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Regioselective role of the hydrazide moiety in the formation of complex pyrrole–pyrazole systems

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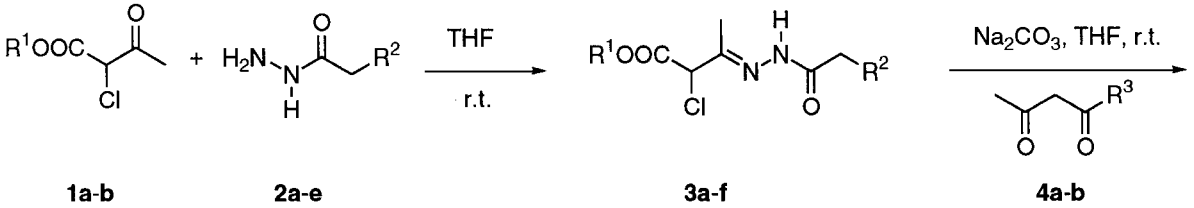
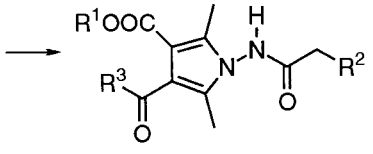
Abstract—The treatment of alkyl 2-chloroacetoacetate with ethyl 3-hydrazino-3-oxopropionate, (4-chlorobenzenesulphonyl)acetic acid hydrazide, 4-nitrophenylacetic acid hydrazide, phenylacetic acid hydrazide, thiophene-3-acetic acid hydrazide or indole-3-acetic acid hydrazide leads to the corresponding hydrazone derivatives. In the presence of sodium carbonate, these compounds react at room temperature with acetoacetanilide or 2,4-pentanedione to give the corresponding 1-aminopyrrole rings through the relevant 1,2-diaza-1,3-butadiene intermediates. In the presence of sodium methoxide, the activated methylene group present on the 1-amino side chain of the heterocycles obtained from ethyl 3-hydrazino-3-oxopropionate or 4-nitrophenylacetic acid hydrazide attacks at room temperature 1,2-diaza-1,3-butadienes affording the respective hydrazonic 1,4-adducts. Under basic conditions, these adducts cyclise at room temperature providing —NH—CO—CH-bridged pyrrole–pyrazole systems. In the case of (4-chlorobenzenesulphonyl)acetic acid hydrazide, the corresponding 1-aminopyrrole does not add a further molecule of 1,2-diaza-1,3-butadiene giving rise to 1*H*-pyrrole and 2-oxohydrazone derivatives as identified compounds. Under the same reaction conditions, the NH group of 1-aminopyrroles derived from phenylacetic acid hydrazide, thiophene-3-acetic acid hydrazide or indole-3-acetic acid hydrazide adds at room temperature 1,2-diaza-1,3-butadienes producing another type of hydrazonic 1,4-adduct. Under basic conditions, these adducts cyclise at room temperature giving rise to different N-bonded pyrrole–pyrazole systems. © 2001 Published by Elsevier Science Ltd.

1. Introduction

The synthetic usefulness of 1,2-diaza-1,3-butadienes as building blocks in organic chemistry has been well documented.[1–6] In a previous preliminary paper, we reported the sequential construction of widely functionalized pyrrole–pyrrole or pyrrole–pyrazole systems from conjugated azoalkenes.[7] In that report, we described an easy protocol



1a-b **2a-e** **3a-f** **4a-b**



5a-g

1	R^1	2	R^2	3	R^1	R^2	4	R^3	5	R^1	R^2	R^3
a	Me	a	CO_2Et	a	Me	CO_2Et	a	NHPh	a	Me	CO_2Et	NHPh
b	Et	b	4-Cl-$PhSO_2$	b	Me	4-Cl-$PhSO_2$	b	Me	b	Me	CO_2Et	Me
		c	4-NO_2-Ph	c	Et	4-NO_2-Ph			c	Me	4-Cl-$PhSO_2$	NHPh
		d	Ph	d	Et	Ph			d	Et	4-NO_2-Ph	Me
		e	Thien-3-yl	e	Et	Thien-3-yl			e	Et	Ph	Me
		f	Indol-3-yl	f	Me	Indol-3-yl			f	Et	Thien-3-yl	Me
									g	Me	Indol-3-yl	Me

Scheme 1.

Keywords: hydrazides; hydrazones; 1,2-diaza-1,3-butadienes; pyrroles; pyrazoles.

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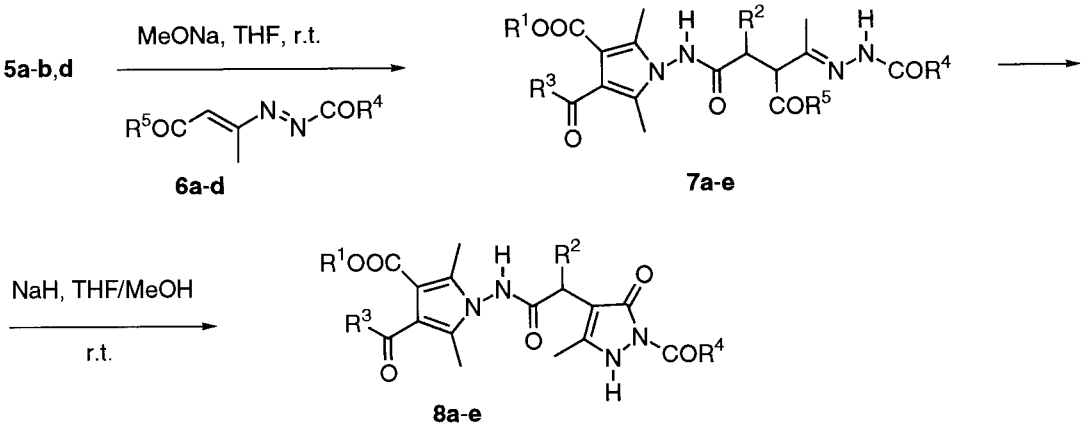
Table 1. Yield and reaction time of pyrroles (**5a–g**), 1,4-adducts (**7a–i**) and pyrrolo-pyrazoles (**8a–i**)

