

Indolyl substituted 4-oxobut-2-enoic acids. Synthesis and *aza*-Michael additions

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Abstract: The synthesis of three new substituted 4-heteroaryl-4-oxobut-2-enoic acids with indole ring substituted in positions 3-, 5- and 7- is described. The addition of these Michael acceptors to 4-(1-phenylsulphonylpyrrol-3-yl)-4-oxobut-2-enoic acid in conjugate addition was explored using both racemic and chiral amines. In tandem with the crystallization-induced asymmetric transformation (CIAT) protocol the effective methodology for the synthesis of enantiomerically highly enriched substituted 2-amino-4-heteroaryl-4-oxobutanoic acids as multifunctional homotryptophan analogues was developed.

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1 Introduction

Aryl- and heteroarylsubstituted (*E*)-4-oxobut-2-enoic acids and their derivatives represent an important class of compounds with interesting pharmacologic indications including anti-ulcer and cytoprotective properties [1], kynurenine-3-hydroxylase [2] and human cytomegalovirus protease inhibiting activity [3]. Several naturally occurring acylacrylic acids show notable antibiotic activity [4, 5]. Moreover as we have demonstrated in our

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recent papers the aroyl-[6] or heteroaroylacrylic [7] acids are a useful synthons for the preparation of γ -oxo- and γ -hydroxysubstituted α -amino acids and acylacrylic subunit appears to have a broad potential as a crystallization-induced asymmetric transformation (CIAT) template [8, 9].

The aim of this paper is the preparation of new indolylsubstituted (*E*)-4-oxobut-2-enoic acids **2-4** and their application along with the pyrrolyl analogue **1** (Figure 1) as the reactive Michael acceptors in the synthesis of some 4-heteroaryl derivatives of 2-amino-4-oxobutanoic acids **5-8** using *aza*-Michael addition as a key step.

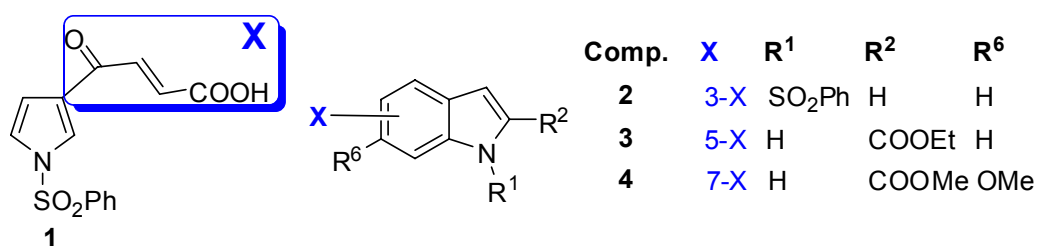


Fig. 1 4-Heteroaryl-4-oxobutenoic acids **1-4**.

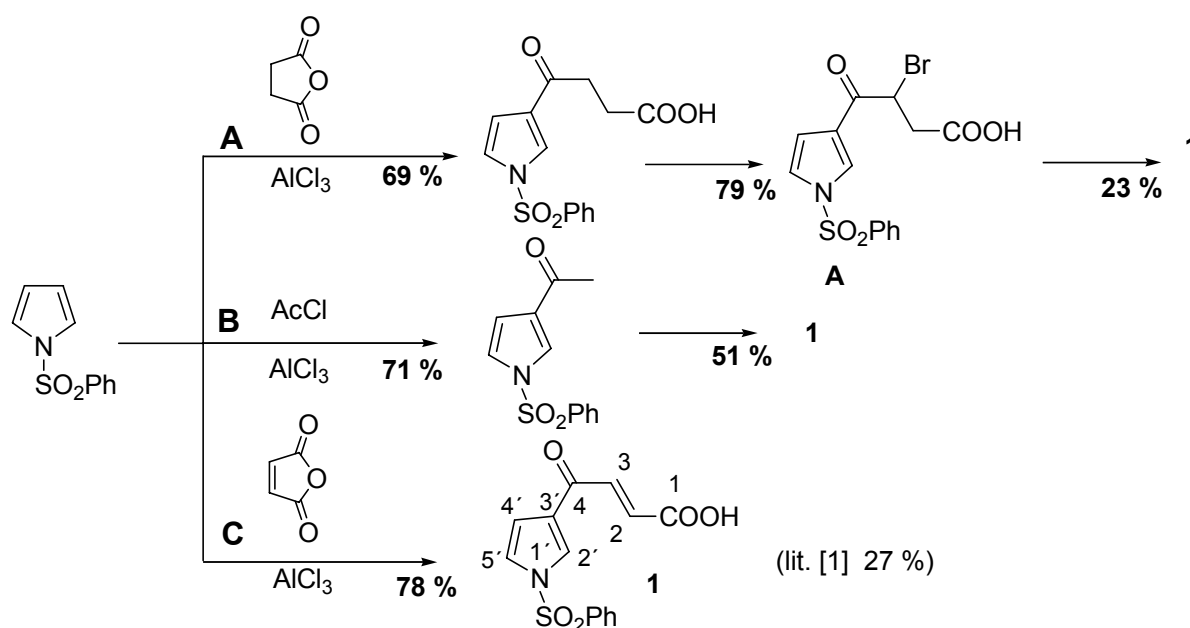
The pyrrolyl derivative **1** has been previously prepared by Bianchi [1] in a 27% yield *via* Friedel-Crafts (F-C) acylation of the corresponding 1-phenylsulfonylpyrrole with maleic anhydride and AlCl₃. However, attempt to use (F-C) methodology in the indolyl series was unsuccessful. The known (*E*)-3-indolyl-4-oxobut-2-enoic acid was synthesized from 1-indolylmagnesium bromide and maleic anhydride albeit in a modest 6.6% yield [1].

2 Results and discussion

2.1 Synthesis of oxobutenoic acids **1-4**

Because of described low yield in the synthesis of derivate **1**, we were looking for a new synthetic strategy to these compounds (Scheme 1). The acylation of 1-phenylsulphonylpyrrole with succinic anhydride (method A) affords the regioisomeric mixture of the desired 4-(1-phenylsulphonylpyrrol-3-yl)-4-oxobutanoic acid and the 2-regioisomer. Fortunately the crystallization of the raw mixture from toluene furnished the desired 3-substituted regioisomer in good yield and purity. However, a subsequent bromination and elimination sequence provided the desired unsaturated acid **1** in low yield. An alternative two-step sequence (method B) using acetyl chloride in the (F-C) reaction followed by condensation with glyoxylic acid, allowed us to generate the desired derivative in increased yield. In addition this (F-C) was found to proceed with better regioselectivity. Finally an improved (F-C) based on the Bianchi method (method C) afforded **1** in a 78% yield after crystallization, simply by changing the solvent.

All attempts using 1-phenylsulfonylindole in (F-C) reactions led to the formation of complex mixtures of product, thus the indolyl analogue **2** was prepared by method B, namely condensation of acetyl derivative with glyoxylic acid in boiling acetic acid -



Scheme 1 Synthetic pathways for 4-(1-phenylsulphonylpyrrol-3-yl)-4-oxobutenoic acid **1**.

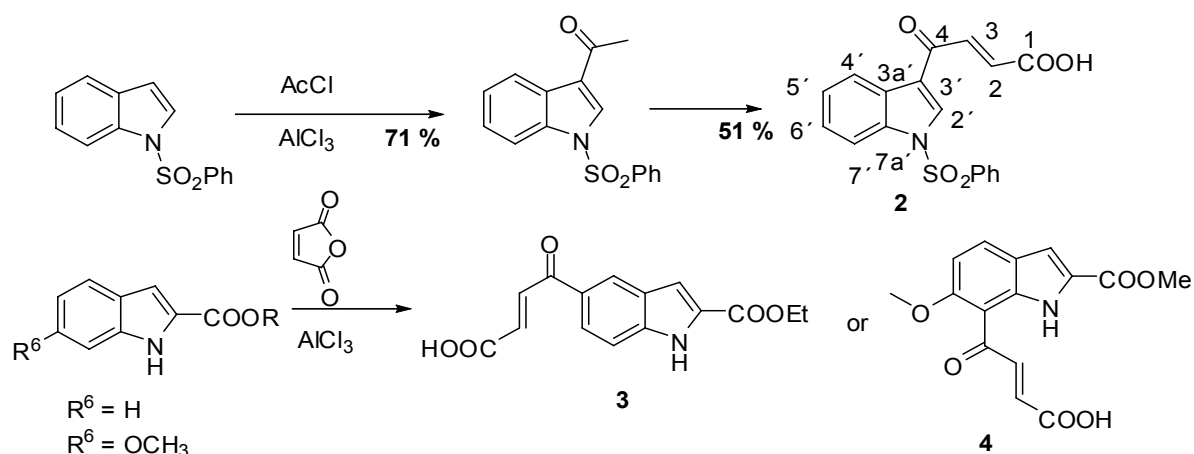
hydrochloric acid mixture.

