents for the treatment of the symptoms of arthritis. As leukotrienes are potent mediators of inflammation and chemotactic agents, inhibition of 5-lipoxygenase has been claimed as a putative treatment for asthma and allergic disorders [6]. However, cyclooxygenase inhibitors show severe side effects, mainly gastrointestinal discomfort, which are directly related to their mechanisms of action [7, 8]. To avoid the adverse effects of NSAIDs, the development of compounds which selectively inhibit the isoenzym cyclooxygenase-2 [9] or are dual inhibitors of both cyclooxygenase and 5-lipoxygenase [10], are under discussion with the objective of achieving a better safety profile in terms of gastric tolerance as compared to classical NSAIDs.

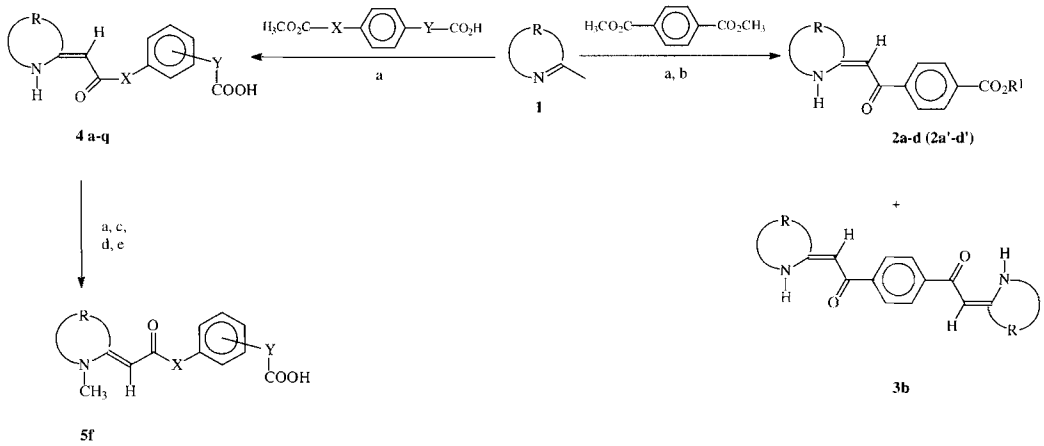
These investigations were based on the assumption that the aryl enaminone moiety may mimic parts of arachidonic acid and thus inhibit biotransformation to eicosanoids. According to data reported in the literature [6] and our own results [10] an additional acidic function within the molecule is needed to inhibit the enzymes. Keeping the aryl enaminone as the basic structure, a series of compounds with different positions of the acidic group [1] were synthesized and evaluated for their potency in inhibiting bovine cyclooxygenase and 5-lipoxygenase. The synthesis and stereochemical characteristics of a series of pyrrolidino-, isoquinolino- and indolo-enaminones structurally analogous to non-steroidal anti-inflammatories are presented here.

Results and Discussion

Synthetic and Structural Aspects

α-Alkyl cycloimines usually react as ambident nucleophiles at their nitrogen atom, exocyclic β-C-atom or (and) endocyclic β-C-atom, electrophiles are therefore suitable partners [11]. Reaction of monoesters and lithiated cycloimines lead to *Z-s-Z* enaminones [12] which undergo ring transformation to aminoalkyl isoxazoles in the presence of hydroxylamine [13, 14].

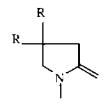
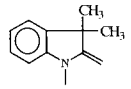
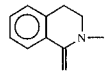
Starting materials to synthesize the enaminones **2**–**11** were the corresponding cycloimines and the monoesters and diesters, which were commercially available or were prepared according to the literature [15]. However, using an excess of the diester to which the α-lithiated imine was dropped (inverse method), the 1:2 product **3** (exemplary shown for **3b**, see Experimental) was formed in yield of 20–50%. According to



a) BuLi, THF, −78 °C; b) K_2CO_3, MeOH; c) H^+, MeOH; d) KO*t*Bu, DMS; e) NaOH

comp.		R	R^1	X	Y
2 a	Pyr	H	CH_3	–	–
2 a'	Pyr	H	H	–	–
2 b	Pyr	CH_3	CH_3	–	–
2 b'	Pyr	CH_3	H	–	–
3 b	Pyr	CH_3	–	–	–
2 c	Ind	–	CH_3	–	–
2 c'	Ind	–	H	–	–
2 d	Iso	–	CH_3	–	–
2 d'	Iso	–	H	–	–
4 a	Pyr	H	–	$-CH_2$	–
4 b	Pyr	H	–	$-CH_2O$	–
4 c	Pyr	CH_3	–	$-CH_2$	–
4 d	Pyr	CH_3	–	$-CH_2O$	–
4 e	Pyr	H	–	–	4-CH_2-

comp.		R	R^1	X	Y
4 f	Pyr	CH_3	–	–	4-CH_2-
4 g	Pyr	CH_3	–	–	4-OCH_2-
4 h	Pyr	CH_3	–	–	3-OCH_2-
4 i	Pyr	CH_3	–	–	4-CH_2CH_2-
4 j	Pyr	CH_3	–	–	4-$CH(CH_3)$-
4 k	Pyr	CH_3	–	–	4-CH_2SCH_2-
4 l	Pyr	CH_3	–	–	4-$CH_2SCH_2CH_2$-
4 m	Ind	–	–	$-CH_2O$	–
4 n	Ind	–	–	–	4-CH_2
4 o	Ind	–	–	–	4-OCH_2
4 p	Ind	–	–	–	4-CH_2SCH_2-
4 q	Iso	–	–	–	4-CH_2-
5 f	Pyr	CH_3	–	–	4-CH_2-

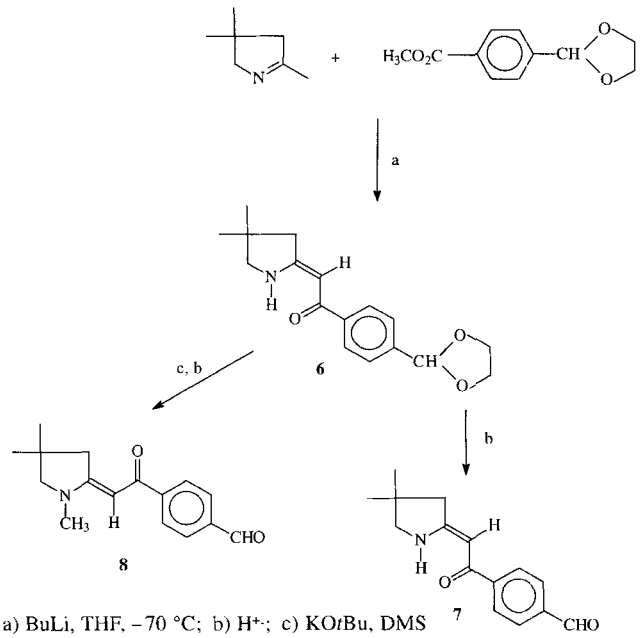
Pyr = 
Ind = 
Iso = 

Scheme 1

Bachi [16] and our own results [12], the proton at the nitrogen atom which forms an H-bridge to the oxygen of the carbonyl group is characterized by a significant down field shift (δ/ppm 9.7–11.5), thus proving the *Z*-configuration. Independent of the conditions applied, only the *Z*-isomer was obtained, and no *E*/*Z*-isomerism or enamine-imine tautomerism was observed by NMR spectroscopy. The vinylic proton resonates at δ/ppm 5.5–5.7 in the pyrrolidine series and at δ/ppm 6.1–6.5 in the benzo annulated compounds. The chemical shifts of the ring methylen protons α to the semicyclic C=C-bond depend on the configuration (*i.e.* anisotropic effects of the keto function), thus the nuclear Overhauser enhancement data, successfully applied in the pyrrolidino enaminone series [12], were used to assign the *Z*-s-*Z*-configuration to all enaminones **2**, **3** correlating the proton resonance signals of C-3 (pyrrolidine moiety) and the vinylic proton. Formation of the 4-carboxybenzoyl cation and hydrogen abstraction gave typical ms-fragments; the molecule ions were detected with medium to high relative intensities (see Experimental).