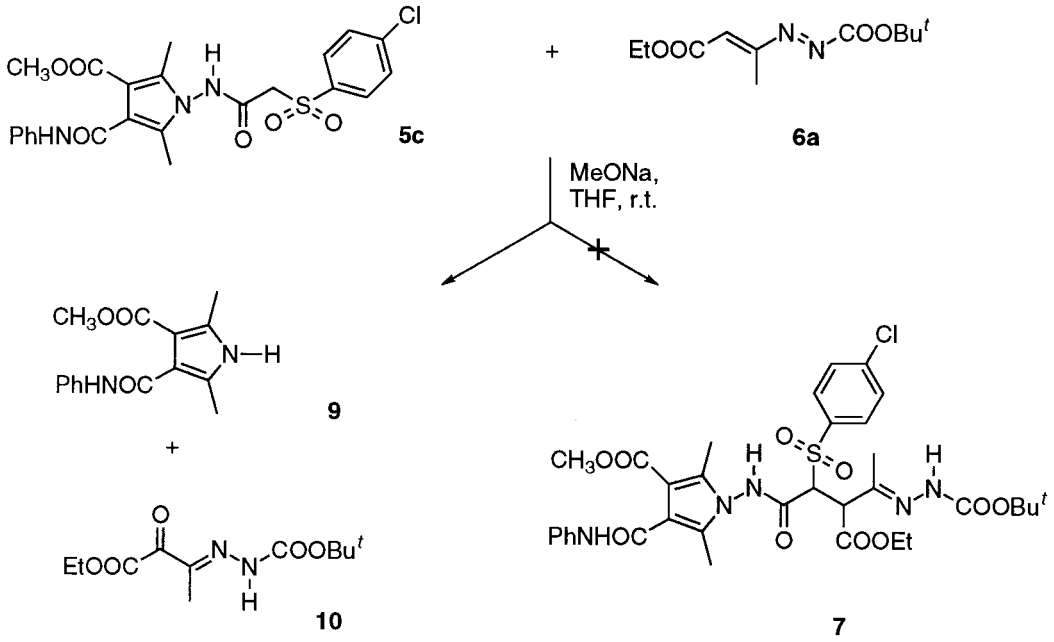
5	Yield[a] (%)	Reaction time (h)	M.p.[b] (°C)	7	Yield[a] (%)	Reaction time (h)	8	Yield[a] (%)	Reaction time (h)
a	70	20	175–177	**a**	60	48	**a**	62	36
b	51	18	90–92	**b**	66	36	**b**	67	48
c	88	26	204–206	**c**	86	24	**c**	64	24
d	49	16	161–165	**d**	62	38	**d**	51	48
e	83	12	100–102	**e**	72	40	**e**	46	24
f	64	24	114–115	**f**	71	108	**f**	67	32
g	69	26	165–166	**g**	60	112	**g**	38	24
				h	70	38	**h**	48	6
				i	67	120	**i**	45	9

[a] Yield of pure isolated products.
[b] Melting points are uncorrected.



6	R^4	R^5	7	R^1	R^2	R^3	R^4	R^5	8	R^1	R^2	R^3	R^4
a	OBu^t	OEt	**a**	Me	CO_2Et	NHPh	OBu^t	OEt	**a**	Me	CO_2Et	NHPh	OBu^t
b	OBn	OMe	**b**	Me	CO_2Et	NHPh	OBn	OMe	**b**	Me	CO_2Et	NHPh	OBn
c	OMe	OEt	**c**	Me	CO_2Et	Me	OMe	OEt	**c**	Me	CO_2Et	Me	OMe
d	NH_2	OMe	**d**	Et	4-NO_2-Ph	Me	OBu^t	OEt	**d**	Et	4-NO_2-Ph	Me	OBu^t
e	NHPh	OMe	**e**	Et	4-NO_2-Ph	Me	NH_2	OMe	**e**	Et	4-NO_2-Ph	Me	NH_2
f	NH_2	OEt	**f**	Et	Ph	Me	NHPh	OMe	**f**	Et	Ph	Me	NHPh
g	OMe	OMe	**g**	Et	Ph	Me	NH_2	OEt	**g**	Et	Ph	Me	NH_2
			h	Et	Thien-3-yl	Me	OMe	OMe	**h**	Et	Thien-3-yl	Me	OMe
			i	Me	Indol-3-yl	Me	OMe	OEt	**i**	Me	Indol-3-yl	Me	OMe

Scheme 2.



Scheme 3.

for the synthesis of 1-aminopyrroles bearing an activated methylene group on the *N*-amino side chain. These derivatives were used as *C*-nucleophiles towards 1,2-diaza-1,3-butadienes affording 1,4-hydrazone derivatives that in turn were subjected to a further intramolecular pyrrole or pyrazole closure in which the key role was played by the cyano or carboxylate group, respectively.

2. Results and discussion

Herein, we report two different types of pyrrole–pyrazole systems arising by means of C- or N-bond formation as a consequence of the different substituents present on the hydrazide moiety. In fact, the treatment of methyl 2-chloroacetoacetate (**1a**) or ethyl 2-chloroacetoacetate (**1b**) with ethyl 3-hydrazino-3-oxopropionate (**2a**), (4-chlorobenzenesulphonyl)acetic acid hydrazide (**2b**), 4-nitrophenylacetic acid hydrazide (**2c**), phenylacetic acid hydrazide (**2d**), thiophene-3-acetic acid hydrazide (**2e**) or indole-3-acetic acid hydrazide (**2f**) in THF at room temperature leads to the corresponding α-chlorohydrazone derivatives **3a–f**.[8,9] In the presence of sodium carbonate, these latter compounds react in THF at room temperature with acetoacetanilide (**4a**) or 2,4-pentanedione (**4b**) to give the relevant 1-aminopyrrole rings **5a–g** in good to excellent yields (Scheme 1 and Table 1).

This latter reaction probably occurs via the formation in situ of the conjugated azoalkene intermediate, as shown by the appearance of the typical orange or red colour of such a compound due to the base-promoted dehydrohalogenation of the corresponding α-chlorohydrazone derivative. The subsequent fading of the colour of the reaction mixture occurs when the compound loses the conjugated double bonds by addition of the β-dicarbonyl compound. This hypothesis is also supported by previous analogous findings.[7,9]

The methylene group of the 1-amino side chain of the pyrrole ring directly activated by an ethylcarboxylate group (**5a–b**) or remotely activated by a 4-nitrophenyl group as in derivative **5d** under basic conditions in THF at room temperature attacks the C-4 of 1,2-diaza-1,3-butadienes **6a–d** affording the corresponding hydrazone *C*-adducts **7a–e** as diastereomeric mixtures. Cyclisation of these last derivatives in the presence of freshly generated sodium methoxide in THF/MeOH mixture at room temperature provides —NH—CO—CH-bridged pyrrole–pyrazole systems **8a–e** (Scheme 2 and Table 1). The multiple signals at δ 1.9–2.3 ppm observed in the ^{1}H NMR spectra of **8a–e** are attributable to a rotameric effect. In the DNMR experiments carried out in DMSO-d_6 (293–360 K) they simplify in the expected signals.