In the previous studies on (F-C) acylation of ethyl indolyl-2-carboxylate the regioselectivity varied significantly depending on the reaction conditions used. In most cases, a mixture of regioisomers was obtained [10]. In our hands the F-C acylation of indolyl-2-carboxylic acid esters with maleic anhydride/ AlCl_3 proceeds regioselectively on aromatic ring. The ethyl ester of the indole-2-carboxylic acid generates a crude product consisting primarily of the 5-substituted regioisomer **3**, this may be easily purified by crystallization (total yield of derivative **3** is 81.9%). In the case of 6-methoxy derivative the only isolated product was the 7-substituted acid **4** (80%). This is a special example of such 7-regioselectivity in the electrophilic reactions on substituted indolyl-2-carboxylate [11–13].

The structure of the prepared heteroaryloxobutenoic acids **2–4** was confirmed by NMR spectral measurements. In the case of derivatives **3** and **4** selective INEPT technique was applied to unambiguously confirm the structure.

2.2 *aza*-Michael addition. Synthesis of oxoaminoacids **5–8**

Over the last decade the synthesis of non-proteinogenic unnatural amino acids has attracted significant attention of organic chemists, who have tried to find novel synthetic pathways whilst keeping time and financial requirements as low as possible. From this point of view 4-aryl-4-oxobut-2-enoic acids represent an attractive starting material for the preparation of aryl substituted homophenylalanines along with their γ -oxo- and γ -hydroxy derivatives *via aza*-Michael addition. The use of chiral *N*-nucleophiles in tandem with the CIAT protocol is an inexpensive and industrially attractive pathway to



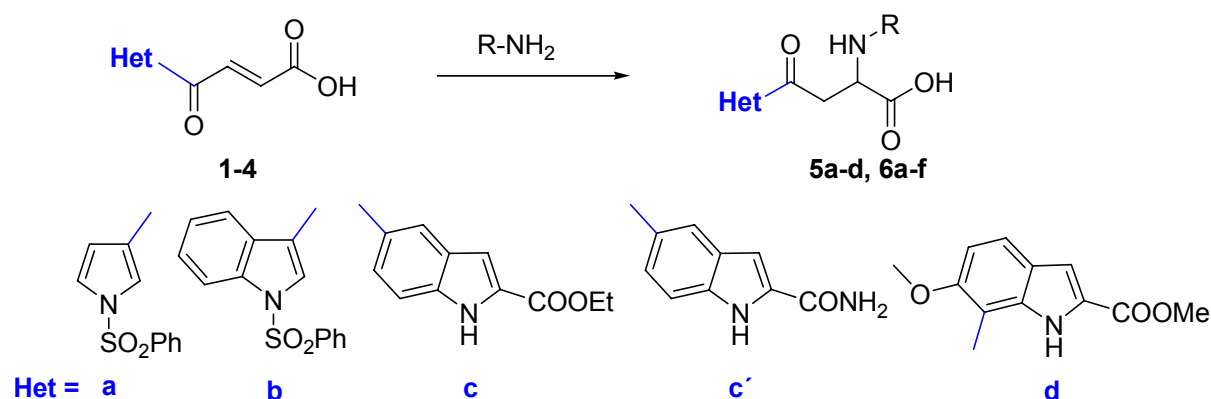
Scheme 2 Preparation of indolylsubstituted 4-oxobutenoic acids **2-4**.

the synthesis of enantiomerically pure α -amino acid derivatives [14–16]. Moreover indole-containing amino acids with their ability to bind cations (the cation – π interaction) represent the peptide residues of high importance in study of membrane processes. Asymmetric synthesis of α -homotryptophan [17], β -homotryptophans [18, 19] and protected tryptophan regioisomers [20] were published recently. Pyrrol-3-yl substituted 2-amino butanoic acid is an important structural fragment of bone collagen cross-links – deoxypyrrroline [21].

In connection with our previous work [22, 23] we have decided to study *aza*-Michael addition on prepared oxobutenoic acids **1-4** and to seek out limitations of CIAT processes in these reaction systems for preparation of enantiomerically pure substituted homotryptophan analogues.

Firstly the addition of ammonia and benzyl amine or furfurylamine ($Fu-NH_2$) was studied (Scheme 3). The reaction conditions are mild (5–72 hours at room temperature) and the respective adducts **5a-d**, **6a-f** were obtained in moderate to good yields (Table 1). The reaction proceeds regioselectively at the 2-position of the oxobutenoic acid moiety. Only α -amino acids were detected in reaction mixture. The amino acids **5,6** were isolated by simple filtration from heterogeneous reaction mixture (benzyl amine and furfurylamine adducts **6a-f**) or *via* adjusting the pH of mixture to 6 and subsequent filtration of the ammonia adducts **5a-d**. In the case of oxobutenoic acid **3** the high excess of ammonia causes the simultaneous ammonolysis of ester function and the isolated product was the corresponding amide **5c'**.

Having optimized the process for the benzyl amine and furfurylamine addition the reactions of racemic phenylethylamine (($\pm$)-PEA), (*S*)-phenylethylamine ((*S*)-PEA) and (*R*)-phenylglycinol was studied in order to develop an effective CIAT protocol (Scheme 4). The success of previously published CIAT on conjugate addition to aroylacrylic acids and their derivatives is based on the formation of only slightly soluble amino acids at their isoelectric point. The solvent also plays an important role when searching for appropriate conditions for CIAT. It is necessary to find solvent in which solubility of the forming amino acid is as low as possible but at a same time high enough to permit the equilibrating



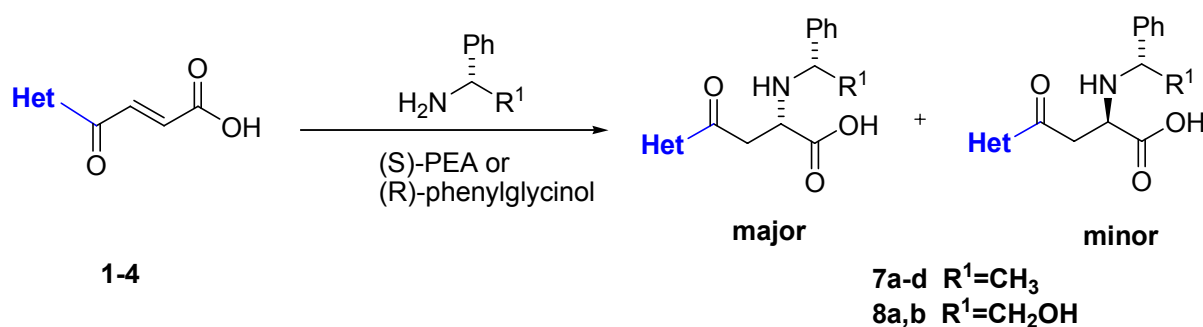
Scheme 3 *aza*-Michael addition of racemic amines on oxobutenoic acids **1-4**.

Table 1 *aza*-Michael addition of racemic amines on oxobutenoic acids **1-4**.

