Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 1411–1416

Four-component tandem protocol for the stereoselective synthesis of highly functionalized [1,4]-thiazines

Sethuraman Indumathi, Raju Ranjith Kumar and Subbu Perumal*

Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai 625 021, India

Received 14 August 2006; revised 10 November 2006; accepted 30 November 2006
Available online 19 December 2006

Abstract—The one-pot, four-component tandem reaction of ethyl 2-[(2-oxo-2-arylethyl)sulfonyl]acetate/ethyl 2-[(2-ethoxy-2-oxoethyl)-sulfonyl]acetate, an aromatic aldehyde and pyrrolidine provides a rapid and facile access to new ethyl 3-aroyl-1-benzyl-2,2-dioxo-4-aryloctahydro-2-pyrrolo[2,1-*c*][1,4]thiazine-1-carboxylates/diethyl 1-benzyl-2,2-dioxo-4-aryloctahydro-2-pyrrolo[2,1-*c*][1,4]thiazine-1,3-dicarboxylates. This reaction shows high stereoselectivity and proceeds in good yields.

1. Introduction

Thiazines occupy a unique place in medicinal chemistry since they display diverse biological properties such as anti-fungal,[1] anti-inflammatory,[2] anti-HIV,[3] anti-psoriatic[4] and anti-tuberculosis.[5] In addition, compounds with a pyrrolidine sub-structure exhibit anti-tumour,[6] anti-asthma and anti-Parkinson[7] activities. The pyrrolothiazine scaffold also shows anti-inflammatory,[8] anti-fungal[9] and anti-microbial[10] activities and acts as potent calcium antagonists selective for cardiovascular tissue.[11]

The above bio-importance of pyrrolidines, thiazines and pyrrolothiazines, in conjunction with our interest in employing novel tandem processes in organic synthesis,[12] led us to report a stereoselective four-component synthesis of novel ethyl 3-aroyl-1-benzyl-2,2-dioxo-4-aryloctahydro-2-pyrrolo-[2,1-*c*][1,4]thiazine-1-carboxylates and diethyl 1-benzyl-2,2-dioxo-4-aryloctahydro-2-pyrrolo[2,1-*c*][1,4]-thiazine-1,3-dicarboxylates via tandem reactions. Tandem multi-component reactions are powerful and elegant for the construction of complex molecules rapidly and efficiently in an eco-friendly manner.[13,14]

2. Results and discussion

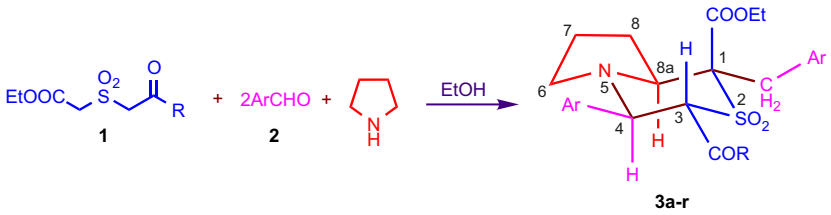
In the present investigation, a mixture of ethyl 2-[(2-oxo-2-arylethyl)sulfonyl]acetate/ethyl 2-[(2-ethoxy-2-oxoethyl)-sulfonyl]acetate **1**, aromatic aldehyde **2** and pyrrolidine in a 1:2:1 molar ratio in ethanol was gently warmed and stirred at ambient temperature for 2–5 days (Scheme 1). Use of 2 mol of pyrrolidine expedited the reaction, which suggests that pyrrolidine acts both as a reactant and base in this reaction. After completion of the reaction (TLC analysis), the mixture was purified through flash column chromatography to afford ethyl 3-aroyl-1-benzyl-2,2-dioxo-4-aryloctahydro-2-pyrrolo[2,1-*c*][1,4]thiazine-1-carboxylates (**3a–i**)/diethyl 1-benzyl-2,2-dioxo-4-aryloctahydro-2-pyrrolo[2,1-*c*][1,4]-thiazine-1,3-dicarboxylates (**3j–r**). This reaction furnishes a single diastereomer of the pyrrolothiazines (**3a–r**) in good yields (61–89%) considering the number of steps involved. Ethyl 2-[(2-oxo-2-arylethyl)sulfonyl]acetate and ethyl 2-[(2-ethoxy-2-oxoethyl)sulfonyl]acetate, **1**, required for the synthesis of the pyrrolothiazines **3** were prepared using a literature procedure.[15,16]

The reaction was studied in different solvents (Table 1). The data shown in Table 1 reveal that in protic solvents, ethanol and methanol, the reaction was completed more rapidly to give a higher yield of **3a** and **3j** than in aprotic solvents, DMF, DMSO or CH_3CN. This solvent effect may presumably arise from the differences in the solvation of polar intermediates involved in the tandem process. This reaction was also investigated using other bases that would not be incorporated into the product. The data presented in Table 2 show that potassium carbonate catalyzes the reaction more efficiently.

The structure of the pyrrolothiazines **3** was deduced from one and two-dimensional NMR spectroscopic data as illustrated for a representative example **3a**. The ^1H NMR spectrum of **3a** gives two doublets related by a H,H-COSY correlation at 6.24 and 4.33 ppm (J=10.8 Hz) assignable, respectively, to H-3 and H-4. These assignments are evident from the HMBC correlation of: (i) H-4 with the *ipso*- and

Keywords: Pyrrolothiazine; Pyrrolidine; Stereoselectivity; Tandem.
* Corresponding author. Tel./fax: +91 452 2459845; e-mail: subbu.perum@gmail.com