In the case of the 4-chlorobenzensulphonyl derivative (**5c**) the reaction with **6a** under the same reaction conditions was also incomplete after several days, giving a complex crude mixture. Unreacted pyrrole derivative with poor amounts of 1*H*-pyrrole **9** and 2-oxohydrazone **10**[10] as degradative and/or oxidative by-products are recovered instead of the expected *C*-adduct **7**, in accordance with our previous findings on analogous compounds (Scheme 3).[6b,j]

Pyrrole derivatives **5e–g** bearing phenyl, thienyl or indolyl residue contain a less activated methylene group on the *N*-amino side chain and produce conjugated adducts **7f–i** by means of *N*-amino attack at the azo-ene system of **6c,e–g**. The pyrazole annulation performed under the same reaction conditions affords —N-bridged pyrrole–pyrazole systems **8f–i** as mixtures of conformers. In fact ^{1}H NMR spectra show diastereotopic protons of the $COCH_2R^2$ group at δ 3.63–4.06 ppm (Scheme 2 and Table 1). By DNMR studies carried out in DMSO-d_6 (293–340 K) their multiplicity disappears to give a singlet. Both pyrazole ring closures involve the amino nitrogen atom (>C═N—*N*H—) of the 1,4-adducts **7a–i** and the

carboxylate group at the carbon in position 4 of the 1,2-diaza-1,3-butadiene molecule **6a–g** with loss of an alcohol molecule (Scheme 2 and Table 1).

3. Conclusion

In conclusion, we report here the synthesis of new and interesting —NH—CO—CH-bridged or —N-bridged pyrrole–pyrazole systems.[11,12] It is noteworthy that this protocol may be useful for the synthesis of compounds possessing antiviral properties (i.e. distamycin, netropsin, tallimustine analogues).[13] The different reaction behaviour observed is attributable to the different electronic effects of the substituents present on the hydrazide derivatives used. When R^2 is an electron-withdrawing group, the C-attack by active methylene at the terminal carbon of the azoalkene molecule is favoured. In the absence of this effect, the N-attack takes place.

4. Experimental

4.1. General

Ethyl 3-hydrazino-3-oxopropionate (**2a**), (4-chlorobenzenesulphonyl)acetic acid hydrazide (**2b**) phenylacetic acid hydrazide (**2d**), thiophene-3-acetic acid hydrazide (**2e**) and indole-3-acetic acid hydrazide (**2f**) were commercial materials and were used without further purification, whereas 4-nitrophenylacetic acid hydrazide (**2c**) was prepared according to a literature procedure. Chlorohydrazone derivatives **3a–f** were synthesised according to our published procedures.[8,9] 1,2-Diaza-1,3-butadienes **6a–g** were synthesised according to published procedures[14,15] and used as isomeric mixtures. Sodium methoxide, sodium hydride and solvents were purchased and used without further purification with the exception of THF, which was distilled from sodium hydroxide. Melting points were determined in open capillary tubes and are uncorrected. IR-FT spectra were obtained as Nujol mulls. Mass spectra were made at an ionising voltage of 70 eV. All ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 MHz and at 50.32 MHz respectively. Chemical shifts (δ_H) are reported relative to TMS as internal standard. All coupling constant (J) values are given in hertz. Chemical shifts (δ_C) are reported relative to DMSO-d_6 or $CDCl_3$ as internal standards in a broad-band decoupled mode; the multiplicities were obtained by using 135° and 90° DEPT experiments to aid in assignment (q=methyl, t=methylene, d=methyne, s=quaternary). The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; br, broad; D_2O exch., exchanged with D_2O; all the NH and NH_2 exchanged with D_2O. Precoated silica gel plates of 0.25 mm were employed for analytical thin layer chromatography and silica gel 35–70 μm for column chromatography.

4.2. General procedure for the preparation of 1-aminopyrrole derivatives 5a–g

α-Chlorohydrazone derivative **3a–f** (1.0 mmol) was added portionwise to a stirred suspension of acetoacetanilide **4a** (1.0 mmol) or 1,3-pentanedione **4b** (1.0 mmol) and anhydrous sodium carbonate (1.5 mmol) in THF (10 ml). The reaction mixture was allowed to stand at room temperature until the complete disappearance of α-chlorohydrazone **3a–f** (12–26 h, monitored by TLC). The reaction solvent was evaporated under reduced pressure, the residue suspended in ethyl acetate and washed in a separatory funnel with 2N HCl (until pH 2) and then with water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue afforded pure 1-aminopyrrole **5a–g** directly by crystallisation from appropriate solvents (see below) or after chromatographic purification on a silica gel column, eluting with cyclohexane–ethyl acetate mixtures.

4.2.1. Methyl 4-(anilinocarbonyl)-1-[(3-ethoxy-3-oxopropanoyl)amino]-2,5-dimethyl-1*H*-pyrrole-3-carboxylate 5a. Colourless crystals from MeOH; mp 175–177°C; δ_H (200 MHz, DMSO-d_6) 1.22 (3H, t, J=7.2 Hz, OCH_2CH_3), 2.13 (3H, s, CH_3), 2.30 (3H, s, CH_3), 3.54 (2H, s, $COCH_2$, D_2O exch.), 3.65 (3H, s, OCH_3), 4.16 (2H, q, J=7.2 Hz, OCH_2CH_3), 7.03 (1H, t, J=7.5 Hz, aromatic), 7.29 (2H, t, J=7.5 Hz, aromatic), 7.66 (2H, d, J=7.5 Hz, aromatic), 10.18 (1H, s, NH), 11.42 (1H, s, NH); δ_C (50.32 MHz, DMSO-d_6) 9.50 (q), 10.31 (q), 13.93 (q), 40.60 (t), 51.02 (q), 61.03 (t), 107.35 (s), 115.88 (s), 119.28 (d), 122.85 (d), 128.50 (d), 130.50 (s), 134.94 (s), 139.68 (s), 163.35 (s), 164.62 (s), 164.77 (s), 166.97 (s); IR: ν_{max} 3297, 3169, 1751, 1724, 1683, 1635, 1596 cm^{-1}; MS: m/z (%) 401 (10) [M$^+$], 309 (100). Anal. Calcd for $C_{20}H_{23}N_3O_6$ (401.1): C, 59.84; H, 5.78; N, 10.47. Found: C, 59.66; H, 5.94; N, 10.57.

4.2.2. Methyl 4-acetyl-1-[(3-ethoxy-3-oxopropanoyl)-amino]-2,5-dimethyl-1*H*-pyrrole-3-carboxylate 5b. Colourless crystals from EtOAc–Et_2O; mp 90–92°C; δ_H (200 MHz, $CDCl_3$) 1.29 (3H, t, J=7.2 Hz, OCH_2CH_3), 1.88 (3H, s, CH_3), 2.18 (3H, s, CH_3), 2.39 (3H, s, $COCH_3$), 3.52 (2H, s, $COCH_2$, D_2O exch.), 3.78 (3H, s, OCH_3), 4.23 (2H, q, J=7.2 Hz, OCH_2CH_3), 10.13 (1H, s, NH); δ_C (50.32 MHz, $CDCl_3$) 9.22 (q), 10.11 (q), 13.99 (q), 31.18 (q), 40.58 (t), 51.23 (q), 61.91 (t), 108.60 (s), 121.49 (s), 131.05 (s), 136.02 (s), 164.58 (s), 165.01 (s), 167.05 (s), 202.58 (s); IR: ν_{max} 3207, 1743, 1718, 1704, 1646 cm^{-1}; MS: m/z (%) 324 (30) [M$^+$], 292 (100). Anal. Calcd for $C_{15}H_{20}N_2O_6$ (324.3): C, 55.55; H, 6.22; N, 8.64. Found: C, 55.40; H, 6.34; N, 8.56.