Starting acid	Adduct	Het	amine	conditions	yield [%]
1	5a	a	NH ₃	water, 24 h, RT	68
2	5b	b	NH ₃	water, 24 h, RT	36
3	5c'	c'	NH ₃	water, 24 h, RT	66
4	5d	d	NH ₃	water, 24 h, RT	59
1	6a	a	Bn-NH ₂	MeOH, 2 d, RT	76
2	6b	b	Bn-NH ₂	MeOH, 3 d, RT	66
3	6c	c	Bn-NH ₂	EtOH, 5h, RT	69
4	6d	d	Bn-NH ₂	MeOH, 5h, RT	74
3	6e	c	Fu-NH ₂	EtOH, 15 h, RT	70
4	6f	d	Fu-NH ₂	MeOH, 15 h, RT	86

processes. The best results in our indolyl- and pyrrolyl- series are outlined in the Scheme 4. In all indolyl substituted examples, the pure diastereomer was afforded in high yield by filtration of the reaction mixture (Table 2). However, the pyrrolyl derivative afforded high yield and purity with racemic ($\pm$)-PEA only. The CIAT process of oxobutenoic acid **1** with enantiomerically pure (*S*)-phenylethylamine proceeds slowly and in all cases mixtures of both diastereomers were isolated from water or dioxane. The application of the (*S*)-PEA in methanol under otherwise unchanged conditions gave rise to a 1:1 mixture of the both diastereomers. As the driving force in CIAT applications is crystallization of the product we anticipate the formation of quasiracemate [24] in this particular example. Fortunately the CIAT protocol of **1** proceeds well with (*R*)-phenylglycinol to give the pyrrolyl substituted oxobutanoic acid **8a** which was isolated in excellent enantiomeric and diastereomeric purity and high yield.

In order to establish the expected stereochemical development on *aza*-Michael addition of chiral amines to oxobutenoic acids, the (*R*)-phenylglycinol addition to oxobutenoic acid **1** and (*S*)-PEA addition to unsaturated acid **4** was monitored by HPLC (NovaPak C18 4 μm , 4.6 $\times$ 250 mm). As can be gleaned from Figure 2, the ratio of both diastere-



Scheme 4 *aza*-Michael addition of chiral amines on heteraryloxobutenoic acids **1-4**.

Table 2 *aza*-Michael addition of chiral amines on oxobutenoic acids **1-4**.

Adduct	Het	amine	conditions	d.r.	yield [%]
7a	a	(±)-PEA	water, 3 d, 40 °C	97:3	81
7a	a	(<i>S</i>)-PEA	water, 3 d, 40 °C	75:25	- ^a
7a	a	(<i>S</i>)-PEA	dioxane, 3 d, 40 °C	80:20	- ^a
7a	a	(<i>S</i>)-PEA	methanol, 3 d, 40 °C	50:50	- ^a
7b	b	(<i>S</i>)-PEA	MeOH, 24 h, 40 °C	99:1	90
7c	c	(<i>S</i>)-PEA	water, 6 h, RT	98:2	68.5
7d	d	(<i>S</i>)-PEA	water, 6 h, RT	99:1	65
8a	a	(<i>R</i>)-phenylglycinol	MeOH, 3 d, 40 °C	99:1	75
8b	b	(<i>R</i>)-phenylglycinol	dioxane, 18 h, 40 °C	98.9:1.1	67
8b	b	(<i>R</i>)-phenylglycinol	MeOH, 4 d, 40 °C	89:11	55

^a not determined

omeric products **8a-major**/**8a-minor** formed in the reaction mixture was approximately 2:1 at initial stages (d.r. = 68:32 after 15 min). However, as the CIAT progressed in time, **8a-major** clearly predominated in the asymmetric transformation with the concomitant decline of the content of its minor diastereoisomer. Thus, after 3 day stirring and subsequent filtration of the heterogeneous reaction mixture we obtained oxoaminoacid **8a** in 75% yield and 9% d.e. (Table 2). The situation is even more illustrative in Figure 3. The addition of (*S*)-PEA on oxobutenoic acid **4** is rapid and within 6 hours the thermodynamic equilibrium in the heterogeneous reaction mixture is reached with the high prevalence of the (*S,S*)-**7d** diastereomer. The formation of the (*R,S*)-diastereomer is faster at the beginning of the reaction and the ratio of (*S,S*)-**7d** : (*R,S*)-**7d** is 19:81 within the first 3 minutes. However the ratio of diastereomers changes rapidly in time (d.r. = 91:9 in the reaction suspension after 5-6 hours) and filtration of the reaction mixture allows to obtain the product in a good yield and excellent diastereomeric purity (65%, d.e. = 98%).

The relative stereochemistry of the newly formed stereogenic centre on carbon C-2 has been assigned tentatively to be (2*S*)- on the basis of all precedent experiments on

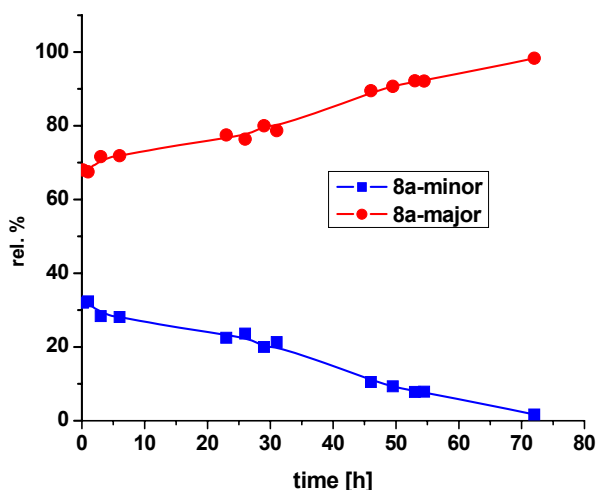


Fig. 2 Diastereomer distribution (HPLC experiments on crude reaction mixture) in (*R*)-phenylglycinol addition to **1**; —●— **8a-major** diastereomer, —■— **8a-minor** diastereomer.

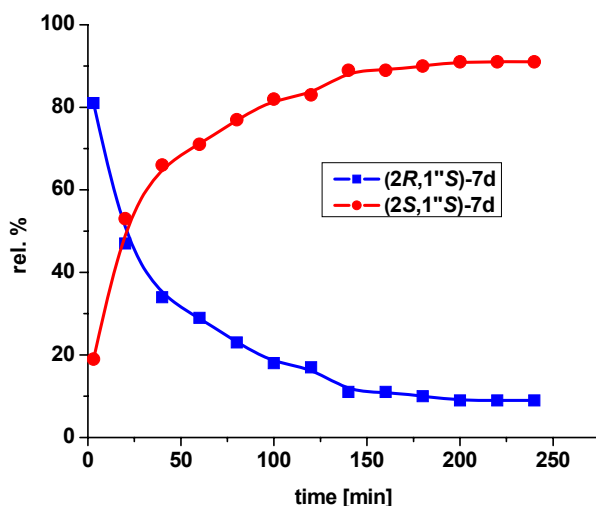


Fig. 3 Diastereomer distribution (HPLC experiment on crude reaction mixture) in (*S*)-PEA addition to (*2E*)-4-[2'-(methoxycarbonyl)-6'-methoxy-1'*H*-indol-7'-yl]-4-oxobut-2-enoic acid **4**; —●— (*S,S*)-**7d**, —■— (*R,S*)-**7d**.

aza-Michael addition to aroyl- and heteroaroyl acrylic acids [6, 7, 15, 22, 23, 25]. In all experiments the experimental claim that the major diastereomer of (*S*)-PEA addition elutes first under the respective HPLC conditions and the major diastereomer from (*R*)-phenylglycinol addition elutes the second one was confirmed.

3 Conclusions

The synthesis of three new indolyl substituted (*E*)-4-oxobut-2-enoic acids was developed and their *aza*-Michael addition were studied. An effective CIAT protocol has been de-

veloped for the preparation of enantiomerically pure indolyl and pyrrolyl substituted γ -oxo- α -aminobutanoic acids. This represents a simple synthetic route to both antipodes of a variety of *N*-functionalized homotryptophan derivatives, useful Trp analogues that we believe merit further exploration in peptide synthesis.