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.11.093



3	R	Ar	Isolated Yield (%)
a	*p*-ClC$_6$H$_4$	C$_6$H$_5$	71
b	*p*-ClC$_6$H$_4$	*p*-CH$_3$C$_6$H$_4$	67
c	*p*-ClC$_6$H$_4$	*p*-ClC$_6$H$_4$	69
d	*p*-ClC$_6$H$_4$	*p*-O$_2$NC$_6$H$_4$	62
e	*p*-ClC$_6$H$_4$	*p*-CH$_3$OC$_6$H$_4$	66
f	*p*-ClC$_6$H$_4$	*o*-CH$_3$C$_6$H$_4$	67
g	*p*-ClC$_6$H$_4$	*p*-FC$_6$H$_4$	67
h	*p*-CH$_3$C$_6$H$_4$	*p*-ClC$_6$H$_4$	63
i	*p*-CH$_3$C$_6$H$_4$	*p*-CH$_3$C$_6$H$_4$	61
j	OEt	C$_6$H$_5$	86
k	OEt	*p*-ClC$_6$H$_4$	84
l	OEt	*p*-CH$_3$C$_6$H$_4$	87
m	OEt	2-thienyl	80
n	OEt	*p*-FC$_6$H$_4$	82
o	OEt	*p*-CH$_3$OC$_6$H$_4$	85
p	OEt	*p*-O$_2$NC$_6$H$_4$	89
q	OEt	*m*-FC$_6$H$_4$	86
r	OEt	*o*-ClC$_6$H$_4$	81

Scheme 1. Synthesis of pyrrolothiazines.

Table 1. Synthesis of pyrrolothiazine in different solvents

Entry	Compd	Solvent	Isolated yield (%)	Reaction time (h)
1	**3a**	Ethanol	71	24
2	**3a**	Methanol	66	24
3	**3a**	DMF	42	48
4	**3a**	DMSO	39	72
5	**3a**	CH$_3$CN	34	72
6	**3j**	Ethanol	86	6
7	**3j**	Methanol	80	8
8	**3j**	DMSO	78	12
9	**3j**	DMF	76	12
10	**3j**	CH$_3$CN	74	12

Table 2. Synthesis of pyrrolothiazine **3a** using different bases in EtOH

Entry	Base (30 mol %)	Yield (%)	Reaction time (h)
1	K_2CO_3	75	12
2	Et_3N	73	15
3	Pyridine	72	18
4	DBU	70	24

ortho-carbons of the aryl ring attached to C-4 at 138.4 and 128.3 ppm, respectively, and (ii) H-3 with the *ipso*-carbon (but not with the *ortho*-carbon) of the aryl ring attached to C-4. Further, H-3 also shows a HMBC correlation with the carbonyl carbon at 187.8 ppm (Fig. 1). The H-3 and H-4 chemical shifts and C,H-COSY correlations assign C-3 and C-4, respectively, to the signals at 69.3 and 67.7 ppm. The *J* value (10.8 Hz) suggests vicinal diaxial coupling between H-3 and H-4 and, hence an equatorial orientation for the benzoyl group at C-3 and the aryl ring at C-4. The 1H triplet at 3.49 ppm (J=8.4 Hz) is assigned to H-8a as it shows a HMBC correlation with C-4. The chemical shift of H-8a and H,H-COSY correlations enables the assignments of the 6-, 7- and 8-CH_2 protons. The 8-CH_2 protons give two multiplets at 2.10–2.15 and 2.33–2.45 ppm. The 6-CH_2 protons appear as multiplets at 2.57–2.62 and 2.17–2.23 ppm. The C,H-COSY correlations assign C-6, C-7 and C-8 to the signals at 53.3, 21.2 and 26.9 ppm, respectively. The 2H singlet at 3.52 ppm, showing a C,H-COSY correlation with the carbon signal at 35.3 ppm, is assigned to the fortuitously isochronous diastereotopic benzylic protons. This assignment of benzylic protons emerges from the HMBC correlations of these protons with: (i) the C-8a carbon at

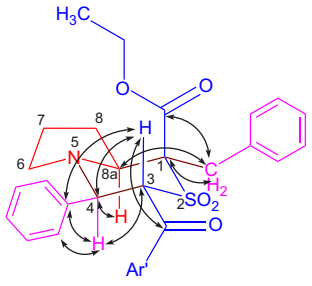


Figure 1. Selected HMBC correlations of **3a**.

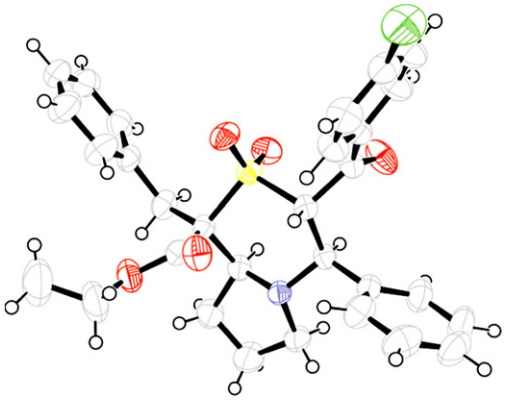


Figure 2. ORTEP diagram of **3a**.

68.6 ppm, (ii) the quaternary carbon C-1 at 77.7 ppm and (iii) the ester carbonyl carbon at 166.5 ppm. The triplet at 1.50 ppm (J=7.1 Hz) and the multiplet at 4.37–4.60 ppm related by a H,H-COSY correlation are assigned to the ester ethyl. The aromatic protons give a multiplet at 7.19–7.81 ppm. The other pyrrolothiazines (**3b–i**) also show similar spectroscopic features. The structure arrived at from an X-ray crystallographic study of a single crystal of **3a** (Fig. 2) is in accord with that assigned from NMR spectroscopic studies. Additionally, the X-ray study reveals axial and equatorial orientations for the ester and benzyl groups at C-1, respectively, and that the pyrrolidine ring is linked to the thiazine ring at C-8a equatorially. The pyrrolothiazines (**3j–r**) bearing two ester functions show similar spectroscopic features except that the benzylic protons are anisochronous. For instance, the benzylic protons of **3j** are anisochronous and appear in the ^{1}H NMR spectrum as an AB spin system with J=14.6 Hz.