4.2.3. Methyl 4-(anilinocarbonyl)-1-{[2-(4-chlorobenzensulphonyl)acetyl]amino}-2,5-dimethyl-1*H*-pyrrole-3-carboxylate 5c. Colourless crystals from MeOH; mp 204–206°C; δ_H (200 MHz, DMSO-d_6) 2.07 (3H, s, CH_3), 2.25 (3H, s, CH_3), 3.37 (3H, s, OCH_3), 4.66 (2H, s, $COCH_2$, D_2O exch.), 7.03 (1H, t, J=7.5 Hz, aromatic), 7.29 (2H, t, J=7.5 Hz, aromatic), 7.67 (2H, d, J=7.5 Hz, aromatic), 7.77 (2H, d, J=8.2 Hz, aromatic), 7.94 (2H, d, J=8.2 Hz, aromatic), 10.16 (1H, s, NH), 11.69 (1H, br s, NH); δ_C (50.32 MHz, DMSO-d_6) 9.42 (q), 10.22 (q), 51.05 (q), 59.01 (t), 107.53 (s), 116.04 (s), 119.32 (d), 122.90 (s), 128.51 (d), 129.49 (d), 130.21 (d), 134.68 (s), 137.52 (s), 139.42 (s), 139.62 (s), 160.64 (s), 163.24 (s), 164.50 (s); IR: ν_{max} 3304, 3172, 1720, 1686, 1636, 1597, 1546, 1339,

1147 cm^{-1}; MS: *m/z* (%) 503 (7) [M^+], 411 (100). Anal. Calcd for $C_{23}H_{22}N_3O_6SCl$ (503.9): C, 54.82; H, 4.40; N, 8.34. Found: C, 54.72; H, 4.38; N, 8.48.

4.2.4. Ethyl 4-acetyl-1-{[2-(4-nitrophenyl)acetyl]amino}-2,5-dimethyl-1*H*-pyrrole-3-carboxylate 5d. Colourless crystals from EtOAc–Et_2O; mp 161–165°C; δ_H (200 MHz, DMSO-d_6) 1.24 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 2.01 (3H, s, CH_3), 2.15 (3H, s, CH_3), 2.28 (3H, s, $COCH_3$), 3.91 (2H, s, $COCH_2$, D_2O exch.), 4.19 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 7.63 (2H, d, *J*=8.8 Hz, aromatic), 8.23 (2H, d, *J*=8.8 Hz, aromatic), 11.44 (1H, s, NH); δ_C (50.32 MHz, DMSO-d_6) 9.56 (q), 9.96 (q), 14.03 (q), 30.86 (q), 39.45 (t), 59.77 (t), 108.76 (s), 120.36 (s), 123.52 (d), 130.59 (d), 131.76 (s), 134.42 (s), 142.59 (s), 146.61 (s), 164.16 (s), 168.81 (s), 196.70 (s); IR: ν_{max} 3178, 1702, 1672, 1666, 1517, 1355 cm^{-1}; MS: *m/z* (%) 387 (20) [M^+], 341 (82), 178 (100). Anal. Calcd for $C_{19}H_{21}N_3O_6$ (387.4): C, 58.91; H, 5.46; N, 10.85. Found: C, 57.85; H, 5.32; N, 10.46.

4.2.5. Ethyl 4-acetyl-1-[(2-phenylacetyl)amino]-2,5-dimethyl-1*H*-pyrrole-3-carboxylate 5e. White powder from Et_2O; mp 100–102°C; δ_H (200 MHz, DMSO-d_6) 1.23 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.96 (3H, s, CH_3), 2.12 (3H, s, CH_3), 2.27 (3H, s, $COCH_3$), 3.69 (2H, s, $COCH_2$), 4.19 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 7.30–7.37 (5H, m, aromatic), 11.35 (1H, s, NH); δ_C (50.32 MHz, DMSO-d_6) 9.54 (q), 9.95 (q), 14.07 (q), 30.88 (q), 39.94 (t), 59.78 (t), 108.72 (s), 120.33 (s), 126.92 (d), 128.49 (d), 129.05 (d), 131.86 (s), 134.50 (s), 134.78 (s), 164.21 (s), 169.78 (s), 196.74 (s); IR: ν_{max} 3182, 1703, 1678, 1657 cm^{-1}; MS: *m/z* (%) 342 (44) [M^+], 296 (100). Anal. Calcd for $C_{19}H_{22}N_2O_4$ (342.4): C, 66.65; H, 6.48; N, 8.18. Found: C, 66.72; H, 6.32; N, 7.98.

4.2.6. Ethyl 4-acetyl-1-{[2-(3-thienyl)acetyl]amino}-2,5-dimethyl-1*H*-pyrrole-3-carboxylate 5f. Colourless crystals from EtOAc–cyclohexane; mp 114–115°C; δ_H (200 MHz, DMSO-d_6) 1.24 (3H, t, *J*=7.0 Hz, OCH_2CH_3), 2.00 (3H, s, CH_3), 2.14 (3H, s, CH_3), 2.28 (3H, s, $COCH_3$), 3.72 (2H, s, $COCH_2$), 4.19 (2H, q, *J*=7.0 Hz, OCH_2CH_3), 7.09 (1H, d, *J*=4.9 Hz, aromatic), 7.38 (1H, d, *J*=1.9 Hz, aromatic), 7.52 (1H, dd, *J*=4.9, 1.9 Hz, aromatic) 11.32 (1H, s, NH); δ_C (50.32 MHz, DMSO-d_6) 9.52 (q), 9.92 (q), 14.03 (q), 30.85 (q), 34.73 (t), 59.75 (t), 108.88 (s), 120.30 (s), 123.07 (d), 128.29 (d), 128.38 (d), 131.82 (s), 134.23 (s), 134.49 (s), 164.18 (s), 169.35 (s), 196.71 (s); IR: ν_{max} 3204, 3117, 3093, 1711, 1696, 1655 cm^{-1}; MS: *m/z* (%) 348 (79) [M^+], 302 (100). Anal. Calcd for $C_{17}H_{20}N_2O_4S$ (348.4): C, 58.60; H, 5.79; N, 8.04. Found: C, 58.44; H, 5.65; N, 8.11.