The same procedure was used to synthesize the homologous derivatives **4**, which were methylated at the nitrogen atom regioselectively [17] according to the reaction sequence shown in Scheme 1. To verify the stereochemistry of **4** and **5** the NMR data were compared, giving evidence that **4** also has *Z*-configuration in contrast to the *E*-configuration of **5** documented by the NOE correlation of the methyl singlet and the signal of the vinylic proton. The s-*Z*-stereochemistry concerning the position of the carbonyl group relative to the C=C-bond of **4** (*i.e.* **4c**, **4f**) was documented by the NMR data, again applying the NOE method: The signals of the ring methylen protons α to the semicyclic C=C-bond and of the aromatic protons at position 2 and 6 correlate with the signal of the vinylic proton; no effects were seen for the NH signal. The s-*Z*-geometry of **5** was deduced from the significant paramagnetic shift of the C-3 proton signals (pyrrolidine moiety) compared to **4**.

To achieve an increased variability at the phenyl ring which bears the essential carboxylic acid functions, the corresponding pyrrolidino enaminones with an aldehyde group at the aromatic ring were prepared as depicted in Scheme 2. Confirmation of the *E*-s-*Z*-configuration was accomplished on the basis of cristallographic data (see



a) BuLi, THF, −70 °C; b) H^+; c) KO*t*Bu, DMS

Scheme 2

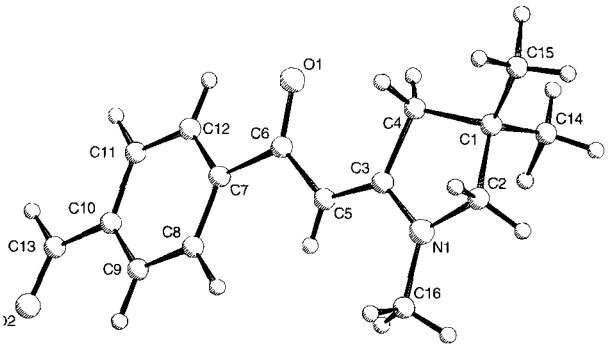
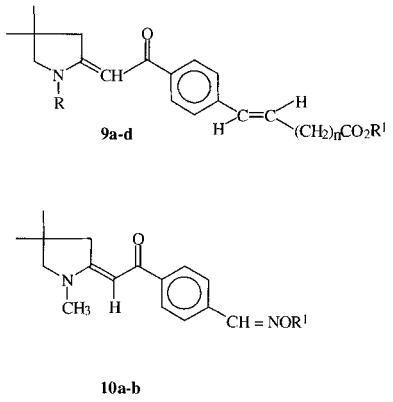


Fig. 1 X-ray analysis (Schakal plot) of 4-[(1,4,4-Trimethyl-pyrrolidin-2-ylidene)-acetyl]-benzaldehyde

Fig. 1) of the N–CH_3 compound **8** [18] whose NMR-data are in agreement with those of **5**, **10**, **11** and **9** (R=CH_3). Employing Wittig reactions to **7** and **8**, the unsaturated acids **9** with *trans* configuration were formed in good yield. The stereochemistry of the exocyclic double bond depends as demonstrated on the substitution of the nitrogen atom, *i.e.* all NH-derivatives show *Z*-s-*Z*-configuration, and the N–CH_3 compounds are inverse at the C=C-bond. According to a procedure given in the literature [19], the aldehyde was transformed to aldoxime **10** and iminooxy acetic acid **11**. The NMR data are in agreement with the *E*-s-*Z*-stereochemistry. Because of the low and not significant anti-inflammatory activities of these compounds, no attempts were made to elucidate the stereochemistry of the oxime moiety.

Anti-inflammatory Activity

Hypothetical enzyme bond conformations of arachidonic acid are postulated for cyclooxygenase [20, 21] and 5-lipoxygenase [22]. It has been shown that a carboxyl group or another acidic function combined with a great hydrophobic area of the molecule are essential for anti-inflammatory activity. On the other hand it should be noted that hydrophobic interactions of the compounds tested and the supplementary binding site of the enzyme are as important as the electronic effects [23].



9	R	R^1	n
a	H	CH_3	0
a'	H	H	0
b	CH_3	CH_3	0
b'	CH_3	H	0
c	H	H	2
d	H	H	4

10	R^1
a	CH_3
b	CH_2CO_2H

Scheme 3

The enaminones synthesized show structural analogy to known anti-inflammatory drugs and they should be able to mimic parts of the arachidonic acid which is oxidized by the enzymes cyclooxygenase and 5-lipoxygenase. If an NH-function remains in the molecules the chelating potency of the enaminone moiety is thought to interact with an iron atom at the active site of the enzymes mentioned. Contrary to these structural features most of the enaminones described have low or no efficacy to inhibit the cyclooxygenase and the 5-lipoxygenase. Medium to low inhibition of the 5-lipoxygenase was shown by the compounds **4h**, **4g**, **4j** (29, 18, 13% inhibition, 10 µM). The most potent cyclooxygenase inhibitor was **4e** (28%, 10µM). A dual inhibition of both cyclooxygenase and 5-lipoxygenase was found for **2c'** (36 and 30%, respectively), which may become a lead structure for further optimisations. When the structural features of these enaminones are compared to clinically used anti-inflammatory drugs, *e.g.* indomethacin or diclofenac, and the carboxylic moiety is fixed together, significant differences in the distribution of lipophilic and hydrophilic domains become obvious. Different distances between the acidic group and the lipophilic domain are achieved and the additional hydrophilic function of the enaminones may disturb the interaction with the active sites of the enzymes. According to accepted models these domains are prerequisites to mimic the steric and electronic demands of arachidonic acid in the folded conformation. Experimental studies to optimise and to elucidate the biological activity of modified enaminones are ongoing.

Experimental

All reagents were of analytical grades, the reactions were carried out in highly pure and anhydrous solvents under a nitrogen atmosphere.

Melting points: Büchi SMP/20 apparatus, uncorrected. – Except where otherwise stated, infrared spectra were measured in KBr, Perkin-Elmer Model 299 Spectrometer. – ^{1}H NMR spectra: $CDCl_3$, Bruker AC 200 MHz spectrometer (TMS as internal standard, chemical shifts δ in ppm in Hz). – All structural assignments were consistent with IR, NMR, and MS data. – Silica gel plates (Merck F_{254}) and silica gel 60 (Merck, 63–200 mesh) or Al_2O_3 90 (Merck, neutral, activity 1) were used for analytical and flash chromatography, respectively.

Enaminones 2–4, 6, 7 (General Procedure)

To 10 mmol of the cycloimine in 10 ml anh THF under N_2 10.1 mmol *n*-butyl-Li was added dropwise while maintaining the temperature at –70 °C. This suspension was injected through a septum to the solution of 12 mmol of the corresponding diester stirring the mixture thereafter 12–24 h (tlc control) at room temperature. The reaction was carefully quenched with 10 ml water and extracted with 50 ml ethyl acetate/ether (1:1 v/v). In case of a monoester 10 mmol cycloimine were lithiated with 20 mmol *n*-butyl-Li. To this solution 7.5 mmol monoester were injected dropwise followed by an additional amount of 7.5 mmol *n*-butyl-Li. The mixture was stirred at room temperature overnight and then carefully acidified with 0.1M HCl. The organic layers were dried and evaporated *in vacuo*, the enaminones were purified by recrystallisation or flash chromatography as stated.