2.1. Mechanism

One plausible mechanism described in Scheme 2 envisages the formation of the pyrrolothiazine **3** via a tandem sequence triggered by Knoevenagel condensation of aromatic aldehyde with ethyl 2-[(2-oxo-2-arylethyl)sulfonyl]acetate/ethyl 2-[(2-ethoxy-2-oxoethyl)sulfonyl]acetate **1** in the presence of pyrrolidine leading to **4** (Scheme 2). Subsequently, conjugate addition of pyrrolidine over **4** could afford **5**. A hydride transfer in **5** from the α-position of pyrrolidine to the β-carbon of the C=C bond could result in the formation of the pyrrolidine iminium **6**, which could undergo cyclization via nucleophilic attack by the stabilized anion to furnish **3**.

3. Conclusions

The present investigation describes a four-component tandem protocol for the stereoselective synthesis of highly substituted pyrrolothiazines from simple starting materials under mild conditions. The medicinal potential of pyrrolothiazines renders them attractive candidates for biological screening. Further scope and versatility of this tandem sequence are currently explored in our group.

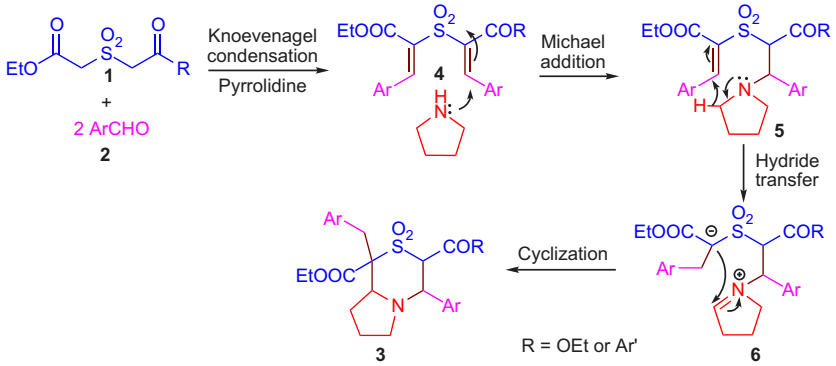
4. Experimental

4.1. General methods

Melting points reported in this work are uncorrected. Flash column chromatography was performed on silica gel (230–400 mesh) using pet ether–ethyl acetate (95:5 v/v) as an eluent. The ^{1}H NMR, ^{13}C NMR, DEPT, H,H-COSY, C,H-COSY and HMBC spectra were recorded on a Bruker (Avance) 300 MHz instrument in $CDCl_3$ using TMS as an internal standard. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. IR spectra were recorded on a JASCO FT IR instrument (KBr pellet in the case of solids and $CHCl_3$ in the case of liquids). Elemental analyses were performed on a Perkin–Elmer 2400 Series II Elemental CHN Analyser.

4.2. General procedure for the preparation of ethyl 3-aroyl-1-benzyl-2,2-dioxo-4-aryloctahydro-2-pyrrolo-[2,1-*c*][1,4]thiazine-1-carboxylates and diethyl 1-benzyl-2,2-dioxo-4-aryloctahydro-2-pyrrolo[2,1-*c*]-[1,4]thiazine-1,3-dicarboxylates

A mixture of ethyl 2-[(2-oxo-2-arylethyl)sulfonyl]acetate/ethyl 2-[(2-ethoxy-2-oxoethyl)sulfonyl]acetate (1.6 mmol), aromatic aldehyde (3.2 mmol) and pyrrolidine (1.6 mmol) was dissolved in ethanol (10 mL), heated until the solution turned yellow and stirred at room temperature for 2–5 days. After completion of the reaction, the crude product was purified using flash column chromatography on silica gel (230–400 mesh) with petroleum ether and ethyl acetate mixture (95:5 v/v) as an eluent.



Scheme 2. Mechanism for the formation of pyrrolothiazines.

4.2.1. Ethyl 1-benzyl-3-(4-chlorobenzoyl)-2,2-dioxo-4-phenyloctahydro-2-pyrrolo[2,1-*c*][1,4]thiazine-1-carboxylate (3a). Isolated as colourless solid. (0.641 g, 71%) mp=159 °C; ν_{max} (KBr) 1728, 1680, 1317, 1142 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.50 (3H, t, J=7.1 Hz), 1.56–1.72 (2H, m), 2.10–2.23 (2H, m), 2.33–2.45 (1H, m), 2.57–2.62 (1H, m), 3.49 (1H, t, J=8.4 Hz), 3.52 (2H, s), 4.33 (1H, d, J=10.8 Hz), 4.37–4.60 (2H, m), 6.24 (2H, d, J=10.8 Hz), 7.19–7.81 (14H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.3, 21.2, 26.9, 35.3, 53.3, 62.5, 67.7, 68.6, 69.3, 77.7, 126.3, 127.4, 128.0, 128.3, 128.7, 128.9, 130.0, 130.5, 130.8, 134.3, 135.7, 138.4, 140.3, 166.5, 187.8. Anal. Calcd for $C_{30}H_{30}ClNO_5S$: C, 65.27; H, 5.48; N, 2.54. Found: C, 65.31; H, 5.42; N, 2.58.