4 Experimental Procedures

All reagents were used as received without further purification unless otherwise specified. (*S*)-Phenylethylamine (99+%, 99% e.e.) was obtained from ACROS, (*R*)-2-amino-2-phenylethanol was prepared from (*R*)-phenylglycine [26]. Melting points were obtained using Kofler hot plate and are uncorrected. Optical rotations were measured with POLAR L- μ P polarimeter (IBZ Messtechnik) with a water-jacked 10.000 cm cell at a wavelength of sodium line D ($\lambda = 589$ nm). Specific rotations are given in units of 10^{-1} deg.cm².g⁻¹ and concentrations are given in g/100 mL. Elemental analyses were performed by the Microanalytical service of Slovak University of Technology. Infrared spectra were recorded on a Philips Analytical PU9800 FTIR spectrometer as KBr discs. ¹H-NMR spectra were recorded on a Varian VXR-300 (299.94 MHz) spectrometer. Chemical shifts (δ) are quoted in ppm and are referenced to the tetramethylsilane (TMS) as internal standard ($\delta_{Me} = 0.00$ for 299.94 MHz). Coupling constants (*J*) are recorded in Hz. The following abbreviations were used throughout to characterise signals multiplicities: s (singlet), d (doublet), t (triplet), m (multiplet), b (broad). Abbreviations with quotation marks mean that the appearance of the signal is different to that theoretically predicted. ¹³C NMR spectra were recorded on a Varian VXR-300 (75.43 MHz) spectrometer. The multiplicities of carbons were assigned from a broadband decoupled analysis used in a conjunction with either APT or DEPT programmes. Chemical shifts are quoted in ppm and are referenced to the tetramethylsilane (TMS) as internal standard ($\delta = 0.00$ ppm for 75.43 MHz). HPLC experiments were carried out using a chromatography system Pye Unicam with PU4225 UV detector. Detection was carried out at 210 nm. The HPLC column used was SEPARON SGX RPS 7 μ m, 250x4 mm (TESSEK). The mobile phase was a 1.5% (v/v) solution of triethylamine in a mixture of acetonitrile and water (from 1:2 to 1:4) adjusted to pH 2.9 with *o*-phosphoric acid, which was pumped through the system at 0.5 - 1.5 mL/min at room temperature. The amount injected was 20 μ l. All data were collected and analyzed using CSW 1.7 software (DATAAPEX).

(E)-4-Oxo-4-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]butenoic acid (1)

Method A: To the well stirred solution of 4-oxo-4-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]butanoic acid [27] (6.25 g, 19 mmol) in chloroform (50 mL) was added dropwise a solution of bromine (3.1 g, 0.98 mL, 19 mmol) in chloroform (10 mL) during 30 min. (HBr was removed with argon). The reaction mixture was then stirred at 25 °C for 3 h. Chloroform was removed under reduced pressure and the remaining oil was dissolved in ether (100 mL). The organic phase was washed with 5% solution of sodium thiosulphate, then with the water (50 mL), dried with sodium sulphate and evaporated *in vacuo* to afford 6.0

g (79%) of the bromo derivative (**A**, Scheme 1) as a pink solid, m.p. 145–147 °C. ^1H NMR (CDCl_3): δ 8.31 (m, 1 H, H_{pyr}), 8.12 (d, 2H, $J = 8.1$, H_{Ar}), 7.63–7.85 (m, 3H, H_{Ar}), 7.43 (m, 1H, H_{pyr}), 6.82 (m, 1H, H_{pyr}), 5.48 (dd, 1H, $J = 5.8$, $J = 8.9$, H-3), 3.36 (dd, 1H, $J_{2A,3} = 8.92$, $J_{2A,2B} = 17.1$, H-2A), 3.04 (dd, 1H, $J_{2B,3} = 5.8$, $J_{2B,2A} = 17.2$ Hz, H-2B). ^{13}C NMR (CDCl_3): δ 188.2 (C=O), 171.1 (COOH), 138.8 (C), 135.4 (=CH), 130.8 (=CH), 128.1 (=CH), 126.7 (C), 122.6 (=CH), 113.4 (=CH), 42.2 (CH-Br), 38.5 (CH_2). The analytically pure compound has been obtained by crystallization from chloroform. The crude 3-bromo-4-oxo-4-(1-(phenylsulfonyl)-1H-pyrrol-3-yl)butanoic acid (6.02 g, 15 mmol) was added to the well stirred solution of sodium acetate (1.6 g, 0.019 mol, 1.3 equiv.) in dry acetic acid (25 mL). The reaction mixture was refluxed for 30 min. (TLC monitoring). The solvent was removed *in vacuo* and water (100 mL) was added. The solution was stirred for 45 min., the water was decanted and toluene (150 mL) was added and refluxed 15 min. To the hot toluene (80 °C) was added *i*-hexane (30 mL) and the solution was allowed to stand overnight. The precipitate was filtered off and dried to afford 1.15 g (23%) of **1** as a yellow solid.

Method B: 3-Acetyl-*N*-(phenylsulfonyl)pyrrole [28] (2.64 g, 10 mmol), and glyoxylic acid monohydrate (0.92 g, 10 mmol), in acetic acid (8 mL) were heated to reflux for 38 h, then cooled to room temperature and stirred overnight at 25 °C. The separated solid was filtered off, washed with cold ethanol (5 mL) and then with ether (5 mL) to give 1.63 g (51%); m.p. 217–222 °C (toluene / *i*-hexane) as yellow solid.

Method C: To a magnetically stirred suspension of aluminium chloride (37.5 g, 0.275 mol) in dichloromethane (100 mL) at 20 °C was added a mixture of *N*-phenylsulfonylpyrrole (8.0 g, 0.08 mol) and maleic anhydride (8.0 g, 0.08 mol) in dichloromethane (50 mL). The mixture was stirred at 25 °C for 8 h and allowed to stand overnight. The mixture was poured onto crushed ice (300 g) containing concentrated hydrochloric acid (50 mL) and stirred for 30 min. The precipitate was filtered off and dried to afford 18.7 g (87%) as a brown solid. Crystallization from a mixture of toluene : *i*-hexane gave 17.8 g (78%) of **1**; m.p. 175–178 °C. ^1H NMR (d_6 -DMSO): δ 8.02 (dd, 1H, $J = 1.6$, $J = 3.1$ Hz, H-2 $_{\text{pyr}}$), 7.63 (d, 1H, $J_{\text{H-B}, \text{H-A}} = 15.4$ Hz, H-B), 7.60–7.79 (m, 5H, H_{Ar}), 7.58 (dd, 1H, $J = 1.8$, $J = 3.6$ Hz, H-5 $_{\text{pyr}}$), 6.65 (d, 1H, $J_{\text{H-A}, \text{H-B}} = 15.4$ Hz, H-A), 6.57 (dd, 1H, $J = 3.8$, $J = 3.2$ Hz, H-4 $_{\text{pyr}}$). ^{13}C NMR (CDCl_3): δ 177.3 (C=O), 166.2 (COOH), 139.8 (q), 138.2 (d), 134.9 (d), 134.5 (q), 134.1 (d), 133.5 (d), 132.4 (d), 130.2 (d), 127.3 (d), 112.2 (d), 101.1 (d).

(E)-4-[(1-Phenylsulfonyl)-1H-indol-3-yl]-4-oxo-but-2-enoic acid (**2**)

3-(Acetyl-*N*-(phenylsulfonyl)indole (4.95 g, 16 mmol), glyoxylic acid monohydrate (1.52 g, 16 mmol), acetic acid (8 mL) and concentrated hydrochloric acid (0.33 mL) were heated to reflux for 3 h, then cooled to room temperature. The separated solid was filtered off, washed with acetic acid and then with ethanol. Yield 4.5 g (80%); m.p. 217–222 °C (acetic acid); ^1H NMR (d_6 -DMSO): δ 13.02 (s, 1H, OH), 9.22 (s, 1H, H_{ind}), 7.31–8.34 (m, 9H, H_{Ar}), 8.07 (d, 1H, $J = 15.4$ Hz, H_B), 6.76 (d, 1H, $J = 15.4$ Hz, H_A). ^{13}C NMR

(d_6 -DMSO): δ 113.2 (C-2_{ind}), 120.6, 122.6, 125.2, 126.3, 127.4, 130.1, 131.8, 134.3, 135.4, 135.9, 136.4, 137.3 (C_{Ar}, C_{ind}), 166.6 (C-1), 184.1 (C-4).

Friedel-Craft's acylation of 1*H*-indole-2-carboxylate derivatives

To a well stirred suspension of anhydrous aluminium chloride (14.57 g, 109.3 mmol) in dry dichloromethane (40 mL) maleic anhydride (4.54 g, 46 mmol) was added in one portion and the resulting mixture was stirred at room temperature for 30 minutes. Then, a solution of indole derivative (42 mmol) in dry dichloromethane (60 mL) was added dropwise over a period of 45 minutes. The mixture was stirred at room temperature for additional 4 hours and poured into ice-water containing concentrated hydrochloric acid (15 mL). The organic layer was separated and aqueous phase was extracted with dichloromethane (3x20 mL). The combined organic layers were washed with brine. After drying over sodium sulphate, the solvent was removed under reduced pressure to give crude substituted 4-oxobutenoic acids.