Hydrolysis of the esters

The suspension of 1 mmol ester, 1g K_2CO_3 and 20 ml anh. MeOH was heated under reflux (tlc control). The solvent was evaporated *in vacuo*, the residue dissolved in water and the solution was acidified with 10% HCl. The carboxylic acids precipitate or were extracted with ethyl acetate.

Methyl 4-(pyrrolidin-2-ylidene-acetyl)-Benzoate (**2a**)

Yield 23% (SiO_2, ether, R_f = 0.5), *m.p.* 178–181°C. – ^{1}H NMR: δ/ppm 2.0–2.2 (m, 2H, H-4), 2.7–2.85 (t, 2H, *J*=7.5, H-3), 3.6–3.7 (t, 2H, *J*=7.5, H-5), 3.95 (s, 3H, CH_3), 5.8 (s, 1H, =CH), 7.9 (d, 2H, AB, *J*=8, H arom.), 8.1 (d, 2H, AB, *J*=8, H arom.), 10.4 (bs, 1H, NH). – IR (KBr): ν/cm^{-1} = 3300 (NH), 1725 (C=O), 1610 (C=O). – MS: *m/z* (%) 245 ($M^{+\cdot}$, 53), 244 ($M^{+\cdot}$–H, 100), 230 ($M^{+\cdot}$–CH_3, 11), 163 ($H_3CO_2C(C_6H_4)CO^+$, 6).

$C_{14}H_{15}NO_3$ Calcd.: C 68.54 H 6.16 N 5.71
(245.32) Found: C 68.32 H 6.20 N 5.62.

Methyl 4-[(4,4-dimethyl-pyrrolidin-2-ylidene)-acetyl]-Benzoate (**2b**)

Yield 25% (SiO_2, ether, R_f = 0.5), *m.p.* 164 °C. – ^{1}H NMR: δ/ppm 1.2 (s, 6H, $(CH_3)_2$), 2.5 (s, 2H, H-3), 3.4 (s, 2H, H-5), 3.9 (s, 3H, CO_2CH_3), 5.75 (s, 1H, =CH), 7.9 (d, 2H, AB, *J*=8.2, H arom.), 8.1 (d, 2H, AB, *J*=8.2), 10.2 (bs, 1H, NH). – IR (KBr): ν/cm^{-1} = 3280 (NH), 1720 (C=O), 1610 (C=O). – MS: *m/z* (%) 273 ($M^{+\cdot}$, 58), 272 ($M^{+\cdot}$–H, 56), 258 ($M^{+\cdot}$–CH_3, 100), 163 ($H_3CO_2C(C_6H_4)CO^+$, 18).

$C_{16}H_{19}NO_3$ Calcd.: C 70.31 H 7.01 N 5.12
(273.33) Found: C 70.05 H 7.12 N 5.02.

2-(4,4-Dimethyl-pyrrolidin-2-ylidene)-1-{4-[(4,4-dimethyl-pyrrolidin-2-ylidene)-acetyl]-phenyl}-Ethanone (**3b**)

Yield 20% (SiO_2, ether, R_f = 0.25), *m.p.* 278 °C. – ^{1}H NMR: δ/ppm 1.1 (s, 12H, $2(CH_3)_2$), 2.5 (s, 4H, 2H-3), 3.4 (s, 4H, 2H-5), 5.8 (s, 2H, 2 =CH), 7.9 (s, 4H, H arom.), 10.2 (bs, 2H, NH). – IR (KBr): ν/cm^{-1} = 3380 (NH), 1600 (C=O). – MS: *m/z* (%) 252 ($M^{+\cdot}$, 71), 351 ($M^{+\cdot}$-H, 100), 337 ($M^{+\cdot}$–CH_3, 60).

$C_{22}H_{28}N_2O_2$ Calcd.: C 74.97 H 8.01 N 7.95
(352.48) Found: C 74.98 H 7.92 N 7.79.

Methyl 4-[(3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-acetyl]-Benzoate (**2c**)

Yield 32% (SiO_2, CH_2Cl_2, R_f = 0.5), *m.p.* 134 °C. – ^{1}H NMR: δ/ppm 1.5 (s, 6H, $(CH_3)_2$), 3.9 (s, 3H, CH_3), 6.05 (s, 1H, =CH), 7.0 (m, 2H, H arom.), 7.25(m, 2H, H arom.), 7.95 (d, 2H, AB, *J*=8, H arom.), 8.1 (d, 2H, AB, *J*=8, H arom.). – IR (KBr): ν/cm^{-1} = 2980 (NH), 1630 (C=O), 1610 (C=O). – MS: *m/z* (%) 321 ($M^{+\cdot}$, 100), 320 ($M^{+\cdot}$–H, 59), 306 ($M^{+\cdot}$–CH_3, 62), 163 ($H_3CO_2C(C_6H_4)CO^+$, 13).

$C_{20}H_{19}NO_3$ Calcd.: C 74.75 H 5.96 N 4.36
(321.38) Found: C 74.51 H 6.08 N 4.40.

Methyl 4-[(3,4-dihydro-2H-isoquinolin-1-ylidene)-acetyl]-Benzoate (**2d**)

Yield 47% (SiO_2, ether, R_f = 0.5), *m.p.* 110 °C. – ^{1}H NMR: δ/ppm 2.9–3.1 (m, 2H, H-4), 3.5–3.65 (m, 2H, H-3), 3.95 (s, 3H, CH_3), 6.32 (s, 1H, =CH), 7.3–7.8 (m, 3H, H arom.), 7.95–8.1 (m, 5H, H arom.). – IR (KBr): ν/cm^{-1} = 3200 (NH), 1710 (C=O), 1610 (C=O). – MS: *m/z* (%) 307 ($M^{+\cdot}$, 70), 306 ($M^{+\cdot}$–H, 100), 163 ($H_3CO_2C(C_6H_4)CO^+$, 73). The 2:1 adduct **3d** (SiO_2, CH_2Cl_2, R_f = 0.2) was not isolated.

$C_{19}H_{17}NO_3$ Calcd.: C 74.25 H 5.58 N 4.56
(307.35) Found: C 73.98 H 5.70 N 4.39.

4-(Pyrrolidin-2-ylidene-acetyl)-benzoic Acid (**2a'**)

Yield 62% (SiO_2, ether/formic acid (1000:1 v/v), R_f = 0.5), *m.p.* 249 °C. – ^{1}H NMR: δ/ppm 1.9 (m, 2H, H-4), 2.75 (t, 2H, *J*=7.5, H-3), 3.7 (t, 2H, *J*=7.5, H-5), 5.8 (s, 1H, =CH), 8.0 (d, 2H, AB, *J*=8, H arom.), 8.1 (d, 2H, AB, *J*=8, H arom.), 10.25 (bs, 1H, NH). – IR (KBr): ν/cm^{-1} = 3300 (NH), 1680 (C=O), 1610 (C=O). – MS: *m/z* (%) 231 ($M^{+\cdot}$, 62), 230 ($M^{+\cdot}$–H, 100), 149 ($HOOCC_6H_4CO^+$, 16).

$C_{13}H_{13}NO_3$ Calcd.: C 67.52 H 5.67 N 6.06
(231.25) Found: C 67.50 H 5.58 N 5.96.

4-[(4,4-Dimethyl-pyrrolidin-2-ylidene)-acetyl]-benzoic Acid (**2b'**)

Yield 60%, ether/formic acid (1000:1 v/v), *m.p.* 208 °C (DIPE). – ^{1}H NMR: δ/ppm 1.2 (s, 6H, $(CH_3)_2$), 2.5 (s, 2H, H-3), 3.4 (s, 2H, H-5), 5.5 (s, 1H, =CH), 7.9 (d, 2H, AB, *J*=8.4, H arom.), 8.1 (d, 2H, AB, *J*=8.4, H arom.), 10.2 (bs, 1H, NH) (400 MHz). – IR (KBr): ν/cm^{-1} = 3300 (NH), 1690 (C=O), 1610 (C=O). – MS: *m/z* (%) 259 ($M^{+\cdot}$, 57), 258 ($M^{+\cdot}$–H, 47), 244 ($M^{+\cdot}$–CH_3, 100), 149 ($HO_2C(C_6H_4)CO^+$, 26).