4.2.2. Ethyl 3-(4-chlorobenzoyl)-1-(4-methylbenzyl)-4-(4-methylphenyl)-2,2-dioxooctahydro-2-pyrrolo[2,1-*c*]-[1,4]thiazine-1-carboxylate (3b). Isolated as colourless solid (0.382 g, 67%) mp=151 °C; ν_{max} (KBr) 1730, 1680, 1315, 1140 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.49 (3H, t, J=7.1 Hz), 1.55–1.69 (2H, m), 1.99–2.13 (1H, m), 2.17 (3H, s), 2.24 (3H, s), 2.30–2.45 (2H, m), 2.57–2.62 (1H, m), 3.46 (1H, t, J=8.4 Hz), 3.48 (2H, s), 4.29 (2H, d, J=10.8 Hz), 4.34–4.55 (2H, m), 6.23 (2H, d, J=10.8 Hz), 6.93–7.77 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.2, 20.9, 21.0, 21.1, 26.8, 34.8, 53.2, 62.3, 67.3, 68.4, 69.2, 77.7, 125.9, 128.5, 128.6, 129.4, 129.6, 129.8, 130.4, 130.5, 131.1, 135.3, 135.6, 136.7, 137.8, 140.1, 166.4, 187.6. Anal. Calcd for $C_{32}H_{34}ClNO_5S$: C, 66.25; H, 5.91; N, 2.41. Found: C, 66.19; H, 5.96; N, 2.48.

4.2.3. Ethyl 3-(4-chlorobenzoyl)-1-(4-chlorobenzyl)-4-(4-chlorophenyl)-2,2-dioxooctahydro-2-pyrrolo[2,1-*c*][1,4]-thiazine-1-carboxylate (3c). Isolated as colourless solid (0.421 g, 69%) mp=166 °C; ν_{max} (KBr) 1732, 1678, 1317, 1140 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.50 (3H, t, J=7.2 Hz), 1.61–1.74 (2H, m), 2.05–2.23 (2H, m), 2.27–2.39 (1H, m), 2.56–2.61 (1H, m), 3.44 (1H, t, J=8.4 Hz), 3.47 (2H, s), 4.32 (2H, d, J=10.7 Hz), 4.40–4.61 (2H, m), 6.18 (2H, d, J=10.7 Hz), 7.16–7.78 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.4, 21.0, 26.8, 34.6, 53.3, 62.7, 66.9, 68.4, 69.1, 77.5, 127.7, 128.2, 128.4, 128.9, 129.4, 130.6, 131.2, 132.2, 132.6, 133.4, 134.1, 135.3, 136.9, 140.8, 166.1, 187.3. Anal. Calcd for $C_{30}H_{28}Cl_3NO_5S$: C, 58.03; H, 4.54; N, 2.26. Found: C, 58.11; H, 4.52; N, 2.29.

4.2.4. Ethyl 3-(4-chlorobenzoyl)-1-(4-nitrobenzyl)-4-(4-nitrophenyl)-2,2-dioxooctahydro-2-pyrrolo[2,1-*c*][1,4]-thiazine-1-carboxylate (3d). Isolated as pale yellow solid. (0.392 g, 62%) mp=176 °C; ν_{max} (KBr) 1728, 1684, 1346, 1140 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.54 (3H, t, J=7.2 Hz), 1.70–1.78 (2H, m), 2.05–2.24 (2H, m), 2.26–2.35 (1H, m), 2.56–2.61 (1H, m), 3.51 (1H, t, J=8.4 Hz), 3.58 (2H, s), 4.46–4.67 (2H, m), 4.51 (1H, d, J=10.5 Hz), 6.23 (1H, d, J=10.5 Hz), 7.27–8.11 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.4, 21.0, 26.8, 35.0, 53.5, 63.2, 66.8, 68.6, 68.9, 77.3, 123.2, 123.7, 124.3, 127.5, 129.1, 130.6, 130.9, 131.9, 134.8, 141.3, 141.7, 145.3, 147.3, 147.7, 165.7, 186.7. Anal. Calcd for $C_{30}H_{28}ClN_3O_9S$: C, 56.12; H, 4.40; N, 6.54. Found: C, 56.05; H, 4.45; N, 6.62.

4.2.5. Ethyl 3-(4-chlorobenzoyl)-1-(4-methoxybenzyl)-4-(4-methoxyphenyl)-2,2-dioxooctahydro-2-pyrrolo[2,1-*c*]-[1,4]thiazine-1-carboxylate (3e). Isolated as viscous paste. (0.401 g, 66%); ν_{max} ($CHCl_3$) 1734, 1684, 1317, 1139 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.50 (3H, t, J=7.1 Hz), 1.58–1.71 (2H, m), 2.04–2.21 (2H, m), 2.31–2.38 (1H, m), 2.57–2.63 (1H, m), 3.44 (1H, t, J=8.4 Hz), 3.46 (2H, s), 3.68 (3H, s), 3.72 (3H, s), 4.26 (1H, d, J=11.0 Hz), 4.39–4.60 (2H, m), 6.20 (1H, d, J=11.0 Hz), 6.65–7.93 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.4, 21.1, 26.8, 34.5, 53.2, 54.9, 55.0, 62.4, 67.0, 68.3, 69.3, 77.7, 112.6, 113.3, 126.1, 128.7, 129.0, 129.1, 129.4, 130.2, 130.5, 131.9, 135.6, 140.3, 158.7, 159.2, 166.5, 187.8. Anal. Calcd for $C_{32}H_{34}ClNO_7S$: C, 62.79; H, 5.60; N, 2.29. Found: C, 62.84; H, 5.68; N, 2.33.

4.2.6. Ethyl 3-(4-chlorobenzoyl)-1-(2-methylbenzyl)-4-(2-methylphenyl)-2,2-dioxooctahydro-2-pyrrolo[2,1-*c*]-[1,4]thiazine-1-carboxylate (3f). Isolated as pale yellow solid (0.382 g, 67%) mp=112 °C; ν_{max} (KBr) 1724, 1682, 1318, 1146 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.41 (3H, t, J=7.2 Hz), 1.47–1.65 (2H, m), 2.07–2.23 (2H, m), 2.44 (3H, s), 2.47 (3H, s), 2.51–2.56 (2H, m), 3.45–3.63 (3H, m), 4.33–4.53 (2H, m), 4.66 (1H, d, J=10.5 Hz), 6.34 (1H, d, J=10.5 Hz), 7.10–7.79 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.1, 20.0, 20.1, 21.5, 27.0, 30.9, 52.4, 61.8, 62.5, 68.7, 68.8, 77.4, 125.8, 126.5, 126.9, 127.1, 127.8, 128.8, 129.6, 130.4, 130.6, 130.7, 133.1, 135.6, 136.6, 136.8, 137.2, 140.3, 167.5, 187.8. Anal. Calcd for $C_{32}H_{34}ClNO_5S$: C, 66.25; H, 5.91; N, 2.41. Found: C, 66.19; H, 5.96; N, 2.48.