4.2.7. Methyl 4-acetyl-1-{[2-(1*H*-indol-3-yl)acetyl]amino}-2,5-dimethyl-1*H*-pyrrole-3-carboxylate 5g. White powder from EtOAc; mp 165–166°C; δ_H (200 MHz, DMSO-d_6) 1.99 (3H, s, CH_3), 2.12 (3H, s, CH_3), 2.27 (3H, s, $COCH_3$), 3.71 (3H, s, OCH_3), 3.80 (2H, s, $COCH_2$), 7.00–7.13 (2H, m, aromatic), 7.31 (1H, s, aromatic), 7.39 (1H, d, *J*=7.5 Hz, aromatic), 7.61 (1H, d, *J*=7.5 Hz, aromatic), 11.00 (1H, s, NH), 11.26 (1H, s, NH); δ_C (50.32 MHz, DMSO-d_6) 9.59 (q), 9.94 (q), 30.41 (t), 30.70 (q), 51.13 (q), 108.04 (s), 108.45 (s), 111.49 (d), 118.34 (d), 118.53 (d), 120.26 (s), 121.18 (d), 124.26 (d), 126.92 (s), 132.15 (s), 134.69 (s), 135.98 (s), 164.70 (s), 170.34 (s), 196.73 (s); IR: ν_{max} 3342, 3234, 3065, 1695, 1660, 1538 cm^{-1}; MS: *m/z* (%) 367 (98) [M^+], 335 (100). Anal. Calcd for $C_{20}H_{21}N_3O_4$ (367.4): C, 65.38; H, 5.76; N, 11.44. Found: C, 65.25; H, 5.69; N, 11.40.

4.3. General procedure for the preparation of hydrazone 1,4-adducts 7a–i

1,2-Diaza-1,3-butadiene **6a–g** (1.0 mmol) dissolved in THF (5 ml) was slowly added to a magnetically stirred solution of the pyrrole derivative **5a,b,d–g** (1.0 mmol) in THF (5 ml) containing a catalytic amount of sodium methoxide. The reaction mixture was allowed to stand at room temperature until the complete disappearance of the reagents (24–120 h, monitored by TLC). The solvent was removed under reduced pressure and the residue, dissolved in ethyl acetate, was washed with water in a separatory funnel. The organic layer, dried over anhydrous Na_2SO_4, was evaporated in vacuo. Derivatives **7a–i** were obtained as diastereomeric mixtures after a chromatographic purification on a silica gel column (cyclohexane–ethyl acetate mixtures as eluent) followed by crystallisation from appropriate solvents.

7a. White powder from Et_2O–petroleum ether (40–60°C); δ_H (200 MHz, DMSO-d_6) 1.15–1.26 (6H, m, 2×OCH_2CH_3), 1.43–1.47 (9H, m, OBu^t), 1.94–2.27 (9H, m, 3×CH_3), 3.64 (3H, s, OCH_3), 3.89–4.01 (1H, m, CH), 4.08–4.19 (4H, m, 2×OCH_2CH_3), 4.21–4.37 (1H, m, CH, D_2O exch.), 7.03 (1H, t, *J*=7.3 Hz, aromatic), 7.30 (2H, t, *J*=7.3 Hz, aromatic), 7.68 (2H, d, *J*=7.3 Hz, aromatic), 9.79 (1H, br s, NH), 10.16 (1H, br s, NH), 11.88 (1H, br s, NH); δ_C (50.32 MHz, DMSO-d_6) 9.05 and 9.30 (2q), 9.86 and 10.06 (2q) 13.75 (q), 13.86 (q), 16.43 and 16.83 (2q), 28.02 (q), 50.40 (d), 51.03 (q), 52.34 (d), 61.17 and 61.28 (2t), 61.48 and 61.69 (2t), 79.30 and 79.41 (2s), 107.23 and 107.38 (2s), 115.76 and 115.94 (2s), 119.29 (d), 122.86 (d), 128.49 (d), 130.17 and 130.72 (2s), 134.86 and 135.26 (2s), 139.66 (s), 146.05 and 146.64 (2s), 152.73 (s), 163.27 (s), 165.19 and 164.54 (2s), 166.10 and 166.99 (2s), 167.57 (s), 169.42 (s); IR: ν_{max} 3289, 3194, 3133, 1747, 1707, 1658, 1640, 1599 cm^{-1}. Anal. Calcd for $C_{31}H_{41}N_5O_{10}$ (324.4): C, 57.84; H, 6.42; N, 10.88. Found: C, 57.70; H, 6.50; N, 10.72.

7b. White powder from MeOH; δ_H (200 MHz, DMSO-d_6) 1.14–1.25 (3H, m, OCH_2CH_3), 1.83–2.24 (9H, m, 3×CH_3), 3.64 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 3.93–4.01 (1H, m, CH), 4.15–4.21 (2H, m, OCH_2CH_3), 4.29–4.36 (1H, m, CH, D_2O exch.), 5.14–5.19 (2H, m, OCH_2Ph), 6.99–7.08 (1H, m, aromatic), 7.25–7.36 (7H, m, aromatic), 7.65–7.72 (2H, m, aromatic), 10.14 and 10.15 (1H, 2 s, NH), 10.26 (1H, br s, NH), 11.33 (1H, s, NH); δ_C (50.32 MHz, DMSO-d_6) 9.03 and 9.35 (2q), 9.84 and 10.04 (2q), 13.85 and 14.06 (2q), 16.48 and 16.57 (2q), 50.47 (d), 51.02 (q), 52.15 (d), 61.59 and 61.79 (2t), 65.86 (t), 107.36 and 107.41 (2s), 115.99 (s), 119.28 (d), 122.89 (d), 127.92 (d), 128.32 (d), 128.38 (d), 128.53 (d), 130.17 and 130.26 (2s), 147.01 and 147.52 (2s), 153.71 (s), 163.29 (s), 164.29 and 165.11 (2s), 166.04 and 166.93 (2s), 167.51 (s), 169.99 (s); IR: ν_{max} 3172, 3033, 1747, 1721, 1707, 1680, 1650, 1599 cm^{-1}. Anal. Calcd for $C_{33}H_{37}N_5O_{10}$ (663.7): C, 59.72; H, 5.62; N, 10.55. Found: C, 59.58; H, 5.68; N, 10.46.

7c. Colourless crystals from EtOAc; δ_H (200 MHz, $CDCl_3$)

1.22–1.31 (6H, m, 2×OCH$_2$C*H*$_3$), 1.91–2.41 (12H, m, 3×CH$_3$ and COCH$_3$), 3.73 (3H, s, OCH$_3$), 3.79 (3H, s, OCH$_3$), 4.06–4.26 (5H, m, 2×OC*H*$_2$CH$_3$ and CH), 4.55–4.60 (1H, m, CH, D$_2$O exch.), 8.06 and 8.18 (1H, 2 br s, NH), 10.05 (1H, br s, NH); IR: ν_{max} 3293, 3229, 3178, 1759, 1745, 1732, 1712, 1685, 1645 cm^{-1}. Anal. Calcd for $C_{23}H_{32}N_4O_{10}$ (524.5): C, 52.67; H, 6.15; N, 10.68. Found: C, 52.58; H, 6.18; N, 10.56.