(2*E*)-4-[2'-(ethoxycarbonyl)-1'*H*-indol-5'-yl]-4-oxobut-2-enoic acid (3)

Yield = 9.9 g (81.9%), m.p. = 197-199 °C (acetone). ¹H NMR (d_6 -DMSO): δ 8.55 (s, 1H, H-4'); 8.02 (d, 1H, $J_{3,2}$ = 15.9 Hz, H-3); 7.93 (d, 1H, $J_{6',7'}$ = 8.7 Hz, H-6'); 7.57 (d, 1H, $J_{7',6'}$ = 8.7 Hz, H-7'); 7.35 (s, 1H, H-3'); 6.69 (d, 1H, $J_{2,3}$ = 15.9 Hz, H-2); 4.37 (q, 2H, CH₂); 1.35 (t, 3H, CH₃). ¹³C NMR (d_6 -DMSO): δ 188.5 (C-4), 166.4 (C-1), 160.9 (COOEt), 140.0 (C-3a'), 136.7 (C-3), 132.0 (C-2), 129.4 (C-2'), 129.3 (C-5'), 126.3 (C-7a'), 126.0 (C-4'), 124.4 (C-6'), 113.2 (C-7'), 109.8 (C-3'), 60.8 (CH₂), 14.3 (CH₃). IR: ν 3208, 1709, 1661, 1613, 1578, 1537, 1410, 1391, 1391, 1341, 1292, 1275, 1247, 1175, 1122. Calc. for C₁₅H₁₃NO₅ (287.27) C, 62.72; H, 4.56; N, 4.88. Found: C, 62.25; H, 4.56; N, 4.90.

(2*E*)-4-[2'-(methoxycarbonyl)-6'-methoxy-1'*H*-indol-7'-yl]-4-oxobut-2-enoic acid (4)

Yield = 10.2 g (80.0%), m.p. = 214 – 215 °C (methanol), ¹H NMR (d_6 -DMSO): δ 8.00 (d, 1H, $J_{4',5'}$ = 9.1 Hz, H-4'); 7.94 (d, 1H, $J_{3,2}$ = 15.6 Hz, H-3); 7.24 (d, 1H, $J_{3',NH}$ = 2.4 Hz, H-3'); 7.13 (d, 1H, $J_{5',4'}$ = 9.0 Hz, H-5'); 6.59 (d, 1H, $J_{2,3}$ = 15.6 Hz, H-2); 4.00 (s, 3H, OCH₃); 3.87 (s, 3H, OCH₃); ¹³C NMR (d_6 -DMSO): δ 189.8 (C-4), 166.8 (C-1), 161.0 (C-6'), 160.1 (COOCH₃), 141.7 (C-3), 136.6 (C-3a'), 131.0 (C-4'), 130.0 (C-2), 127.3 (C-2'), 122.4 (C-7a'), 109.3 (C-7'), 109.1 (C-3'), 107.9 (C-5'), 57.0 (OCH₃), 52.0 (OCH₃). IR: ν 3436, 2951, 1723, 1701, 1626, 1580, 1532, 1501, 1439, 1246, 1210, 1167, 1118, Calc. for C₁₅H₁₃NO₆ (303.27): C, 59.41; H, 4.32; N, 4.62. Found: C, 59.03; H, 4.36; N, 4.64.

4-Heteroaryl-4-oxo-2-aminobutanoic acids (5a-d)

To a solution of ammonium hydroxide (12%, 30 mL) the corresponding 4-aryl-4-oxobut-2-enoic acid 2.8 mmol was added. The mixture was stirred at room temperature for 24 hours. After removing the excess of ammonia at diminished pressure, the pH of reaction mixture was adjusted to 6.0 with the 4 M hydrochloric acid and the suspension was stirred for 2 hours. The precipitate was filtered off and dried.

2-Amino-4-oxo-4-[1'-(phenylsulfonyl)-1'*H*-pyrrol-3'-yl]butanoic acid (5a)

Yield 0.61 g (68%); m.p. 170–171 °C. ¹H NMR (*d*₆-DMSO + DCl): δ 7.98–8.12 (m, 2H, H_{Ar}), 7.92 (t, 1H, *J* = 3.2 Hz, H_{Pyrr}), 7.7–7.76 (m, 1H, H_{Ar}), 7.60–7.69 (m, 2H, H_{Ar}), 7.58 (bs, 1H, H_{Pyrr}), 6.54 (t, 1H, *J* = 3.4 Hz, H_{pyrr}), 4.18 (t, 1H, *J* = 5.5 Hz, 2-H), 3.83 (dd, 1H, *J* = 4.2 Hz, *J* = 18.4 Hz, 3-H_B), 3.72 (dd, 1H, *J* = 5.8 Hz, *J* = 18.3 Hz, 3-H_B). ¹³C NMR (*d*₆-DMSO + DCl): δ 185.3 (C-4), 169.8 (C-1), 138.9 (C_{Ar}, C_{Pyrr}), 135.2, 132.3, 129.8, 128.8, 127.1, 112.1 (C_{Pyrr}), 49.3 (C-2), 38.8 (C-3).

2-Amino-4-oxo-4-[1'-(phenylsulfonyl)-1'*H*-indol-3'-yl]butanoic acid (5b)

Yield 0.38 g (36%); m.p. 162–165 °C. ¹H NMR (CD₃COCD₃ + DCl): δ 8.54–8.66 (m, 1H, H_{Ar}), 8.12–8.24 (m, 1H, H_{Ar}), 7.61–7.74 (m, 1H, H_{Ar}), 7.11–7.51 (m, 6H, H_{Ar}), 6.85 (bs, 1H, 2-H_{ind}), 4.18 (t, 1H, *J* = 7.5 Hz, H-2), 2.57 (dd, 1H, *J*_{3A,2} = 7.6 Hz, *J*_{3A,3B} = 15.5 Hz, H-3B), 2.47–2.56 (m, 1H, H-3A). ¹³C NMR (CD₃COCD₃ + DCl): δ 185.2 (C=O), 170.1 (COOH), 139.3, 135.1 (C_{Ar}), 132.9 (C-2_{ind}), 132.3, 129.9, 128.8, 127.0 (C_{Ar}), 112.1 (C-3_{ind}), 49.5 (C-2), 39.0 (C-3).

2-Amino-4-[2'-(methoxycarbonyl)-6'-methoxy-1'*H*-indol-7'-yl]-4-oxobutanoic acid (5d)

Yield = 0.53 g (59%), m.p. = 207–211 °C (dec.). ¹H NMR (*d*₆-DMSO+DCl): δ 10.72 (s, 1H, COOH); 8.52 (m, 1H, NH), 7.95 (d, 1H, *J* = 8.7 Hz, H-4'); 7.17 (s, 1H, H-3'); 7.05 (d, 1H, *J* = 9.0 Hz, H-5'); 4.31 (bs, 1H, H-2), 3.97 (s, 3H, OCH₃), 3.82 (s, 3H, OCH₃), 3.71 (d, 2H, *J* = 4.2 Hz, H-3). ¹³C NMR (*d*₆-DMSO+DCl): δ 197.5 (C-4), 171.0 (C-1), 161.6, 161.0 (COOMe, C-6'), 136.9, 127.2, 122.7, 108.6 (C-2', C-7', C-3a', C-7a'), 131.7, 109.5, 108.0 (C-3', C-4', C-5'), 57.4, 52.6 (2xOCH₃), 48.6 (C-2), 44.6 (C-3).

2-Amino-4-(2'-carbamoyl-1'*H*-indol-5'-yl)-4-oxobutanoic acid (5c')

Yield = 0.51 g (66%), m.p. = >250 °C (dec.). ¹H NMR (*d*₆-DMSO+DCl): δ 11.99 (s, 1H, COOH); 8.48 (m, 1H, NH); 8.38 (s, 1H, H-4'); 7.79 (d, 1H, *J* = 8.8 Hz, H-7'); 7.53 (d, 1H, *J* = 8.7 Hz, H-6'); 7.34 (s, 1H, H-3'); 4.31 (bs, 1H, H-2); 3.78 (d, 2H, *J* = 4.4 Hz, H-3). ¹³C NMR (*d*₆-DMSO+DCl): δ 196.1 (C-4), 170.8 (C-1), 162.9 (CONH₂), 139.8, 134.0, 128.5, 127.2 (C-2', C-5', C-8', C-9'), 125.0, 123.5, 113.2, 106.1 (C-3', C-4', C-6', C-7'), 49.1 (C-2), (C-3) not detected.