4.2.7. Ethyl 3-(4-chlorobenzoyl)-1-(4-fluorobenzyl)-4-(4-fluorophenyl)-2,2-dioxooctahydro-2-pyrrolo[2,1-*c*][1,4]-thiazine-1-carboxylate (3g). Isolated as yellow solid. (0.389 g, 67%) mp=147 °C; ν_{max} (KBr) 1730, 1684, 1315, 1147 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.50 (3H, t, J=7.1 Hz), 1.67–1.74 (2H, m), 2.05–2.23 (2H, m), 2.28–2.40 (1H, m), 2.57–2.62 (1H, m), 3.42 (1H, t, J=8.4 Hz), 3.48 (2H, s), 4.32 (1H, d, J=10.7 Hz), 4.40–4.61 (2H, m), 6.19 (1H, d, J=10.7 Hz), 6.88–7.77 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.4, 21.1, 26.9, 34.5, 53.3, 62.7, 66.9, 68.5, 69.4, 77.6, 114.8, 115.1, 128.9, 129.8, 129.9, 130.5, 132.5, 132.6, 134.2, 134.3, 135.5, 140.7, 160.7, 163.9, 166.3, 187.6. Anal. Calcd for $C_{30}H_{28}ClF_2NO_5S$: C, 61.27; H, 4.80; N, 2.38. Found: C, 61.30; H, 4.84; N, 2.32.

4.2.8. Ethyl 1-(4-chlorobenzyl)-4-(4-chlorophenyl)-3-(4-methylbenzoyl)-2,2-dioxooctahydro-2-pyrrolo[2,1-*c*]-[1,4]thiazine-1-carboxylate (3h). Isolated as yellow solid. (0.419 g, 63%) mp=127 °C; ν_{max} (KBr) 1735, 1679, 1319, 1148 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.51 (3H, t, J=7.2 Hz), 1.60–1.74 (2H, m), 2.04–2.14 (2H, m), 2.30 (3H, s), 2.32–2.39 (1H, m), 2.56–2.61 (1H, m), 3.42–3.46 (3H, m), 4.34 (1H, d, J=10.7 Hz), 4.38–4.58 (2H, m), 6.20 (1H, d, J=10.7 Hz), 7.09–7.40 (6H, m), 7.72 (2H, d, J=8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.4, 21.0, 21.6, 26.8, 34.7, 53.4, 62.6, 66.9, 68.5, 68.8, 77.2, 127.8, 128.1, 128.4, 129.3, 129.4, 131.3, 132.3, 132.8, 133.3, 133.9, 134.6, 137.1, 145.2, 166.2, 187.7. Anal. Calcd for $C_{31}H_{31}Cl_2NO_5S$: C, 62.00; H, 5.20; N, 2.33. Found: C, 61.95; H, 5.26; N, 2.37.

4.2.9. Ethyl 3-(4-methylbenzoyl)-1-(4-methylbenzyl)-4-(4-methylphenyl)-2,2-dioxooctahydro-2-pyrrolo[2,1-*c*]-[1,4]thiazine-1-carboxylate (3i). Isolated as yellow solid.

(0.422 g, 61%) mp=158 °C; ν_{max} (KBr) 1734, 1689, 1315, 1145; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.51 (3H, t, J=7.1 Hz), 1.58–1.68 (2H, m), 2.04–2.13 (2H, m), 2.19 (3H, s), 2.25 (3H, s), 2.28 (3H, s), 2.56–2.63 (2H, m), 3.43–3.47 (3H, m), 4.30 (1H, d, J=10.8 Hz), 4.46–4.54 (2H, m), 6.23 (1H, d, J=10.8 Hz), 6.96–7.74 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.3, 20.8, 21.0, 21.4, 21.5, 26.5, 35.8, 55.1, 61.9, 67.9, 68.4, 69.2, 77.6, 128.2, 128.8, 129.6, 129.9, 130.0, 130.9, 131.4, 132.2, 137.0, 138.7, 139.3, 139.6, 140.1, 166.7, 185.6. Anal. Calcd for $C_{33}H_{37}NO_5S$: C, 70.81; H, 6.66; N, 2.50. Found: C, 70.87; H, 6.59; N, 2.55.

4.2.10. Diethyl 1-benzyl-2,2-dioxo-4-phenyloctahydro-2-pyrrolo[2,1-*c*][1,4]thiazine-1,3-dicarboxylate (3j). Isolated as yellow solid. (0.875 g, 86%) mp=146 °C; ν_{max} (KBr) 1735, 1719, 1319, 1138 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.96 (3H, t, J=7.2 Hz), 1.42 (3H, t, J=7.1 Hz), 1.57–1.69 (2H, m), 2.02–2.13 (2H, m), 2.27–2.36 (1H, m), 2.56–2.62 (1H, m), 3.40 (1H, t, J=8.4 Hz), 3.47 (1H, d, J=14.6 Hz), 3.53 (1H, d, J=14.6 Hz), 3.97 (2H, q, J=7.2 Hz), 4.06 (1H, d, J=10.8 Hz), 4.37–4.48 (2H, m), 5.04 (1H, d, J=10.8 Hz), 7.24–7.44 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.7, 14.2, 21.1, 26.8, 35.3, 53.4, 62.1, 62.4, 67.5, 68.6, 69.9, 77.6, 127.4, 128.0, 128.5, 129.1, 129.7, 130.9, 134.4, 138.2, 162.1, 166.0. Anal. Calcd for $C_{26}H_{31}NO_6S$: C, 64.31; H, 6.43; N, 2.88. Found: C, 64.27; H, 6.48; N, 2.82.