$C_{15}H_{17}NO_3$ Calcd.: C 69.48 H 6.61 N 5.40
(259.30) Found: C 69.19 H 6.55 N 5.28.

4-[(3,3-Dimethyl-1,3-dihydro-indol-2-ylidene)-acetyl]-benzoic Acid (**2c'**)

Yield 85% (SiO_2, ether, R_f = 0.3), *m.p.* 248 °C.– ^{1}H NMR:

δ/ppm 1.5 (s, 6H, $(CH_3)_2$), 6.1 (s, 1H, =CH), 7.0–7.4 (m, 4H, H arom.), 8.05 (d, 2H, AB, J=8, H arom.), 8.25 (d, 2H, AB, J=8, H arom.), 12.0 (bs, 1H, NH) (200 MHz, DMSO-d_6). – IR (KBr): ν/cm^{-1} = 3280 (NH), 1700 (C=O), 1605 (C=O). – MS: m/z (%) 307 ($M^{+\cdot}$, 100), 306 ($M^{+\cdot}$–H, 55), 291 ($M^{+\cdot}$–CH_3, 72), 149 ($HO_2C(C_6H_4)CO^+$, 20).

$C_{19}H_{17}NO_3$	Calcd.:	C 74.25	H 5.58	N 4.56
(307.35)	Found:	C 74.20	H 5.62	N 4.62.

4-[(3,4-Dihydro-2H-isoquinolin-1-ylidene)-acetyl]-benzoic Acid (**2d'**)

Yield 80% (SiO_2, ethyl acetate/formic acid (1000:1 v/v), R_f = 0.5), *m.p.* 259 °C. – ^{1}H NMR: δ/ppm 2.95–3.05 (m, 2H, H-4), 3.5–3.6 (m, 2H, H-3), 6.5 (s, 1H, =CH), 7.3–7.55 (m, 3H, H arom.), 7.95–8.1 (m, 5H, H arom.) (400 MHz, DMSO-d_6). – IR (KBr): ν/cm^{-1} = 3200 (NH), 1690 (C=O), 1610 (C=O). – MS: m/z(%) 293 ($M^{+\cdot}$, 71), 292 ($M^{+\cdot}$–H, 100), 149 ($HO_2C(C_6H_4)CO^+$, 6).

$C_{18}H_{15}NO_3$	Calcd.:	C 73.71	H 5.15	N 4.78
(293.32)	Found:	C 72.92	H 5.40	N 4.72.

4-(2-Oxo-3-pyrrolidin-2-ylidene-propyl)-benzoic Acid (**4a**)

Yield 28% (SiO_2, ether, R_f = 0.1), *m.p.* 185 °C. – ^{1}H NMR: δ/ppm 1.8 (m, 2H, H-4), 2.5 (t, 2H, J=7.5, H-3), 3.4 (t, 2H, J=7.5, H-5), 3.5 (s, 2H, CH_2), 5.0 (s, 1H, =CH), 7.3 (d, 2H, AB, J=8, H arom.), 7.85 (d, 2H, AB, J=8, H arom.), 9.7 (bs, 1H, NH), 12.85 (bs, 1H, COOH) (DMSO-d_6). – IR (KBr): ν/cm^{-1} = 3280 (NH), 1680 (C=O), 1620 (C=O), 1605 (C=O). – MS: m/z (%) 245 ($M^{+\cdot}$, 2), 110 ($M^{+\cdot}$–$H_2C(C_6H_4)COOH$, 100).

$C_{14}H_{15}NO_3$	Calcd.:	C 68.56	H 6.16	N 5.71
(245.28)	Found:	C 68.50	H 6.20	N 5.51.

4-[(3-Pyrrolidin-2-ylidene)-2-oxo-propoxy]-benzoic Acid (**4b**)

Yield 32% (SiO_2, ethyl acetate/formic acid (1000:1 v/v), R_f = 0.3), *m.p.* 208 °C. – ^{1}H NMR: δ/ppm 1.9 (m, 2H, H-4), 2.5 (t, 2H, J=7.5, H-3), 3.5 (t, 2H, J=7.5, H-5), 4.4 (s, 2H, OCH_2), 5.3 (s, lH, =CH), 6.8 (d, 2H, AB, J=8, H arom.), 7.85 (d, 2H, AB, J=8, H arom.), 9.7 (bs, 1H, NH), 12.85 (bs, 1H, COOH) (DMSO-d_6). – IR (KBr): ν/cm^{-1} = 3250 (NH), 1680 (C=O), 1605 (C=O). – MS: m/z(%) 261 ($M^{+\cdot}$, 10), 179 ($HOOC(C_6H_4)OCH_2CO^+$, 7), 110 ($M^{+\cdot}$–$H_2CO(C_6H_4)COOH$, 100).

$C_{14}H_{15}NO_4$	Calcd.:	C 64.36	H 5.79	N 5.36
(261.28)	Found:	C 64.09	H 5.90	N 5.28.

4-[3-(4,4-Dimethyl-pyrrolidin-2-ylidene)-2-oxo-propyl]-benzoic Acid (**4c**)

Yield 32% (SiO_2, ethyl acetate, R_f = 0.4), *m.p.* 176 °C. – ^{1}H NMR: δ/ppm 1.0 (s, 6H, $(CH_3)_2$), 2.4 (s, 2H, H-3), 3.3 (s, 2H, H-5), 3.55 (s, 2H, CH_2), 5.0 (s, 1H, =CH), 7.4 (d, 2H, AB, J=8, H arom.), 7.85 (d, 2H, AB, J=8, H arom.), 9.5 (bs, 1H, NH), 12.8 (bs, 1H, COOH) (DMSO-d_6); IR (KBr): ν/cm^{-1} = 3350 (NH), 1680 (C=O), 1625 (C=O). – MS: m/z (%) 273 ($M^{+\cdot}$, 3), 138 ($M^{+\cdot}$–$CH_2(C_6H_4)COOH$, 100).

$C_{16}H_{19}NO_3$	Calcd.:	C 70.31	H 7.01	N 5.12
(273.33)	Found:	C 70.08	H 7.24	N 5.06.

4-[3-(4,4-Dimethyl-pyrrolidin-2-ylidene)-2-oxo-propoxy]-benzoic Acid (**4d**)

Yield 42% (SiO_2, ethyl acetate/formic acid (1000:1 v/v), R_f = 0.6), *m.p.* 158 °C. – ^{1}H NMR: δ/ppm 1.0 (s, 6H, $(CH_3)_2$), 2.25 (s, 2H, H-3), 3.2 (s, 2H, H-5), 4.38 (s, 2H, OCH_2), 5.2 (s, 1H, =CH), 6.8 (d, 2H, AB, J=8.4, H arom.), 7.35 (d, 2H, AB, J=8.4), 9.7 (bs, 1H, NH), ($CDCl_3$+5% DMSO-d_6). – IR (KBr): ν/cm^{-1} = 3280 (NH), 1690 (C=O), 1605 (C=O). – MS: m/z (%) 289 ($M^{+\cdot}$, 6), 196 (4), 152 ($M^{+\cdot}$–$O(C_6H_4)COOH$, 100).

$C_{16}H_{19}NO_4$	Calcd.:	C 66.42	H 6.62	N 4.84
(289.33)	Found:	C 66.36	H 6.45	N 4.60.