***N*-Substituted 2-amino-4-heteroaryl-4-oxobutanoic acids (6a-f)**

To the stirred solution of 4-aryl-4-oxobutanoic acid (2.8 mmol) in methanol or ethanol benzyl amine (0.63 g, 5.9 mmol) or furfurylamine (0.57 g, 5.9 mmol) was added in one portion. The mixture was stirred at room temperature (for reaction times, see Table 1). The precipitate was filtered off, washed with methanol (10 mL) and diethyl ether (2 × 10 mL) and dried under reduced pressure (50 Pa, 50 °C).

2-Benzylamino-4-oxo-4-(1'-(phenylsulfonyl)-1'*H*-pyrrol-3'-yl)butanoic acid (6a)

Yield 0.88 g (76%); ^1H NMR ($\text{CD}_3\text{COCD}_3 + \text{DCl}$): δ 7.95–8.05 (m, 2H, H_{Ar}), 7.91 (dd, 1H, $J=1.7$ Hz, $J=3.2$ Hz, H_{Pyr}), 7.58–7.754 (m, 5H, H_{Ar}), 7.56 (dd, 1H, $J=1.7$ Hz, $J=3.4$ Hz, H_{Pyr}), 7.36–7.44 (m, 3H, H_{Ar}), 6.52 (t, 1H, $J=3.4$ Hz, H_{Pyr}), 4.54 ("t", 1H, $J=5.4$, H-2), 4.39 (bs, 2H, H-1"), 3.85 (ABq, 2H, H-3). ^{13}C NMR ($\text{CD}_3\text{COCD}_3 + \text{DCl}$): δ 185.4 (C-4), 170.4 (C-1), 140.2, 136.0, 133.3, 133.1, 132.6, 132.3, 131.1, 130.8, 130.6, 129.8, 128.1, 113.1 (C-Ar, C-Pyr), 55.9 (C-2), 51.9 (C-1"), 39.7 (C-3). Calc. for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_5\text{S}$ (412.46): C, 61.15; H, 4.89; N, 6.79, S, 7.77. Found: C, 61.85; H, 5.01; N, 6.60.

2-Benzylamino-4-oxo-4-[1'-(phenylsulfonyl)-1H-indol-3'-yl]butanoic acid (6b)

Yield 0.85 g (66%); m.p. 203–206 °C. ^1H NMR (d_6 -DMSO + DCl): δ 8.90 (bs, 1H, H-2'), 8.10–8.17 (m, 3H, H-5', H_{Ar}), 7.91 (d, 1H, $J = 7.9$ Hz, H-4'), 7.71 ('t', 1H, $J = 7.4$ Hz, H-6'), 7.62 (d, 2H, $J = 7.9$ Hz, H-7', H_{Ar}), 7.52–7.68 (m, 2H, H_{Ar}), 7.32–7.44 (m, 5H, H_{Ar}), 4.36 ("t", 1H, $J = 5.6$ Hz, H-2), 4.27 (d, 1H, $J = 13.2$ Hz, H-1"A), 4.24 (d, 1H, $J = 13.2$ Hz, H-1"B), 3.93 (dd, 1H, $J = 6.2$ Hz, $J = 17.2$ Hz, H-3B), 3.78 (dd, 1H, $J = 5.4$ Hz, $J = 17.3$ Hz, H-3A). ^{13}C NMR (d_6 -DMSO + DCl): δ 191.0 (C-4), 169.1 (C-1), 137.8, 136.1, 135.8, 133.9, 130.8, 130.5, 129.2, 127.2, 126.2, 125.2, 122.3, 119.4, 113.4 ($\text{C}_{\text{Ar}} + \text{C}_{\text{Ind}}$), 54.1 (C-2), 49.6 ($\text{CH}_2\text{-N}$), 40.3 (C-3). Calc. for $\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_5\text{S}$ (462.52): C, 64.92; H, 4.79; N, 6.06, S, 6.93. Found: C, 65.25; H, 4.95; N, 6.20.

2-Benzylamino-4-(2'-ethoxycarbonyl-1'H-indol-5'-yl)-4-oxobutanoic acid (6c)

Yield = 0.76 g (69%), m.p. = 189–191 °C (ethanol). ^1H NMR (d_6 -DMSO+DCl): δ 12.37 (s, 1H, COOH); 8.47 (s, 1H, H-4'); 7.89 (d, 1H, $J = 8.4$ Hz, H-6'); 7.58 (m, 3H, H_{Ar} , H-7'); 7.43 (m, 3H, H_{Ar}); 7.36 (bs, 1H, H-3'); 4.32 (m, 6H, OCH_2 , NCH_2 , H-3); 3.87 (d, 1H, $J_{2,3} = 4.2$ Hz, H-2) 1.35 (t, 3H, CH_3). ^{13}C NMR (d_6 -DMSO+DCl): δ 194.8 (C-4), 169.7 (C-1), 160.9 (COOEt), 139.9, 131.6, 129.4, 128.5, 126.2 (C-2', C-5', C-3a', C-7a', C-Ph), 130.4, 129.1, 128.9, 124.9, 124.0, 112.9, 109.6 (C-3', C-4', C-6', C-7', C_{Ar}), 60.8 (OCH_2), 54.1 (C-2), 49.8 (N-CH_2), 37.8 (C-3), 14.3 (CH_3). Calc. for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_5$ (394.42): C, 66.99; H, 5.62; N, 7.10. Found: C, 66.25; H, 5.75; N, 7.20.

2-Benzylamino-4-(6'methoxy-2'-methoxycarbonylindol-7'-yl)-4-oxobutanoic acid (6d)

Yield = 0.85 g (74%), m.p. = 187–188 °C (methanol). ^1H NMR (d_6 -DMSO+DCl): δ 10.82 (s, 1H, COOH); 8.04 (d, 1H, $J = 8.7$ Hz, H-4'); 7.58 (m, 2H, H_{Ar}); 7.41 (m, 3H, H_{Ar}); 7.28 (s, 1H, H-3'); 7.16 (d, 1H, $J = 9.0$ Hz, H-5'); 4.31 (m, 4H, H-3 and $\text{CH}_2\text{-Ph}$); 4.03 (s, 3H, OCH_3); 3.88 (s, 3H, OCH_3); 3.81 d, 1H, $J_{2,3} = 3.6$ Hz, H-2). ^{13}C NMR (d_6 -DMSO+DCl): δ 196.7 (C-4), 169.9 (C-1), 161.0, 160.4 (COOMe, C-6'), 136.7, 131.6, 127.0, 122.3, 108.4 (C-2', C-7', C-3a', C-7a', C_{Ar}), 131.0, 130.4, 129.0, 128.6, 108.9, 107.7 (C-3', C-4', C-5', C_{Ar}), 57.0, 54.4 a 52.1 (C-2, 2x OCH_3), 50.3 (CH_2Ph), 44.1 (C-3). IR: ν 3438, 2949, 1713, 1641, 1627, 1608, 1579, 1530, 1498, 1446, 1385, 1333, 1318, 1242, 1174, 1168, 1113, 1080. Calc. for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_6$ (410.42): C, 64.38; H, 5.40; N, 6.83. Found: C, 63.95; H, 5.41; N, 6.60.

4-[2'-(Ethoxycarbonyl)-1'*H*-indol-5'-yl]-2-[(furan-2''-yl)methylamino]-4-oxobutanoic acid (6e)

Yield = 0.75 g (70%), m.p. = 189–191 °C (ethanol). ¹H NMR (*d*₆-DMSO+DCl): δ 8.34 (s, 1H, H-4'); 7.82 (d, 1H, *J*_{6',7'} = 8.4 Hz, H-6'); 7.69 (s, 1H, H-3'); 7.56 (d, 1H, *J*_{7',6'} = 8.4 Hz, H-7'); 7.31 (s, 1H, H-5''); 6.67 (bs, 1H, H-3''); 6.47 (bs, 1H, H-4''); 4.31 (m, 4H, OCH₂, NCH₂); 4.01 (m, 1H, H-2); 3.80 (m, 2H, H-3); 1.27 (t, 3H, CH₃). ¹³C NMR (*d*₆-DMSO+DCl): δ 195.6 (C-4); 169.9 (C-1); 161.5, 145.5, 140.5, 129.8, 128.8, 126.7 (COOEt, C-2', C-5', C-7a', C-3a', C-2''); 145.1, 125.6, 124.5, 113.7, 113.5, 111.8, 110.3 (C-3', C-4', C-6', C-7', C-3'', C-4'', C-5''); 61.6 (OCH₂); 42.8 (NCH₂); 35.4 (C-3); 54.3 (C-2); 14.8 (CH₃). Calc. for C₂₀H₂₀N₂O₆ (384.38): C, 62.49; H, 5.24; N, 7.29. Found: C, 63.05; H, 5.41; N, 7.45.