4.2.11. Diethyl 1-(4-chlorobenzyl)-4-(4-chlorophenyl)-2,2-dioxooctahydro-2-pyrrolo[2,1-*c*][1,4]thiazine-1,3-dicarboxylate (3k). Isolated as yellow solid. (0.977 g, 84%) mp=152 °C; ν_{max} (KBr) 1734, 1716, 1317, 1134 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.99 (3H, t, J=7.1 Hz), 1.39 (3H, t, J=7.2 Hz), 1.53–1.64 (2H, m), 1.99–2.15 (2H, m), 2.23–2.26 (1H, m), 2.53–2.58 (1H, m), 3.31–3.36 (1H, m), 3.39 (1H, d, J=14.7 Hz), 3.46 (1H, d, J=14.7 Hz), 3.96 (2H, q, J=7.2 Hz), 4.03 (1H, d, J=11.1 Hz), 4.33–4.49 (2H, m), 4.97 (1H, d, J=11.1 Hz), 7.17–7.35 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.3, 13.8, 20.6, 26.3, 34.2, 52.9, 61.9, 62.3, 66.3, 68.1, 69.4, 76.3, 127.7, 128.9, 130.5, 131.8, 132.4, 132.8, 133.8, 136.4, 161.5, 165.3. Anal. Calcd for $C_{26}H_{29}Cl_2NO_6S$: C, 56.32; H, 5.27; N, 2.53. Found: C, 56.36; H, 5.21; N, 2.61.

4.2.12. Diethyl 1-(4-methylbenzyl)-4-(4-methylphenyl)-2,2-dioxooctahydro-2-pyrrolo[2,1-*c*][1,4]thiazine-1,3-dicarboxylate (3l). Isolated as yellow solid. (0.938 g, 87%) mp=136 °C; ν_{max} (KBr) 1738, 1716, 1318, 1136 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.99 (3H, t, J=7.1 Hz), 1.43 (3H, t, J=7.2 Hz), 1.56–1.65 (2H, m), 2.01–2.13 (3H, m), 2.29 (3H, s), 2.31 (3H, s), 2.57–2.63 (1H, m), 3.36–3.41 (1H, m), 3.44 (1H, d, J=14.7 Hz), 3.51 (1H, d, J=14.7 Hz), 3.96 (2H, q, J=7.1 Hz), 4.03 (1H, d, J=11.1 Hz), 4.41–4.45 (2H, m), 5.04 (1H, d, J=11.1 Hz), 7.05–7.33 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.5, 13.9, 20.8, 20.9, 21.3, 26.5, 34.7, 53.1, 61.7, 62.2, 67.0, 68.3, 69.8, 77.4, 126.4, 128.4, 129.6, 130.4, 131.1, 135.1, 136.5, 137.9, 161.9, 165.8. Anal. Calcd for $C_{28}H_{35}NO_6S$: C, 65.47; H, 6.87; N, 2.73. Found: C, 65.51; H, 6.95; N, 2.70.

4.2.13. Diethyl 2,2-dioxo-4-(2-thienyl)-1-(2-thienylmethyl)octahydro-2-pyrrolo[2,1-*c*][1,4]thiazine-1,3-dicarboxylate (3m). Isolated as yellow solid. (0.835 g, 80%) mp=140 °C; ν_{max} (KBr) 1736, 1718, 1319, 1151 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.04 (3H, t, J=7.2 Hz), 1.47 (3H, t, J=7.2 Hz), 1.61–1.68 (2H, m), 2.03–2.19 (3H, m), 2.77–2.82 (1H, m), 3.24–3.29 (1H, m), 3.69 (2H, s), 4.03 (2H, q, J=7.2 Hz), 4.39 (1H, d, J=10.9 Hz), 4.48 (2H, q, J=7.2 Hz), 5.06 (1H, d, J=10.9 Hz), 6.86–7.27 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.5, 13.9, 20.4, 26.5, 29.9, 52.9, 62.0, 62.6, 67.8, 70.4, 71.3, 76.8, 125.2, 125.9, 126.2, 126.7, 129.2, 135.2, 141.3, 161.6, 165.1. Anal. Calcd for $C_{22}H_{27}NO_6S_3$: C, 53.10; H, 5.47; N, 2.81. Found: C, 53.16; H, 5.39; N, 2.87.

4.2.14. Diethyl 1-(4-fluorobenzyl)-4-(4-fluorophenyl)-2,2-dioxooctahydro-2-pyrrolo[2,1-*c*][1,4]thiazine-1,3-dicarboxylate (3n). Isolated as yellow solid. (0.898 g, 82%) mp=120 °C; ν_{max} (KBr) 1734, 1715, 1319, 1136 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.98 (3H, t, J=7.1 Hz), 1.41 (3H, t, J=7.1 Hz), 1.59–1.65 (2H, m), 2.02–2.15 (2H, m), 2.25–2.29 (1H, m), 2.53–2.59 (1H, m), 3.31–3.37 (1H, m), 3.41 (1H, d, J=15.3 Hz), 3.48 (1H, d, J=15.3 Hz), 3.96 (2H, q, J=7.1 Hz), 4.04 (1H, d, J=11.1 Hz), 4.37–4.44 (2H, m), 4.98 (1H, d, J=11.1 Hz), 6.88–7.40 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.6, 14.1, 20.9, 26.6, 34.4, 53.3, 62.2, 62.5, 66.7, 68.4, 69.9, 77.4, 114.6, 114.9, 129.9, 130.0, 132.4, 132.5, 133.9, 134.0, 160.4, 160.8, 162.0, 163.6, 164.1, 165.7. Anal. Calcd for $C_{26}H_{29}F_2NO_6S$: C, 59.87; H, 5.60; N, 2.69. Found: C, 59.92; H, 5.66; N, 2.61.