7d. White powder from Et$_2$O; δ_H (200 MHz, DMSO-d_6) 1.18–1.29 (6H, m, 2×OCH$_2$C*H*$_3$), 1.44 (9H, s, OBu^t), 1.48, 1.62 and 1.72 (6H, 3 s, 2×CH$_3$), 2.12, 2.23, 2.26 and 2.28 (6H, 4 s, CH$_3$ and COCH$_3$), 4.12–4.25 (5H, m, CH and 2×OC*H*$_2$CH$_3$), 4.69 (1H, d, *J*=11.7 Hz, CH, D$_2$O exch.), 7.72 (2H, d, *J*=8.5 Hz, aromatic), 8.20 (2H, d, *J*=8.5 Hz, aromatic), 9.54 (1H, s, NH), 11.76 (1H, s, NH); IR: ν_{max} 3284, 3193, 1743, 1715, 1681, 1651, 1605, 1521, 1348 cm^{-1}. Anal. Calcd for $C_{30}H_{39}N_5O_{10}$ (629.6): C, 57.23; H, 6.24; N, 11.12. Found: C, 57.28; H, 6.18; N, 11.26.

7e. White powder from EtOAc–Et$_2$O; δ_H (200 MHz, DMSO-d_6) 1.15–1.27 (3H, m, OCH$_2$C*H*$_3$), 1.47, 1.61 and 1.66 (6H, 3 s, 2×CH$_3$), 2.12, 2.22, 2.25 and 2.27 (6H, 4 s, CH$_3$ and COCH$_3$), 3.68 (3H, s, OCH$_3$), 4.12–4.32 (3H, m, CH and OC*H*$_2$CH$_3$), 4.86 (1H, d, *J*=11.7 Hz, CH, D$_2$O exch.), 6.22 (2H, br s, NH$_2$), 7.72 (2H, d, *J*=8.5 Hz, aromatic), 8.20 (2H, d, *J*=8.5 Hz, aromatic), 9.10 (1H, s, NH), 11.80 (1H, s, NH); IR: ν_{max} 3407, 3388, 3178, 1736, 1702, 1666, 1646, 1569, 1351 cm^{-1}. Anal. Calcd for $C_{25}H_{30}N_6O_9$ (558.5): C, 53.77; H, 5.41; N, 15.05. Found: C, 53.65; H, 5.52; N, 15.23.

7f. White powder from THF; δ_H (200 MHz, DMSO-d_6) 1.16–1.25 (3H, m, OCH$_2$C*H*$_3$), 1.63 and 1.65 (3H, 2 s, CH$_3$), 2.02, 2.16, 2.20, 2.29, 2.31 and 2.33 (9H, 6 s, 2×CH$_3$ and COCH$_3$), 3.32 (2H, br s, COCH$_2$), 3.74 (3H, s, OCH$_3$), 4.12–4.22 (2H, m, OC*H*$_2$CH$_3$), 5.50 and 5.54 (1H, 2 s, CH), 6.96–7.06 (3H, m, aromatic), 7.24–7.31 (5H, m, aromatic), 7.53 (2H, d, *J*=7.9 Hz, aromatic), 8.87 and 8.89 (1H, 2 s, NH), 9.96 (1H, s, NH); IR: ν_{max} 3324, 3195, 3132, 3092, 3061, 3029, 2963, 1759, 1743, 1716, 1707, 1678, 1622, 1596 cm^{-1}. Anal. Calcd for $C_{31}H_{35}N_5O_7$ (589.6): C, 63.15; H, 5.98; N, 11.88. Found: C, 63.00; H, 5.98; N, 11.75.

7g. Yellowish foam; δ_H (200 MHz, DMSO-d_6) 1.14–1.29 (6H, m, 2×OCH$_2$C*H*$_3$), 1.60 (3H, s, CH$_3$), 1.98, 2.09, 2.17, 2.28, 2.31 and 2.32 (9H, 6 s, 2×CH$_3$ and COCH$_3$), 3.29 (2H, br s, COCH$_2$), 4.12–4.26 (4H, m, 2×OC*H*$_2$CH$_3$), 5.21 and 5.24 (1H, 2 s, CH), 6.42 (2H, br s, NH$_2$), 7.01–7.05 (2H, m, aromatic), 7.22–7.29 (3H, m, aromatic), 9.43 (1H, s, NH); IR: ν_{max} 3480, 3361, 3304, 3220, 1748, 1716, 1701, 1686, 1656, 1638, 1576 cm^{-1}. Anal. Calcd for $C_{26}H_{33}N_5O_7$ (527.5): C, 59.19; H, 6.30; N, 13.27. Found: C, 59.30; H, 6.18; N, 13.32.

7h. White foam; δ_H (200 MHz, DMSO-d_6) 1.25 (3H, t, *J*=7.0 Hz, OCH$_2$C*H*$_3$), 1.77 (3H, s, CH$_3$), 2.03, 2.08, 2.21, 2.27, 2.30 and 2.31 (9H, 6 s, 2×CH$_3$ and COCH$_3$), 3.29 (2H, br s, COCH$_2$), 3.65 (3H, s, OCH$_3$), 3.70 (3H, s, OCH$_3$), 4.21 (2H, q, *J*=7.0 Hz, OC*H*$_2$CH$_3$), 5.15 and 5.19 (1H, 2 s, CH), 6.86 (1H, d, *J*=4.9 Hz, aromatic), 7.13 (1H, d, *J*=1.9 Hz, aromatic), 7.45 (1H, dd, *J*=4.9, 1.9 Hz, aromatic) 10.21 (1H, s, NH); IR: ν_{max} 3286, 3101, 1751, 1687, 1537 cm^{-1}. Anal. Calcd for $C_{24}H_{30}N_4O_8S$ (534.6): C, 53.92; H, 5.66; N, 10.48. Found: C, 53.74; H, 5.62; N, 10.56.

7i. White powder from EtOAc–Et$_2$O; δ_H (200 MHz, DMSO-d_6) 1.08–1.16 (3H, m, OCH$_2$C*H*$_3$), 1.78 (3H, s, CH$_3$), 1.99, 2.05, 2.16, 2.23, 2.28 and 2.30 (9H, 6 s, 2×CH$_3$ and COCH$_3$), 3.34 (2H, br s, COCH$_2$), 3.64 (3H, s, OCH$_3$), 3.75 (3H, s, OCH$_3$), 4.05–4.16 (2H, m, OC*H*$_2$CH$_3$), 5.04 and 5.09 (1H, 2 s, CH), 6.95–7.10 (3H, m, aromatic), 7.27–7.36 (2H, m, aromatic), 10.17 (1H, s, NH), 10.98 (1H, s, NH); IR: ν_{max} 3294, 3178, 1752, 1735, 1710, 1683, 1575 cm^{-1}. Anal. Calcd for $C_{28}H_{33}N_5O_8$ (567.6): C, 59.25; H, 5.86; N, 12.34. Found: C, 59.17; H, 6.02; N, 12.45.