[4-(Pyrrolidin-2-ylidene-acetyl)-phenyl]-acetic Acid (**4e**)

Yield 42% (SiO_2, ether/formic acid (1000:1 v/v), R_f = 0.2), *m.p.* 190 °C. – ^{1}H NMR: δ/ppm 1.9 (m, 2H, H-4), 2.7 (t, 2H, J=7.5, H-3), 3.6 (m, 5H, J=7.5, H-5, CH_2), 5.8 (s, 1H, =CH), 7.25 (d, 2H, AB, J=8, H arom.), 7.75 (d, 2H, AB, =8, H arom.), 10.1 (bs, 1H, NH) (DMSO-d_6). – IR (KBr): ν/cm^{-1} = 3350 (NH), 1695 (C=O), 1610 (C=O). – MS: m/z (%) 245 ($M^{+\cdot}$, 48), 244 ($M^{+\cdot}$–H, 100).

$C_{14}H_{15}NO_3$	Calcd.:	C 68.56	H 6.16	N 5.71
(245.28)	Found:	C 68.52	H 6.10	N 5.59.

{4-[(4,4-Dimethyl-pyrrolidin-2-ylidene)-acetyl]-phenyl}-acetic Acid (**4f**)

Yield 43% (SiO_2, ether/formic acid (1000:1 v/v), R_f = 0.3), *m.p.* 187 °C. – ^{1}H NMR: δ/ppm 1.0 (s, 6H, $(CH_3)_2$), 2.5 (s, 2H, H-3), 3.3 (s, 2H, H-5), 3.65 (s, 2H, CH_2), 5.75 (s, 1H, =CH), 7.3 (d, 2H, AB, J=8, H arom.), 7.8 (d, 2H, AB, J=8, H arom.), 10.05 (bs, 1H, NH), 12.4 (bs, 1H, COOH) (DMSO-d_6). – IR (KBr): ν/cm^{-1} = 3280 (NH), 1710 (C=O), 1605 (C=O). – MS: m/z (%) 273 ($M^{+\cdot}$, 67), 258 ($M^{+\cdot}$–CH_3, 100).

$C_{16}H_{19}NO_3$	Calcd.:	C 70.31	H 7.01	N 5.12
(273.33)	Found:	C 69.50	H 6.94	N 5.01.

4-[(4,4-Dimethyl-pyrrolidin-2-ylidene)-acetyl]-phenoxy}-acetic Acid (**4g**)

Yield 42% (SiO_2, ether/formic acid (1000:1 v/v), R_f = 0.3), *m.p.* 154 °C. – ^{1}H NMR: δ/ppm 1.2 (s, 6H, $(CH_3)_2$), 2.5 (s, 2H, H-3), 3.4 (s, 2H, H-5), 4.15 (s, 2H, OCH_2), 5.7 (s, 1H, =CH), 6.8 (d, 2H, AB, J=8, H arom.), 7.8 (d, 2H, AB, J=8, H arom.), 10.0 (bs, 1H, NH). – IR (KBr): ν/cm^{-1} = 3320 (NH), 1735 (C=O), 1605 (C=O). – MS: m/z (%) 289 ($M^{+\cdot}$, 53), 288 ($M^{+\cdot}$–H, 100).

$C_{16}H_{19}NO_4$	Calcd.:	C 66.42	H 6.62	N 4.84
(289.33)	Found:	C 66.39	H 6.51	N 4.71.

{3-[(4,4-Dimethyl-pyrrolidin-2-ylidene)-acetyl]-phenoxy}-acetic Acid (**4h**)

Yield 38% (SiO_2, ether/formic acid (1000:1 v/v), R_f = 0.3), *m.p.* 157 °C. – ^{1}H NMR: δ/ppm 1.15 (s, 6H, $(CH_3)_2$), 2.49 (s, 2H, H-3), 3.37 (s, 2H, H-5), 4.71 (s, 2H, OCH_2), 5.68 (s, 1H, =CH), 7.05–7.40 (m, 4H, H arom.). – IR (KBr): ν/cm^{-1} = 3320 (NH), 1720 (C=O), 1610 (C=O). – MS: m/z (%) 289 ($M^{+\cdot}$, 79), 288, 274 ($M^{+\cdot}$–CH_3, 100).

$C_{16}H_{19}NO_4$	Calcd.:	C 66.42	H 6.62	N 4.84
(289.33)	Found:	C 66.50	H 6.48	N 4.69.

{4-[(4,4-Dimethyl-pyrrolidin-2-ylidene)-acetyl]-phenyl}-propionic Acid (**4i**)

Yield 45% (SiO_2, ether/formic acid (1000:1 v/v), R_f = 0.2), *m.p.* 135 °C. – ^{1}H NMR: δ/ppm 1.15 (s, 6H, $(CH_3)_2$), 2.5 (m(s; t), 4H, H-3, CH_2), 2.85 (t, 2H, CH_2), 3.4 (s, 2H, H-5), 5.75 (s, 1H, =CH), 7.25 (d, 2H, AB, J =8, H arom.), 7.75 (d, 2H, AB, =8, H arom.), 9.9 (bs, 1H, NH), (DMSO-d_6). – IR

(KBr): ν/cm^{-1} = 3300 (NH), 1735 (C=O), 1600 (C=O). – MS: *m/z* (%) 287 ($M^{+\cdot}$, 62), 286 ($M^{+\cdot}$–H, 100).

$C_{17}H_{21}NO_3$	Calcd.:	C 71.06	H 7.37	N 4.87
(287.36)	Found:	C 70.65	H 7.32	N 4.79.

2-{4-[(4,4-Dimethyl-pyrrolidin-2-ylidene)-acetyl]-phenyl}-propionic Acid (**4j**)

Yield 38% (SiO_2, ether/formic acid (1000:1 v/v), R_f = 0.4), *m.p.* 168 °C. – ^{1}H NMR (DMSO-d_6): δ/ppm 1.15 (s, 6H, $(CH_3)_2$), 1.4 (d, 3H, HC-CH_3), 2.5 (s, 2H, H-3), 3.45 (s, 2H, H-5), 3.75 (q, 1H, CH), 5.75 (s, 1H, =CH), 7.4 (d, 2H, AB, *J*=8, H arom.), 7.8 (d, 2H, AB, *J*=8, H arom.), 10.0 (bs, 1 H, NH), 12.4 (bs, 1H, COOH). – IR (KBr): ν/cm^{-1} = 3250 (NH), 1715 (C=O), 1605 (C=O). – MS: *m/z* (%) 287 ($M^{+\cdot}$, 65), 286 ($M^{+\cdot}$–H, 100), 177 ($^+OC(C_6H_4)CH(CH_3)CO_2H$, 22).

$C_{17}H_{21}NO_3$	Calcd.:	C 71.06	H 7.37	N 4.87
(287.36)	Found:	C 70.76	H 7.33	N 4.79.

{4-[(4,4-Dimethyl-pyrrolidin-2-ylidene)-acetyl]-benzsulfanyl}-acetic Acid (**4k**)

Yield 26% (SiO_2, ether/formic acid (1000:1 v/v), R_f = 0.4), *m.p.* 162 °C. – ^{1}H NMR: δ/ppm 1.15 (s, 6H, $(CH_3)_2$), 2.5 (s, 2H, H-3), 3.05 (s, 2H, CH_2COOH), 3.4 (s, 2H, H-5), 3.85 (s, 2H, SCH_2), 5.7 (s, 1H, =CH), 7.35 (d, 2H, AB, *J*=8, H arom.), 7.8 (d, 2H, AB, *J*=8, H arom.), 10.05 (bs, 1H, NH). – IR (KBr): ν/cm^{-1} = 3180 (NH), 1715 (C=O), 1605 (C=O). – MS: *m/z* (%) 319 ($M^{+\cdot}$, 80), 318 ($M^{+\cdot}$–H, 99), 304 ($M^{+\cdot}$–CH_3/OH, 100).