2-[(Furan-2''-yl)methylamino]-4-[2'-(methoxycarbonyl)-6'-methoxy-1'*H*-indol-7'-yl]-4-oxobutanoic acid (6f)

Yield = 0.96 g (86%), m.p. = 183–185 °C (methanol). ¹H NMR (*d*₆-DMSO+DCl): δ 7.99 (d, 1H, *J*_{4',5'} = 9.0 Hz, H-4'); 7.68 (d, 1H, *J*_{5'',4''} = 1.2 Hz, H-5''); 7.21 (s, 1H, H-3'); 7.08 (d, 1H, *J*_{5',4'} = 9.0 Hz, H-5'); 6.66 (d, 1H, *J*_{3'',4''} = 3.0 Hz, H-3''); 6.45 (dd, 1H, *J*_{4'',3''} = 3.0 Hz, *J*_{4'',5''} = 1.2 Hz, H-4''); 4.31 (m, 3H, H-2 and NCH₂); 3.96 (s, 3H, OCH₃); 3.81 (s, 3H, OCH₃); 3.74 (d, 2H, *J* = 4.2 Hz, H-3). ¹³C NMR (*d*₆-DMSO+DCl): δ 197.1 (C-4); 170.0 (C-1); 161.6, 161.1, 145.5, 136.8, 127.2, 122.6, 108.6 (COOMe, C-2', C-6', C-7', C-3a', C-7a', C-2''); 131.9, 113.6, 111.7, 110.1, 109.5, 108.6 (C-3', C-4', C-5', C-3'', C-4'', C-5''); 57.5, 54.5, 52.7 (2x OCH₃, C-2); 44.4, 43.0 (NCH₂, C-3). Calc. for C₂₀H₂₀N₂O₇ (400.38): C, 60.00; H, 5.03; N, 7.00. Found: C, 60.95; H, 5.91; N, 7.20.

(±)-(2*SR*,1''*SR*)-4-Oxo-2-[1''-(phenylethylamino)]-4-[1'-(phenylsulfonyl)-1'*H*-pyrrol-3'-yl]butanoic acid (7a)

A suspension of 4-oxo-4-(1'-(phenylsulfonyl)-1'*H*-pyrrol-3'-yl)butenoic acid (0.3 g, 1 mmol) in water (10 mL) was introduced in an ultrasound bath and subsequently treated with one portion (±)-1-phenylethylamine (0.19 g, 1.6 mmol). The mixture was heated at 40 °C for 3 days (HPLC control). The precipitated product was filtered off, washed with 2 x 5 mL methanol and dried under diminished pressure at 50 °C. Yield 0.34 g (81%, d.r. 97:3, mobile phase: phosphate buffer/ acetonitrile 2:1 +13.5 mL triethylamine, pH=3); m.p. 190–193 °C. ¹H NMR (CD₃COCD₃ + DCl): δ 7.91–7.98 (m, 2H, H_{Ar}), 7.87 (dd, 1H, *J* = 1.62 Hz, *J* = 3.2 Hz, H_{Pyr}), 7.63–7.78 (m, 1H, H_{Ar}), 7.53–7.63 (m, 4H, H_{Ar}), 7.42–7.51 (m, 4H, H_{Ar} + H_{Pyr}), 6.50 (t, 1H, *J* = 3.3 Hz, H_{Pyr}), 4.76 (q, 1H, *J* = 7.1 Hz, H-1''), 3.96 (t, 1H, *J*_{2,3A} = 6.6 Hz, H-2), 3.68 (dd, 1H, *J*_{3B,2} = 6.8 Hz, *J*_{3B,3A} = 18.3 Hz, H-3B), 3.57 (dd, 1H, *J*_{3A,2} = 4.5 Hz, *J*_{3A,3B} = 18.2 Hz, H-3A), 1.76 (d, 3H, *J* = 6.8 Hz, H-2''). ¹³C NMR (CD₃COCD₃ + DCl): δ 183.6 (C-4), 169.3 (C-1), 139.4 (C_{Ar}, C_{Pyr}), 136.4, 135.0, 131.8, 130.1, 129.8, 129.6, 128.7, 128.5, 127.0, 112.1 (C_{Pyr}), 59.1 (C-1''), 53.5 (C-2), 39.2 (C-3), 20.3 (C-2''). Calc. for C₂₂H₂₂N₂O₅S (426.49): C, 61.96; H, 5.20; N, 6.57; S, 7.52. Found: C, 62.05; H, 5.31; N, 6.60.

(2*S*, 1''*S*)- 4-Oxo-2-[1''-(phenylethylamino)]-4-[1'-(phenylsulfonyl)-1'*H*-indol-3'-yl]butanoic acid (7b)

The mixture of acid **2** (0.36 g, 1.0 mmol) and (*S*)-PEA (0.15 mL, 1.2 mmol) in methanol (10 mL) was stirred at 40 °C for 5 h. The precipitate was filtered off and washed consecutively with methanol and diethyl ether, and dried to afford 0.45 g (90%; d.r.>99:1) of **7b**, m.p. 215–217 °C; $[\alpha]_D^{25} = +33.7$ ($c = 1$, MeOH/HCl = 3:1). ^1H NMR (CD_3COCD_3 + DCl): δ 8.67 (s, 1H, H_{ind}) 8.17 (d, 1H, $J = 8.9$ Hz, H_{Ar}), 8.11 (d, 1H, $J = 8.9$ Hz, 1H, H_{Ar}), 7.95 (d, 1H, $J = 7.9$ Hz, H_{Ar}), 7.29–7.69 (m, 10H, H_{Ar}), 4.76 (q, 1H, $J = 6.5$ Hz, H-1''), 3.78 (m, 1H, H-2), 3.36 (m, 1H, H-3_B), 3.27 (m, 1H, H-3_A), 1.81 (d, 3H, $J = 6.4$ Hz, H-2''). ^{13}C NMR (CD_3COCD_3 + DCl): δ 192.6 (C-4), 170.8 (C-1), 138.4 (C_{Ar} , C_{ind}), 136.9, 136.6, 136.2, 135.4, 130.9, 130.6, 128.4, 127.1, 123.6, 120.8, 114.2, 60.3 (C-1''), 54.5 (C-2), 40.6 (C-3), 20.4 (C-2''). Calc. for $\text{C}_{26}\text{H}_{24}\text{N}_2\text{O}_5\text{S}$ (476.54): C, 65.53; H, 5.08; N, 5.88; S, 6.73. Found: C, 65.95; H, 5.21; N, 5.60.

(2*S*, 1''*S*)- 4-[2'-(Ethoxycarbonyl)-1'*H*-indol-5'-yl]-2-(1''-phenylethylamino)-4-oxobutanoic acid (7c)

Yield = 0.34 g (68.5%; d.r. = 98:2), m.p. = 196–198 °C (ethanol); $[\alpha]_D^{20} = +67.8$ ($c = 0.5$, MeOH/HCl = 3:1) ^1H NMR (d_6 -DMSO+DCl): δ 8.38 (s, 1H, H-4'); 7.78 (d, 1H, $J_{6,7'} = 8.4$ Hz, H-6'); 7.55 (m, 3H, H-Ph); 7.41 (m, 3H, H-7' and H_{Ar}); 7.30 (s, 1H, H-3'); 4.58 (m, 1H, H-2); 4.26 (q, 2H, OCH_2); 3.81 (m, 3H, H and H-3); 1.62 (d, 3H, $J = 6.0$ Hz, H-2''); 1.28 (t, 3H, CH_3). ^{13}C NMR (d_6 -DMSO+DCl): δ 194.9 (C-4); 169.6 (C-1); 161.4, 140.2, 136.5, 129.7, 128.0, 126.6 (COOEt , C-Ph, C-2', C-5', C-3a', C-7a'); 129.8, 129.6, 128.6, 125.4, 124.4, 113.3, 110.1 (C-3', C-4', C-6', C-7', 3x C_{Ar}); 61.4 (OCH_2); 58.5, 53.0 (C-2, C-1''); 51.3 (C-3); 20.6 (C-2''); 14.8 (CH_3). IR: ν 3308, 3033, 2991, 1683, 1617, 1575, 1534, 1477, 1456, 1387, 1358, 1340, 1318, 1302, 1293, 1261, 1213, 1203, 1169, 1124, 1078, 1018. Calc. for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_5$ (408.45): C, 67.63; H, 5.92; N, 6.86. Found: C, 66.95; H, 5.71; N, 6.60.