4.4. General procedure for the preparation of pyrrolopyrazole derivatives 8a–i

To a magnetically stirred solution of 1,4-adduct **7a–i** (1.0 mmol) in a 1:1 mixture of THF–MeOH (10 ml) was added sodium hydride 60% pure in mineral oil (1.1 mmol). The reaction mixture was allowed to stand at room temperature until the complete disappearance of hydrazone compounds **7a–i** (6–48 h, monitored by TLC). THF was removed under reduced pressure and the residue was suspended in ethyl acetate, acidified in a separatory funnel with 2N HCl until pH 1 and then washed with water. The organic layer, dried over anhydrous Na$_2$SO$_4$, was evaporated in vacuo. The crude reaction mixture was crystallised from appropriate solvents as in the case of **8a–c** or purified by chromatography and subsequent crystallisation as for compounds **8d–i**. Compounds **8a–i** were obtained as mixtures of conformers, as revealed by DNMR experiments in DMSO-d_6 (293–360 K).

8a. White powder from Et$_2$O–MeOH; δ_H (200 MHz, DMSO-d_6) 1.21 (3H, t, *J*=7.2 Hz, OCH$_2$C*H*$_3$), 1.53 (9H, s, OBu^t), 2.02, 2.14, 2.19 and 2.33 (9H, 4 s, 3×CH$_3$), 3.63 and 3.65 (3H, 2 s, OCH$_3$), 4.19 (2H, q, *J*=7.2 Hz, OC*H*$_2$CH$_3$), 4.64 (1H, s, CH, D$_2$O exch.), 7.03 (1H, t, *J*=7.7 Hz, aromatic), 7.29 (2H, t, *J*=7.7 Hz, aromatic), 7.67 (2H, d, *J*=7.7 Hz, aromatic), 10.16 (1H, s, NH), 11.58 (1H, br s, NH), 11.72 (1H, br s, NH); δ_C (50.32 MHz, DMSO-d_6) 9.46 (q), 10.26 (q), 11.90 (q), 13.93 (q), 27.64 (q), 45.08 (d), 51.05 (q), 61.65 (t), 84.03 (s), 96.53 (s), 107.39 (s), 115.82 (s), 119.27 (d), 119.37 (s), 122.93 (d), 128.53 (d), 130.72 (s), 135.14 (s), 139.59 (s), 146.42 (s), 151.89 (s), 163.25 (s), 164.63 (s), 166.54 (s), 167.87 (s); IR: ν_{max} 3170, 3120, 1755, 1730, 1695, 1665, 1635, 1610, 1590 cm^{-1}. Anal. Calcd for $C_{29}H_{35}N_5O_9$ (597.6): C, 58.28; H, 5.90; N, 11.72. Found: C, 58.36; H, 5.78; N, 11.64.

8b. Whitish powder from EtOAc–Et$_2$O; δ_H (200 MHz, DMSO-d_6) 1.20 (3H, t, *J*=7.0 Hz, OCH$_2$C*H*$_3$), 2.01, 2.15, 2.19 and 2.33 (9H, 4 s, 3×CH$_3$), 3.63 and 3.64 (3H, 2 s, OCH$_3$), 4.19 (2H, q, *J*=7.0 Hz, OC*H*$_2$CH$_3$), 4.66 (1H, s, CH, D$_2$O exch.), 5.40 (2H, s, OC*H*$_2$Ph), 7.02 (1H, t, *J*=7.2 Hz, aromatic), 7.25–7.51 (7H, m, aromatic), 7.67 (2H, d, *J*=7.2 Hz, aromatic), 10.18 (1H, s, NH), 11.60 (1H, s, NH), 12.01 (1H, br s, NH); δ_C (50.32 MHz, DMSO-d_6) 9.49 (q), 10.30 (q), 12.00 (q), 13.94 (q), 45.07 (d), 51.05 (q), 61.67 (t), 68.08 (t), 96.47 (s), 107.42 (s), 115.90 (s), 119.34 (d), 119.38 (s), 122.89 (d), 127.92 (d), 128.29 (d),

128.47 (d), 128.53 (d), 130.40 (s), 134.79 (s), 135.11 (s), 139.70 (s), 147.90 (s), 153.01 (s), 163.35 (s), 164.65 (s), 166.53 (s), 167.83 (s); IR: ν_{max} 3288, 3187, 1770, 1736, 1694, 1642, 1600, 1577 cm^{-1}. Anal. Calcd for $C_{32}H_{33}N_5O_9$ (631.6): C, 60.85; H, 5.27; N, 11.09. Found: C, 60.74; H, 5.14; N, 11.09.

8c. Colourless crystals from MeOH; δ_H (200 MHz, DMSO-d_6) 1.20 (3H, t, J=7.0 Hz, OCH_2CH_3), 1.98, 2.11, 2.14, 2.24 and 2.28 (12H, 5 s, 3×CH_3 and $COCH_3$), 3.73 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.19 (2H, q, J=7.0 Hz, OCH_2CH_3), 4.66 (1H, s, CH, D_2O exch.), 11.61 (1H, s, NH), 12.02 (1H, br s, NH); δ_C (200 MHz, DMSO-d_6) 9.50 (q), 9.86 (q), 11.89 (q), 13.89 (q), 30.70 (q), 44.95 (d), 51.15 (q), 53.90 (q), 61.64 (t), 96.20 (s), 108.60 (s), 120.37 (s), 120.63 (s), 132.04 (s), 134.63 (s), 148.44 (s), 152.61 (s), 164.61 (s), 166.55 (s), 167.79 (s) 196.55 (s); IR: ν_{max} 3172, 3127, 1780, 1741, 1702, 1650, 1577, 1541 cm^{-1}. Anal. Calcd for $C_{21}H_{26}N_4O_9$ (478.5): C, 52.72; H, 5.48; N, 11.71. Found: C, 52.64; H, 5.46; N, 11.65.

8d. Yellow powder from Et_2O; δ_H (200 MHz, DMSO-d_6) 1.24 (3H, t, J=7.0 Hz, OCH_2CH_3), 1.51 (9H, s, OBu^t), 1.97, (3H, s, CH_3), 2.05, (3H, s, CH_3), 2.18, (3H, s, CH_3), 2.27 (3H, s, $COCH_3$), 4.19 (2H, q, J=7.0 Hz, OCH_2CH_3), 5.07 and 5.15 (1H, 2 s, CH, D_2O exch.), 7.87 (2H, d, J=8.7 Hz, aromatic), 8.20 (2H, d, J=8.7 Hz, aromatic), 11.67 (2H, br s, 2 NH); IR: ν_{max} 3197, 1760, 1701, 1683, 1652, 1606, 1595, 1521, 1348 cm^{-1}. Anal. Calcd for $C_{28}H_{33}N_5O_9$ (583.6): C, 57.63; H, 5.70; N, 12.00. Found: C, 57.50; H, 5.78; N, 11.82.