$C_{17}H_{21}NO_3S$	Calcd.:	C 63.92	H 6.63	N 4.39
(319.42)	Found:	C 63.97	H 6.85	N 4.29.

3-{4-[(4,4-Dimethyl-pyrrolidin-2-ylidene)-acetyl]-benzenesulfanyl}-propionic Acid (**4l**)

Yield 24% (SiO_2, ether/formic acid (1000:1 v/v), R_f = 0.5), *m.p.* 121 °C. – ^{1}H NMR: δ/ppm 1.15 (s, 6H, $(CH_3)_2$), 2.5 (s, 2H, H-3), 2.6 (m, 4H, CH_2CH_2), 3.4 (s, 2H, H-5), 3.7 (s, 2H, SCH_2), 5.7 (s, 1H, =CH), 7.35 (d, 2H, AB, *J*=8, H arom.), 7.8 (d, 2H, AB, *J*=8, H arom.), 10.0 (bs, 1H, NH). – IR (KBr): ν/cm^{-1} = 3320 (NH), 1710 (C=O), 1610 (C=O); MS: *m/z* (%) 333 ($M^{+\cdot}$, 82), 332 ($M^{+\cdot}$–H, 100).

$C_{18}H_{23}NO_3S$	Calcd.:	C 68.84	H 6.95	N 4.20
(333.45)	Found:	C 64.17	H 6.77	N 4.06.

4-[3-(3,3-Dimethyl-1,3-dihydro-indol-2-ylidene)-2-oxo-propoxy]-benzoic Acid (**4m**)

Yield 35% (SiO_2, DIPE/formic acid (1000:1 v/v), R_f = 0.1), *m.p.* 241 °C. – ^{1}H NMR: δ/ppm 1.4 (s, 6H, $(CH_3)_2$), 4.75 (s, 2H, CH_2O), 5.6 (s, 1H, =CH), 6.95–7.4 (m, 6H, H arom.), 7.9 (d, 2H, AB, *J*=8, H arom.), 11.5 (bs, 1H, NH/COOH), 12.6 (s, 1H, NH/COOH) (DMSO-d_6). – IR (KBr): ν/cm^{-1} = 3280 (NH), 1680 (C=O), 1605 (C=O). – MS: *m/z* (%) 337 ($M^{+\cdot}$, 18), 186 ($M^{+\cdot}$–$CH_2O(C_6H_4)COOH$, 100).

$C_{20}H_{19}NO_4$	Calcd.:	C 71.20	H 5.68	N 4.15
(337.38)	Found:	C 71.10	H 5.43	N 4.00.

{4-[(3,3-Dimethyl-1,3-dihydro-indol-2-ylidene)-acetyl]-phenyl}-acetic Acid (**4n**)

Yield 55%; *m.p.* 233 °C. – ^{1}H NMR: δ/ppm 1.4 (s, 6H, $(CH_3)_2$), 3.65 (s, 2H, CH_2), 6.28 (s, 1H, =CH), 6.9–7.3 (m, 4H, H arom.), 7.35 (d, 2H, AB, *J*=8, H arom.), 7.95 (d, 2H, AB, *J*=8, H arom.), (DMSO-d_6). – IR (KBr): ν/cm^{-1} = 3210 (NH), 1715 (C=O), 1615 (C=O). – MS: *m/z* (%) 321 ($M^{+\cdot}$, 100), 320 ($M^{+\cdot}$–H, 74), 163 ($^+OC(C_6H_4)CH_2COOH$, 20).

$C_{20}H_{19}NO_3$	Calcd.:	C 74.75	H 5.96	N 4.36
(321.38)	Found:	C 74.71	H 5.91	N 4.20.

{4-[(3,3-Dimethyl-1,3-dihydro-indol-2-ylidene)-acetyl]-phenoxy}-acetic Acid (**4o**)

Yield 43% (SiO_2, ether/formic acid (1000:1 v/v), R_f = 0.2), *m.p.* 192 °C. – ^{1}H NMR: δ/ppm 1.4 (s, 6H, $(CH_3)_2$), 4.8 (s, 2H, OCH_2), 6.4 (s, 1H, =CH), 7.0 (d, 2H, AB, *J*=8, H arom.), 7.1–7.4 (m, 4H, H arom.), 8.0 (d, 2H, AB, *J*=8, H arom.), 11.7 (bs, 1H, NH/COOH), 13.1 (bs, 1H, NH/COOH) (DMSO-d_6). – IR (KBr): ν/cm^{-1} = 3280 (NH), 1720 (C=O), 1600 (C=O). – MS: *m/z* (%) 337 ($M^{+\cdot}$, 100), 336 ($M^{+\cdot}$–H, 65), 179 ($HOOCCH_2OC_6H_4CO^+$, 12).

$C_{20}H_{19}NO_4$	Calcd.:	C 71.20	H 5.68	N 4.15
(337.38)	Found:	C 70.93	H 5.63	N 4.18.

{4-[(3,3-Dimethyl-1,3-dihydro-indol-2-ylidene)-acetyl]-benzylsulfanyl}-acetic Acid (**4p**)

Yield 39% (SiO_2, ethyl acetate, R_f = 0.6), *m.p.* 190 °C. – ^{1}H NMR: δ/ppm 1.5 (s, 6H, $(CH_3)_2$), 3.1 (s, 2H, CH_2), 3.9 (s, 2H, CH_2), 6.0 (s, 1H, =CH), 6.95–7.4 (m, 4H, H arom.), 7.4 (d, 2H, AB, *J*=8, H arom.), 7.9 (d, 2H, AB, *J*=8, H arom.). – IR (KBr): ν/cm^{-1} = 3400 (NH), 1705 (C=O), 1690 (C=O). – MS: *m/z* (%) 367 ($M^{+\cdot}$, 100), 366 ($M^{+\cdot}$–H, 65), 209 ($^+OC(C_6H_4)CH_2SCH_2COOH$, 4).

$C_{21}H_{21}NO_3S$	Calcd.:	C 68.64	H 5.76	N 3.81
(367.46)	Found:	C 68.15	H 5.54	N 3.78.

{4-[3,4-Dihydro-2H-isoquinolin-1-ylidene)-acetyl]-phenyl}-acetic Acid (**4q**)

Yield 49% (SiO_2, ether/formic acid (1000:1 v/v), R_f = 0.3), *m.p.* 219 °C. – ^{1}H NMR: δ/ppm 2.95–3.05 (m, 2H, H-4), 3.5–3.6 (m, 2H, H-3), 3.65 (s, 2H, CH_2), 6.5 (s, 1H, =CH), 7.3–7.55 (m, 4H, H arom.), 7.95–8.1 (m, 2H, H arom.), 11.7 (bs, 1H, NH/COOH), 12.4 (bs, 1H, NH/COOH) (DMSO-d_6). – IR (KBr): ν/cm^{-1} = 3200 (NH), 1710 (C=O), 1610 (C=O). – MS: *m/z* (%) 307 ($M^{+\cdot}$, 60), 306 ($M^{+\cdot}$–H, 100), 163 ($^+OC(C_6H_4)CH_2COOH$, 10).

$C_{19}H_{17}NO_3$	Calcd.:	C 74.25	H 5.58	N 4.56
(307.35)	Found:	C 74.34	H 5.61	N 4.40.

2-(4,4-Dimethyl-pyrrolidin-2-ylidene)-1-(4-[1,3]-dioxolan-2-yl-phenyl)-Ethanone (**6**)

Yield 35% (SiO_2, ether, R_f = 0.3), *m.p.* 113 °C. – ^{1}H NMR: δ/ppm 1.15 (s, 6H, $(CH_3)_2$), 2.5 (s, 2H, H-3), 3.45 (s, 2H, H-5), 4.0–4.2 (m, 4H, CH_2CH_2), 5.72 (s, 1H, =CH), 5.82 (s, 1H, CH), 7.5 (d, 2H, AB, *J*=8, H arom.), 7.9 (d, 2H, AB, *J*=8, H arom.), 10.1 (bs, 1H, NH). – IR (KBr): ν/cm^{-1} = 3300 (NH), 1615 (C=O). – MS: *m/z* (%) 287 ($M^{+\cdot}$, 29), 286 ($M^{+\cdot}$–H, 41), 138 ($M^{+\cdot}$–$(OCH_2CH_2O)(C_6H_4)CO$, 100), 105 ($C_6H_4CO^+$, 57).