4-[2'-(Methoxycarbonyl)-6'-methoxy-1'*H*-indol-7'-yl]-2-(1''-phenylethylamino)-4-oxobutanoic acid (7d)

Yield = 0.33 g (65%; d.r. = 99:1), m.p. = 162–165 °C (methanol); $[\alpha]_D^{20} = +13.3$ ($c = 0.5$, MeOH/HCl = 3:1) ^1H NMR (d_6 -DMSO+DCl): δ 7.94 (d, 1H, $J_{4,5'} = 8.4$ Hz, H-4'); 7.63–7.47 (m, 5H, H_{Ar}); 7.19 (s, 1H, H-3'); 7.05 (d, 1H, $J_{5,4'} = 8.7$ Hz, H-5'); 4.76 (q, 1H, $J = 6.9$ Hz, H-1''), 4.13 (t, 1H, $J_{2,3} = 4.2$ Hz, H-2); 4.03 (s, 3H, OCH_3); 3.96 (s, 3H, OCH_3); 3.88–3.80 (m, 2H, H-3); 1.81 (d, 3H, $J = 6.9$ Hz, H-2''). ^{13}C NMR (d_6 -DMSO+DCl): δ 187.7 (C-4); 161.2, 153.6, 152.8, 130.7, 128.6, 127.3, 118.9, 114.4 (C-1, COOCH_3 , C-2', C-6', C-7', C-3a', C-7a', C_{Ar}); 122.8, 121.2, 120.9, 119.4, 100.5, 98.4 (C-3', C-4', C-5', 3x C_{Ar}); 51.0, 47.7, 45.8, 43.1 (2x OCH_3 , C-2, C-1''); 36.2 (C-3); 11.0 (C-2''). IR: ν 3433, 2946, 2845, 1727, 1712, 1629, 1579, 1535, 1498, 1436, 1388, 1362, 1240, 1227, 1180, 1227, 1180, 1168, 1118. Calc. for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_6$ (424.45): C, 65.08; H, 5.70; N, 6.60. Found: C, 65.55; H, 5.81; N, 6.80.

(2*S*, 1''*R*)-2-(2''-Hydroxy-1''-phenylethylamino)-4-oxo-4-(1'-(phenylsulfonyl)-1'*H*-pyrrol-3'-yl)butanoic acid (8a)

To the stirred solution of 4-[(1'-phenylsulfonyl)-1'*H*-pyrrol-3'-yl]-4-oxobut-2-enoic acid (0.3 g, 1.0 mmol) in methanol (10 mL) (*R*)-phenylglycinol (0.15 g, 1.1 mmol) was added in one portion. The mixture was stirred at 40 °C for 3 days. The precipitate was filtered off, washed with methanol (10 mL) and diethyl ether (2 x 10 mL) and dried under reduced pressure (50 Pa, 50 °C). Yield = 0.33 g (75%, d.r 99:1, HPLC); m.p. 195-197 °C; $[\alpha]_D^{25} = +14.1$ (methanol / hydrochloric acid 3:1, *c*=1). ¹H-NMR (CD₃COCD₃/DCl): δ 8.02 (bs, 1H, H-2'); 7.98-8.0 (m, 2H, H_{Ar}); 7.74 (t, 2H, *J* = 7.4 Hz, H_{Ar}); 7.63 (t, 2H, *J* = 7.6 Hz, H_{Ar}); 7.48 (m, 5H, H_{Ar}); 7.40 (dd, 1H, *J* = 1.2 Hz, *J* = 3.7 Hz, H-5'); 6.52 (t, 1H, *J* = 3.7 Hz, H-4'); 4.68 (dd, 1H, *J* = 5.0 Hz, *J* = 8.9, H-1''); 4.11 (dd, 1H, *J* = 4.5 Hz, *J* = 6.4 Hz, H-2); 4.03 (dd, 1H, *J* = 11.9 Hz, *J* = 5.0 Hz, H-2''A); 3.99 (dd, 1H, *J* = 11.9 Hz, *J* = 8.9 Hz, H-2''B); 3.59 (dd, 1H, *J* = 19.3 Hz, *J* = 6.8 Hz, H-3B); 3.48 (dd, 1H, *J* = 18.9 Hz, *J* = 4.3, H-3A). ¹³C-NMR (CD₃COCD₃/DCl): δ 185.0 (C-4); 170.2 (C-1); 139.5; 132.9; 132.5; 132.3; 131.2; 130.5; 130.0; 129.8; 129.3; 127.5; 112.5 (C_{Ar}, C_{pyr}); 65.9 (C-1''); 64.5 (C-2''); 54.5 (C-2); 39.7 (C-3). Calc. for C₂₂H₂₂N₂O₆S (442.48): C, 59.72; H, 5.01; N, 6.33; S, 7.25. Found: C, 60.05; H, 5.31; N, 7.40.

(2*S*, 1''*R*)-2-(2''-Hydroxy-1''-phenylethylamino)-4-oxo-4-(1'-(phenylsulfonyl)-1'*H*-indol-3'-yl)butanoic acid (8b)

To the stirred solution of 4-[(1'-benzenesulfonyl)-1'*H*-indol-3'-yl]-4-oxobut-2-enoic acid (0.35 g, 1.0 mmol) in dioxane (10 mL) (*R*)-phenylglycinol (0.288 g, 2.1 mmol) was added in one portion. The mixture was stirred at 40 °C for 18 h. The precipitate was filtered off, washed with methanol (10 mL) and ether (2 x 10 mL) and dried under reduced pressure (50 Pa, 50 °C) to afford **8b** 0.33 g (67%, d.r 1.1: 98.9, HPLC); m.p. 195-197 °C; $[\alpha]_D^{25} = +27.5$ (*c* = 1, MeOH/HCl = 3:1); ¹H-NMR (CD₃COCD₃/DCl): δ 8.67 (bs, 1H, H-2'); 8.23 (dd, 1H, *J* = 1.1 Hz, *J* = 7.4 Hz, H-4'); 8.12 (dd, 1H, *J* = 1.4 Hz, *J* = 7.5 Hz, H-6'); 7.99 (dd, 1H, *J* = 1.2 Hz, *J* = 7.5 Hz, H-7'); 7.68-7.75 (m, 1H, H-5'); 7.56-7.65 (m, 5H, H_{Ar}); 7.50-7.54 (m, 3H, H_{Ar}); 7.33-7.46 (m, 2H, H_{Ar}); 4.77 (dd, 1H, *J* = 4.9 Hz, *J* = 8.6 Hz, H-1''); 4.32 (dd, 1H, *J* = 4.2 Hz, *J* = 6.1 Hz, H-2); 4.05 (dd, 1H, *J* = 11.8 Hz, *J* = 5.0 Hz, H-2''A); 4.01 (dd, 1H, *J* = 11.9 Hz, *J* = 3.3 Hz, H-2''B); 3.86 (dd, 1H, *J* = 18.5 Hz, *J* = 6.2 Hz, H-3B); 3.73 (dd, 1H, *J* = 18.6 Hz, *J* = 4.1, H-3A). ¹³C-NMR (CD₃COCD₃/DCl): δ 192.8 (C-4); 171.1 (C-1); 138.4; 136.2; 135.1; 132.6; 131.1; 130.9; 130.6; 129.9; 128.4; 127.0; 126.1; 123.6; 120.8; 114.3 (C_{Ar}, C_{Ind}); 66.4 (C-1''); 63.8 (C-2''); 55.3 (C-2); 41.2 (C-3). Calc. for C₂₆H₂₄N₂O₆S (492.54): C, 63.40; H, 4.91; N, 5.69; S, 6.51. Found: C, 63.05; H, 5.45; N, 6.60.

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