4.2.15. Diethyl 1-(4-methoxybenzyl)-4-(4-methoxyphenyl)-2,2-dioxooctahydro-2-pyrrolo[2,1-*c*][1,4]thiazine-1,3-dicarboxylate (3o). Isolated as yellow solid. (0.973 g, 85%) mp=118 °C; ν_{max} (KBr) 1734, 1716, 1317, 1138 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.98 (3H, t, J=7.1 Hz), 1.41 (3H, t, J=7.1 Hz), 1.54–1.63 (2H, m), 2.01–2.09 (2H, m), 2.23–2.31 (1H, m), 2.55–2.60 (1H, m), 3.29–3.35 (1H, m), 3.43 (1H, d, J=14.4 Hz), 3.51 (1H, d, J=14.4 Hz), 3.73 (3H, s), 3.76 (3H, s), 3.87 (1H, d, J=10.9 Hz), 3.96 (2H, q, J=7.1 Hz), 4.36–4.45 (2H, m), 4.98 (1H, d, J=10.9 Hz), 6.75–7.33 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.7, 14.2, 21.0, 26.7, 34.4, 53.2, 54.9, 55.1, 61.9, 62.3, 66.8, 68.3, 70.0, 77.6, 113.2, 114.2, 114.9, 126.2, 130.3, 131.8, 158.6, 159.4, 162.1, 165.9. Anal. Calcd for $C_{28}H_{35}NO_8S$: C, 61.63; H, 6.47; N, 2.57. Found: C, 61.66; H, 6.42; N, 2.63.

4.2.16. Diethyl 1-(4-nitrobenzyl)-4-(4-nitrophenyl)-2,2-dioxooctahydro-2-pyrrolo[2,1-*c*][1,4]thiazine-1,3-dicarboxylate (3p). Isolated as yellow solid. (1.075 g, 89%) mp=168 °C; ν_{max} (KBr) 1736, 1714, 1314, 1151 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.02 (3H, t, J=6.9 Hz), 1.45 (3H, t, J=6.8 Hz), 1.66–1.75 (2H, m), 2.05–2.23 (3H, m), 2.53–2.58 (1H, m), 3.38–3.44 (1H, m), 3.51 (1H, d, J=14.4 Hz), 3.63 (1H, d, J=14.4 Hz), 3.94–4.07 (2H, m), 4.22 (1H, d, J=10.7 Hz), 4.37–4.51 (2H, m), 5.01 (1H, d, J=10.7 Hz), 7.59–8.19 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.6, 14.1, 20.8, 26.5, 34.8, 53.3, 62.6, 62.9, 66.4, 68.5, 69.4, 77.2, 122.9, 123.5, 127.9, 131.7, 141.9, 145.1, 146.9, 147.7, 161.4, 165.1. Anal. Calcd for $C_{26}H_{29}N_3O_{10}S$: C, 54.25; H, 5.08; N, 7.30. Found: C, 54.31; H, 5.12; N, 7.27.

4.2.17. Diethyl 1-(3-fluorobenzyl)-4-(3-fluorophenyl)-2,2-dioxooctahydro-2-pyrrolo[2,1-*c*][1,4]thiazine-1,3-dicarboxylate (3q). Isolated as yellow solid. (0.942 g, 86%)

mp=110 °C; ν_{max} (KBr) 1732, 1720, 1410, 1145 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.96 (3H, t, J=7.2 Hz), 1.40 (3H, t, J=7.2 Hz), 1.59–1.65 (2H, m), 2.01–2.15 (2H, m), 2.20–2.27 (1H, m), 2.56–2.61 (1H, m), 3.32–3.38 (1H, m), 3.40 (1H, d, J=14.7 Hz), 3.49 (1H, d, J=14.7 Hz), 3.96 (2H, q, J=7.2 Hz), 4.04 (1H, d, J=10.5 Hz), 4.36–4.47 (2H, m), 4.99 (1H, d, J=10.5 Hz), 6.83–7.31 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.3, 13.8, 20.6, 26.3, 34.5, 52.9, 61.9, 62.3, 66.5, 68.1, 69.4, 76.4, 113.7, 114.0, 117.1, 117.4, 126.4, 128.9, 129.0, 136.3, 136.4, 140.3, 140.4, 160.2, 161.5, 163.5, 165.3. Anal. Calcd for $C_{26}H_{29}F_2NO_6S$: C, 59.87; H, 5.60; N, 2.69. Found: C, 59.92; H, 5.66; N, 2.61.

4.2.18. Diethyl 1-(2-chlorobenzyl)-4-(2-chlorophenyl)-2,2-dioxooctahydro-2-pyrrolo[2,1-*c*][1,4]thiazine-1,3-dicarboxylate (3r). Isolated as paste. (0.943 g, 81%); ν_{max} ($CHCl_3$) 1740, 1730, 1318, 1139 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.92 (3H, t, J=7.2 Hz), 1.09 (3H, t, J=7.1 Hz), 1.31–1.44 (2H, m), 1.99–2.22 (2H, m), 2.45–2.61 (2H, m), 3.44–3.49 (1H, m), 3.56 (1H, d, J=16.2 Hz), 3.66 (1H, d, J=16.2 Hz), 3.92 (2H, q, J=7.2 Hz), 4.12–4.23 (2H, m), 4.75 (1H, d, J=11.1 Hz), 5.12 (1H, d, J=11.1 Hz), 7.21–7.60 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.3, 13.4, 21.1, 26.9, 30.1, 51.9, 60.9, 61.9, 62.1, 67.8, 68.6, 76.5, 126.3, 127.3, 128.0, 128.8, 129.0, 129.2, 129.4, 131.5, 132.5, 133.8, 134.7, 135.3, 161.3, 165.9. Anal. Calcd for $C_{26}H_{29}Cl_2NO_6S$: C, 56.32; H, 5.27; N, 2.53. Found: C, 56.36; H, 5.21; N, 2.61.