$C_{17}H_{21}NO_3$	Calcd.:	C 71.06	H 7.37	N 4.87
(287.36)	Found:	C 70.89	H 7.35	N 4.68.

4-[(4,4-Dimethyl-pyrrolidin-2-ylidene)-acetyl]-Benzaldehyde (**7**)

Yield 75% (SiO_2, DIPE, R_f = 0.15), *m.p.* 137 °C. – ^{1}H NMR: δ/ppm 1.15 (s, 6H, $(CH_3)_2$), 2.5 (s, 2H ,H-3), 3.37 (s, 2H, H-5), 5.72 (s, 1H, =CH), 7.88 (d, 2H, AB, *J*=8, H arom.), 7.95 (d, 2H, AB, *J*=8, H arom.), 10.0 (s, 1H, CHO), 10.19 (bs, 1H,

NH), (400 MHz). – IR (KBr): ν/cm^{-1} = 3250 (NH), 1695 (C=O), 1605 (C=O) MS. – *m/z* (%) 243 (M^+·, 60), 242 (M^+·–H, 41), 228 (M^+·–CH_3, 100), 133 ($OHC(C_6H_4)CO^+$, 25).

$C_{15}H_{17}NO_2$	Calcd.:	C 74.05	H 7.04	N 5.76
(243.31)	Found:	C 74.20	H 6.95	N 5.62.

Regioselective N-Methylation of Enaminones (General Procedure)

To 2 mmol of the enaminone in 10 ml anh DMF under N_2 2 mmol KO*t*Bu were added while maintaining the temperature below 30 °C. After 10 min 2 mmol dimethyl sulfate (DMS) in 2 ml anh. DMF were injected with a syringe. After 12 h at room temperature the solution was diluted with ice water and extracted with ethyl acetate/ether (1:1 v/v). The combined organic layers were dried and than evaporated *in vacuo*. The residue was purified by flash chromatography as stated.

{4-[(1,4,4-Trimethyl-pyrrolidin-2-ylidene)-acetyl]-phenyl}-acetic Acid (**5**)

Yield 60% (SiO_2, ether/formic acid (1000:1 v/v), R_f = 0.3), *m.p.* 155 °C. – ^1H NMR: δ/ppm 1.14 (s, 6H, $(CH_3)_2$), 2.92 (s, 3H, NCH_3), 3.2 (s, 4H, H-3, H-5), 3.61 (s, 2H, CH_2), 5.58 (s, 1H, =CH), 7.23 (d, 2H, AB, *J*=8, H arom.), 7.72 (d, 2H, AB, *J*=8, H arom.). – IR (KBr): ν/cm^{-1} = 1700 (C=O). – MS: *m/z* (%) 301 (M^+·, 3), 286 (M^+·–CH_3, 16), 272 (100), 163 ($HOOCCH_2C_6H_4CO^+$, 17).

$C_{17}H_{21}NO_3$	Calcd.:	C 71.06	H 7.37	N 4.87
(287.36)	Found:	C 71.10	H 7.25	N 4.75.

4-[(1,4,4-Trimethyl-pyrrolidin-2-ylidene)-acetyl]-Benzaldehyde (**8**)

Yield 90%, *m.p.* 89 °C. – (DIPE) ^1H NMR: δ/ppm 1.15 (s, 6H, $(CH_3)_2$), 3.0 (s, 3H, NCH_3), 3.19 (s, 2H, CH_2), 3.2 (s, 2H, CH_2), 5.65 (s, 1H, =CH), 7.85 (d, 2H, AB, *J*=8, H arom.), 8.1 (d, 2H, AB, *J*=8, H arom.), 10.0 (s, 1H, CHO) (200 MHz, $CDCl_3$). – IR (KBr): ν/cm^{-1} = 1700 (C=O), 1620 (C=O). – MS: *m/z* (%) 242 (M^+·–CH_3, 93), 133 ($OHC(C_6H_4)CO^+$, 34), 42 (C_2H_2O,100).

$C_{16}H_{19}NO_2$	Calcd.:	C 74.86	H 7.44	N 5.44
(257.33)	Found:	C 74.39	H 7.54	N 5.38.

Wittig Reaction (General Procedure)

To the suspension of 2.2 mmol phosphonium salt in 5 ml anh. THF 7.2 mmol KO*t*Bu in 5 ml anh THF were added at −40 °C. The corresponding aldehyde was added at room temperature, and after stirring for 12 h the solution was acidified with 5% HCl and extracted with ethyl acetate/ether (1:1 v/v). The combined organic layers were dried, evaporated *in vacuo*, the residue purified by flash chromatography.

Methyl 3-{4-[(4,4-Dimethyl-pyrrolidin-2-ylidene)-acetyl-phenyl}-Acrylate (**9a**)

Yield 90% (SiO_2, ether, R_f = 0.4), *m.p.* 138 °C. – ^1H NMR: δ/ppm 1.16 (s, 6H, $(CH_3)_2$), 2.49 (s, 2H, H-3), 3.36 (s, 2H, H-5), 3.78 (s, 3H, CO_2CH_3), 5.73 (s, 1H, =CH), 6.41–6.49 (d, 1H, *J*=16, =CH–CO_2), 7.52 (d, 2H, AB, *J*=8, H arom.), 7.77 (d, 1H, *J*=16, -CH=), 7.85 (d, 2H, AB, *J*=8, H arom.), 10.12 (bs, 1H, NH). – IR (KBr): ν/cm^{-1} = 3280 (NH), 1705 (C=O), 1660 (C=O).

$C_{18}H_{21}NO_3$	Calcd.:	C 72.22	H 7.07	N 4.68
(299.37)	Found:	C 72.12	H 7.00	N 4.48.

Methyl 3-{4-[(1,4,4-Trimethyl-pyrrolidin-2-ylidene)-acetyl-phenyl}-Acrylate (**9b**)

Yield 90% (SiO_2, ether, R_f = 0.35), *m.p.* 120 °C. – ^1H NMR: δ/ppm 1.13 (s, 6H, $(CH_3)_2$), 2.93 (s, 3H, NCH_3), 3.19 (s, 4H, H-3, H-5), 3.78 (s, 3H, CO_2CH_3), 5.63 (s, 1H, =CH), 6.45 (d, 1H, *J*=16, =CH–CO), 7.51 (d, 2H, AB, *J*=8, H arom.), 7.68 (d, 1H, *J*=16, CH=), 7.87 (d, 2H, AB, *J*=8, H arom.). – IR (KBr): ν/cm^{-1} = 1705 (C=O), 1640 (C=O). – MS: *m/z* (%) 313 (M^+·, 35), 312 (M^+·–H, 5), 298 (M^+·–CH_3, 100), 189 ($^+OC(C_6H_4)CH{=}CHCO_2CH_3$, 17).

$C_{19}H_{23}NO_3$	Calcd.:	C 72.82	H 7.40	N 4.47
(313.40)	Found:	C 72.52	H 7.28	N 4.29.