8e. Light yellow powder from Et_2O; δ_H (200 MHz, DMSO-d_6) 1.19–1.26 (3H, m, OCH_2CH_3), 1.55 and 1.69 (3H, 2 s, CH_3), 2.06–2.28 (9H, m, 2×CH_3 and $COCH_3$), 4.04–4.21 (2H, m, OCH_2CH_3), 5.84 and 5.92 (1H, 2 s, CH, D_2O exch.), 6.11 and 6.86 (2H, 2 br s, NH_2) 7.05, 7.82, 8.00 and 8.17 (4H, 4 d, J=8.5 Hz, aromatic), 9.03 (1H, s, NH), 11.48 (1H, br s, NH); IR: ν_{max} 3355, 3219, 1734, 1699, 1688, 1653, 1637, 1572, 1522, 1349 cm^{-1}. Anal. Calcd for $C_{24}H_{26}N_6O_8$ (526.5): C, 54.75; H, 4.98; N, 15.96. Found: C, 54.90; H, 4.96; N, 15.87.

8f. White powder from Et_2O; δ_H (200 MHz, DMSO-d_6) 1.20–1.26 (3H, m, OCH_2CH_3), 1.70 and 1.81 (3H, 2 s, CH_3), 1.93, 2.04, 2.16 and 2.26, (9H, 4 s, 2×CH_3 and $COCH_3$), 3.68–3.96 (2H, m, $COCH_2$), 4.16–4.21 (2H, m, OCH_2CH_3), 7.08–7.27 (8H, m, aromatic), 7.56–7.62 (2H, m, aromatic), 10.01 and 10.10 (1H, 2 br s, NH), 12.32 (1H, br s, NH); IR: ν_{max} 3264, 3169, 2986, 1735, 1702, 1686, 1662, 1619, 1604 cm^{-1}. Anal. Calcd for $C_{30}H_{31}N_5O_6$ (557.6): C, 64.62; H, 5.60; N, 12.56. Found: C, 64.58; H, 5.68; N, 12.56.

8g. Whitish powder from Et_2O; δ_H (200 MHz, DMSO-d_6) 1.19–1.27 (3H, m, OCH_2CH_3), 1.73 and 1.86 (3H, 2 s, CH_3), 1.98, 2.03, 2.18, 2.26 and 2.32 (9H, 5 s, 2×CH_3 and $COCH_3$), 3.63–3.96 (2H, m, $COCH_2$), 4.15–4.22 (2H, m, OCH_2CH_3), 7.16–7.33 (5H, m, aromatic), 8.07 and 8.19 (2H, 2 br s, NH_2), 11.44 (1H, br s, NH); IR: δ_{max} 3350, 3218, 1750, 1732, 1718, 1699, 1685, 1669, 1655, 1576 cm^{-1}. Anal. Calcd for $C_{24}H_{27}N_5O_6$ (481.5): C, 59.87; H, 5.65; N, 14.54. Found: C, 59.78; H, 5.62; N, 14.49.

8h. Light pink powder from Et_2O; δ_H (200 MHz, DMSO-d_6) 1.23 (3H, t, J=7.0 Hz, OCH_2CH_3), 1.62 (3H, s, CH_3), 2.03, 2.11, 2.15, 2.25 and 2.29 (9H, 5 s, 2×CH_3 and $COCH_3$), 3.65–3.78 (4H, m, OCH_3 and $COCH_aH_b$), 3.99 (1H, d, J=16.0 Hz, $COCH_aH_b$), 4.16 (2H, q, J=7.0 Hz, OCH_2CH_3), 6.88 (1H, d, J=4.9 Hz, aromatic), 7.15 (1H, d, J=1.9 Hz, aromatic), 7.44 (1H, dd, J=4.9, 1.9 Hz, aromatic), 11.52 (1H, br s, NH); IR: ν_{max} 3353, 3105, 1748, 1734, 1698, 1669, 1559, 1540 cm^{-1}. Anal. Calcd for $C_{23}H_{26}N_4O_7S$ (502.5): C, 54.97; H, 5.21; N, 11.15. Found: C, 54.96; H, 5.11; N, 11.20.

8i. Beige powder from Et_2O; δ_H (200 MHz, DMSO-d_6) 1.54 and 1.56 (3H, 2 s, CH_3), 1.88 and 1.96 (3H, 2 s, CH_3), 2.16, 2.22, 2.25 and 2.28 (6H, 4 s, CH_3 and $COCH_3$), 3.68 (3H, s, OCH_3), 3.77–3.83 (4H, m, OCH_3 and $COCH_aH_b$), 4.06 (1H, d, J=14.0 Hz, $COCH_aH_b$), 6.89–7.09 (3H, m, aromatic), 7.31–7.46 (2H, m, aromatic), 10.92 (1H, s, NH), 11.52 (1H, br s, NH); IR: ν_{max} 3349, 3301, 1736, 1685, 1616 cm^{-1}. Anal. Calcd for $C_{26}H_{27}N_5O_7$ (521.5): C, 59.88; H, 5.22; N, 13.43. Found: C, 59.88; H, 5.18; N, 13.48.

4.4.1. Methyl 4-(anilinocarbonyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylate 9. White powder from EtOAc–cyclohexane; mp 206–210°C; δ_H (200 MHz, DMSO-d_6) 2.31 (3H, s, CH_3), 2.38 (3H, s, CH_3), 3.70 (3H, s, OCH_3), 7.01 (1H, t, J=7.5 Hz, aromatic), 7.29 (2H, t, J=7.5 Hz, aromatic), 7.66 (2H, d, J=7.5 Hz, aromatic), 10.76 (1H, s, NH), 11.51 (1H, br s, NH); δ_C (200 MHz, DMSO-d_6) 12.47 (q), 13.55 (q), 51.10 (q), 108.03(s), 116.24 (s), 119.10 (d), 122.62 (d), 128.58 (d), 131.63 (s), 134.79 (s), 139.79 (s), 163.36 (s), 166.42 (s); IR: ν_{max} 3209, 3126, 1674, 1653, 1598 cm^{-1}. MS: *m/z* (%) 272 (14) [M^+], 180 (100), 150 (28). Anal. Calcd for $C_{15}H_{16}N_2O_3$ (272.3): C, 66.16; H, 5.92; N, 10.29. Found: C, 66.28; H, 5.90; N, 10.23.

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