4.3. X-ray crystallographic determination of compound 3a

Data were collected at room temperature on an Enraf-Nonius MACH 3 four-circle diffractometer (Mo Kα radiation, λ=0.71073 Å). The data collection, integration and data reduction for **3a** were performed using CAD-4 EXPRESS[17] and XCAD4[18] programs and an empirical absorption correction was applied using μ scan method.[19] The unit cell parameters were determined by least square fitting of 25 randomly selected strong reflections and an empirical absorption correction was applied using the azimuthal scan method. The structure was solved by direct methods (SHELXS 97)[20] and subsequent Fourier synthesis and refined by full matrix least squares on SHELXL 97[21] for all non-hydrogen atoms for **3a**. All hydrogen atoms were placed in calculated positions.

4.3.1. Compound 3a. $C_{30}H_{30}ClNO_5S$, M=552.06, Triclinic, Space group P-1, a=10.596 Å, b=11.587 Å, c=12.118 Å, V=1335.5 $Å^3$, Z=2, F(000)=580, μ=0.263 mm^{-1}, D_c=1.373 mg/m^3. The reflections collected were 5535 of which 4699 unique [$R_{(int)}$=0.0163]; 3194 reflections $I>2\sigma(I)$, R_1=0.0335 and ωR_2=0.0863 for 3194 [$I>2\sigma(I)$] and R_1=0.0697 and ωR_2=0.1001 for all (4699) intensity data. Goodness of fit=1.009, residual electron density in the final Fourier map was 0.235 and −0.224 e $Å^{-3}$. CCDC number is 608117.

Acknowledgements

S.P. thanks the Council of Scientific and Industrial Research, New Delhi for a major research project no. 01(1926/04/EMR II) and the Department of Science and Technology, New Delhi for funds under: (i) IRHPA programme for the purchase of a high resolution NMR spectrometer and (ii) FIST programme and the University Grants Commission, New Delhi for funds under the DRS and ASIST programmes. The authors are thankful to the reviewers for the mechanistic suggestions.

References and notes

1. Reddy, D. B.; Reddy, S.; Reddy, N. S.; Reddy, M. V. R. *Indian J. Chem., Sect. B* **1991**, *30*, 529.
2. Srivatsava, S. K.; Yadav, R.; Srivatsava, S. D. *Indian J. Chem., Sect. B* **2004**, *43*, 399.
3. Arranz, M. E.; Diaz, J. A.; Ingate, S. T.; Witvrouw, M.; Pannecouque, C.; Balzarini, J.; De Clercq, E.; Vega, S. *Bioorg. Med. Chem.* **1999**, *7*, 2811.
4. Moriyama, H.; Tsukida, T.; Inoue, Y.; Yokota, K.; Yoshino, K.; Kondo, H.; Miura, N.; Nishimura, S. *J. Med. Chem.* **2004**, *47*, 1930.
5. Koketsu, M.; Tanaka, K.; Takenaka, Y.; Kwong, C. D.; Ishihara, H. *Eur. J. Pharm. Sci.* **2002**, *15*, 307.
6. Hemming, K.; Patel, N. *Tetrahedron Lett.* **2004**, *45*, 7553.
7. Bundy, G. L.; Banitt, L. S.; Dobrowolski, P. J.; Palmer, J. R.; Schwartz, T. M.; Zimmermann, D. C.; Lipton, M. F.; Mauragis, M. A.; Veley, M. F.; Appell, R. B.; Clouse, R. C.; Daugs, E. D. *Org. Process Res. Dev.* **2001**, *5*, 144.
8. Mylari, B. L.; Carty, T. J.; Moore, P. F.; Zembrowski, W. J. *J. Med. Chem.* **1990**, *33*, 2019.
9. Armenise, D.; Trapani, G.; Stasi, F.; Morlacchi, F. *Arch. Pharm.* **1998**, *331*, 54.
10. Armenise, D.; Trapani, G.; Arrivo, V.; Morlacchi, F. *Farmaco* **1991**, *46*, 1023.
11. Campiani, G.; Garofalo, A.; Fiorini, I.; Botta, M.; Nacci, V.; Tafi, A.; Chiarini, A.; Budriesi, R.; Bruni, G.; Romeo, M. R. *J. Med. Chem.* **1995**, *38*, 4393.
12. (a) Alex Raja, V. P.; Perumal, S. *Tetrahedron* **2006**, *62*, 4892; (b) Savitha Devi, N.; Perumal, S. *Tetrahedron* **2006**, *62*, 5931; (c) Srinivasan, M.; Perumal, S. *Tetrahedron* **2006**, *62*, 7726.
13. (a) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.—Eur. J* **2000**, *6*, 3321; (b) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3169; (c) Domling, A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 318; (d) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471.
14. (a) *Tandem Organic Reactions*; Ho, T. L., Ed.; Wiley: New York, NY, 1992; (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131; (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115; (d) Linghu, X.; Nicewicz, D. A.; Johnson, J. S. *Org. Lett.* **2002**, *4*, 2957.
15. Reddy, D. B.; Reddy, M. M.; Reddy, P. V. R. *Indian J. Chem., Sect. B* **1993**, *32*, 1018.
16. Baliah, V.; Rangarajan, T. *J. Chem. Soc., Chem. Commun.* **1954**, 3068.
17. Enraf-Nonius. *CAD-4 EXPRESS Version 5.0*; Enraf-Nonius: Delft, The Netherlands, 1994.
18. Harms, K.; Wocadio, S. *XCAD4*; University of Marburg: Marburg, Germany, 1995.
19. North, A. C. T.; Philips, D. C.; Mathews, F. S. *Acta Crystallogr., Sect. A* **1968**, *24*, 351.
20. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **1990**, *46*, 467.
21. Sheldrick, G. M. *SHELXL 97*; University of Gottingen: Gottingen, Germany, 1997.