3-{4-[(4,4-Dimethyl-pyrrolidin-2-ylidene)-acetyl-phenyl}-acrylic Acid (**9a'**)

Yield 60% (SiO_2, ether/formic acid (1000:1 v/v), R_f = 0.3), *m.p.* 215 °C. – ^1H NMR: δ/ppm 0.85 (s, 6H, $(CH_3)_2$), 2.2 (s, 2H, H-3), 3.0 (s, 2H, H-5), 5.4 (s, 1H, =CH), 6.1 (d, 1H, *J*=16, =CH–CO), 7.15 (d, 2H, AB, *J*=8, H arom.), 7.25 (d, 1H, *J*=16, CH=), 7.5 (d, 2H, AB, *J*=8, H arom.), 9.8 (bs, 1H, NH) ($CDCl_3$+5% DMSO-d_6). – IR (KBr): ν/cm^{-1} = 3300 (NH), 1680 (C=O), 1630 (C=O). – MS: *m/z* (%) 285 (M^+·, 10), 284(M^+·–H, 13), 270 (M^+·–CH_3, 14), 175 ($^+OC(C_6H_4)CH{=}CHCO_2H$, 4), 103 ($C_6H_4CH{=}CH_2$, 100).

$C_{17}H_{19}NO_3$	Calcd.:	C 71.56	H 6.71	N 4.91
(285.34)	Found:	C 71.28	H 6.55	N 4.79.

3-{4-[(1,4,4-Trimethyl-pyrrolidin-2-ylidene)-acetyl]-phenyl}-acrylic Acid (**9b'**)

Yield 69% (SiO_2, ether/formic acid (1000:1 v/v), R_f = 0.3), *m.p.* 229 °C. – ^1H NMR δ/ppm 0.85 (s, 6H, $(CH_3)_2$), 2.65 (s, 3H, NCH_3), 2.8 (s, 2H, CH_2), 2.9 (s, 2H, CH_2), 5.35 (s, 1H, =CH), 6.1 (d, 1H, *J*=16, =CH–CO), 7.2 (d, 2H, AB, *J*=8, H arom.), 7.3 (d, 1H, *J*=16, CH=), 7.55 (d, 2H, AB, *J*=8, H arom.) ($CDCl_3$+5% DMSO-d_6). – IR (KBr): ν/cm^{-1} = 1685 (C=O), 1620 (C=O). – MS: *m/z* (%) 299 (M^+·, 42), 298 (M^+·–H, 6), 284 (M^+·–CH_3, 100), 175 ($^+OC(C_6H_4)CH{=}CHCO_2H$, 18).

$C_{18}H_{21}NO_3$	Calcd.:	C 72.22	H 7.07	N 4.68
(299.37)	Found:	C 7202	H 7.12	N 4.53.

5-{-[(4,4-Dimethyl-pyrrolidin-2-ylidene)-acetyl]-phenyl}-pent-4-enoic Acid (**9c**)

Yield 38% (SiO_2, ether/formic acid (1000:1 v/v), R_f = 0.3), *m.p.* 123 °C. – ^1H NMR: δ/ppm 1.15 (s, 6H, $(CH_3)_2$), 2.3–2.7 (m, 6H, H-3, CH_2CH_2), 5.1–5.85 (m(s), 2H, =CHCO, =CH-), 6.5 (d, 1H, -CH=), 7.4 (d, 2H, AB, *J*=8, H arom.), 7.9 (d, 2H, AB, *J*=8, H arom.), 10.0 (s, 1H, NH), 12.2 (s, 1H, COOH) (DMSO-d_6). – IR (KBr): ν/cm^{-1} = 3200 (NH), 1715 (C=O), 1605 (C=O). – MS: *m/z* (%) 313 (M^+·, 75), 312 (M^+·–H, 100), 298 (M^+·–CH_3, 74).

$C_{19}H_{23}NO_3$	Calcd.:	C 72.82	H 7.40	N, 4.47
(313.40)	Found:	C 72.88	H 7.35	N, 4.35.

7-{4-[4,4-Dimethyl-pyrrolidin-2-ylidene)-acetyl]-phenyl}-hept-6-enoic Acid (**9d**)

Yield 45% (SiO_2, ether, R_f = 0.5), *m.p.* 104 °C. – ^1H NMR: δ/ppm 1.15 (s, 6H, $(CH_3)_2$), 1.4–1.7 (m, 4H, CH_2–CH_2), 2.1–

2.4 (m, 4H, CH_2, CH_2), 2.5 (s, 2H, H-3), 3.45 (s, 2H, H-5), 5.1–5.85 (m(s), 2H, =CHCO, =CH-), 6.5 (d, 1H, -CH=), 7.4 (d, 2H, AB, *J*=8, H arom.), 7.9 (d, 2H, AB, *J*=8, H arom.), 10.0 (s, 1H, NH), (DMSO-d_6). – IR (KBr): ν/cm^{-1} = 3280 (NH), 1725 (C=O), 1605 (C=O). – MS: *m/z* (%) 341 ($M^{+\cdot}$, 52), 340 ($M^{+\cdot}$–H, 100), 326 ($M^{+\cdot}$–CH_3, 57), 231 ($^+OC(C_6H_4)CH{=}CH(CH_2)_4COOH$, 13).

$C_{21}H_{27}NO_3$	Calcd.:	C 73.87	H 7.97	N 4.10
(341.45)	Found:	C 73.80	H 7.81	N 4.02.

Oximation of Aldehydes (General Procedure)

0.6 mmol aldehyde, 500 mg $BaCO_3$ and 1 mmol hydroxylamine derivative were refluxed in 15 ml EtOH for 3 h. EtOH was evaporated and water added to the residue. The aqueous layer was extracted with CH_2Cl_2, the combined organic layers were dried and evaporated *in vacuo*. The products were purified by flash chromatography (SiO_2, Ether).

4-[(1,4,4-Trimethyl-pyrrolidin-2-ylidene)-acetyl]-phenyl-O-methyl-Aldoxime (**10**)

Yield 72% (SiO_2, ether, R_f = 0.3), *m.p.* 124 °C. – ^1H NMR: δ/ppm 1.15 (s, 6H, $(CH_3)_2$), 2.95 (s, 3H, NCH_3), 3.20 (s, 4H, H-3, H-5), 3.97 (s, 3H, OCH_3) 5.65 (s, 1H, =CH), 7.6 (d, 2H, AB, *J*=9, H arom.), 7.85 (d, 2H, AB, *J*=9, H arom.), 8.1 (s, 1H, CH=N). – IR (KBr): ν/cm^{-1} = 1620 (C=O). – MS: *m/z* (%) 286 ($M^{+\cdot}$, 49), 285 ($M^{+\cdot}$–H, 5), 271 ($M^{+\cdot}$–CH_3, 100).

$C_{17}H_{22}N_2O_2$	Calcd.:	C 71.30	H 7.74	N 9.78
(286.37)	Found:	C 71.12	H 7.58	N 9.55.

4-[(1,4,4-Trimethyl-pyrrolidin-2-ylidene)-acetyl]-phenyl-aldiminoxy acetic Acid (**11**)

Yield 53% (SiO_2, ether/formic acid (1000:1 v/v), R_f = 0.4), *m.p.* 146 °C. – ^1H NMR: δ/ppm 1.15 (s, 6H, $(CH_3)_2$), 2.95 (s, 3H, NCH_3), 3.2 (s, 4H, H-3, H-5), 4.7 (s, 2H, CH_2), 5.62 (s, 1H, =CH), 7.5 (d, 2H, AB, *J*=9, H arom.), 7.85 (d, 2H, AB, *J*=9, H arom.), 8.17 (s, 1H, CH=N). – IR (KBr): ν/cm^{-1} = 1740 (C=O). – MS: *m/z* (%) 330 ($M^{+\cdot}$, 3), 329 ($M^{+\cdot}$–H, 12), 315 ($M^{+\cdot}$–CH_3, 22), 238 (100).

$C_{18}H_{22}N_2O_4$	Calcd.:	C 65.44	H 6.71	N 8.48
(330.38)	Found:	C 65.28	H 6.75	N 8.24.

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